RESEARCH ARTICLE

Evaluation of Wound Healing Potential of *Zizyphus jujuba* in Rats

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ABSTRACT

The healing potential of a topically applied extract derived from the bark of *Ziziphus jujuba* was assessed using both incision and excision wound models in albino rats over 20 days. For this study, the rats were categorized into four distinct groups, each group receiving ongoing treatment with 0.5%, 1%, and methanolic extract of *Ziziphus jujuba*, applied at a dosage of mg/cm2. The test duration encompassed 20 days, during which the diameter of the wounds was measured on days 0, 8, 12, 16, and 20th. Additionally, biopsies were collected from two rats within each group. The findings of the study highlighted that the administration of the lower-dose group of methanolic extract of *Ziziphus jujuba* (E1 0.5% w/w) was associated with a significant ($p< 0.01$) reduction in wound area. Moreover, the histopathological assessment also corroborated this observation. Notably, during the second and third weeks of the study, the tissues exhibited significant ($p< 0.01$) improvement in comparison to most other groups. Interestingly, the group treated with a higher dose of the methanolic extract of *Ziziphus jujuba* (E2 1% w/w) displayed the most substantial wound shrinkage and organization. This suggests that the application of the higher extract concentration led to more pronounced wound contraction and enhanced tissue organization.

Keywords Excision wound model,Incision wound model, Wound, Healing, and *Ziziphus jujuba*

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INTRODUCTION

A wound represents a disturbed condition of bodily tissue resulting from physical, chemical, microbial, or immunological factors, and its recovery occurs through either regeneration or fibroplasia.[1] In regions with inadequate hygiene, wound infections prevail as a prevalent concern, particularly in developing nations.[2] The initiation of wound healing commences immediately after injury and can persist for differing durations, contingent on the wound's severity. This complex sequence of events can be divided into three primary stages: the initial inflammatory phase, followed by the proliferation phase and concluding with the subsequent remodeling phase. These phases collectively determine the strength and visual characteristics of the healed tissue.[3] Wound healing, a multifaceted physiological process, is a critical facet of the body's response to tissue injury, aiming to restore structural and functional integrity to damaged areas. It encompasses a series of orchestrated events involving intricate cellular and molecular interactions, with the ultimate goal of re-establishing homeostasis and preventing infection. This intricate process is essential for maintaining the body's structural integrity and overall health.[4] The dynamic nature of wound healing involves various overlapping phases, each characterized by distinct cellular activities and molecular signaling pathways. These phases include hemostasis, inflammation, proliferation, and remodeling.[3-4] Hemostasis involves the rapid formation of a clot to prevent excessive bleeding, while the inflammatory phase engages immune cells to ward off potential pathogens and initiate tissue cleanup. Subsequently, the proliferation phase entails the migration and proliferation of cells essential for rebuilding tissue, and the remodeling phase involves tissue maturation and the alignment of collagen fibers to regain strength.[4] Numerous factors intricately influence the trajectory of wound healing, including the wound's type, depth, location, and the individual's overall health. Additionally, underlying conditions such as diabetes, vascular diseases, and immunodeficiency can significantly impact the healing process. Advancements in molecular biology, cellular research, and medical technologies have unveiled new insights into the cellular players, cytokines, growth factors, and signaling pathways involved in wound healing, enabling the development of innovative therapeutic strategies to expedite and optimize this process.[2-5] Numerous traditional medicinal applications exist, often not reliant on comprehensive knowledge of their constituents. As per Ayurvedic principles, the bitter and cooling attributes of *Ziziphus jujuba's* root make it effective in alleviating coughs, biliousness, and headaches.[6] The bark of this plant possesses curative properties for boils, and it proves beneficial in addressing dysentery and diarrhea concerns.[7] The leaves are known for their antipyretic qualities and their potential to aid in weight reduction. *Z.*

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Table 1: Pharmacognostic studies

Parameters	(Mean±S.D.)
Moisture content (%w/w)	2.01±0.05
Total ash value (%w/w)	2.5±0.05
Acid insoluble ash (%w/w)	0.010±0.001
Sulfated ash (%w/w)	0.0001±0.0002
Inorganic Content (ppm)	Calcium (30±3.0), Potassium (41±3.51), Sodium (72±4.04)
Extractive Values (%w/w) are mentioned in a separate table	Petroleum ether (0.2±0.11 Chloroform (0.2±0.02), Methanol (1.1±0.10), Water (0.8±0.028)

Table 2: Qualitative Preliminary Phytochemical Screening of Extracts

Phytochemicals/Phytoconstituents	Methanolic Extract
Alkaloids	Present
Volatile oil	Present
Glycosides (Saponins, Cardiac)	Present
Flavonoids	Present
Tannins	Present
Fixed oils and fats	Absent

jujuba's fruit offers cooling, tonic, digestible, aphrodisiac, and laxative properties, countering sensations of burning, quenching thirst, mitigating vomiting, and exhibiting promise in tuberculosis and blood disorder treatments. Moreover, its seeds are credited with treating ocular ailments and aiding in leucorrhoea.[8] Within the traditional healing practices of the Bastar region, dried leaves and powdered bark are employed by practitioners to dress wounds.[7] For equivalent purposes, fresh leaves are also harnessed. External application of an aqueous leaf paste serves to alleviate sensations of burning. Roots find utility in addressing dysentery; their administration, combined with cow's milk, continues until recovery is achieved. Among the elderly, a mixture of fresh leaf juice and buffalo's milk was traditionally employed to mitigate the severity of smallpox.

In bygone times, seeds were commonly utilized to address eye afflictions. To counteract throat hoarseness, customary healers suggest placing fresh roots of this plant in the mouth. Furthermore, traditional practitioners employ fresh leaves in conjunction with cumin to manage urinary infections.[8] The fruit serves as an antidote for countering aconite poisoning, alleviating abdominal discomfort during pregnancy, and finding application externally as both poultices and wound treatments. The kernels, on the other hand, contribute to increased muscle mass and vigor, exhibiting sedative properties.[8] Notably, *Ziziphus jujuba* fruits boast substantial vitamin content, including vitamins C, B1 (thiamine), and B2 (riboflavin).[10] In comparison to other consumable fruits, consuming just one bur fruit daily would sufficiently meet the recommended dietary intake of Vitamin C as well as Vitamin B complex for an adult male, as endorsed through FAO/WHO guidelines. Furthermore, *Ziziphus jujuba* is recognized for its elevated Vitamin P (bioflavonoid) content, which notably augments the efficacy of Vitamin C. This plant exhibits medicinal attributes encompassing antibacterial, anti-inflammatory, and antioxidant properties. It additionally stimulates bile production, enhances circulation, and serves as a preventive measure against allergies. The presence of Pectin-A in Z. jujuba fruit has also been documented.[11] From a chemical perspective, it encompasses units of 2, 3, and 6-tri-o-acetyl D lactose. Pectin boasts various pharmaceutical qualities, including binding to bile acids, reducing plasma cholesterol levels, and demonstrating anti-diarrheal effects.[12] In this current investigation, the methanolic extract of *Ziziphus jujuba*, reputed for its potential wound-healing properties, was chosen to assess its effectiveness in treating wounds. The study focused on evaluating the wound healing capabilities of both aqueous and methanolic extracts using excision wound models conducted on Wister albino rats.

MATERIAL AND METHODS

Plant material

The wood was procured from Vaijanath from Wild (Karjat Maharashtra, India) and the plant was authenticated at St. Xavier's College (Blatter Herbarium) Mumbai with the specimen number (SH-252). The branch of the tree that was infesting free was chosen and was separated from the main tree. The collection was done in May and June. The branch was then cut into pieces and the bark was separated from the wood.

Pharmacognostic profile/studies

The crude drug was subjected to proximate analysis which included the total ash value, inorganic ion content, and moisture content.[13,16]

Extraction

The 1kg shade-dried wood of *Zizyphus jujuba* powder was extracted with methanol and subjected to Soxhlet extraction for 4 hours. The extract was collected after 4 hours and concentrated using a rotary flash evaporator not exceeding 50^0C and dried in a vacuum oven at a temperature not exceeding 50^0C and was stored at 2-8^0C.[13]

Preliminary phytochemical analysis

The plant material underwent an initial phytochemical examination to identify different components present in the plant. Various qualitative chemical tests for carbohydrates Glycosides Tannins Alkaloids Steroids and Flavonoids were performed to detect their presence in the extract.[13]

Formulation of herbal gel

Various polymers were screened for the preparation of gel and the final selected was Carbopol-974P. The gel consisted of the gelling agent (2%w/w) Humectants (30%w/w) Preservatives (0.1%w/w). The stated quantity of Carbopol 974P was soaked in 50ml water for complete hydration for 2 hours. After complete hydration stated amount of humectant was added followed by the addition of the base (TEA) to obtain the clear gel. The extract with the desired concentration was dissolved in the minimum amount of water and then mixed in the gel base by geometric proportions to obtain the formulation with the specified drug concentration.

Animals used

Male and female Wister albino rats, weighing between 150 and 200 grams, were kept in standard environmental conditions with a temperature of 25±0.5°C and a 12-hour light/12-hour dark cycle for the duration of the study. They were provided with a standard pellet diet and had unrestricted access to water. The rats were divided into four main groups: Control, Standard, and Test groups. The Control group received a plain gel base treatment. The Standard group was treated with Betadine® ointment. The Test groups received treatments with extracts incorporated into the plain gel base. All animal experiments were conducted with the approval of the Institutional Animal Ethical Committee under Registration No: 704/C/02/CPCSEA. The total methanolic extract was used for assessing wound healing activity. The animals were allowed to acclimatize for 8-10 days before the experiments began.

Study design

The animals were divided into the following groups for the assessment of the wound healing action by both the models viz. excision and incision. Control (CT): The Simple gel base without extract was utilized as the control preparation in the investigation. Standard (SD): Betadine ointment containing 10 %w/w Povidone iodine was used as the standard for the study. E1: test preparations were utilized viz. the carbopol gel containing methanolic extract in the concentration of 0.5 % w/w, E2: test preparations were utilized viz. the carbopol gel containing methanolic extract in the concentration of 1.0 %w/w,

Evaluation of wound healing activity

Incision wound models

The rats were given ketamine anesthesia at a dosage of 80mg per kilogram of body weight through an intraperitoneal injection. Afterward, a 6cm long incision was made along the paravertebral area of the rats' shaved backs while they remained anesthetized. These incisions were closed using interrupted sutures, employing surgical thread and a curved needle. Subsequently, the wounds of the rats in different groups were treated with topical gel application for 8 days. On the 8th day after the initial wound was made, the sutures were removed, and the tensile strength of the healed tissue was measured using a

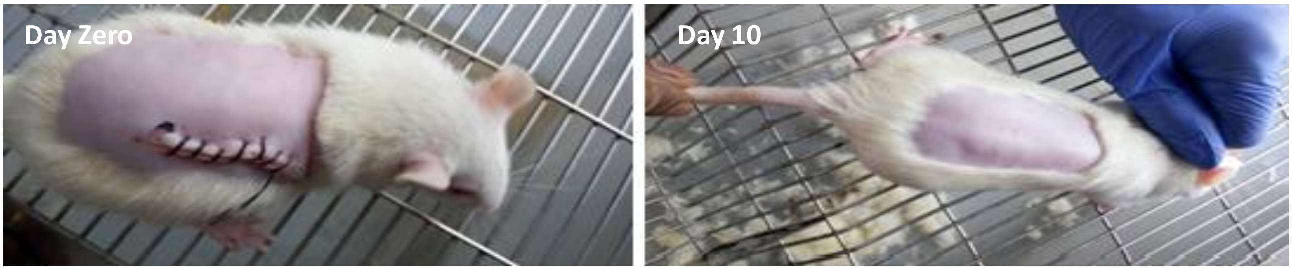

Figure 1: Wound healing potential by incision model.

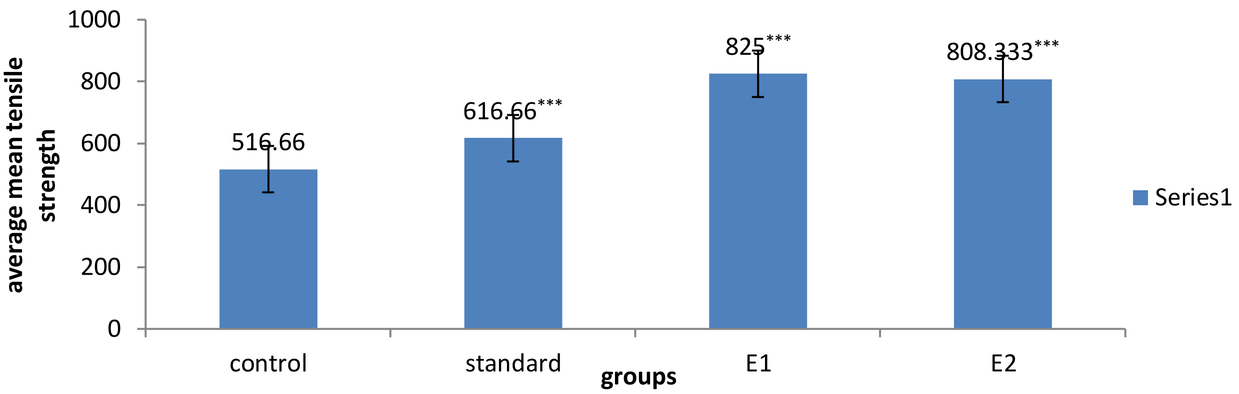

Figure 2: Comparative effect of topical application of the gel containing 0.5%w/w and 1%w/w total methanolic extract on the tensile strength by incision wound on Wister rats

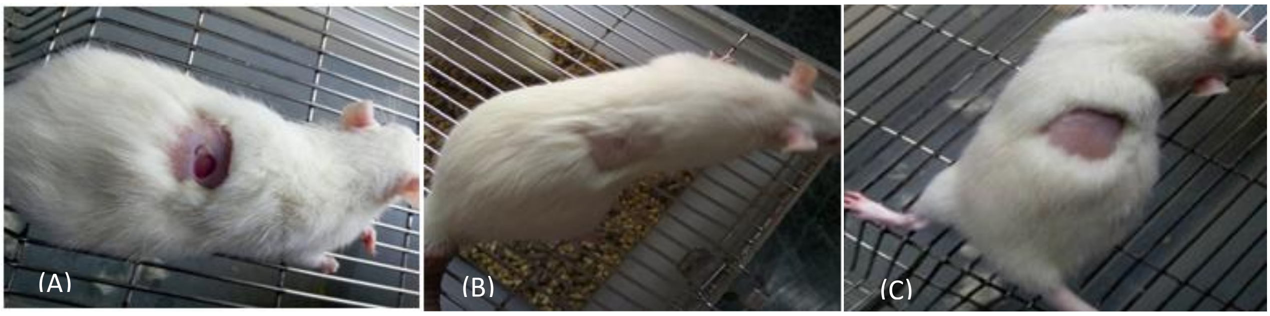

Figure 3: Wound healing potential by excision model (A) Day Zero; (B) Completely Healed wound of 0.5%w/w after 16 days; (C) Completely Healed wound of 1.0%w/w after 20 days.

Table 3:Effect of topical application of the gel containing 0.5%w/w and 1%w/w total methanolic extract on the tensile strength by incision wound on Wister rats

Groups	Average mean tensile strength(gm)						Mean±SD
	1	2	3	4	5	6	
CT	500	550	500	500	500	550	516.66±25.81
STD	650	600	600	600	650	600	616.66±20.41***
E1	850	800	850	800	800	850	825±27.38***
E2	700	750	800	900	800	900	808.34±80.18***

(N=6 animals in each group; the treated groups are compared by ANOVA test concerning the control group ***P<0.01. CT: Control group; STD: Povidone Iodine Ointment (5% w/w); E1: 0.5% w/w spray dried methanolic extract dispersed in 2%w/w Carbopol 974P; E2: 1.0% w/w spray dried methanolic extract dispersed in 2%w/w Carbopol 974P)

Table 4 :Effect of topical application of the various formulations of the methanolic extract of the wood of *Zizyphus jujuba* on percent epithelization on the excised wounds on the rats

Groups	% Mean contractions				
	4th day	8th day	12th day	16th day	20th day
Control	10.23±0.25	15.238±0.23	35.54±0.56	70.375±0.74	90.56±0.1575
Standard	22.11±0.70*	30.533±1.078*	70.99±0..71*	90.085±0..67*	100***
E1	24.45±0.78*	40.2±0.56*	80.10±0..021*	99.98±0.99*	100***
E2	30.533±1.07*	55.14±0.19*	90.10±0.12*	100*	100***

(N=6 animals for each group. The treated groups are compared by ANOVA test with the control group. ***P<0.01; Control: Plain 2% Carbopol 974P gel; Standard: Betadine (povidone-iodine 10 %w/w); E1:0.5% extract dispersed in the 2%w/w Carbopol 974P gel base; E2: 1.0% extract dispersed in the 2%w/w Carbopol 974P gel base)

Table 5: Effect of topical application of the various formulations of the methanolic extract of the wood of *Zizyphus jujuba* on hydroxyproline content on the excised wounds on the rats

Groups	Hydroxyproline content (µg/500mg)					
	1	2	3	4	5	Mean ± S.D
Control	4.34	3.04	4.34	4.6	4.7	4.204±0.67
Standard	18.84	24.73	23.08	26.95	26.9	24.1±3.35***
E1	53.3*	53.6*	54.4*	56.5*	55.01*	54.562±1.27***
E2	124.63*	121.6*	122.7*	123.69*	123.01*	123.126±1.13***

(11th Day post wounding; Plain Carbopol Base: 4.204µg/500mg; Standard: (Betadine Ointment): 24.1µg/500mg; E1 (0.5% extract dispersed in the 2%w/w Carbopol 974P gel base): 54.562µg/500mg; E2 1.0% extract dispersed in the 2%w/w Carbopol 974P gel base): 123.126µg/500mg)

tensiometer on the 10th day following the initial wound creation.[13-16]

Excision wound model

The rats were administered ketamine anesthesia at a dosage of 80mg per kilogram of body weight through an intraperitoneal injection. A circular wound with a diameter of 8 millimeters and an area of 200 square millimeters was then created on the shaved back of the anesthetized rats using a biopsy punch. Any bleeding was addressed by blotting with sterile gauze, and the wounds were cleaned with sterile water. The day of wound creation was marked as day zero. From that day onward, the wounds were treated with the topical application of the gel until they were fully healed. The wounds were closely observed, and their size was measured by tracing them onto tracing paper until complete epithelization occurred.[13-15]

Assessment of biochemical parameter

The excision wounds were inflicted on the back of the Albino rats and treated appropriately as per the previously reported method. To monitor the healing process biochemical parameters viz hydroproline content in granulation tissue of the wound were determined on day 11th by colorimetric method. The content of the hydroxyproline content of the granulation tissue was compared in different groups.[16]

Statistical *I*nvestigation

A statistical analysis was performed using one-way analysis of variance (ANOVA) to evaluate the significance of variations among different sets of values. The comparison between the control group and the group treated with the drug showed a statistically significant distinction. The presented values are represented as the mean value accompanied by the standard error of the mean (±SEM).[13]

RESULTS

Pharmacognostic profile/studies

The Pharmacognostic studies were performed and the results are shown in Table 1.

Preliminary phytochemical analysis

The methanolic extracts of the plant indicated the presence of alkaloids, flavonoids, glycosides, phenolic compounds, and tannins within *Zizyphus jujube* as provided in Table 2.

Wound healing potential by incision model

The experiment involved comparing the tensile strength of healing skin among different groups: the control group, the test group, and the standard group. The results demonstrated a significant ($p<0.01$) increase in the test group's tensile strength compared to the other groups, as indicated in Figure 1 and Figure 2. This suggests that in the incision wound model, the application of E1 and the standard treatment led to a noteworthy enhancement in skin tensile strength (with a statistical significance of $p<0.01$) compared to the animals in the control group, as presented in Table 3. The collected data consistently supported the conclusion that both E1 and E2 gels possess remarkable wound-healing properties. Notably, E1 exhibited superior wound healing potential compared to E2. The observed increase in tensile strength can be attributed to the levels of collagen present and the formation of stable connections both within and between collagen molecules. The greater tensile strength is likely the result of an amplified synthesis of collagen fibers, responsible for forming robust cross-links. In essence, the animals treated with E1 and E2 demonstrated heightened tensile strength due to an augmented production of collagen fibers and subsequently enhanced cross-linking.[15,16]

Wound healing potential by excision model

In this particular investigation, the research focused on evaluating the wound contraction rate using an excision wound model, which involves measuring the area of wound healing in square millimeters ($200mm^2$). The process involved calculating the percentage of wound contraction by monitoring changes in the wound area at specific time intervals, as visually depicted in Figure 3 and Figure 4 and quantified in Table 4. The designated time points for analysis were the 4th, 8th, 12th, 16th, and 20th days post-treatment with the methanolic extract. On the 16th day following the initial injury, the control group animals exhibited a healing rate of 70.375±0.74%, which might be attributed to the natural immunity of the animals. In contrast, the groups treated with the extract (E1 & E2) demonstrated significantly enhanced healing rates, reaching 99.98±0.99% and 100% healing respectively on the same day. By the 20th day, the healing rates for the extract-treated groups were 90.56±0.1575% and 100%. Upon comparison with the control group, the extract exhibited highly significant wound healing activity (with a statistical significance of $P<0.001$). Notably, the wound healing efficacy of the extract was comparable to that of the reference standard (Povidone iodine). The accelerated epithelization process within a shorter timeframe appears to be responsible for the reduction in wound area. This phenomenon has been substantiated through in vivo studies, indicating that animals treated with E1 experienced a more rapid reduction in wound area compared to those treated with E2.[13-15]

Determination of hydroxyproline content

Hydroxyproline, an amino acid predominantly present in collagen, a significant component of the extracellular matrix within tissues such as the skin, plays a crucial role in providing structural integrity and aiding in wound healing. The quantity of hydroxyproline in tissues serves as an

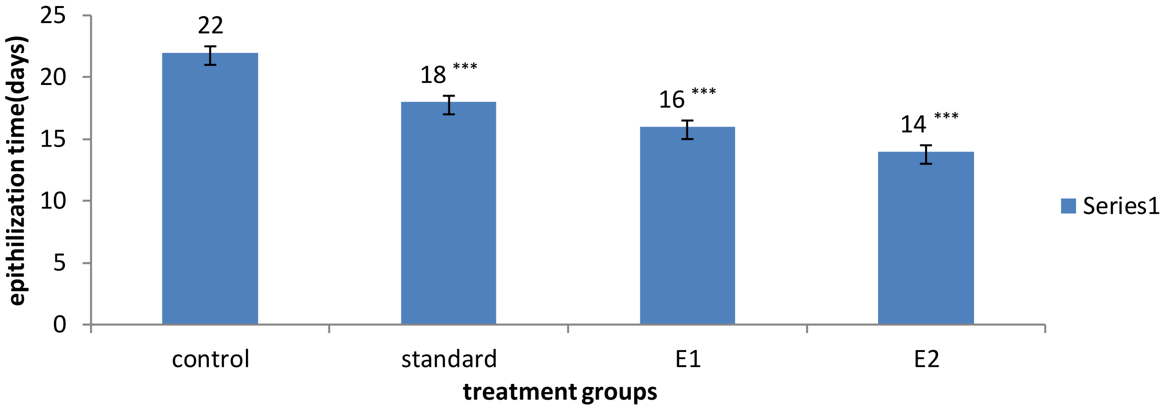

Figure 4: Effect of topical application of the various formulations of the methanolic extract of the wood of *Zizyphus jujuba* on percent epithelization on the excised wounds on the rats

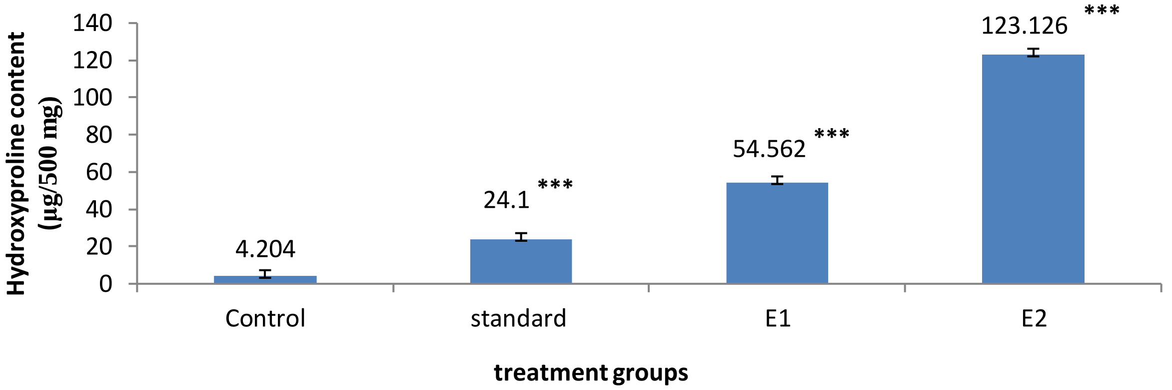

Figure 5: Effect of topical application of the various formulations of the methanolic extract of the wood of *Zizyphus jujuba* on hydroxyproline content on the excised wounds on the rats

informative marker for assessing collagen turnover and the process of collagen synthesis. The observed augmentation in protein levels, specifically hydroxyproline (a component of collagen), as depicted in Figure 5 and detailed in Table 5, in the treated animals indicates that the administered extracts had positive effects on various aspects of tissue healing. This includes the stimulation of cellular proliferation, the formation of granulation tissue, and the acceleration of epithelization, which collectively contribute to effective wound healing. The notable increase in protein content within the treated group is primarily attributed to an enhanced synthesis of collagen. This phenomenon is directly linked to the application of the methanol bark extract of *Ziziphus jujuba*. The extract's influence on augmenting collagen synthesis is a key factor responsible for the observed rise in protein levels, affirming its role in promoting wound healing processes.[14,16]

DISCUSSION

Wound healing represents an intricate and dynamic sequence of events aimed at restoring damaged tissues to their normal state as closely as possible. A critical process within this context is wound contracture, initiated during the fibroblastic stage of healing, where the wound area undergoes reduction. Subsequently, in the maturational point, the last stage of wound healing, the wound further contracts, resulting in a diminished appearance of scar tissue. Notably, the granulation tissue formed in the latter part of the proliferative phase comprises fibroblasts, collagen, edema, and newly formed small blood vessels.[13] The methanolic bark extract of *Ziziphus jujuba* has demonstrated notable effects, particularly an increase in protein content and wound closure. It is conceivable that one or more of the phytochemical constituents within the methanol bark extract of *Z. jujuba* might be responsible for these wound-healing properties. Recent investigations involving other plant extracts have revealed that certain phytochemicals, such as flavonoids, possess wound healing-promoting qualities primarily due to their astringent and antimicrobial properties. These properties play a role in wound contraction and the acceleration of epithelization.[13-15] The observed wound-healing potential of the methanol bark extract of *Z. jujuba* is likely attributed to the presence of various phytoconstituents within the plant. The accelerated wound-healing process could be a consequence of the individual or synergistic effects of these phytoconstituents.[16] Notably, tannins, which rank third in quantity among the estimated phytochemicals in *Z. jujuba*, possess astringent and antimicrobial properties. Consequently, it can be inferred that the observed wound-healing activity of the methanol bark extract of *Z. jujuba* is, in part, attributed to its tannin and flavonoid contents, which appear to contribute to wound contraction and an increased rate of epithelization.[16] One of the key findings of this study was the accelerated wound closure rate observed in the *Zizyphus jujuba* treated group compared to the control group.[17,27] The *Zizyphus jujuba* treated wounds exhibited significantly faster reepithelialization and contraction, indicating its potential to enhance the early stages of wound healing.[18-24] The presence of antioxidants in *Zizyphus jujuba* can help protect cells from oxidative damage, which can delay wound healing. This antioxidative capacity is attributed to compounds like quercetin and kaempferol found in the plant.[19-25] Collagen is a key component of the extracellular matrix, and its synthesis is critical for wound closure and scar formation. Some studies have suggested that *Zizyphus jujuba* extracts may stimulate collagen production, thereby promoting tissue remodeling and wound closure.[20,26-38] This effect can potentially lead to improved wound healing outcomes. Angiogenesis, the formation of new blood vessels, is crucial for delivering nutrients and oxygen to the wound site. Some research suggests that *Zizyphus jujuba* extracts may promote angiogenesis by upregulating angiogenic factors like vascular endothelial growth factor (VEGF).[21,22,28-32]

CONCLUSION

In our current research, we investigated the impact of various phytochemicals on two distinct wound models. These models encompassed an examination of different compounds and their effects on wound healing. Specifically, we focused on the methanolic extract derived from the dried whole plant of *Zizyphus jujuba*. Our findings revealed that the methanolic extract of *Zizyphus jujuba* exhibited significant wound-healing properties in both wound models. The observed wound healing effects were attributed to multiple factors. Firstly, the extract appeared to mitigate tissue damage caused by the generation of free radicals. Additionally, it displayed positive effects on the antioxidant status of the tissue, which is crucial for promoting the healing process. Furthermore, the extract demonstrated the ability to expedite the deposition of collagen, a fundamental protein for tissue structure and regeneration. It also facilitated the formation of other essential constituents of connective tissue, contributing to the overall healing process. One noteworthy aspect of the methanolic extract from *Zizyphus jujuba* is its affordability, safety, and effectiveness. In comparison to synthetic topical antibacterial agents commonly used, this extract proved to be a viable and efficient alternative. Its potential to foster wound healing, particularly for minor injuries and during surgical dressing procedures, positions it as a valuable option.

Acknowledgments

Sincere gratitudeto my grandfather **(**Late) Vaidya Bhau Sule (Ashok M Sule) for providing me the opportunity to do research on his medication.

Data availability

The research is patented by the name" Medicinal Composition**"** (Application no:201721036561) dated 14th October 2017

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