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Therapeutic potential of *Ziziphus spina–christi*: A natural antiseptic, antioxidant, and anti–inflammatory properties

Potencial terapéutico de *Ziziphus spina–christi*: Un antiséptico natural con propiedades antioxidantes y antiinflamatorias

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ABSTRACT

Ziziphus spina–christi, a medicinal plant widely distributed in Algeria and belonging to the *Rhamnaceae* family, is commonly employed to treat various ailments due to its multiple biological properties. This research sought to assess the biological activities of the hydroethanolic extract of its leaves, including antioxidant, antibacterial, and wound healing properties, in addition to quantifying its bioactive compounds to develop a natural antiseptic solution. In an experimental model with rats, different concentrations of the extract (5, 10, and 15%) were applied and compared with positive (Betaderme), negative (untreated) controls, and an additional control group. Additionally, the xylene–induced edema model was used to assess anti–inflammatory efficacy, administering doses of 250, 400, and 600 mg·kg^{-1} and comparing its effects with the standard anti–inflammatory NIFLUMENE (250 mg·kg^{-1}). The results showed a high presence of active compounds (FTC: 1.06 ± 0.03 mg QE·g^{-1}; extraction yield: 13.6%), strong antioxidant activity (IC_{50}: 0.004 ± 0.004 mg·mL^{-1}), and significantly accelerated wound healing with the 10% solution (96.25 ± 7.5%), even higher than Betaderme. Furthermore, the dose of 400 mg·kg^{-1} demonstrated the greatest reduction in inflammation (65.11%). These results demonstrate Ziziphus spina–christi's medicinal potential as a strong natural antiseptic.

Key words: *Ziziphus spina–christi;* hydroethanolic extract; antioxidant activity; wound healing; natural antiseptic solution

RESUMEN

Ziziphus spina–christi, una planta medicinal ampliamente distribuida en Argelia y perteneciente a la familia *Rhamnaceae*, se utiliza tradicionalmente para tratar diversas dolencias debido a sus múltiples propiedades biológicas. Este estudio tiene como objetivo evaluar las actividades biológicas del extracto hidroetanólico de sus hojas, incluyendo propiedades antioxidantes, antibacterianas y cicatrizantes, además de cuantificar sus compuestos bioactivos para desarrollar una solución antiséptica natural. En un modelo experimental con ratas, se aplicaron distintas concentraciones del extracto (5, 10 y 15 %) y se compararon con controles positivo (Betaderme), negativo (sin tratamiento) y un grupo adicional control. También se evaluó la actividad antiinflamatoria mediante el modelo de edema ótico inducido por xileno, administrando dosis de 250, 400 y 600 mg·kg^{-1} y comparando sus efectos con el antiinflamatorio estándar NIFLUMENE (250 mg·kg^{-1}). Los resultados mostraron una alta presencia de compuestos activos (CFT: 1,06 ± 0,03 mg QE·g^{-1}; rendimiento de extracción: 13,6 %), una fuerte actividad antioxidante (CI_{50}: 0,004 ± 0,004 mg·mL^{-1}) y una cicatrización significativamente acelerada con la solución al 10 % (96,25 ± 7,5 %), superior incluso a Betaderme. Además, la dosis de 400 mg·kg^{-1} presentó la mayor inhibición de inflamación (65,11 %). Estos hallazgos resaltan el potencial terapéutico de *Ziziphus spina–christi* como un eficaz agente antiséptico natural.

Palabras clave: *Ziziphus spina–christi;* extracto hidroetanólico; actividad antioxidante; cicatrización de heridas; solución antiséptica natural

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INTRODUCTION

Conventional health care systems all around the world have traditionally relied heavily on medicinal plants. Their widespread use over thousands of years is largely attributed to their accessibility and generally low risk of side effects [1]. In recent years, interest in herbal medicine has also grown significantly in developed countries. Although natural medicine practices, often based on plant extracts, are not always fully accepted within conventional medical circles [2, 3, 4, 5] they are not inherently contradictory to modern treatments [6].

Nowadays, antiseptics are a crucial component of medical care. They are commonly employed across various medical specialties, including burn care, wound management, preventive surgical treatments, and diagnostic procedures. Their effectiveness against bacteria, viruses, and fungi is fundamental to their role as disinfectants [7]. The plant *Ziziphus spina–christi* L., sometimes referred to as Jujube, is a plant renowned for its numerous health advantages; Due to its antibacterial effects and the secondary metabolites presence, jujube can be developed into an effective antiseptic [8]

Z. spina–christi is an edible plant commonly referred to as *Christ's thorn*, *Jujube*, *Nabka*, and *Sidr*. It belongs to the Rhamnaceae family and thrives mainly in arid and warm climates [9]. Sudan, Ethiopia, Somalia, Eritrea, Chad, Kenya, Djibouti, Mali, Libya, Mauritania, Senegal, Nigeria, Tunisia, Algeria, and Zimbabwe are among the African countries where the plant is indigenous [10].

The biological activities of *Z. spina–christi* have been investigated, and literature reviews indicate that the plant possesses anti–inflammatory, antibacterial, antioxidant, antifungal, antimalarial and anticancer properties [10]. Additionally, in Iranian folk medicine, the leaves are utilized to treat skin conditions like acne and atopic dermatitis, as well as to serve as anti–inflammatory, antifungal, and antiseptic agents [11]. The primary phytochemical compounds identified in this plant are flavonoids, alkaloids, and saponins [12].

The objective of this research is to create a natural antiseptic solution using an extract of *Z. spina–christi* plant leaves and assess its anti–inflammatory and antioxidant properties, which make it a viable option for the creation of a safe and efficient antiseptic for use in medicine.

MATERIALS AND METHODS

Preparation of ZSC extract

The leaves of *Z. spina–christi* (ZSC) were gathered in M'sila, Algeria. In order to get rid of any undesirable particles, the plant leaves were gathered from their natural environment and cleaned with tap water. The leaves were then individually pulverized in a professional blender (Condor, CMX1400DN, Algeria) and left to dry at ambient temperature in the shade.

Prior to maceration, the plant was carefully weighed using a standard electronic balance (Kern, ALJ220,4NM, Philippines). The plant components were extracted using a solvent consisting of an 80% aqueous ethanol solution for a duration of 72 hours (h) [13].

The extract powder was dried in the oven at at 40°C (Memmert UM200, Germany). Next, the plant extract's yield as a percentage was determined. The following equation was used to get the extraction yield (%):

$$\text{Extraction yield}\left(\%\right) = \frac{\text{Weight of the crude extract}}{\text{Weight of the powdered sample}} \times 100$$

Total flavonoid

According to [14], the aluminum complexation method was employed to determine the total amount of flavonoids. One mL of plant extract was combined with one mL of $AlCl_3$ solution, and the flavonoid levels were measured by incubating the mixture at room temperature for ten minutes. The intensity of the resultant yellowish–orange was quantified spectrophotometrically at 410 nm using a Shimadzu UV 1800 spectrophotometer (Japan) with pure water serving as the blank. The experiment was carried out three times to guarantee accuracy.

Z. spina–christi's total flavonoid content is expressed as mg of quercetin equivalents per g of extract (mg QE·g^{-1} of extract) after being compared to a calibration curve made with quercetin as the standard.

Antioxidant activity

DPPH radical

Using the radical scavenging method of 2,2-diphenyl-1-picrylhydrazyl (DPPH), the *in vitro* antioxidant activity of leaf extract samples was evaluated [15]. A 1250 µl DPPH solution was mixed with 50 µL of solution extract. The mixture was left in the dark for 30 minutes at room temperature. The absorbance of the resulting solution was measured at 517 nm using spectrophotometry. The experiment was carried out three times by using Cint (interior concentration in examiner tube). The radical scavenging activity was calculated using the formula.

$$\frac{(\mathrm{A\_control} - \mathrm{A\_sample})}{\mathrm{A\_control}} \times 100$$

Where $\mathrm{A\_sample}$ and $\mathrm{A\_control}$ represent the absorbance of the DPPH solution alone and the DPPH solution plus the sample at various concentrations, respectively.

To get the IC_{50} value, or the concentration required to reduce the initial DPPH concentration by 50%, a linear concentration/percentage inhibition curve was constructed. For comparison, Butylated Hydroxytoluene (BHT) served as the reference standard.

Preparation of the antiseptic solution

To determine the appropriate dosage, we prepared three solutions with different concentrations. First solution (5%); Second solution (10%); Third solution (15%) where 5, 10, and 15 g of ZSC were mixed with glycerol, ethanol and distilled water. After that, A pH meter was used to determine each solution's pH, and the results were as follows:

Solution	5%	10%	15%
pH	6.40	6.20	5.90

All values fall within the range of 5 to 6, which is considered the desired range for the preparation of a disinfectant solution.

In vivo study

Animals

To assess wound healing activities, white Wistar rats (*Rattus norvegicus*) weighing 150–180 g (PS 600. R2, Germany) were chosen. Each group employed five rats. Following acclimatization, with a temperature of 23 ± 2°C, a humidity of 50 ± 5%, and cycles of light and dark lasting 10 and 14 h, respectively, the rats were kept in controlled conditions. The animals were kept in cages with unrestricted access to water and sterile food (animal feed).

The Institutional Animal Ethics Committee gave its clearance before the animals were used in the experimental study.

Study design

A modification of [16] approach was used to examine the *in vivo* wound healing activity of the solutions prepared using ZSC hydroethanolic extract. Lidocaine Razes 2% (0.4 mL) was used to anesthetize rats both before and during the wound–creation process. An electric clipper was used to shave each rat's dorsal skin. Each animal had a vertical incision made using a sterile surgical scalpel, with each lesion ranging in length from 1 to 1.5 cm. The wound was left uncovered in a public setting.

From among the animals, six groups of five rats each were chosen at random for use in an experimental wound model. Groups 1, 2, and 3 were given Solution 1 (5%), Solution 2 (10%), and Solution 3 (15%). Betaderme solution was administered to Group 4, the positive control. Group 5, the negative control, received no treatment, whereas Group 6, often known as the control group, received only distilled water.

For 15 d, the solutions were topically administered to the wound site once every d. Using a graduated ruler, the wound length was measured every day for the duration of the treatment. The following formula was used to determine wound contraction, which was expressed as a percentage decrease in the initial size of the wound:

$$\text{Wound closure}\left(\%\right) = \frac{(A_0 - A\_d)}{A_0} \times 100$$

Where A_0 is the first area of the wound on day 0 (the day of wounding), and A_d is the area of the wound on day d.

Anti–inflammation study

Study Design: Xylene–induced ear edema model

The Xylene–induced ear edema model is a widely used experimental approach for assessing acute localized inflammatory responses in animals. Xylene provokes significant vasodilation and tissue swelling, making it a reliable agent for evaluating the anti–inflammatory potential of test substances [17, 18].

With minor adjustments, the approach of [19] was used to evaluate the extract from *Z. spina–christi*'s anti–inflammatory properties. The remaining thirty rats, which ranged in weight from 150 to 180 g, were randomly assigned to six groups. A rat's ear's inner and outer surfaces was treated with 0.02 mL of pure xylene, usually an hour after oral administration of plant extracts at different doses, causes acute edema.

The concentration of 250 mg·mL^{-1} of ZSC extract that was given to the first group, 400 mg·mL^{-1} to the second group, and 600 mg·mL^{-1} to the third group. Edema formation in the treated ears was quantitatively measured, and the inhibition rate was computed to ascertain the extract's relative effectiveness in reducing inflammation in comparison to the standard treatment. The results were compared to those of NIFLUMENE® 250 mg, a well–known anti–inflammatory reference drug (positive control), and the other group (negative control) was given only water.

The ear thickness was determined using a digital caliper. The following formula was used to determine the percentage of ear edema inhibition:

$$\text{Inhibition}\left(\%\right) = \frac{(Dn - D)}{Dn} \times 100$$

Where D represents the variation in the treated group's ear edema thickness, Dn is the variation in the negative group's ear edema thickness.

Statistical study

For statistical analysis, Graph Pad Prism (version 5.01 for Windows) was used. All results in vitro were examined using Excel's one–way analysis and computed as mean ± SD for three measurements [10]. In contrast, in vivo trials utilized a one–way ANOVA for analysis and the Tukey test, with the mean ± SEM. It was decided that the $P<0.05$ was statistically significant.

RESULT AND DISCUSSION

Phenolic content of *Ziziphus spina–christi* leaf extracts

The dry weight, relative to wet weight of the leaves extracted from ZSC represented 13.6% (TABLE I). Considering the total flavonoid, the leaves contain a high level with a precision of (1.06 ± 0.03mg QE·g^{-1} of extract)

TABLE I
Dried Vegetable Product obtained from ZSC leaves

Weight of the dried pulverized pan material (g)	Weight of dried extract (g)	Yield (%)	TFC (mg QE·g^{-1} of extract)
150	20.4	13.6	1.06 ± 0.03

mg QE·g^{-1} of extract: mg quercetin equivalents per g of extract. TFC: total flavonoid content

The yield of the jujube leaf hydroethanolic extract was 13.6%. Comparatively for methanolic extraction, the yield of the leaves, as a dry product, was 20.64% in an Iraqi study [20], 28% with an ethanol water (70%) combination after two weeks [21], and 32.5% in another methanolic extraction [22] than ethanolic extraction, which yielded lower yields (4.71%) [23]. Since each type of solvent

has unique polarity and solubilizing characteristics that impact its capacity to extract plant components, these variations are mostly caused by the solvent type [24]. In general, methanol produces more, whereas ethanol produces less. Geographical, climatic, soil, and harvesting conditions all have an impact on biological activity and phenolic content of ZSC leaf extracts. Notably, the total phenolic content is greatly influenced by the extraction technique (ethanolic vs. aqueous) [25].

Biological activities

Antioxidant activity

The findings shown that a decrease in absorbance indicated the plant antioxidants' ability to lower the DPPH radical. (FIG. 1). The IC_{50} value was determined to be 0.004 ± 0.004 mg·mL^{-1}, in comparison to the control sample (BHT), which had an IC_{50} of 0.031.

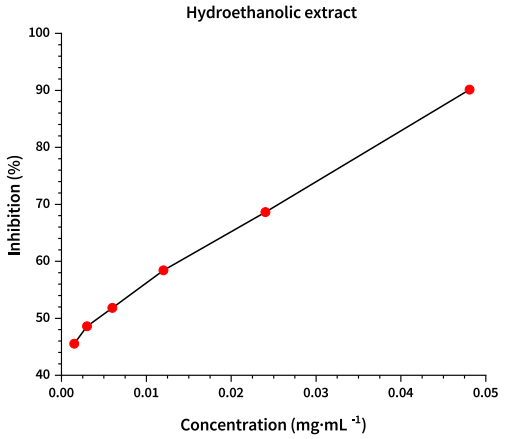

FIGURE 1. Determination of the antioxidant activity of the hydroethanolic extract of *Ziziphus spina-christi*. Concentration interior in examiner tube

Because of their high phenolic content, medicinal plants such as ZSC are being extensively researched for their antioxidant qualities [26]. With substantial flavonoid contents (1.06 mg), this investigation verified high antioxidant activity in its hydroethanolic leaf extract. Higher amounts of phenol and flavonoids were found in water extracts (35.69 ± 5.38 mg GAE·g^{-1} and 26.60 ± 2.25 mg RE·g^{-1}, respectively) [27], whereas methanolic extracts had the maximum phenolic content (52.5 mg GAE·g^{-1}) when compared to ethanolic and aqueous extracts [28, 29].

The composition of compounds varies by species; ZSC is primarily composed of luteolin and quercetin, whilst other species of *Ziziphus* contain caffeic, salvulinic, or chlorogenic acids. Total phenolics, flavonoids, and tannins are closely associated with antioxidant activity [25].

Methanolic extracts exhibited the highest antioxidant effect (IC_{50}=21.4 µg·mL^{-1}), followed by aqueous (24.2 µg·mL^{-1}) and ethanolic (54.3 µg·mL^{-1}), according to a study conducted in Jordan [29]. Phytochemicals like flavonoids, which counteract free radicals with their structural characteristics, are responsible for the antioxidant power [30].

Hydroethanolic solvents are perfect for optimizing antioxidant extraction efficiency since they are very good at extracting both polar and semi–polar substances [25].

In vivo study

Wound healing activity

TABLE II shows the results of wound healing after damage for each treated group. Likewise, no appreciable changes in body weight were seen in treatment with 5% and 15% doses (FIG. 2).

TABLE II
Variation of the body weights of rats among the experimental period

Groups	Body weights on day (M ± SEM)				
	3–days	6–days	10–days	13–days	15–days
C1	176.22 ± 18.44^{ns}	176.22 ± 18.44^{ns}	176.22 ± 18.44^{ns}	176.22 ± 18.44^{ns}	176.22 ± 18.44^{ns}
C2	176.64 ± 11.51^{ns}	176.64 ± 11.51^{ns}	176.64 ± 11.51^{ns}	176.64 ± 11.51^{ns}	176.64 ± 11.51^{ns}
C3	173.4 ± 17.24^{ns}	173.4 ± 17.24^{ns}	173.4 ± 17.24^{ns}	173.4 ± 17.24^{ns}	173.4 ± 17.24^{ns}
C^{+}	172.40 ± 13.02^{ns}	172.40 ± 13.02^{ns}	172.40± 13.0^{ns}	172.40 ± 13.02^{ns}	172.40 ± 13.02^{ns}
C^{-}	165.44 ± 17.73^{ns}	165.44 ± 17.73^{ns}	165.44 ± 17.73^{ns}	165.44 ± 17.73^{ns}	165.44 ± 17.73^{ns}
T	172.28 ± 5.98	183.18 ± 4.56	184.16 ± 8.40	185.14 ± 10.50	196.07 ± 13.97

Values are expressed as mean ± SEM (n = 6). ns: not significant, * P<0.05, ** P<0.01, *** P<0.001. C1: group1, C2: group2, C3: group3, C^{+}: positive control, C^{-}: not treated, T: control

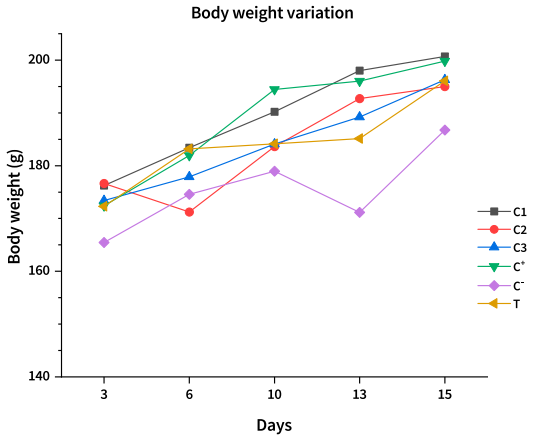

FIGURE 2. Body weight variation. C1: group 1; C2: group 2; C3: group 3; C^{+}: positive control; C^{-}: not treated; T: control

Statistical results

Furthermore, no statistically significant alterations were observed in body weight over the course of the 15 d observation period following the administration of the antiseptic solution at a 10% concentration

When ZSC solution was applied topically to rat wounds in this investigation, the healing process was accelerated by 15 d (TABLE III, FIG. 3). From 6 to 15 d, the second group, which received the 10% solution, demonstrated the greatest rate at which the wound contracts and a discernible decrease in wound size. The group with the longest time was third, which was given the 15% solution, came next.

TABLE III
Hydroethanolic extract's effects solutions of *Ziziphus spina–christi* on wound healing in rats

Groups	Wound closure on day (M ± SEM)				
	3–days	6–days	10–days	13–days	15–days
C1	48.75 ± 11.08**	56.25 ± 9.46*	65.0 ± 11.54*	76.25 ± 18.42^{ns}	81.25 ± 12.50^{ns}
C2	35.0 ± 18.25***	50.0 ± 17.79**	56.25 ± 14.93*	72.5 ± 15.54^{ns}	96.25 ± 7.50^{ns}
C3	48.75 ± 10.30**	62.5 ± 14.43^{ns}	75.0 ± 0^{ns}	78.75 ± 4.78^{ns}	90.0 ± 12.24^{ns}
C^{+}	50.0 ± 0**	56.25 ± 12.50*	56.25 ± 12.50**	56.25 ± 12.50*	56.25 ± 12.50**
C^{-}	41.66 ± 14.43***	43.33 ± 16.07**	41.66 ± 14.33***	41.66 ± 14.43**	41.66 ± 14.43***
T	100.0 ± 0	100.0 ± 0	100.0 ± 0	100.0 ± 0	100.0 ± 0

Values are expressed as mean ± SEM (n = 6). ns: not significant, * P<0.05, ** P<0.01, *** P<0.001. C1: group1, C2: group2, C3: group 3, C^{+}: positive control, C^{-}: not treated, T: control

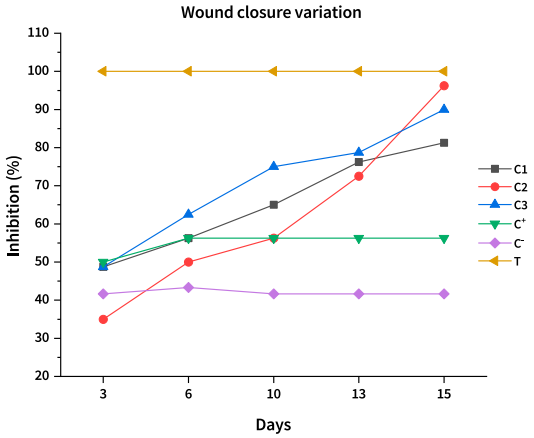

FIGURE 3. Assessment of treatment efficacy in wound healing acceleration. C1: group 1; C2: group 2; C3: group 3; C^{+}: positive control; C^{-}: not treated; T: control

Comparing the first solution 5% to the second and third groups, the former demonstrated comparatively poorer healing rates. On the other hand, the group that received betaderme treatment started to heal by day six, whereas the group that was not treated (negative control) did not exhibit any symptoms of recovery until day twelve (FIG. 4). Overall, the test formulation outperformed Betaderme, the reference solution, in terms of wound contraction ability.

When tissue is damaged, the body's typical response is wound healing, which includes myofibroblast–driven wound contraction, granulation tissue development, and cell regeneration [31]. The body's own cellular defense mechanisms are regulated by the biological response, which aids in wound healing [32].

The ethanolic extract of *Ziziphus mauritiana* markedly improved wound healing in albino rats, which is consistent with other studies. By 16 d, the animals treated with a 5% w/w extract ointment had a significantly higher rate of wound contraction than both control and standard treatments, and their results were similar to those of animals treated with nitrofurazone (Nitrofurazone ointment (0.2% w/w) was used as a standard drug) [16, 27].

Increased collagen concentration and fiber stability that promotes wound healing may be the cause of treated wounds' increased tensile strength. It improved contraction of the wound, either through improved myofibroblast contractile properties or increased

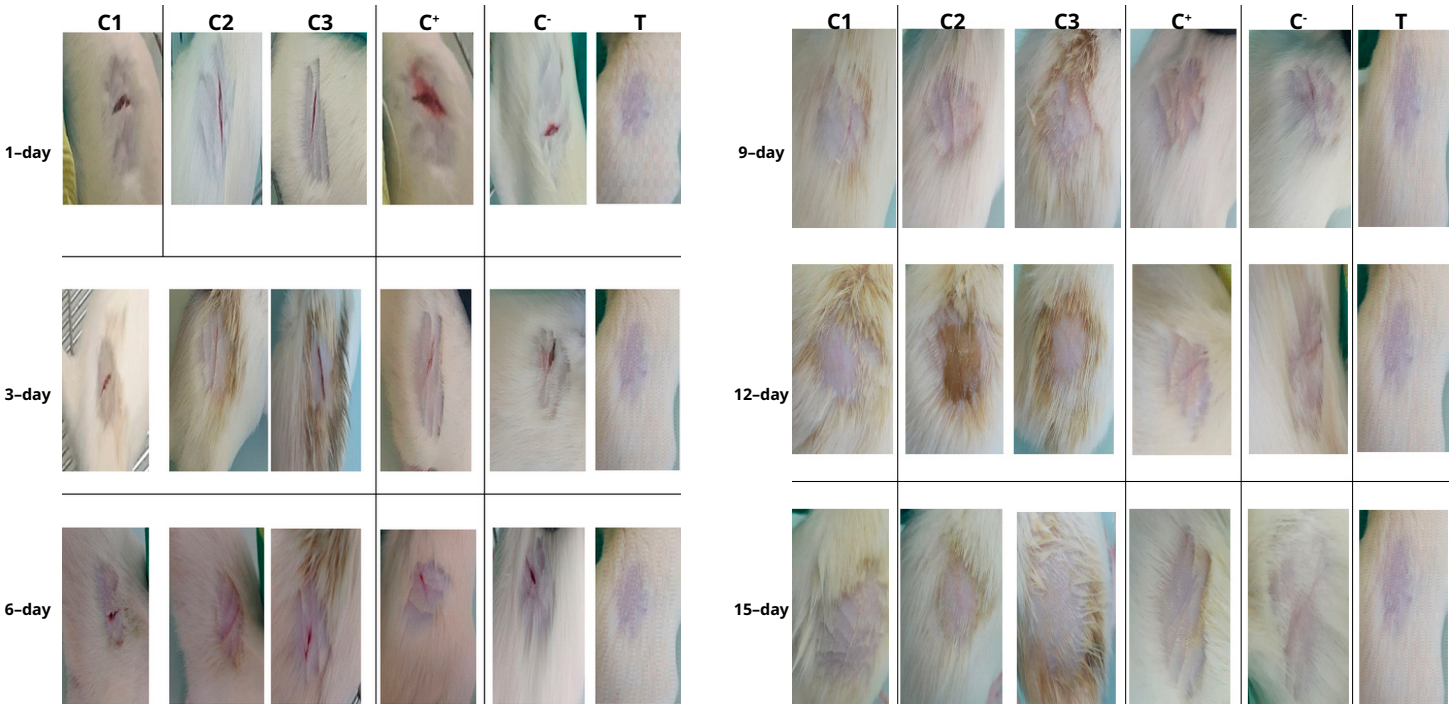

Figure 4. Macroscopic changes in the area and look of the wound during the healing process on days 1, 3, 6, 9, 12, and 15 post–treatments. C1: group 1; C2: group 2; C3: group 3; C^{+}: positive control; C^{-}: not treated; T: control

quantity of myofibroblasts that were drawn to the wound site. Additionally, it was encouraging epithelialization by either boosting the survival of epithelial cells or facilitating their proliferation [32].

Anti–inflammation study

After applying Xylene, the rat ear became noticeably red, signifying an inflammatory reaction. But after an hour, this redness progressively went away, indicating that the irritating effects of xylene were beginning to lessen. ZSC extract's anti–inflammatory qualities are responsible for this improvement; at different concentrations, it dramatically decreased inflammation in comparison to the not treated group, this had a high level of significance (P<0.001) reduction (TABLE IV).

TABLE IV
Effect of *Ziziphus spina christi* extract on ear thickness

Animal treatment groups	M ± SEM	Inhibition %
Group1	0.54 ± 0.01^{ns}	63.55
Group2	0.52 ± 0.01^{ns}	65.11
Group3	0.54 ± 0.01^{ns}	63.77
Positive control (Niflumene)	0.53 ± 0.15^{ns}	64.44
Not treated	$1.45 \pm 0.05^{***}$	3.33
Control	0.52 ± 0.01	100

The development of ear edema was significantly inhibited at all ZSC extract doses. The second concentration of the extract (400 mg·kg^{-1}) outperformed the other concentrations with an inhibition rate of 65.11%. The third concentration (600 mg·kg^{-1}) followed with 63.77%, while the first concentration (250 mg·kg^{-1}) generated 63.55%. In contrast, the inhibition rate for the positive group was 64.44%. In comparison to the control groups, the negative control group, which was given water, had the lowest inhibition rate, at just 3.33% (FIG. 5).

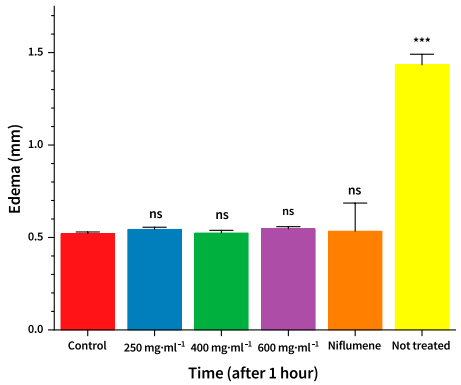

FIGURE 5. Anti–inflammatory effect of extract. Values are expressed as mean ± SEM (n = 6). ns: not significant; * P<0.05 ; ** P<0.01 ; *** P<0.001

The body uses inflammation as a defense mechanism against pathogens. It is primarily brought on the stimulation of Inducible Nitric Oxide Synthase (iNOS) by pro–inflammatory mediators like nitric oxide and involves white blood cell infiltration, edema, and granuloma formation [33].

A typical paradigm for assessing anti–inflammatory drugs is mice with xylene–induced ear edema, which is caused by phospholipase A2 activity and results in acute inflammation characterized by vasodilation and skin swelling. It has been demonstrated that there was a suppressed the generation of NO and the release of pro–inflammatory mediators, such as TNF–α and IL-6, when lipopolysaccharide (LPS) was present. Additionally, it significantly inhibited the translocation of NF–κB to the nucleus as well as the production and enzymatic activity of iNOS and COX-2. [34, 35].

Previous research [36] demonstrated the pharmacological potential of *Ziziphus mauritiana* by demonstrating that a methanolic leaf extract dramatically reduced rat paw edema caused by carrageenan, attaining a 71.8% inflammation reduction at 400 mg·kg^{-1}. Further demonstrating the anti–inflammatory properties of the Ziziphus genus, pentacyclic triterpenes from Ziziphus oxyphylla, in particular zizybrenalic acid, reduced the ear edema caused by xylene by 58.6% at 50 mg·kg^{-1} [37].

In addition, Triterpenes, in particular, and natural products in general are among the promising substances as analgesics and anti–inflammatory agents [38, 39].

CONCLUSIONS

Ziziphus spina–christi is among the plants that are most frequently utilized in traditional medicine due to its multiple therapeutic properties, particularly its antiseptic, and antioxidant effects.

Biological tests also confirmed its role in accelerating wound healing compared to reference solutions, demonstrating the extract's ability to promote the rapid and safe regeneration of damaged skin tissue.

These findings highlight the potential of *Z. spina–christi* extract as a natural agent to support tissue repair by speeding up wound healing. The extract may be a useful ingredient in the creation of botanical–based antibacterial and wound care products due to its efficiency in speeding up the healing process. This supports the development of safer, plant–derived substitutes for traditional chemical therapies in skin health and wound care, thereby reinforcing the research's practical application.

Ethical approval

According to the Council for International Organizations of Medical Sciences' (CIOMS) ethical requirements, the study that used animals complied. The Algerian Executive Directive (no. 10–90 JORA, dated 18 March 2004) prescribed ethical health research standards, and these protocols were approved in accordance with them. They also comply with the provisions of Law No. 88–08, issued on 26 January 1988, which addresses veterinary medicine activities and the protection of animal health (approval no. JORA: 004 of 27–01–1988).

Conflict of interest

There are no conflicts of interest related to this work.

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