RESEARCH ARTICLE

Evaluation of Curcumin Effect on Wound Healing in Rat Model

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ABSTRACT

Background: skin wound healing consists of a series of meticulously orchestrated, time-dependent, complex steps including inflammation, proliferation, and wound remodeling. Wounds that do not follow this time course are complicated. Skin wounds and their complications impose a major threat to the patients and the health systems and are a heavy burden on the global economy. Many researchers have directed their attention to studying the wound healing properties of natural products because of their safety, accessibility, low price, and fewer side effects. One of these phytomedicines is Curcumin. The active constituent of *Curcuma longa* has been widely studied for its anti-inflammatory, antioxidant, and antimicrobial properties.

The current study aims at exploring the wound healing properties of Curcumin in DMSO gel and comparing its effectiveness as a topical medicine to β-sitosterol ointment by using excisional full-thickness skin wounds in the rat model.

Methods: After the initiation of a full-thickness 2 cm diameter wound at their dorsal skin, forty male rats were divided randomly into 4 equal groups: the positive control, the Dimethyl sulfoxide (DMSO) gel, the β-sitosterol ointment, and the curcumin 4% gel groups. The groups were subdivided into A, and B subgroups and received their designed treatment for 7 and 14 days, respectively. Skin and blood samples were collected on the seventh and fourteenth days after wound initiation. Wound healing was evaluated by measuring the percentages of wound closure, the serum concentrations of IL-6, H/E staining for histopathological analysis, and the immunohistochemical assessment of MMP-9.

Results: During both test intervals, the curcumin-treated group showed accelerated wound closure, lowered levels of IL-6, enhanced collagen deposition and epithelialization, and modulated scores of MMP-9 in comparison to the positive control, DMSO gel, and β-sitosterol ointment groups.

Conclusions: Curcumin in DMSO gel significantly augmented wound healing by improving various parameters of the repair process. The 4% curcumin gel had a higher therapeutic wound healing potential compared to β-sitosterol ointment.

Keywords: Collagen deposition, Curcumin, DMSO, IL-6, Re-epithelialization, Matrix metalloproteinase (MMP-9).

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INTRODUCTION

The skin is the body's largest organ; it forms up to 15% of the adult's total body weight. It is a complex dynamic organ made up of an integral arrangement of cells, tissues, and matrix elements that provides a wide array of functions and offers continuous protection of the organism from the surrounding environmental conditions. Thus, preserving its integrity requires complicated mechanisms, and without these, assaults from injuries, burns, and surgical incisions can lead to serious complications.[1] The skin has the ability for self-regeneration and can withstand limited physical and chemical assaults. When this limit is breached, a skin wound is inevitable.

Wounds are one of the confusing clinical problems, with early and late complications, and are a common reason for morbidity and mortality.[2] Once the skin integrity is violated, the body undergoes a dynamic process to achieve tissue repair with the re-establishment of skin function and barrier. Wound repair is one of the most complicated processes in multicellular organisms. It is a natural biological procedure made of a series of independent processes where epidermal and dermal cells, Extracellular matrix (ECM), growth factors, cytokines, and plasma-derived proteins act simultaneously to initiate wound healing.[3] It involves a chain of carefully controlled actions and steps that correlate with the presence of various cell types in the wound area during different stages of the healing process.[4] Although healing is a continuous process, it is arbitrarily separated into four time-dependent steps.[5] These are (i) the coagulation and hemostasis phase; (ii) the inflammatory phase; (iii) the proliferative; and (iv) the remodeling phase.

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Wounds and their complications are a major concern for the health care providers and may seriously jeopardize the quality of the affected person's life. Thus, the attempt to quickly close the skin lesions with an ideal functional and aesthetic outcome would be the goal of any planned treatment.[6]

The desire for an optimal wound dressing has resulted in a surge of interest in traditional treatments and phytochemicals, which are plant-based products, that promote wound healing.[7] Many studies have been conducted on the wound healing properties of natural products with antioxidant, anti-inflammatory, pro-collagen synthesis, and antibacterial activities.

Curcumin ($C_{21}H_{20}O_6$) is a natural polyphenolic compound. It is an extract of Turmeric which is the powder of rhizome of the *Curcuma Longa* plant which belongs to the Zingiberaceae family. This plant is native in Southern Asia and is widely cultivated in the warm parts of the globe, mainly in India and China.[8] Curcumin gives turmeric its yellow color. Its chemical structure was described by Milobedska in 1910 as 1,7-bis (4-hydroxy3-methoxyphenyl)-1,6-heptadiene-3,5-dione.[9] It is soluble in ethanol, methanol, acetone, and dimethyl sulfoxide but insoluble in ether and water.[10]

During the last three decades, extensive medical research has shown that Curcumin can modulate several signaling pathways, alter gene expression, and interact directly with target molecules to result in anti-inflammatory,[11] antioxidant,[12] antiviral, antimicrobial, antifungal,[13] anticarcinogenic activities and other plentiful benefits to human health.[14] There is much evidence supporting curcumin status as safe. U.S. Food and Drug Administration has categorized the curcumin molecule as 'Generally Regarded As Safe'.[9] Clinical trials on humans have demonstrated its good tolerability and maximum safety profiles even at high doses ranging from 4000 to 8000 mg/day[15] and even to 12,000 mg/day.[16] However, its therapeutic activity is limited by its hydrophobicity causing poor solubility, permeability, and bioavailability, and by its photosensitivity, both act as major barriers against wider clinical applications.[17]

The current study aims at exploring the wound healing properties of curcumin gel and comparing its effectiveness as a topical medicine to β-sitosterol ointment by using excisional full-thickness skin wounds in the rat model.

Study Design

A prospective, randomized, experimental design involving four groups of rats was used for the evaluation of the effects of topical curcumin gel on wound healing progression compared to its vehicle gel and a standard on surgically induced full-thickness excisional wounds. The review board of the

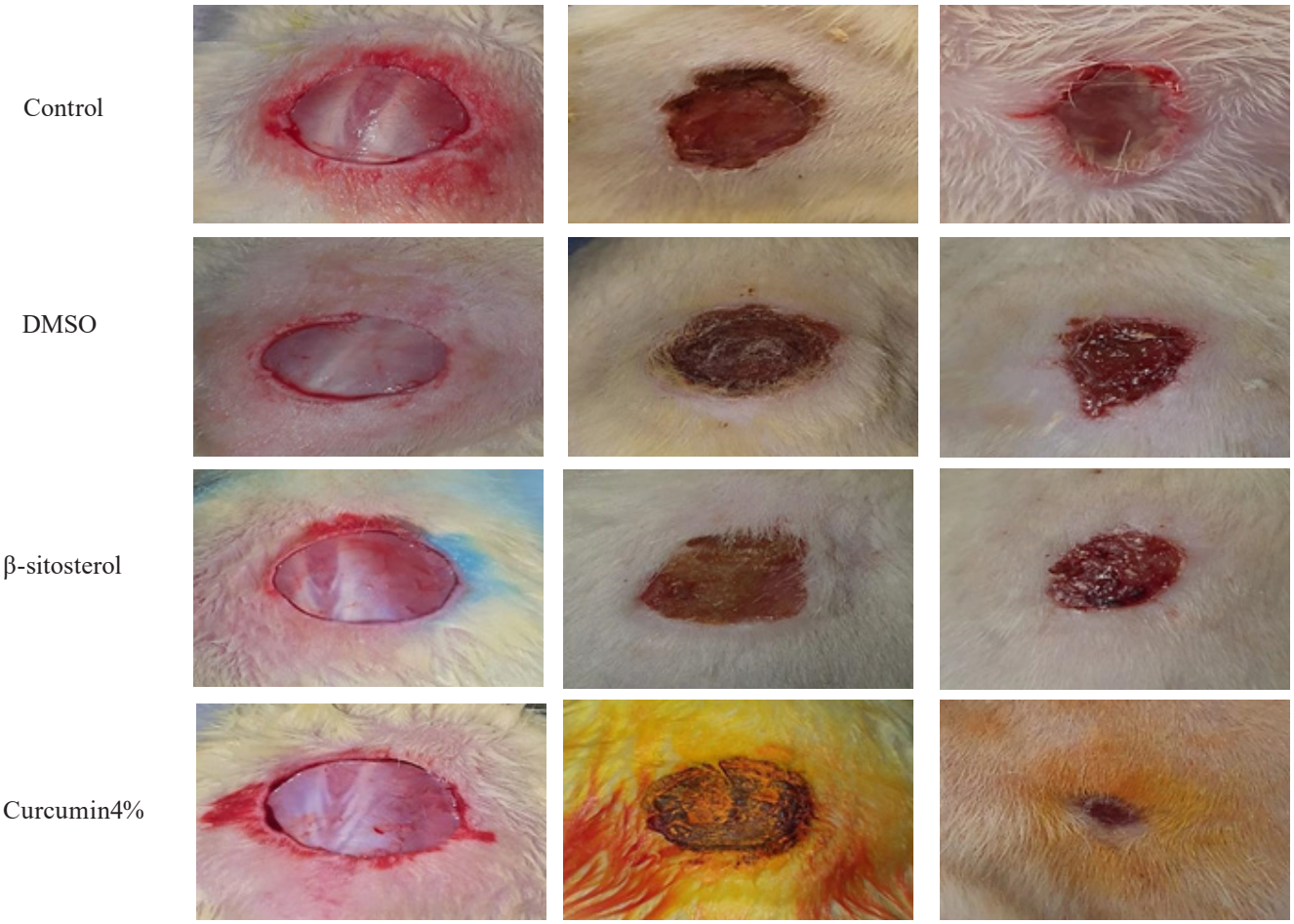


Figure 1: Wound closure of studied groups at days zero, seven, and fourteen.

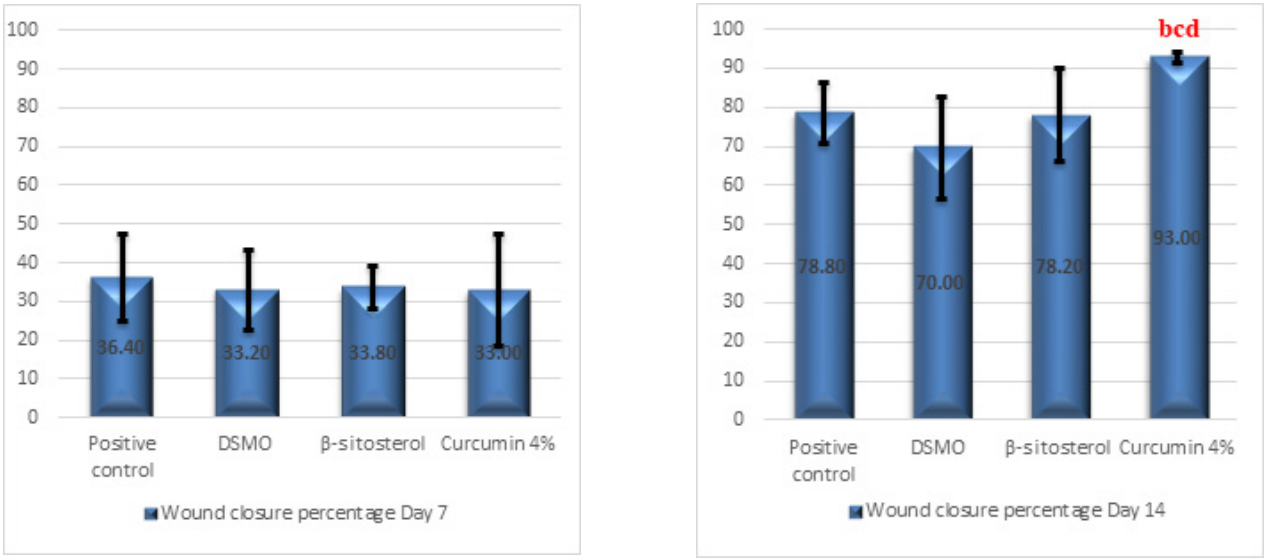


Figure 2: The mean wound closure percentage of the studied groups. **a:** is higher in curcumin gel group. **b:** is significant to the control group. **c:** is significant to the DMSO group. **d:** is significant to the β-sitosterol group.

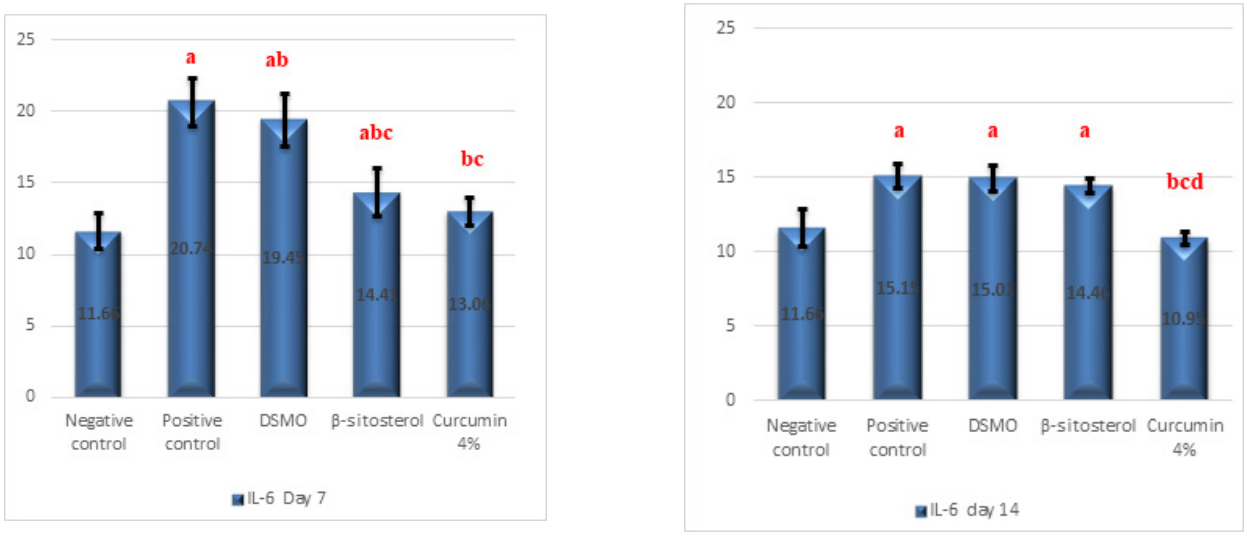


Figure 3: Interleukin-6 mean levels in experimental groups. **a:** is significant to the healthy group. **b:** is significant to the control group. **c:** is significant to the DMSO group. **d:** is significant to the β-sitosterol group.

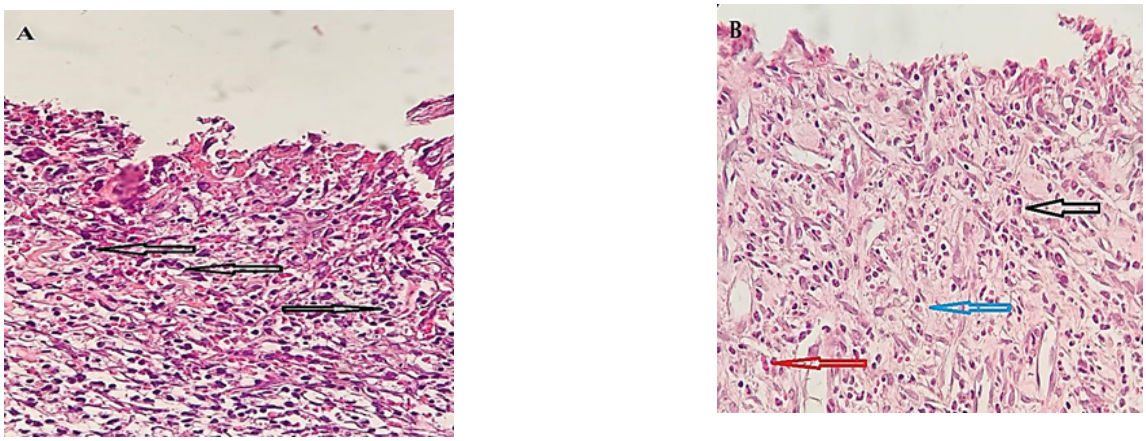
department of clinical laboratory sciences in the College of pharmacy of Mustansiriyah University approved the study design. The study covered the period from December 2020 to January 2021.

Experimental Animals

Forty-five healthy and active Wistar albino male rats were purchased from and cared for in the unit of the animal house of the Veterinary Medicine College of Baghdad University. They were about eight to twelve weeks of age and (250–300 gm) of weight. They were housed in individual, standard, cleaned, and disinfected polyethylene cages. The animal care unit was well-ventilated with temperature control (22 ± 2°C) and a 12/12 hours light to dark cycle. Free pellet food and drinking water were ensured. Rats were left to acclimatize for one week before the surgical procedure; during this time, their well-being, feeding, and activity were checked daily to exclude unfit rats. Ethical approval for animal use was granted by the Animal Ethics Committee/College of Pharmacy/ Mustansiriyah University, No. 21, 30/11/2020.

Forty rats were used to accomplish the full-thickness excisional wound according to previous reports6 under general anesthesia by intramuscular injections of 1.1 mg/kg of xylazine and 15 mg/kg of ketamine.[18] The rat dorsal regions were shaved and disinfected with ethanol 70%. The circular 2 cm diameter full-thickness excisional wound was induced with a sterile surgical set. The wounds were left undressed to receive their planned treatment.[6,19] Wounded rats were housed individually

Positive control group



DMSO group

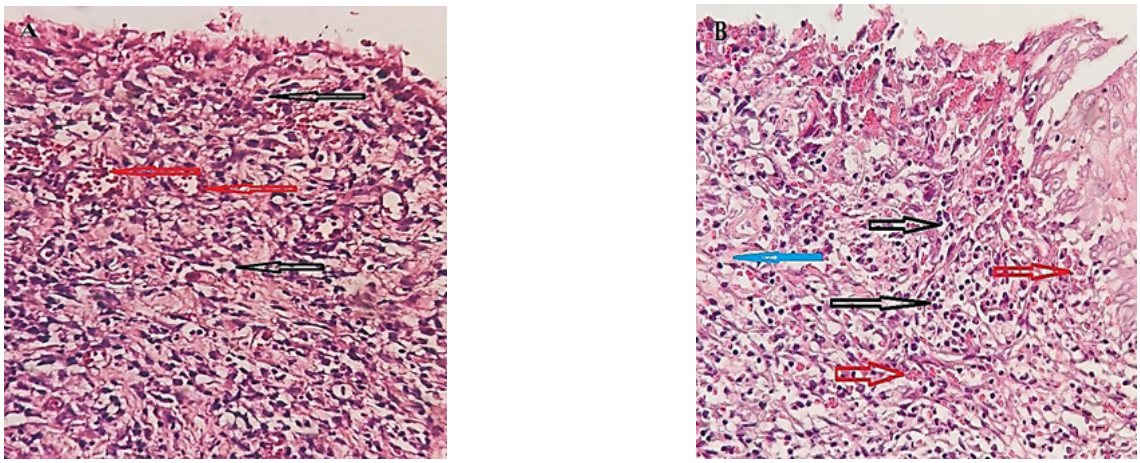


Figure 4 (A): light microscopic section of wound areas of the studied groups (40X). **A:** subgroup A. **B:** subgroup B. The black arrow represents inflammatory cells. The red arrow represents neovascularization. The green arrow represents reepithelialization. The Blue arrow represents collagen.

to prevent traumatic wound damage and licking of the wounds by other animals.[20]

Preparation of Curcumin Gel

Curcumin gel was prepared by a simple dispersion method modified from previous reports,[21] 4 grams of pure curcumin powder (Curcumin GRG: Natural yellow 3: 99.9%, Avonchem /UK) was accurately weighed. These were gradually dissolved in 15 mL of DMSO solvent (DMSO liquid, 99.9%, DMSO store/ USA) and the weight was completed to 100 grams by adding a ready-made Pharma-Grade DMSO medi-gel (carbomer, deionized water, and dimethylsulfoxide, DMSO store/USA) resulting in a clear, dark-orange, and free of precipitate, 4% curcumin in DMSO gel.

Animal Grouping, Topical Treatment, and Samples Collection

Immediately after the surgical procedure, 40 rats were randomly divided into 4 equal groups. the untreated animals' group was the positive control group, the DMSO gel group received the vehicle gel topically once daily, the β-sitosterol ointment group received this ointment topically twice daily,[22] and the curcumin group received topical 4% curcumin gel once daily.[23] Each group was subdivided into A and B subgroups. The 40 rats were euthanized by a high dose of the same anesthetics on the 7th (for the A subgroup) and the 14th postoperative day (for the B subgroup). In addition, 5 rats were used as a negative control group, their blood samples were collected as a source for the basal levels of the ELISA biomarkers study.

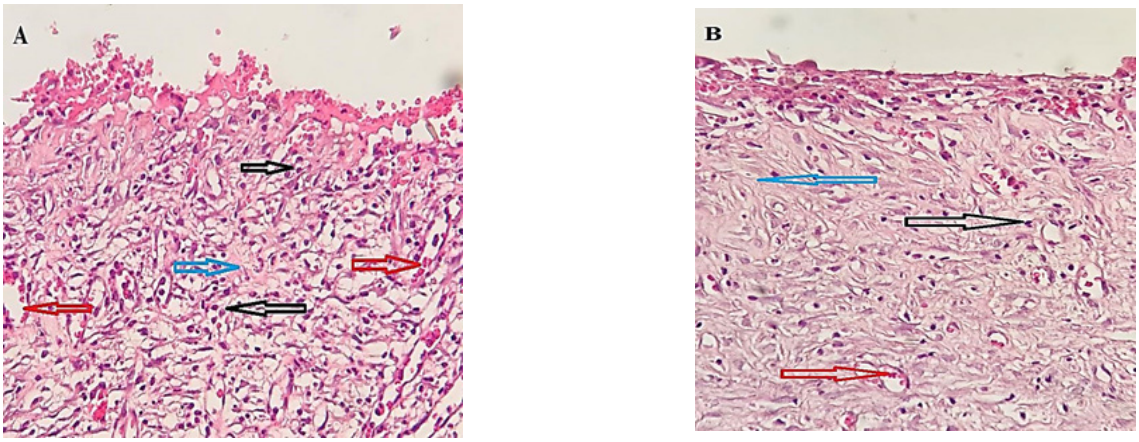
At each time point, wounds dimensions were measured by a ruler (the most extended length and the longest perpendicular width),[24] for the assessment of wound closure, blood samples were collected by cardiac puncture for the ELISA study, and skin wound samples were collected by excising the wound with its granulation tissue and a 5 mm margin of normal skin to be submitted for the histopathological and the immunohistopathological assessment.

Measurements of the Wound Closure Percentage

The wound area at day 0 was regarded as 100%, and the wound area closure percentages were expressed according to the Wilson Formula.

The percentage of the wound closure equals (area of the wound at postoperative day zero - area of the wound at the

β-sitosterol group



Curcumin 4% gel group

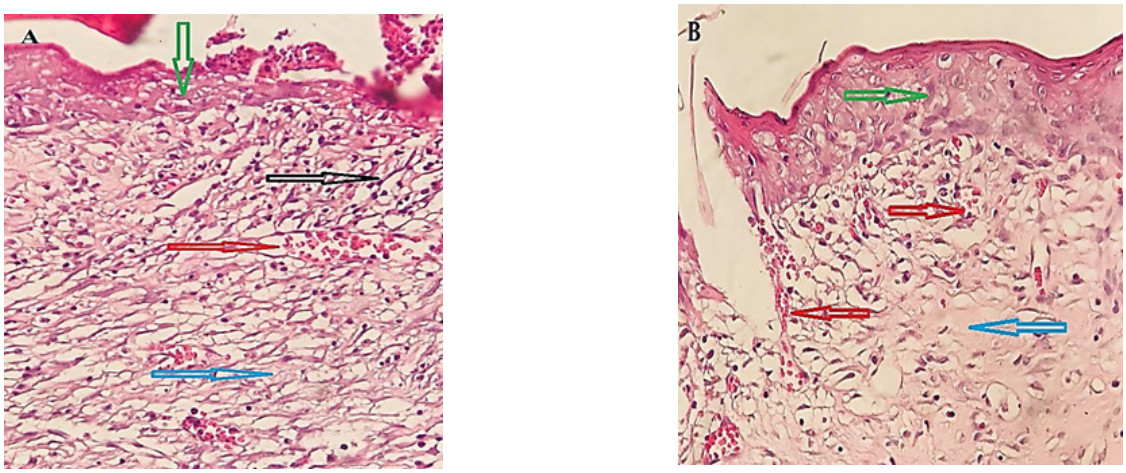


Figure 4(B): light microscopic section of wound areas of the studied groups (40X). A: subgroup A. B: subgroup B. The black arrow represents inflammatory cells. The red arrow represents neovascularization. The green arrow represents reepithelialization. The blue arrow represents collagen.

relevant day) divided by (area of the wound at postoperative day 0) × 100.[25]

ELISA Markers Study

Serum levels of interleukin-6 (IL-6) were evaluated using enzyme-linked immunosorbent assay (ELISA) kits (SunLong, Biotech. LTD/China) according to the manufacturer's instructions.

Histopathology

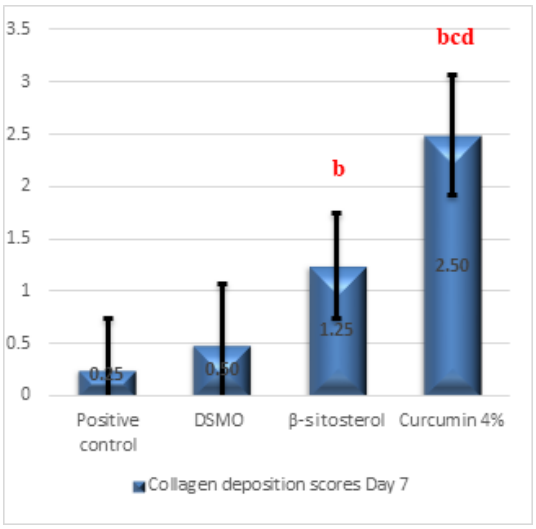
The collected samples were separately fixed in 10% formalin, dehydrated through graded alcohol series, cleared in xylene, and embedded in paraffin wax. Serial sections of 5 µm were cut and stained with hematoxylin and eosin. The sections were examined under a light microscope and photomicrographs were taken. To assess the degrees of wound healing, a histological score was used to assess the degree of collagen deposition (none=0, minimal=1, mild=2, and abundant=3) and reepithelialization (none=0, partial=1, thin and complete surface=2, and thick and complete surface=3) as described by Karadag.[26]

Immunohistochemistry

To assess the MMP-9 scores in the harvested samples, a primary antibody (Rat Anti- MMP9 antibody, ab76003, Abcam, UK), a secondary antibody (Rabbit specific HRP/DAB, ab64261, Abcam, Uk), DAB, and hematoxylin staining were used according to the manufacturer's guide. The positive cells were observed for brownish color under light microscopy and the extent of the reaction was graded as follows: 0= undetected, 1= when 1% to 25% cells stained; weak intensity, 2= when 26% to 50% cells stained, medium intensity, 3= when 51% to 100% cells stained, dense brown.[27]

Statistical Analysis

The numerical data retrieved from studied parameters were transferred to the Excel datasheet as mean ± SD, and analysis was made by using IBM SPSS software package version 27.0. Differences among studied groups were assessed by the One Way Analysis of Variance (ANOVA) and Least Significant Difference test (LSD).[28,29] A p-value of ≤ 0.05 was considered significant.



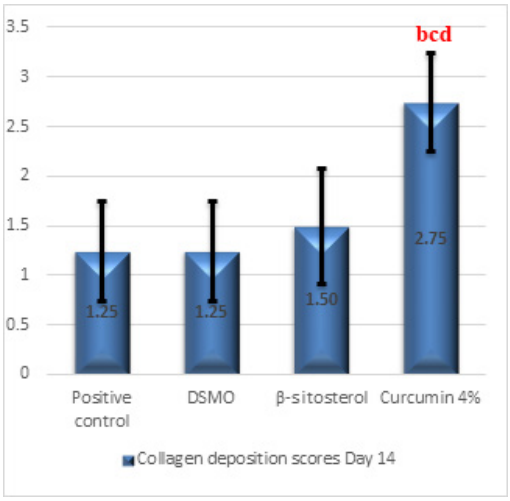
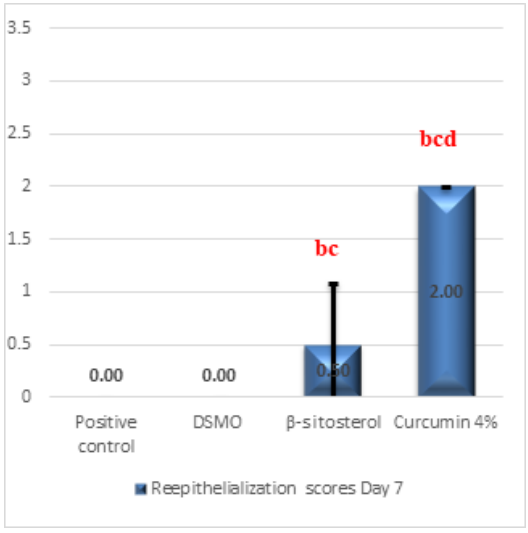


Figure 5: Collagen deposition scores in studied groups. **a:** is significantly higher in curcumin gel group. **b:** is significant to the control group. **c:** is significant to the DMSO group. **d:** is significant to the β-sitosterol group.



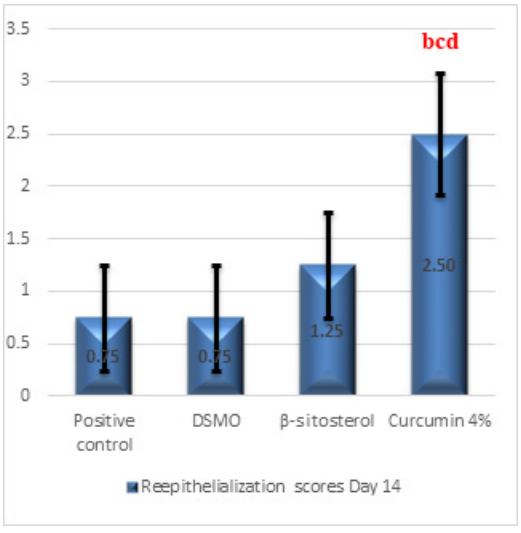


Figure 6: Re-epithelialization scores in studied groups. **a:** is significantly higher in curcumin gel group. **b:** is significant to the control group. **c:** is significant to the DMSO group. **d:** is significant to the β-sitosterol group.

RESULTS

Clinical Observations on Wound Closure

The wound healing of the curcumin-treated group was characterized by early formation and rejection (on the seventh to the tenth day) of thick scabs in comparison to the other groups. In addition, the Granulation tissue of the curcumin-treated group was thicker, well-formed, healthy-red, and elevated at the time of biopsy collection on day seven compared with other groups as seen in Figure 1.

Wound Closure Percentage

On day seven, all groups have shown a mild reduction in the wound surface area (the positive control: 36.4 ± 11.28, the DMSO group: 33.2 ± 10.26, the β-sitosterol group: 33.8 ± 5.63 and the curcumin 4% gel group: 33.0 ± 14.4, but no significant differences were found among the groups. On day 14, the curcumin gel group showed a higher wound closure percentage (93.0 ± 1.22), compared to the control group (78.8 ± 7.66), the DMSO group (70.0 ± 13.04), and the β-sitosterol group (78.2 ± 11.84) which was statistically significant to the three groups ($p \leq 0.05$) (Figure 2).

Measurement of the Level of Interleukin-6

On day seven, the three groups (the positive control: 20.74 ± 1.67, the DMSO group: 19.45 ± 1.80, the β-sitosterol group: 14.41 ± 1.72) had significantly higher levels of IL-6 than the negative control group (11.66 ± 1.23), while the curcumin gel group (13.06 ± 0.96) had a nonsignificant difference to the negative control (p=0.1). On day 14, the recorded levels of IL-6 remained significantly elevated ($p \leq 0.05$) in the positive

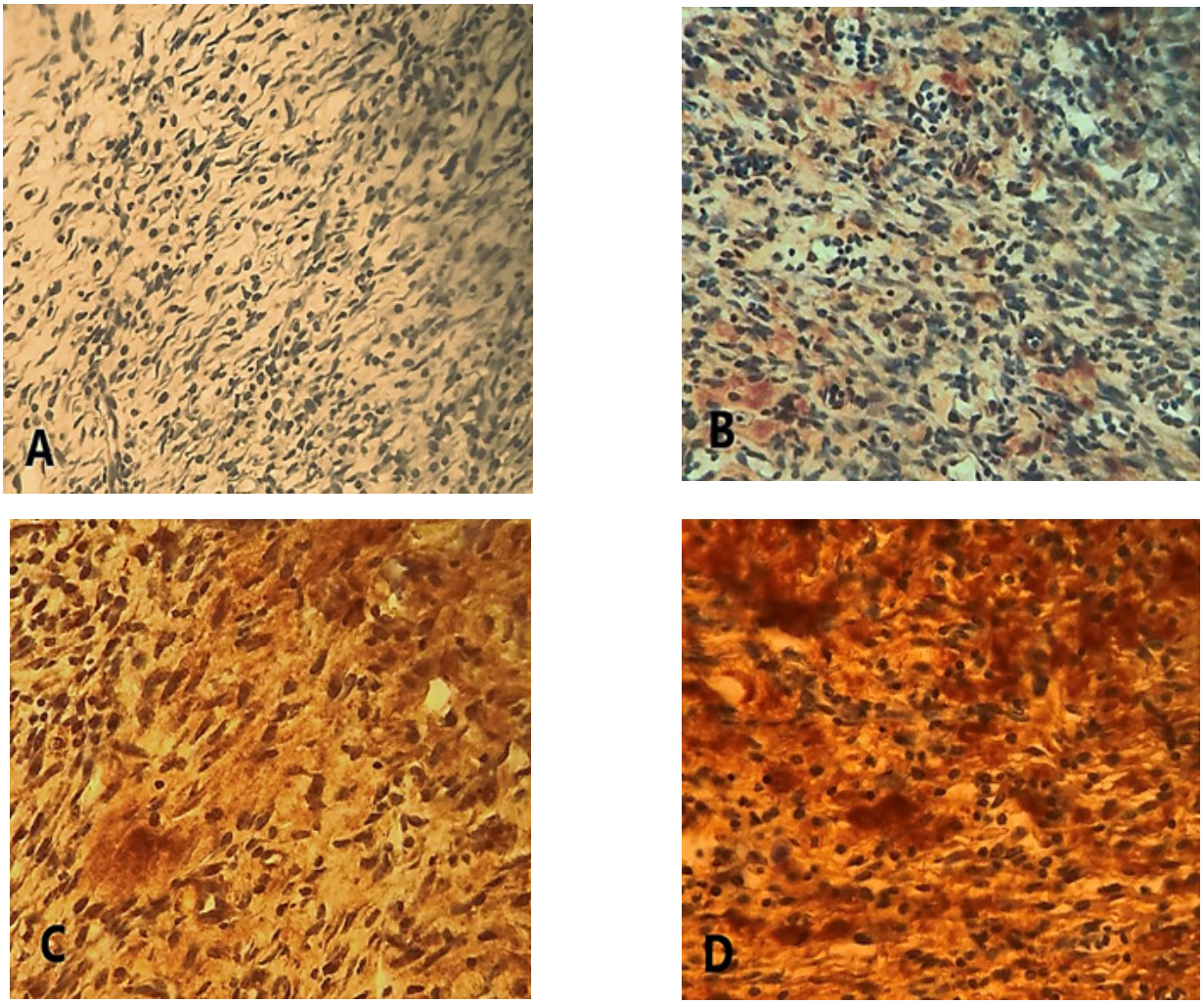


Figure 7: The Matrix Metalloprotease-9 immunohistopathological score slides images (40X) **A:** Score 0 in the healthy group skin samples. **B:** score 1 (low-intensity score) in the Curcumin 4% gel group at day 14. **C:** Score 2 (medium-intensity score) in the DMSO gel group at day 14. **D:** Score 3 (dense) in the positive control group at day 14.

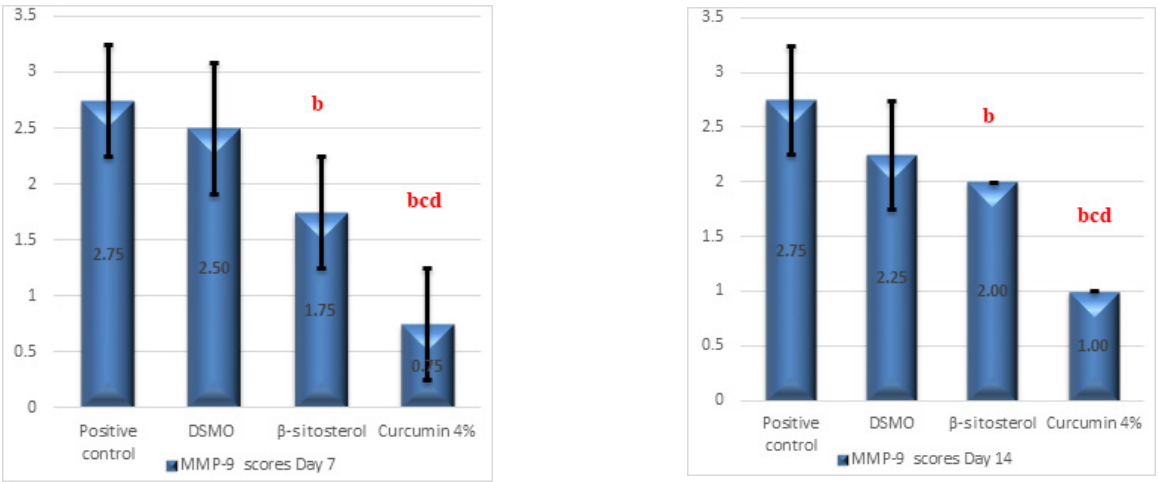


Figure 8: The matrix metalloprotease-9 scores in the studied groups. **a:** is significantly lower in curcumin gel group. **b:** is significant to the control group. **c:** is significant to the DMSO group. **d:** is significant to the β-sitosterol group

control group (15.15 ± 0.82), the DMSO group (15.01 ± 0.88), and the β-sitosterol group (14.46 ± 0.5) while those of the curcumin gel group (10.95 ± 0.39) were almost equal to the negative control group (11.66 ± 1.23) (p= 0.43) (Figure 3).

Collagen Deposition

On day seven, the curcumin gel group had significantly higher collagen deposition scores (2.50 ± 0.58) than the rest of the test groups (the positive control: 0.25±0.50, the DMSO: 0.50±0.58, the β-sitosterol group: 1.25 ± 0.50). On day 14, collagen deposition scores increased in all test groups compared to day 7 (the positive control group: 1.25 ± 0.50, the DMSO group: 1.25 ± 0.50, the β-sitosterol group: 1.50 ± 0.58, and the curcumin gel group: 2.75 ± 0.50). However, the curcumin gel group had shown significantly higher scores compared to the other test groups (Figures 4 and 5).

Re-epithelialization

On day seven, new epithelium started to regenerate in the curcumin 4% gel (2.00±) which was significantly higher than, the positive control group (0), the DMSO group (0), and the β-sitosterol group (0.50 ± 0.58) where ($p \leq 0.05$). On day 14, the curcumin-treated group showed significantly higher scores of epithelial regeneration (2.50 ± 0.58) than the other groups (the positive control group: 0.75 ± 0.50, the DMSO group: 0.75 ± 0.50, the β-sitosterol group: 1.25 ± 0.50) (Figures 4 and 6).

Measurement of the Intensity Scores of Matrix Metalloprotease-9 (MMP-9)

On day seven: all groups had shown an upsurge in MMP-9 level. However, the Curcumin 4% gel group (0.75 ± 0.50) had statistically significant less MMP-9 scores than the positive control group (2.75 ± 0.50), the DMSO group (2.50 ± 0.58), and the β-sitosterol ointment group (1.75 ± 0.50) with p-values of (≤ 0.05). On day 14, despite being slightly higher than the scores on day 7, the MMP-9 scores of the curcumin gel group (1.00) were significantly lower than those recorded in the other groups (the positive control group: 2.75 ± 0.50, the DMSO group: 2.25 ± 0.50, and the β-sitosterol ointment group: 2.00) (Figures 7 and 8).

DISCUSSION

Skin wounds are one of the major concerns for medical personnel and may seriously affect the life of the involved individuals with increased morbidity and mortality. In addition, wounds create an ongoing problem for global health systems due to expensive costs and non-effective treatments. In the USA alone, there are more than 5.7 million chronic wounds cases with an estimated yearly treatment cost of 20 billion dollars, and the international marketing for wound care products is rising sharply from 13 billion dollars in 2008 with a predicted yearly growth of 4%.[30]

In the last twenty years, there has been a growing interest in using phytochemical therapies in treating wounds due to their natural origin, acceptability, lower cost, and lower incidence of side effects.[31] Many plant-based and traditional therapies have been tested for their effect on wounds and wound healing properties targeting faster wound recovery, less scar formation, and better aesthetic results; these plants include; *Aloe vera*, *Arctium lappa, Boswellia sacra, Cinnamomum cassia, Curcuma longa*, and others.[5,7]

Gel forms of topical applications are characterized by their easy administration, the better residence time of the drug on the skin, enhanced bioavailability, non-greasy nature, and better drug release.[21] Dimethyl sulfoxide (DMSO) was used in the gel preparation as a solvent to Curcumin and as a drug diffusion enhancer.[32]

Effect of Topical Curcumin on Wound Closure Percentage

Wound contraction is the centripetal advancement of the full-thickness wound margins to assist earlier wound closure. Clinical observation of wound contraction by visual evaluation and consistent measurements is considered a reliable indicator of wound healing.[33] In the current study, curcumin topical treatment was associated with a significantly higher wound closure percentage than the other groups on the 14th day. Mohanty *et al.* also stated that at least eight days are needed to accurately compare wound contraction measurements differences between curcumin-treated and other groups of rats because the contraction was minimal before the eighth day.[34] However, Kant V. *et al.* found significantly higher wound contraction rates in curcumin-treated diabetic rat wounds than control and gel groups at day seven.[35]

Thick scabs, formed early in the course of curcumin treatment (also seen in Kant V. *et al*.'s study),[33] might have fixed the wound margins and delayed wound closure in the curcumin-treated group on day seven of the present study. Yen *et al.* found that in a dose-dependent manner, Curcumin accelerated wound contraction in mice by inducing alpha-smooth muscle actin (α-SMA) expression by fibroblasts causing them to differentiate into myofibroblasts.[23]

Effects of Topical Curcumin on Interleukin-6 (IL-6)

Interleukin-6 is the cytokine regarded as one of the major contributors to stimulating wide varieties of acute-phase proteins in inflammation. In addition to neutrophil chemoattraction, it also stimulates keratinocytes mitogenic activity, which is related to scar development.

In this study, topical application of 4% curcumin gel reduced the levels of IL-6 to normal values from day seven, while the values in other groups remained significantly higher than negative controls even at day 14. This finding agrees with that of Bhubhani *et al*. who found that curcumin nanoparticle hydrogels reduced the level of IL-6 in wounded rats from the 4th day of his study in comparison to the control rats,[36] and Sun *et al.* who also found that topical Curcumin reduced the IL-6 level in the first 84 hours after inducing psoriasis-like inflammation in mice.[37] However, Yang *et al*. noticed that topical curcumin treatment has no apparent effect on IL-6 in the first seven days of treating diabetic rats' wounds and attributed this to very high levels of IL-6 in diabetic wounds.[38]

This effect of Curcumin on IL-6 is mediated by suppressing the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation pathway.[39]

By modulating the level of IL-6, Curcumin can control the inflammation and optimize the wound repair process. Rolfe *et al.* found that low IL-6 levels were associated with scarless wound healing in fetal skin wounds[40] while, Lee et al. have linked delayed wound healing in diabetic rats to increased induction and expression of IL-6.[41] Johnson et al. have clarified the relation of atypical levels of IL-6 to hypertrophic scarring, keloids, and many fibrotic conditions of the skin.[42]

Effects of Topical Curcumin on Collagen Deposition

Collagens are a vital component in all the phases of wound repair. They are a product of fibroblast. Being a major component of connective tissue, they give the regenerating tissues their structural framework and tensile strength and provide an environment for tissue renewal. The scar tissue, which is the final result of wound healing, is mainly composed of collagens; thus, improving collagen synthesis and deposition would be ideal for wound healing.[39]

In the present study, curcumin treatment significantly increased collagen deposition from the 7th to the 14th day of the experiment compared to the other test groups. This finding agrees with Mitic *et al.* who noticed that collagen deposition started earlier (at day 7 of his study) in the curcumin-treated group of rats' tooth extraction sites.[43] He also noticed that curcumin treatment significantly improved the alignment, thickness, and architectural regularity of the deposited collagen fascicles compared to other studied groups. Qian *et al.* also proved that topical Curcumin improved burn-wound healing by increasing collagen deposition from the 4th to the 12th day of their experiment on excision wounds in rats.[44] On the contrary, Chun-Bin *et al.* showed that Curcumin reduced collagen deposition in human lung fibroblast *in-vitro* via autophagy.[45]

Effects of Topical Curcumin on Re-epithelialization

Reepithelialization is the process in which the wound is resurfaced with the regenerated new epithelium. It occurs during the proliferative stage of wound healing and begins 16-24 hours after being wounded.[46] Re-epithelialization involves the proliferation and migration of keratinocytes from the wound margins and skin appendages (sebaceous glands and hair follicles) to reconstruct the epithelial defect and restore the skin's barrier function.[47]

In the current study, Curcumin significantly improved epithelial regeneration from the 7th day of its topical application to the 14th day compared to the other test groups. This finding is consistent with that of Meizarini *et al.* who showed that keratinocytes' activity (as an indicator of reepithelialization) was at its peak on day seven of his experiment of topical application of zinc oxide-turmeric extract dressing on wounded rats and that reepithelialization was complete in the treated group by the 14th day of his experiment compared to the non-treated group.[46] Leng *et al.* have also concluded that curcumin nanoparticles topical application on excisional wounds in rats enhanced reepithelialization on the 6th day and that epidermis was similar to the normal skin by the 15th day of the experiment.[48]

Effects of Topical Curcumin on Matrix Metalloproteinase-9 (MMP-9)

Matrix Metalloproteinases are neutral proteinases, that constitute a family of more than 25, multi-gene, members. They are zinc-dependent endopeptidases involved in the breakdown of the ECM, nonmatrix components, and the basement membrane. Gelatinase-B or MMP-9 is primarily released on the degranulation of leukocytes during the inflammatory stage of wound healing. Macrophages, monocytes, and fibroblasts also release it during the wound healing process. Like the other group's members, it is involved in the early stages of wound healing during inflammation, debridement of the injured tissues, and epithelial regeneration, and in the later stages by mediating angiogenesis and connective tissue remodeling.[49] TNF-α partly regulates the activity, activation, and even synthesis of MMP-9.[50] Proper levels of MMP-9 were associated with early resolution of acute wounds thus, preventing wound healing process complications including delayed and non-healing wounds.[51] Excessive levels of MMP-9 were found to delay wound healing by inhibiting the attachment of migrating epithelial and endothelial cells and interfering with the basement membrane formation thus, delaying reepithelialization and angiogenesis.[52] However, MMP-9 depletion can be deleterious to wound healing since it interferes with its physiological functions.[53]

The present study has shown that topical curcumin application can modulate the levels of MMP-9 by significantly lowering them compared to the other test groups. This is in agreement with Kant V. and his group who noted that topical application of Curcumin accelerated wound healing in diabetic rats by significantly balancing the expression of MMP-9 in different phases of wound healing.[35] Yen *et al.* had also shown that topical curcumin application accelerated the healing of mice wounds by modulating the MMP-9 expression and proved that this effect of Curcumin is mediated through the inhibition of TNF-α.[23] In addition, Curcumin is regarded as a natural MMP broad-spectrum inhibitor by chelating catalytic zinc ions in the active sites of metalloproteinases.[54]

CONCLUSIONS

Curcumin in DMSO gel in a once-daily application for 14 days proved very effective in the treatment of full-thickness excisional wounds in the rat model by reducing the wound closure time, increasing collagen deposition, and enhancing reepithelialization. These effects of Curcumin were mediated by manipulation and modulation of IL-6 and MMP-9. The improvement of wound healing by curcumin gel was not related to the biological properties of the DMSO gel vehicle and its therapeutic potentials in wound healing were superior to the β-sitosterol ointment.

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