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RESEARCH ARTICLE

PHARMACOLOGICAL EVALUATION OF HERBAL FORMULATION UNDER SIMULATED REAL- LIFE USAGE CONDITIONS IN EXPERIMENTAL WOUND HEALING MODEL

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ABSTRACT

The process of wound healing is a complicated physiological undertaking that includes inflammation, proliferation, and the remodeling of tissue. Oxidative stress, decreased angiogenesis, microbial infection, and reduced collagen synthesis are all factors that contribute to the considerable delay in wound healing that is associated with diabetes mellitus. The use of herbal medicines as alternative therapeutic agents has become more popular due to the fact that they are not only safe but also affordable and have pharmacological action that targets several targets. In the current study, the objective was to create and assess a topical herbal gel formulation for diabetic wound healing that contained extract of Nyctanthes arbor-tristis. The formulation was intended to be used under settings that were mimicked to be used in real life. After collecting, shade drying, powdering, and extracting the leaves of Nyctanthes arbor-tristis with ethanol using the Soxhlet extraction method, the leaves were gathered. In the preliminary screening of phytochemicals, the presence of flavonoids, alkaloids, tannins, glycosides, phenolic compounds, and saponins was established. In order to analyze the physicochemical properties of herbal gel formulations (F1, F2, and F3), Carbopol 934 was used as the gelling agent. The formulations were examined for pH, viscosity, spreadability, extrudability, homogeneity, washability, grittiness, syneresis, drug content, and stability. Over the course of six hours, an in-vitro drug diffusion investigation demonstrated sustained drug release. The F2 formulation had the highest possible drug content (98.4%) and the most regulated drug release pattern of all the formulations. An excision wound model was utilized in diabetic rats for the purpose of conducting pharmacological assessment experiments. At day 0, day 3, day 7, day 10, and day 14, the percentage of wound contraction was measured. A wound contraction rate of 91% was seen in the test group that was treated with herbal gel, in comparison to 63% in the control group and 96% in the conventional medicine group. The safety of the formulation was validated by the skin irritation investigation. As a consequence of the antioxidant, antibacterial, and anti-inflammatory characteristics of phytoconstituents, the findings suggest that the herbal gel made from Nyctanthes arbor-tristis contains substantial wound healing activity. The formulation remained stable in conditions that were approximated to be a real-life usage scenario, which suggests that it is suitable for therapeutic application in the actual world. When it comes to the treatment of diabetic wounds, the herbal gel that was produced has the potential to be a safe, effective, and cost-efficient solution.

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INTRODUCTION

WOUND HEALING: Wound healing is a natural biological process through which the body repairs damaged tissue and restores normal skin structure. It is a complex and continuous process involving coordination between different types of cells, growth factors, cytokines, and extracellular matrix components.

The wound healing process occurs in three main stages:

1. **INFLAMMATION PHASE –** Immediately after injury, the body activates the immune response. White blood cells remove microorganisms, dead cells, and debris to prevent infection.
2. **PROLIFERATION PHASE** – New tissue begins to form. Fibroblast cells produce collagen, blood vessels develop (angiogenesis), and granulation tissue forms to cover the wound.
3. **REMODELING PHASE –** Collagen fibers reorganize, tissue strength increases, and the wound gradually closes with scar formation. Any disturbance in these stages may delay healing and lead to chronic wounds. Diseases such as diabetes mellitus significantly affect wound healing by

increasing oxidative stress, prolonging inflammation, reducing blood supply, and increasing risk of microbial infection.

PHARMACOLOGICAL ASPECTS OF WOUND HEALING

ROLE OF OXIDATIVE STRESS: Oxidative stress plays an important role in delayed wound healing, especially in diabetic conditions. During injury, excessive production of reactive oxygen species (ROS) damages cells, proteins, and tissues. High oxidative stress slows down fibroblast activity and delays formation of new tissue. Antioxidant enzymes such as superoxide dismutase (SOD) and catalase help neutralize harmful free radicals. Drugs or herbal medicines having antioxidant activity can reduce oxidative stress and promote faster healing.

ROLE OF INFECTION: Infection is one of the major causes of delayed wound healing. Microorganisms such as Staphylococcus aureus and Pseudomonas aeruginosa commonly infect wounds and prolong inflammation. These bacteria release toxins that damage tissues and slow down healing. Therefore, antimicrobial activity is an important property of wound healing drugs.

ROLE OF COLLAGEN IN TISSUE REPAIR: Collagen is an important structural protein responsible for strength and elasticity of skin. During wound healing, fibroblast cells synthesize collagen which helps in tissue repair and wound contraction. Hydroxyproline is commonly measured in pharmacological studies as an indicator of collagen formation.

MULTI-TARGET ACTION OF HERBAL DRUGS

Herbal medicines act through multiple mechanisms unlike synthetic drugs which usually act on a single target.

Herbal drugs show:

1.Anti-inflammatory activity
2.Antioxidant activity
3.Antimicrobial activity
4.Collagen synthesis promoting activity
5.Angiogenesis promoting activity

These combined effects make herbal medicines useful in complex conditions like diabetic wounds.

IMPORTANCE OF STUDYING REAL-LIFE USAGE CONDITIONS

In real clinical practice, patients do not always use medicines regularly as prescribed. Many patients: forget to apply medicine, skip doses, apply lower quantity, stop treatment early. However, most experimental pharmacological studies are conducted under ideal conditions where medicines are given regularly in fixed doses. Because of this difference, drug effectiveness observed in laboratory studies may not exactly match clinical outcomes. Therefore, studying drug activity under simulated real-life conditions provides more practical and clinically relevant results.

DIABETES MELLITUS AND WOUND HEALING: Diabetes mellitus is a chronic metabolic disorder characterized by increased blood glucose levels. Diabetes negatively affects many physiological processes including wound healing. Diabetic wounds heal slowly due to several reasons:

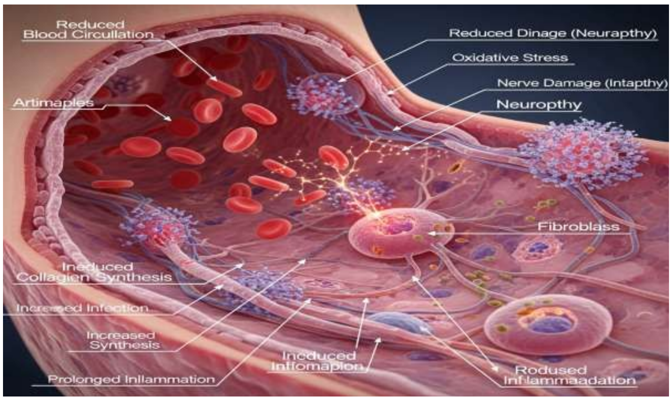


Figure 1. Reasons for Diabetic wound heal slow

High glucose levels increase reactive oxygen species production and delay tissue regeneration. Diabetic patients are also more susceptible to bacterial infections which further slowdown healing. Therefore, diabetic wounds require medicines that act on multiple targets such as inflammation, oxidative stress, microbial infection, and tissue repair.
Factors Affecting Wound Healing

- **Oxidative Stress:** Excess production of free radical damages cells and delays healing.
- Infection: **Microbial growth prolongs inflammation and prevents tissue repair.**
- Collagen Formation: **Proper collagen synthesis improves wound contraction and tissue strength.**

Role of Herbal Formulations in Wound Healing. Herbal medicines have been used traditionally for wound treatment due to their safety and effectiveness. Many medicinal plants show wound healing activity, such as: Nyctanthes arbor-tristis Herbal drugs help in:

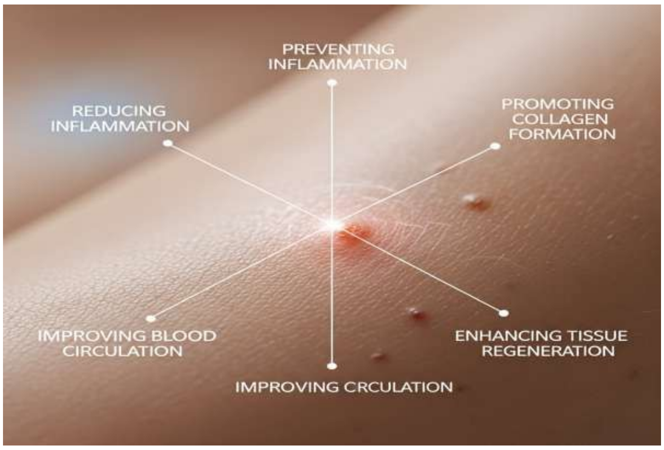


Figure 2. Activities of wound healing by medicinal Plants

Because herbal medicines act through multiple pathways, they are considered suitable for treating chronic wounds.
Real-Life Usage Conditions in Drug Therapy

In practical conditions, patients may not strictly follow treatment schedules. Common problems include:

1. irregular application of medicine low dose application

2. interrupted treatment poor compliance

Such variations affect therapeutic effectiveness. Therefore, studying drug activity under simulated real-life usage conditions helps in understanding actual drug performance.

2. Plant Profile: Nyctanthes arbor-tristis (Parijata)

Nyctanthes arbor-tristis, commonly known as Parijata or Night Jasmine, is a medicinal plant belonging to family Oleaceae. It is widely distributed in tropical and subtropical regions of India. The plant is commonly found in home gardens, temple premises, and herbal gardens. Taxonomical Classification

Kingdom: Plantae
Family: Oleaceae
Genus: Nyctanthes
Species: Nyctanthes arbor-tristis

Phytochemical Constituents

The plant contains several bioactive compounds such as Flavonoids, Glycosides, Phenolic compounds, Alkaloids, Tannins, Essential oils

Pharmacological Activities

Nyctanthes arbor-tristis shows various pharmacological activities:

1.Anti-inflammatory
2.Antioxidant
3.Antimicrobial
4.Antidiabetic
5.Analgesic

These properties make the plant suitable for evaluation in diabetic wound healing models.

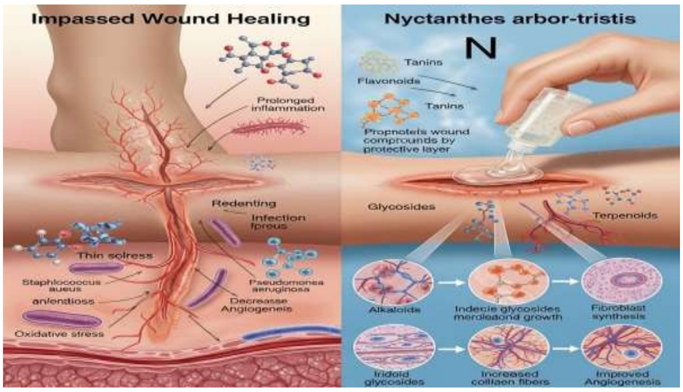


Figure 3. Comparison of wound healing by Impassed and Nyctanthes arbor-tristi

Multi-target Pharmacological Action of Herbal Drugs

Table 1. Herbal medicines act on multiple factors responsible for delayed wound healing.

Problem	Herbal Action
Oxidative stress	antioxidant activity
Infection	antimicrobial activity
Inflammation	anti-inflammatory action
Low collagen	increased collagen synthesis
Poor blood supply	angiogenesis stimulation

Translational gap refers to the difference between experimental results and actual clinical outcomes. Many drugs show good results in laboratory studies but fail to produce similar effects in clinical practice due to variability in patient behaviour and environmental factors. Including real-life conditions in pharmacological research helps improve clinical relevance. Most research studies evaluate drugs under controlled laboratory conditions with regular dosing schedules. However, very limited studies evaluate drug effectiveness under real-life conditions such as:

1. Irregular dosing
2. Interrupted treatment
3. Low dose therapy

Drug effectiveness depends not only on pharmacological properties but also on patient compliance. Irregular use of medicines may reduce therapeutic effectiveness. Therefore, this study evaluates pharmacological activity of herbal formulation under real-life usage patterns to obtain clinically relevant results.

MATERIALS AND METHODS

Fresh leaves of Nyctanthes arbor-tristis were collected from local herbal garden and authenticated by a qualified taxonomist in the Department of Pharmacognosy. The plant material was washed with tap water followed by distilled water to remove adhering dirt and impurities. Carbopol 934 was used as gelling agent due to its high viscosity, stability, and compatibility with topical formulations. Propylene glycol was used as solvent and penetration enhancer to improve drug diffusion through skin.

Methyl paraben and propyl paraben were used as antimicrobial preservatives to prevent microbial contamination during storage. Triethanolamine was used as neutralizing agent to adjust pH of gel formulation and to achieve desired consistency. Ethanol was used as extraction solvent due to its ability to dissolve wide range of phytoconstituents such as flavonoids, phenols, and glycosides. Distilled water was used as vehicle. Standard drug povidone iodine ointment was used for comparison in pharmacological study. Streptozotocin or alloxan was used for induction of diabetes in experimental animals. All chemicals used in the study were of analytical grade.

Preparation of Plant Material: Collected leaves of Nyctanthes arbor-tristis were washed thoroughly to remove dust and foreign matter. Leaves were shade dried at room temperature (25–30°C) for 7–10 days to prevent degradation of thermolabile phytoconstituents. Shade drying helps preserve bioactive compounds by avoiding direct sunlight exposure.

Dried leaves were pulverized using mechanical grinder to obtain coarse powder. Powdered material was passed through sieve number 40 to ensure uniform particle size which improves extraction efficiency. Powder was stored in airtight container protected from moisture and light until further use. Percentage yield of extract was calculated.

Preparation of Extract: Extraction of powdered plant material was carried out using Soxhlet extraction method. About 100 g of powdered drug was placed in Soxhlet apparatus and extracted with 500 ml ethanol for 6–8 hours. Soxhlet extraction ensures continuous extraction of phytoconstituents by repeated washing of plant material with fresh solvent. Ethanol was selected as solvent due to its ability to extract both polar and moderately non-polar phytochemicals such as flavonoids, tannins, phenolic compounds, glycosides, and alkaloids. Extract was filtered using Whatman filter paper to remove insoluble plant residues.

Filtrate was concentrated using rotary evaporator under reduced pressure to remove solvent and obtain semisolid extract. Extract was further dried in desiccator to remove residual moisture. Dried extract was weighed and percentage yield was calculated. Extract was stored in airtight container at refrigerated temperature until further use.

Formulation of Herbal Gel: Herbal gel formulation was prepared using Carbopol 934 as polymeric gelling agent. Three formulations were prepared containing different concentrations of plant extract:

F1 – 1% extract
F2 – 3% extract
F3 – 5% extract

Procedure: Required quantity of Carbopol 934 was slowly dispersed in distilled water with continuous stirring to prevent lump formation. The dispersion was allowed to hydrate for 24 hours to obtain clear gel base. Methyl paraben and propyl paraben were dissolved in small quantity of warm distilled water to ensure uniform distribution. Plant extract was dissolved in propylene glycol which acts as cosolvent and penetration enhancer. Extract solution was added slowly to hydrated polymer dispersion with continuous stirring to obtain uniform mixture.

Triethanolamine was added dropwise to adjust pH between 6 and 7. Neutralization of Carbopol results in formation of gel network structure which increases viscosity.Gel was mixed thoroughly to obtain smooth and homogeneous consistency without formation of air bubbles. Prepared gel formulations were stored in airtight containers.

Evaluation of Herbal Gel Formulation: Prepared gel formulations were evaluated for physicochemical parameters to determine quality, stability, and suitability for topical application.

Physical Appearance: Gel formulations were visually observed for color, odor, transparency, texture, and presence of particulate matter.

Homogeneity: Homogeneity was evaluated by visual inspection and by rubbing small quantity of gel between fingers to detect lumps or aggregates.

pH Determination: pH of gel formulation is important for compatibility with skin. 1 g gel was dispersed in distilled water and pH was measured using calibrated digital pH meter at room temperature.

Viscosity: Viscosity determines spreadability and retention of gel at application site. Viscosity was measured using Brookfield viscometer at controlled temperature.

Spreadability: Spreadability indicates ease of application of gel on skin surface. Gel sample was placed between two glass slides and weight was applied. Time required for separation of slides was recorded. Spreadability ensures uniform distribution of formulation on wound surface.

Extrudability: Extrudability determines ease with which gel can be removed from tube. Gel was filled in collapsible tube and pressure was applied to extrude gel.

Drug Content: Drug content uniformity ensures equal distribution of extract in formulation.

Known quantity of gel was dissolved in suitable solvent and absorbance was measured using UV spectrophotometer.

Consistency: Consistency was evaluated visually by observing smoothness and thickness of gel.

Washability: Washability indicates ease of removal of gel from skin surface using water.

Grittiness: Grittiness was evaluated by rubbing gel between fingers to detect presence of coarse particles.

Syneresis Study: Syneresis refers to separation of liquid from gel during storage. Gel formulations were stored at room temperature and refrigerated condition and observed for phase separation.

In-vitro Drug Diffusion Study: In-vitro drug diffusion study was performed to determine release pattern of phytoconstituents from gel formulation. Diffusion study was carried out using diffusion membrane and phosphate buffer as receptor medium. Gel sample was placed on membrane and receptor compartment was filled with buffer solution. Samples were withdrawn at predetermined time intervals and replaced with fresh buffer. Samples were analyzed using UV spectrophotometer. Percentage drug release was calculated. Drug diffusion study indicates sustained release behavior of formulation.

Stability Study under Simulated Real-Life Usage Conditions Stability study was performed to evaluate physical stability of gel formulation under conditions similar to real-life use. Gel formulation was stored under following conditions:

Simulated real-life usage conditions included

1. repeated opening and closing of container
2. handling during storage
3. exposure to environmental temperature variation Formulations were observed for changes in:
4. colour
5. Odour
6. pH
7. consistency
8. phase separation
9. Stability study helps predict shelf life and storage conditions of formulation.

Pharmacological Evaluation

Experimental Animals: Healthy rats were used for wound healing study. Animals were housed under standard laboratory conditions with controlled temperature and humidity. Animals were provided standard diet and water ad libitum.

Induction of Diabetes: Diabetes was induced using Streptozotocin or Alloxan which selectively destroys pancreatic beta cells resulting in hyperglycemia. Blood glucose levels were monitored to confirm induction of diabetes.

Excision Wound Model: Animals were anesthetized using suitable anesthetic agent. Dorsal surface of rat was shaved and cleaned with antiseptic solution. Circular wound was created using sterile surgical blade.

Animals were divided into experimental groups:

Control group – untreated
Standard group – treated with povidone iodine Test group – treated with herbal gel formulation.

Measurement of Wound Contraction Wound are was measured on day:0,3,7,10,14 Reduction in wound size indicates healing progress. Percentage wound contraction was calculated

Epithelialization Period: Number of days required for complete healing of wound was recorded. Shorter epithelialization period indicates faster healing.

Skin Irritation Study: Gel formulation was applied on shaved dorsal skin and observed for redness, irritation, or inflammation. Absence of irritation indicates safety of formulation.

Statistical Analysis: Experimental data were expressed as mean ± standard deviation. Statistical analysis was performed using ANOVA. Differences between groups were considered significant at $p < 0.05$. Statistical analysis helps determine reliability and significance of results.

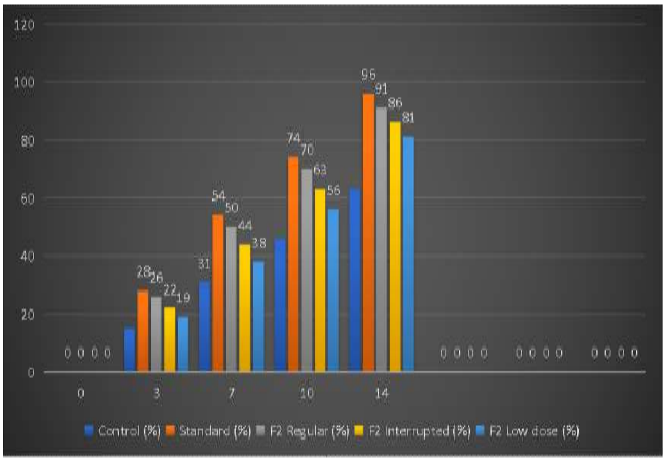
RESULTS

Effect of Formulation on Wound Contraction

1. The wound healing activity of the optimized herbal gel formulation was evaluated using excision wound model in diabetic rats. Wound area was measured on days 0, 3, 7, 10, and 14 to determine the rate of wound contraction.
2. The results showed progressive reduction in wound size in all experimental groups during the study period. The untreated control group showed slow reduction in wound area indicating delayed healing due to diabetic condition. The standard group treated with povidone iodine showed faster wound contraction compared to control group.
3. The test group treated with Nyctanthes arbor-tristis herbal gel (F2) showed significant reduction in wound area compared to control group. The rate of wound contraction increased gradually from day 3 to day 14 indicating enhanced tissue regeneration.
4. The optimized formulation (F2) showed wound contraction comparable to standard drug, indicating significant wound healing potential of herbal gel.
5. In diabetic conditions, delayed wound healing is mainly due to prolonged inflammatory phase, reduced collagen synthesis, oxidative stress, and impaired angiogenesis. The improved wound contraction observed in test group indicates effectiveness of phytoconstituents in promoting tissue repair.

Table 2. Wound Area Measurement (mm²)

Day	Control (mm²)	Standard (Povidone iodine) (mm²)	TestF2 Regular (mm²)	TestF2 Interrupted (mm²)	Test F2 Low dose (mm²)
0	500 ± 0.0	500 ± 0.0	500 ± 0.0	500 ± 0.0	500 ± 0.0
3	425 ± 5	360 ± 4	370 ± 5	390 ± 6	405 ± 7
7	345 ± 6	230 ± 5	250 ± 6	280 ± 5	310 ± 8
10	270 ± 5	130 ± 4	150 ± 5	185 ± 6	220 ± 7
14	185 ± 4	20 ± 2	45 ± 3	70 ± 5	95 ± 6



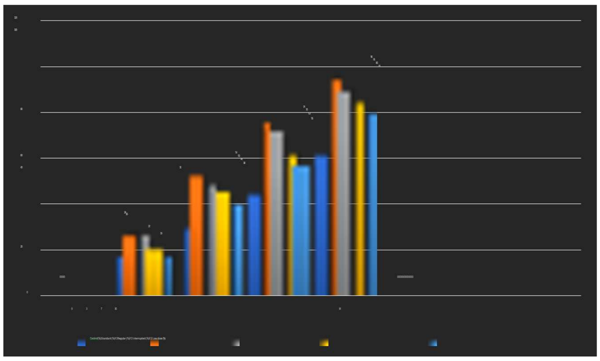
Graph 1. Graphical representation of wound area measurement

Percentage Wound Contraction: Percentage wound contraction was calculated to evaluate healing efficiency of formulation. The control group showed slower wound contraction due to impaired healing associated with diabetic condition.

1. The standard group showed maximum wound contraction indicating effective wound healing activity.
2. The test group treated with Nyctanthes arbor-tristis gel showed significant increase in percentage wound contraction compared to control group.
3. Higher percentage wound contraction indicates increased fibroblast proliferation, collagen synthesis, and epithelial regeneration.
4. Improved wound contraction in herbal gel treated group suggests pharmacological activity of plant extract in promoting tissue repair.

Table 3. Percentage Wound Contraction

Day	Control (%)	Standard (%)	F2Regular (%)	F2Interrupted (%)	F2 Low dose (%)
0	0	0	0	0	0
3	15	28	26	22	19
7	31	54	50	44	38
10	46	74	70	63	56
14	63	96	91	86	81



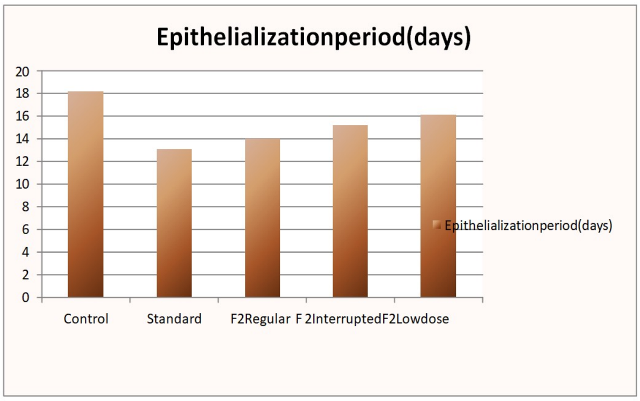
Graph-2. Graphical representation of wound contraction

Epithelialization Period

1. Epithelialization period refers to number of days required for complete closure of wound surface by new epithelial tissue.
2. The control group showed longer epithelialization period indicating delayed wound healing. The standard group showed shorter epithelialization period due to faster tissue regeneration. The test group treated with herbal gel showed reduced epithelialization period compared to control group.
3. Reduced epithelialization time indicates faster regeneration of epithelial tissue and improved healing process.
4. Shorter epithelialization period in herbal gel treated group confirms effectiveness of formulation in accelerating wound healing.

Table 4. Epithelialization Period

Group	Epithelialization period (days)
Control	18.2 ± 0.4
Standard	13.1 ± 0.3
F2 Regular	14.0 ± 0.5
F2 Interrupted	15.2 ± 0.6
F2 Low dose	16.1 ± 0.7



Graph 3. Epithelization of wound

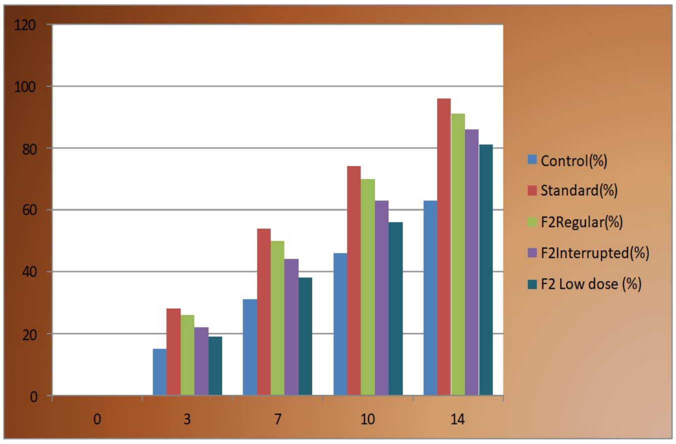
Comparison of Healing Rate between Groups: Comparison of healing rate showed that herbal gel treated group exhibited significantly improved healing compared to untreated control group. The healing effect observed in herbal gel treated group may be attributed to presence of bioactive phytoconstituents such as flavonoids, tannins, phenolic compounds, and glycosides. Flavonoids and phenolic compounds exhibit antioxidant activity which reduces oxidative stress at wound site. Reduction in oxidative stress promotes fibroblast proliferation and collagen synthesis.
Tannins contribute to wound contraction by forming protective layer over wound surface and promoting epithelial regeneration. Antimicrobial activity of phytoconstituents helps prevent microbial infection which delays wound healing. Anti-inflammatory activity reduces prolonged inflammation and promotes faster healing.

Effect under Simulated Real-Life Usage Conditions: The wound healing activity was evaluated under simulated real-life usage conditions such as repeated application and handling of formulation. The formulation maintained therapeutic effectiveness under simulated conditions indicating stability and consistency of pharmacological activity. Simulated real-life conditions provide realistic prediction of clinical effectiveness of formulation.

The herbal gel maintained significant wound healing activity despite exposure to practical usage variations.

Table 5. Mean ± SD values of Percentage Wound Contraction under Simulated Real-Life Usage Conditions

Day	Control (%)	Standard (%)	F2Regular (%)	F2Interrupted (%)	F2 Low dose (%)
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
3	15 ± 1	28 ± 2	26 ± 2	22 ± 1	19 ± 2
7	31 ± 2	54 ± 3	50 ± 2	44 ± 2	38 ± 3
10	46 ± 2	74 ± 2	70 ± 3	63 ± 2	56 ± 2
14	63 ± 3	96 ± 1	91 ± 2	86 ± 3	81 ± 2



Graph 4. Comparative Bar Graph of Percentage Wound Contraction for Control, Standard and F2 Treatment Groups

Skin Irritation Study: Skin irritation study was performed to evaluate safety of formulation. Gel formulation was applied on shaved dorsal skin surface of animals and observed for signs of irritation such as redness, swelling, or inflammation. No visible irritation or allergic reaction was observed. Absence of irritation indicates safety and suitability of formulation for topical application. Overall Wound Healing Result Nyctanthes arbor-tristis herbal gel showed significant wound healing activity in diabetic wound model.

Parameter	Observation
Redness	Absent
Swelling	Absent
Irritation	Absent

The results indicate that herbal gel possesses significant pharmacological potential for diabetic wound healing.

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