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Original Article

Wound Healing Potential of Curcumin and Colostrum-Loaded Liposomes in Diabetic Foot Ulcers

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ABSTRACT

Background: Diabetic Foot Ulcers (DFUs), a serious diabetes consequence, are caused primarily by hyperglycemia, oxidative stress, and chronic inflammation. This study aims to evaluate the therapeutic potential of liposome-based formulations containing curcumin, colostrum, or both for oral and topical delivery in DFU management. **Materials and Methods:** The thin film hydration approach was used to develop the liposomes, and their pharmaceutical characteristics were assessed. These liposomes were modified into hydrogels. Efficacy was evaluated in diabetic rats by measuring blood glucose, body weight, antioxidant status (SOD, CAT, GSH, MDA), HbA1c, insulin, TNF-α levels, wound contraction, histopathology, and TNF-α protein expression. **Results:** Liposome-loaded hydrogels were pH-compatible and rheologically suitable for topical use. Glycemic control was significantly improved (p<0.0001) with the colostrum-curcumin combination in oral and topical therapy. A highly significant improvement in antioxidant levels (p<0.0001) was noticed in both oral and topical administration of curcumin and colostrum combination, compared to the positive control group. In addition, the combination reduced the TNF-α levels considerably in oral (64.3%) and topical (77.1%). Higher wound contraction, rapid re-epithelialization, and collagen deposition were also observed with the combination. **Conclusion:** In conclusion the developed curcumin-colostrum-loaded liposomes showed a synergistic effect and could be a novel delivery platform for DFU therapy.

Keywords: Colostrum, *Curcuma*, Liposomes, Oral, Topical, Hydrogel, Inflammatory Marker, Oxidative Injury, Foot Ulcers.

INTRODUCTION

Diabetic Foot Ulcers (DFUs) are a critical consequence of diabetes mellitus, profoundly impacting patients' health and quality of life.[1,2] DFUs arise from various contributing causes, including diminished sensibility, vascular impairment, alterations in microcirculation, and/or anatomical abnormalities in the foot, including the creation of plantar calluses.[3,4] Foot ulcers are one of the main complications of diabetes mellitus with 34% of patients at risk.[4] In addition, about 15% of diabetic patients with foot ulcers undergo lower extremity amputation.[5] DFUs affect both minor areas of the foot and major regions above the foot. The rate of infection is very high in diabetic patients after foot ulcers occur. It also affects the patient's social and economic position, including emotional distress, social isolation, and unemployment.[6] Several studies have reported that almost one-quarter of the population may experience DFUs.[4,7] According to a meta-analysis, 6% of diabetic people worldwide have persistent foot ulcers.[8] People with diabetes are often unaware of foot injuries due to peripheral sensory neuropathy. In addition, motor neuropathy and vascular damage lead to foot deformities and poor circulation, contributing to the formation of chronic, non-healing wounds. The mechanisms behind the aberrant wound healing process in diabetes are intricate and involve the interplay of several cell types, chronic inflammation, poor angiogenesis, irregular proliferation and migration of keratinocytes, and atypical extracellular matrix remodeling.[9,10] Thus, it is crucial to comprehend these intricate processes in order to develop successful treatment strategies.

In this context, natural compounds are being explored for their potential to enhance DFU management by improving wound healing and reducing complications.[11,12] Nutraceuticals are bioactive compounds derived from food sources, including vitamins, antioxidants, and herbal extracts that offer promising adjunctive benefits in DFU treatment due to their antioxidant, anti-inflammatory, and wound-healing properties.[13-16] Colostrum

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and curcumin have emerged as notable active drugs in DFU management.[17,18] Growth factors, including epidermal growth factor, Transforming Growth Factor-beta (TGF-β), insulin-like growth factor-1, and Platelet-Derived Growth Factor (PDGF), are present in colostrum, the nutrient-rich first milk produced by mammals. These factors are essential for wound healing, as they promote cell proliferation, angiogenesis, collagen synthesis, and epithelialization.[18-20] Additionally, colostrum possesses immunomodulatory and antimicrobial properties through components such as lactoferrin as well as antioxidant enzymes like Glutathione (GSH) and Superoxide Dismutase (SOD), which help mitigate oxidative stress and support tissue repair.[21-23]

Curcumin, derived from turmeric, has shown significant therapeutic potential for DFUs by inhibiting pro-inflammatory cytokines, reducing oxidative stress, and enhancing antioxidant defenses through increased activities of Glutathione Peroxidase (GPx), Catalase (CAT) and SOD.[24,25] It promotes tissue regeneration by modulating growth factors like vascular endothelial growth factor, PDGF and TGF-β, and demonstrates antimicrobial properties, reducing biofilm formation and DFU infection risk.[26] Despite the individual promise of colostrum and curcumin, further research is required to establish optimal formulations and dosing strategies for effective DFU treatment. In this context, nanovesicular carriers like liposomes have demonstrated significant potential in delivering various phytochemicals.[27] Liposomes are nanoscale, biocompatible vesicles made of phospholipid bilayers that have drawn a lot of interest as medication delivery carriers, especially for DFUs and other chronic wounds.[28-30] Owing to their structural adaptability, hydrophilic and lipophilic drugs can be encapsulated, improving stability, bioavailability, and targeted administration to wound areas.[31] It is likely that the liposome formulation may provide various benefits when it comes to DFUs, such as regulated medication release, extended retention at the site of injury, and the capacity to pass through compromised skin barriers. Because of these characteristics, liposomes are a perfect carrier for delivering natural bioactive substances like curcumin and colostrum. However, it is essential to have a practical and robust platform to facilitate the clinical translation of liposomes in topical therapy. In this context, hydrogels offer a promising strategy as carriers for liposomes in topical applications. Typically, the hydrogels are three-dimensional polymer networks and are hydrophilic in nature, and are well established in the fields of drug delivery.[32] Owing to their high water content and tunable viscoelastic properties, hydrogels have been thoroughly investigated for the topical therapy of drugs, including liposomal formulations.[33-36] More significantly, the successful combination of liposomes into polymeric hydrogels has the potential to synergistically combine the advantages of both systems.[37-39] Thus, the current study aims to investigate the wound healing potential of liposomal formulation of colostrum and curcumin, both individually and in combination, in the management of DFUs via oral and topical routes in chronic diabetes rat models.

MATERIALS AND METHODS

Materials

Curcumin and Streptozotocin (STZ) were purchased from Sigma-Aldrich (Bangalore, India). Colostrum was obtained from Inlife Pharma, Hyderabad, India. Oleic acid, tween 80, carbopol 934, and polyethylene glycol 400 were purchased from Qualikems Fine Chem (Vadodara, India). Povidone-iodine (betadine) ointment USP (10% w/w) was procured from GS Pharmbutor, Rudrapur, India. All other chemicals and reagents used in the study were of analytical grade.

Preparation of liposomes

Liposomes of curcumin and colostrum were prepared by the thin film hydration technique described earlier with minor modifications.[40,41] In short, 10 mL of a solvent system consisting of a mixture of methanol and chloroform (2:1, v/v) was used to dissolve 50 mg of soy lecithin, 10 mg of cholesterol in a 7:3 (mole ratio), and 10 mg of curcumin. In a 250 mL round-bottom flask, 10 mg of colostrum was separately dissolved in 10 mL of a solvent system consisting of a 3:1 v/v ethanol and water mixture. A thin lipid layer formed after the two solutions were combined and the organic solvent was removed using a rotary evaporator that rotated at 120 rpm in a water bath that was set at 45°C and reduced pressure. 10 mL of distilled water were used to hydrate the lipid layer, and the flask was rotated for 1 h. The suspension was then extruded through a polycarbonate membrane with a pore size of 0.2 μm after being sonicated for about 15 min using a bath sonicator. Similarly, liposomes containing colostrum or curcumin alone were prepared by dissolving colostrum (10 mg) or curcumin (10 mg) using their respective solvents.

Preparation of liposome-loaded hydrogel

To develop hydrogel, Carbopol 934 (1% w/v) was dissolved in deionized water under stirring, and the mixture was left for 24 hr to fully hydrate the polymer chains. The dispersion (10 g) was neutralized to pH 7 by dropwise addition of 2% triethanolamine and stirred until a transparent gel appeared.[42] Then the prepared liposomal suspensions of curcumin liposomes, colostrum liposomes, or curcumin-colostrum liposomes were gradually added and mixed (30 min) to get their respective liposomal hydrogels. Similarly, a control gel containing carbopol (1% w/v) liposome without curcumin and colostrum was prepared under the same conditions.

Characterization of liposomes

Determination of particle size

The particle size and Polydispersity Index (PDI) of all three formulations (curcumin liposomes, colostrum liposomes, and

curcumin-colostrum liposomes) were assessed at 25°C using particle analyzer (Beckman zetasizer Delsa Nano C, Switzerland, ver. 3.73/2.30).[43]

Zeta potential analysis

All three formulations were analyzed for zeta potential using a Beckman zetasizer at 25°C.[44] The measurement was made at 25°C using a transparent disposable zeta cell with a count rate of 29.3 kcps.

Entrapment efficiency

About 100 mg of liposomes (curcumin liposomes and curcumin-colostrum liposomes) were dissolved in Triton X-100 and then kept on an orbital shaker at 100 rpm and 37°C for 24 hr to determine the degree of curcumin entrapment.[45] The mixture was centrifuged for 20 min at 4000 rpm. The supernatant was retrieved and measured spectrophotometrically at 425 nm to measure the curcumin content.[46] To determine the drug concentration in the formulation, working dilutions for the calibration curve were used.

Characterization of gel

Determination of pH

Weighed 10 g of curcumin liposomes, colostrum liposomes, and curcumin-colostrum liposomes gel formulation were transferred to separate beakers and the pH was determined using digital pH meter (MP-220, Greifensee, Switzerland).

Spreadability

Slide and drag method were used to assess the spreadability of the liposomal gel formulation.[47] The apparatus has been altered and designed to accommodate two glass slides. The lower slide was fastened to a wooden plate, and the upper slide was connected to a balance by a hook. The spreadability of the gel was tested by sandwiching 2-5 g between two slides and then increasing the weight by placing it on the weight pan. The time it took for the upper plate to move 6 cm after adding 20 g of weight was recorded. The following formula was used to determine the spreadability.

$$\text{Spreadability (g.cm/sec)} = (\text{Weight to upper slide} \times \text{length moved on the glass slide})/\text{Time taken to slide}$$

Viscosity measurements

Using a Brookfield viscometer DV-II model (Middleborough, MA, USA), the viscosity of gels was measured. The viscosity was determined using a helipath stand and a T-bar spindle. The temperature of the medium was 25°C±1.0°C.

Animals

The experimental protocol was approved by the Institutional Animal Ethics Committee (MMCP/IAEC/19/62) and included adult albino Wistar rats of either sex weighing between 200 and 250 g. The animals were obtained from an approved animal house (NIPER, Punjab, India). The animals were kept in a 12:12 light-dark cycle with regular temperatures (24-28°C) and relative humidity (60-70%). Throughout the trial, the animals were given a specific diet and free access to water.

In vivo evaluation

Streptozotocin-induced diabetes and induction of foot ulcer

Diabetes was induced by administration of STZ (40 mg/kg b.w) freshly prepared with citrate buffer via single intraperitoneal injection to the overnight fasted rats in all groups except the normal control group. After 4 days, the rats with high blood glucose levels (>200 mg/dL) were selected as diabetic models for wounds. Hyperglycaemic animals received wounds on day 7. Animals were anesthetized with the topical application of lignocaine and 50.3 mm^2 circular incision was made in the foot using surgical blade. All of the surgical procedures were carried out in an aseptic environment. Animals had their wounds treated with drugs starting from the day of performing the wound (day 7) and continued for a period of 45 days, which is day 52 from starting the experiment.[48,49] The details of various groups for oral and topical therapy used are summarized in Table 1.

Glucose estimation

Blood samples were drawn on 0, 7, 14, 21, and 27 days from the animal's tail. The amount of blood glucose levels was determined using an Accu-Chek glucometer (Roche Diabetes Care GmbH, Germany).[50]

Body weight

Rats in each group were weighed using a digital electronic balance for small animals at various intervals: 0, 7, 14, 21, and 27 days.

Antioxidant assay

SOD, CAT, and reduced GSH were measured using a tissue homogenate (10%) of the granulation tissue made from 0.02 M phosphate-buffered saline. SOD activity was measured using the previously mentioned methodology.[51] The sample's supernatant was determined using spectrophotometry at 480 nm, which measures the oxidation of adrenaline in terms of adrenochrome production. The sample was combined with 0.1 mL of tissue homogenate and 0.5 mL of H_2O_2 in a test tube and incubated in a water bath at 37°C for 60 sec in order to perform CAT analysis. To produce the yellow complex, ammonium molybdate solution (0.5 mL) was then added to the process. A spectrophotometer was used to measure the absorbance at 405 nm.[52] The colorimetric method was used to measure the reduced GSH in the tissue homogenates.[53] In brief, the tissue homogenate (100 µL) was combined with 0.2 M Tris EDTA buffer (0.1 mL), incubated for 15 min at 25°C, and then centrifuged. The reaction mixture was added to 5,5 dithiobis-2-nitrobenzoic acid and incubated at 37°C for 15 min, or until a fairly stable yellow color

formed. The absorbance at 412 nm was then measured using a spectrophotometer.

In order to measure lipid peroxidation levels by quantifying Malondialdehyde (MDA) using the thiobarbituric acid reaction, samples of wound tissue were obtained and homogenized in buffer (Tris-HCl, pH 7.4).[54,55] Then, 1.5 mL of 20% acetic acid, 0.2 mL of 8.1% sodium dodecyl sulfate, 1.5 mL of 0.95% thiobarbituric acid, and 0.6 mL of distilled water were added to 0.2 mL of tissue homogenate. After properly mixing the reaction mixture, it was incubated for 1 h at 95°C in a water bath. After that, 5.0 mL of a butanol/pyridine combination (15:1, v/v) and 1.0 mL of distilled water were added, and the mixture was vortexed. After centrifuging the solution for 10 min at 10,000 × g, the absorbance of the supernatant was measured at 532 nm. Using 1,1,3,3-tetraethoxypropane as a reference, the amount of lipid peroxidation was measured and reported as nanomoles of thiobarbituric acid reactive compounds per milligram of protein.

Determination of glycosylated haemoglobin and proinflammatory cytokines

The 10% homogenate supernatant was centrifuged at 4000 x g for 15 min. A conventional method was used to assess the amounts of glycosylated hemoglobin. [56] ELISA kits were used to measure proinflammatory cytokines (TNF-α and IL-6) in accordance with the manufacturer's instructions.[56,57] The concentration of cytokines was stated in pg/mL.

Wound healing measurement

On the seventh, fifteenth, and twenty-first days following the day of wound induction, the regions of the wound were measured. The changes in the wound region were photographed with a digital camera and subsequently examined with Image J software. The percentage of wound closure was determined using the formula.[58]

$$\% \text{ Wound closure} = (\text{Initial wound area}) - (\text{Nth day wound area})/(\text{Initial wound area}) \times 100$$

Histopathology

Ketamine HCl (100 mg/kg) and xylazine HCl (25 mg/kg) were given intraperitoneally to the animals to induce anesthesia at the completion of the experiment. The afflicted areas' wound-healing tissues were extracted using a biopsy punch. For histopathological investigation, the tissue samples were preserved in 10% buffered formalin and paraffin using conventional laboratory procedures. After that, a tiny 5 µm thick piece was obtained and stained with periodic acid-Schiff dye and hematoxylin and Eosin (H and E). Under a light microscope (magnification x 200), slides were qualitatively inspected for tissue alterations.

Western blot analysis

To evaluate TNF-α, a 30-µg protein sample was electrophoresed in a 10% sodium dodecyl sulfate page gel. After blocking the gel on a polyvinylidine difluoride membrane for 1h at room temperature using a blocking solution (5% skim milk powder in TBST),

Table 1: Grouping of animals for diabetic foot ulcer study by oral and topical therapy.

Groups	Treatment
Oral therapy	
Group 1	Normal control received 0.5% carboxymethyl cellulose.
Group 2	Diabetic control with foot ulcer wounds (STZ 40 mg/kg).
Group 3	Diabetic-induced foot ulcer received metformin.
Group 4	Diabetic-induced foot ulcer received curcumin (1%, low dose per orally, CUR-O-Low).
Group 5	Diabetic-induced foot ulcer received curcumin (2% high dose per orally, CUR-O-High).
Group 6	Diabetic-induced foot ulcer received colostrum (1%, low dose per orally, COL-O-Low).
Group 7	Diabetic-induced foot ulcer received colostrum (2% High dose per orally, COL-O-High
Group 8	Diabetic-induced foot ulcer received colostrum and curcumin (1%, low dose per orally, CURCOL-O).
Topical therapy	
Group 1	Normal control received control gel.
Group 2	Diabetic control with foot ulcer wounds (STZ 60 mg/kg).
Group 3	Diabetic-induced foot ulcer received betadine (BET).
Group 4	Diabetic-induced foot ulcer received curcumin (1%, low dose topical, CUR-T-Low).
Group 5	Diabetic-induced foot ulcer received curcumin (2%, high dose topical, CUR-T-High).
Group 6	Diabetic-induced foot ulcer received colostrum (1%, low dose topical, COL-T-Low).
Group 7	Diabetic-induced foot ulcer received colostrum (2%, high dose topical, COL-T-High).
Group 8	Diabetic-induced foot ulcer received colostrum and curcumin (1%, low dose topical, CUR-COT).

primary antibodies (Abcam, Cambridge, UK, 1:1000) were used to probe the membranes. The following day, secondary antibodies (antimouse or antirabbit at 1:2000) were added to the membranes after they had been cleaned. The chemidoc XRS imaging system (Bio-Rad, Milan, Italy) was used to scan the proteins after they had been augmented with cemiluminescence substrate. The results were represented in standard units, and Image J software was used to assess the band intensity, with β-actin serving as a housekeeping gene.

Statistical analysis

The data were presented as Mean±Standard Error (S.E.M). The Tukey multiple comparison test and two-way ANOVA were used to examine the statistical difference between the means. *p*-values below 0.05 were considered significant.

RESULTS

Evaluation of liposomes

Representative images of particle size and PDI of prepared liposomes are presented in Figure 1. The developed curcumin liposomes, colostrum liposomes and curcumin-colostrum liposomes showed an average particle size of 533.2±2.34 nm, 476.7±1.23 nm and 736.0±2.01 nm, respectively, with corresponding PDI values of 1.000±0.03, 1.000±0.01, and 0.785±0.01. The zeta potential of curcumin liposomes, colostrum liposomes and curcumin-colostrum liposomes was found to be -31.3 mV, -32.2 mV and -32.6 mV, respectively (Figure 2), while the entrapment efficiency was 82.53±1.92% and 83.84±1.13%.

Evaluation of gels

The physicochemical characteristics of the prepared gels are presented in Table 2. The pH values of the prepared liposomal gels were within acceptable limits of 7.0-7.2. Spreadability was determined to be between 10.42 to 12.02 g.cm/sec based on the gels' slide and drag characteristics. The determined viscosity of gels was in the range of 2000 cPs.

In vivo evaluation

Effect of different formulations on glucose levels

The estimated blood glucose levels in various groups are presented in Figure 3. In the oral therapy groups (Figure 3A), blood glucose levels were significantly increased ($p<0.0001$) in all groups except the normal control group. Following the induction of diabetes and the creation of a wound on day 7, glucose levels raised within a range of 344±43.75 to 350±47.62 mg/dL. A gradual decrease in glucose levels was observed by the 14th day in the group treated orally with curcumin (301±30.86 mg/dL) and colostrum (293±29.25 mg/dL), respectively, compared to the positive control group (361±55.49 mg/dL). A slightly significant difference ($p<0.05$) was noted in the group treated with a high dose of the colostrum liposomes relative to the positive control group. On the 21st day, the highest reduction in glucose levels (18.83%) was observed in the high-dose oral colostrum-treated group. Both the colostrum-curcumin combination group and the colostrum alone group demonstrated sharp and statistically significant drops in blood glucose levels during the past two intervals when compared with the positive control group ($p<0.0001$).

In case of the topical application of liposome formulation study (Figure 3B), the betadine-treated group did not exhibit any reduction in blood glucose levels from the 7th to 27th days. A highly significant statistical difference ($p<0.0001$) in glucose reduction was observed at both the 21st and 27th days in animals treated with curcumin and colostrum liposomes, at both low and high doses, compared to the positive control group. Among the different drug-treated groups, the combination of colostrum with curcumin and the colostrum alone-treated group demonstrated the greatest reductions in glucose levels. Overall, the difference was found to be statistically significant.

Effect of different formulations on body weight

The animals' body weight was recorded at various times and is shown in Figure 3. Except for the normal control group, all groups experienced a drop-in body weight following diabetes diagnosis. By the 7th day, the weight of the animals had decreased significantly. However, following oral treatment (Figure 3C), all drug-treated groups have maintained their weight, with

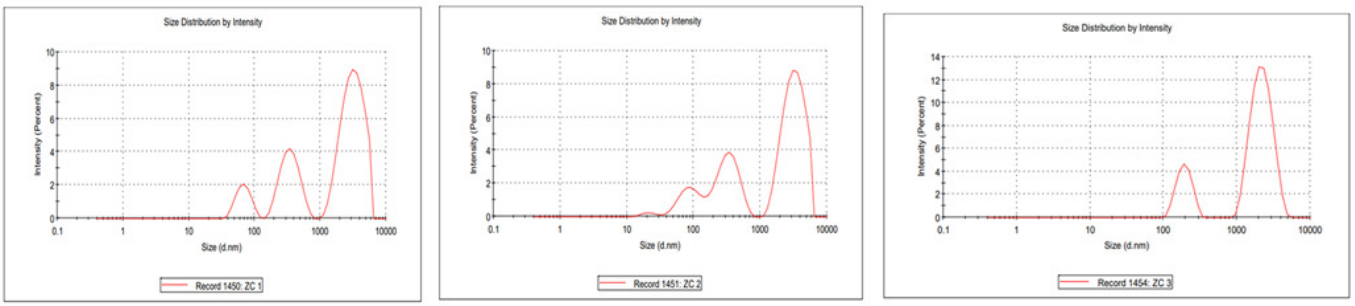

Figure 1: Particle size of curcumin liposomes (a), colostrum liposomes (b) and curcumin-colostrum liposomes (c).

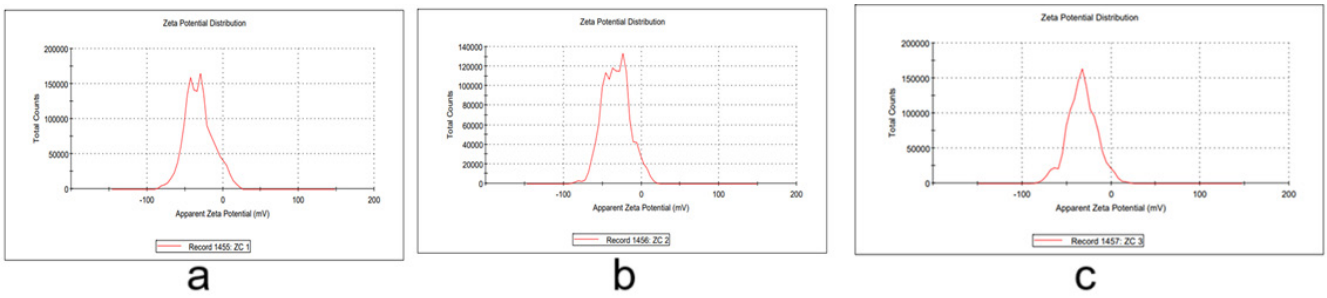

Figure 2: Zeta potential of curcumin liposomes (a), colostrum liposomes (b) and curcumin-colostrum liposomes (c).

Table 2: Physicochemical characteristics of gels.

Formulation	pH	Spreadability (g.cm/sec)	Viscosity (cPs)
Control gel	7.04±0.13	10.48±0.81	1895.14±25.99
Curcumin liposome gel	7.08±0.12	10.42±0.94	1929.17±23.90
Colostrum liposome gel	7.17±0.18	11.06±0.59	1909.83±25.08
Curcumin-colostrum liposome gel	7.05±0.17	12.02±0.78	1939.72±33.07

improvements ranging from 11.83% to 20.71% by the 14th day. The metformin-treated group demonstrated better efficacy in promoting weight regain. Among the treated groups, those receiving high-dose curcumin, high-dose colostrum, and the combination of colostrum and curcumin were particularly effective in maintaining body weight across all intervals. These results were statistically significant (p<0.0001) compared to the positive control group. A similar trend was observed in the topical formulation study (Figure 3D), where the animals' body weight remained stable by the 27th day, also showing a highly significant difference (p<0.0001) from the positive control group. Among the various treated groups, the colostrum-treated group exhibited the highest efficacy in promoting weight regain between the 14th and 27th days.

Antioxidant effect of different formulations on foot ulcer

Effects of colostrum and curcumin alone and in combination on antioxidant enzymes and oxidative stress are presented in Figure 4. The results showed that lipid peroxidation, measured by MDA levels (Figures 4E and 4F), was significantly increased, while antioxidant levels in the foot skin, specifically CAT (Figures 4A and 4B), GSH (Figures 4C and 4D), and SOD (Figures 4G and 4H), were markedly depleted in the positive control group. Furthermore, both oral and topical administration of curcumin and colostrum, individually and in combination, resulted in a highly significant increase in antioxidant levels compared to the positive control group (p<0.0001). In contrast, the betadine-treated group did not exhibit any significant antioxidant effects in the assays.

Effect of different formulations on glycosylated haemoglobin, and proinflammatory cytokines

Figure 5 depicts the glycosylated hemoglobin levels across various treatment groups. The group treated orally (Figure 5A) with a high dose of colostrum showed a modest but statistically significant improvement (p<0.05) on both the 14th and 21st days. In contrast, the metformin-treated group (4.33±1.30 mg/g) and the group that received the combination of colostrum and curcumin (5.20±1.49 mg/g) exhibited highly significant improvements compared to the positive control group (12.68±2.65 mg/g). In case of the topical application study (Figure 5B), no significant improvement was seen in any treated groups when compared to the positive control group.

The data on insulin levels indicates (Figure 5) that the oral formulation (Figure 5C) of colostrum and curcumin, both at low and high doses, as well as their combination, resulted in insulin levels approaching normal values. These changes were statistically significant (p<0.0001) when compared to the positive control group. However, topical formulations (Figure 5D), whether individual (colostrum or curcumin) or in combination, did not produce significant changes in insulin levels compared to the positive control.

TNF-α level in tissues was markedly elevated in the positive control group compared to all other treated groups (Figure 5). The oral treated group (Figure 5E) with a combination of curcumin and colostrum showed a 64.3% reduction in TNF-α level by the end of the experiment. Similarly, in the topical treatment study (Figure 5F), colostrum alone led to a 64.2% reduction, while the combination of colostrum and curcumin produced a 77.1% reduction, indicating strong anti-inflammatory effects.

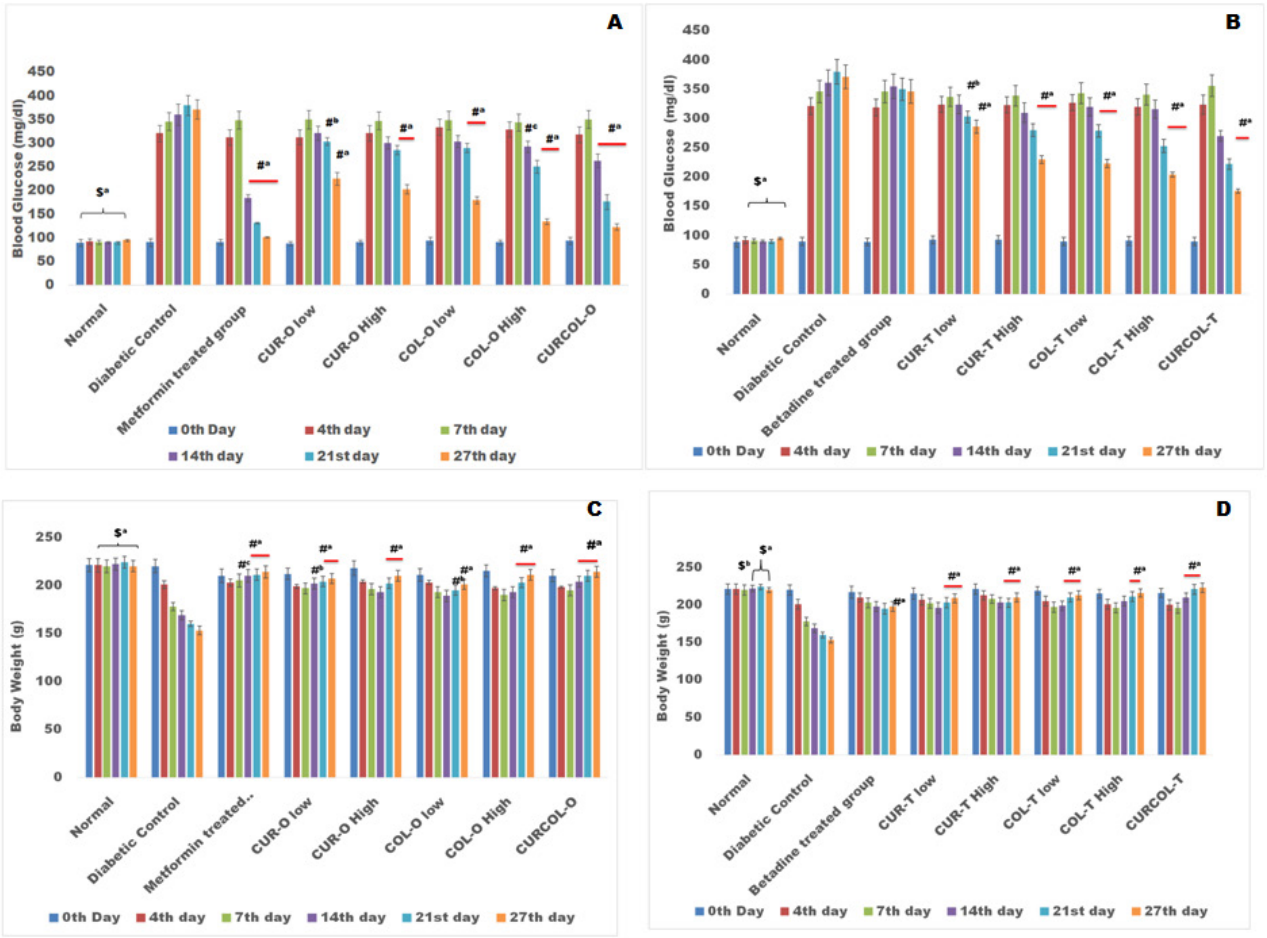

Figure 3: Effect of colostrum and curcumin individually and in combination on blood glucose level (Figures 3A and 3B) and body weight (Figures 3C and 3D). A one-way ANOVA and the Tukey-Kramer multiple comparisons test were used to statistically analyze the data. For each group (*n*=6), the values are Mean±SEM, and a *p* value of less than 0.05 was deemed significant. $ Normal vs. positive group, # Positive control vs. all treatment groups. *p* values of a <0.001, b <0.01, and c <0.05.

Effect of different formulations on wound contraction

After wound induction in diabetic animals, wound contraction was measured at different intervals and presented in Figures 6A and 6B. Figure 7 displays representative photographs of wound closures in different treated groups. By the 15th day, all orally treated groups (Figure 7A) showed a reduction in wound size. The greatest reductions at this stage were observed in the metformin-treated group (38.16%) and the low-dose curcumin group (19.74%). On the 21st day, the combination group (colostrum with curcumin) showed the highest wound contraction, achieving 85.93% reduction. In the topical formulation study (Figure 7B), the combination treatment also showed superior wound healing, with 61.51% contraction by the 15th day and 96.38% by the 27th day.

Histopathological changes

Histopathological examination of the wound-healing process in different experimental groups would reveal remarkable variations in tissue regeneration and cellular activity (Figures 8A and B). In the normal group, the wound healing followed the typical course: early infiltration of inflammatory cells such as neutrophils by day 3, followed by fibroblast proliferation and the initiation of re-epithelialization. By day 7, the normal group exhibited well-organized granulation tissue, increased collagen deposition, and a marked reduction in inflammatory cells, signifying a movement toward wound closure. By day 15, histological analysis of the normal group showed complete re-epithelialization with an intact epidermal layer and minimal scarring.

The treated groups, particularly those receiving betadine, metformin, curcumin high dose oral, colostrum high dose topical, and curcumin high dose topical, demonstrated notable histological improvements compared to the diabetic control group. On day 3, these groups exhibited reduced inflammation and increased fibroblast proliferation, contributing to more developed granulation tissue. By day 7, histopathological sections showed enhanced collagen deposition and better tissue organization, consistent with the observed increase in wound contraction. By day 15, high-dose treatment groups displayed near-complete re-epithelialization and mature collagen formation, closely resembling the histological characteristics

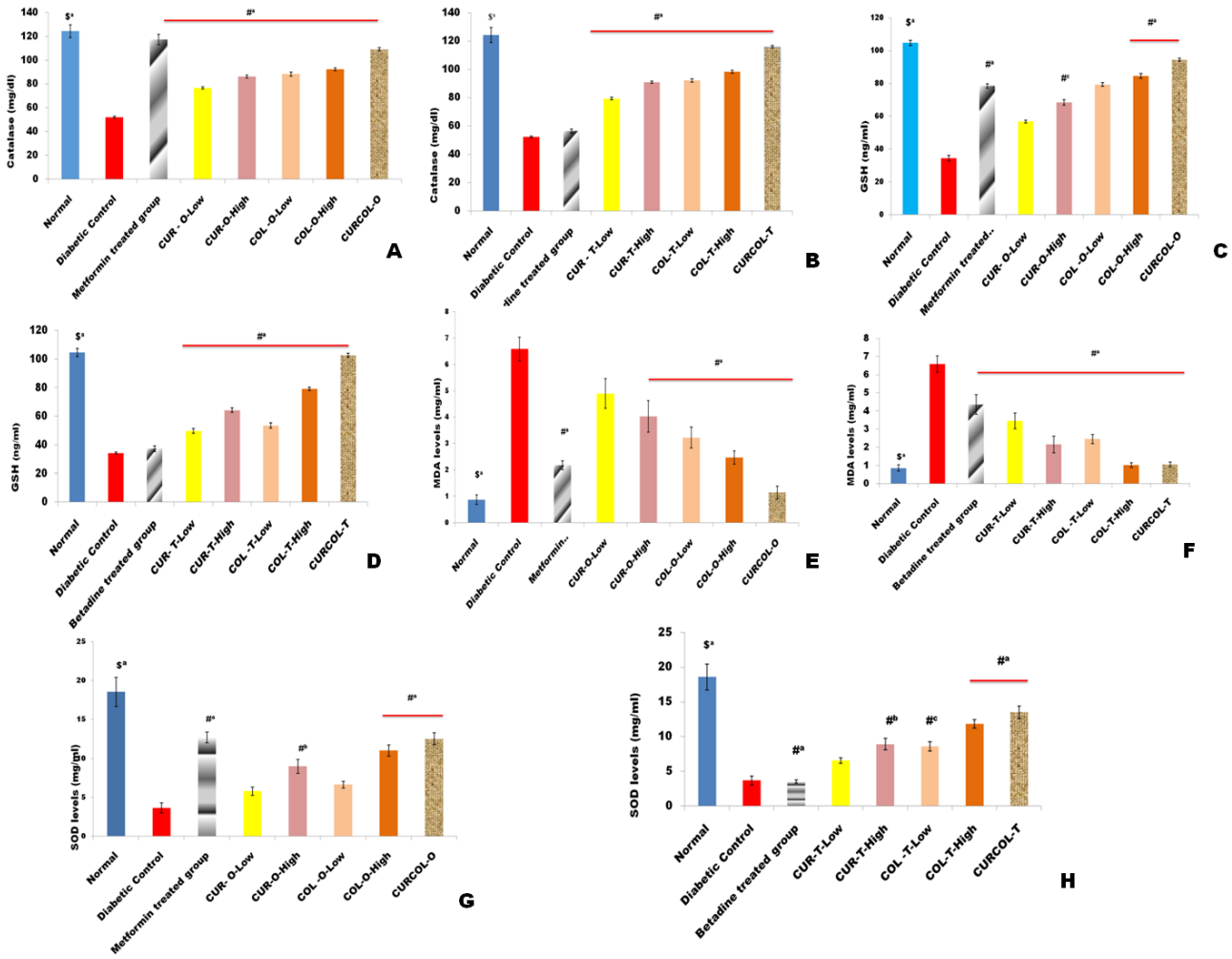

Figure 4: Effect of colostrum and curcumin individually and in combination on antioxidant enzymes (Figures 4A, 4B, 4C, 4D, 4G and 4H) and oxidative stress (Figures 4E and 4F). A one-way ANOVA and the Tukey-Kramer multiple comparisons test were used to statistically analyze the data. For each group (n=6), the values are Mean±SEM, and a p value of less than 0.05 was deemed significant. $ Normal vs. positive group, # Positive control vs. all treatment groups. p values of a <0.001, b <0.01, and c <0.05.

of the normal group. These findings align with the accelerated wound contraction observed in the study.

Effect of different formulations on protein expression of TNF-α in experimental rats

Western blot analysis was used to assess TNF-α protein expression in the foot ulcer tissues of all experimental groups. A marked upregulation of TNF-α was observed in the positive control group compared to the normal control group (Figure 9A). Conversely, diabetic rats treated with oral (Figure 9B) and topical formulations (Figure 9C) of colostrum and curcumin, either individually or in combination, exhibited significant downregulation of TNF-α protein expression relative to the positive control group. This reduction suggests an anti-inflammatory effect of the treatments, further supporting their role in promoting wound healing.

DISCUSSION

Diabetes mellitus is a chronic illness that can lead to DFUs. The prevalence of diabetes is currently 135.6 million people, and it is predicted to rise to 195.2 million by 2030 due to the increasing number of patients with the disease.[59] On the other hand, DFUs affect around 18.6 million people globally.[60] The multiple pathways responsible for the occurrence of this disease, such as oxidative stress, inflammatory markers, and increased advanced end products in the body, lead to DFU. Different categories of marketed formulations are available to tackle this disease, but due to some limitations, like adverse drug effects are unable to completely treat this disease. This research aims to analyze the wound healing efficacy of oral and topical formulations of curcumin and colostrum alone and in combination in experimental DFUs.

The incorporation of liposomes into hydrogel matrices is a unique and increasingly essential approach to improved drug delivery, especially for chronic and difficult to treat lesions

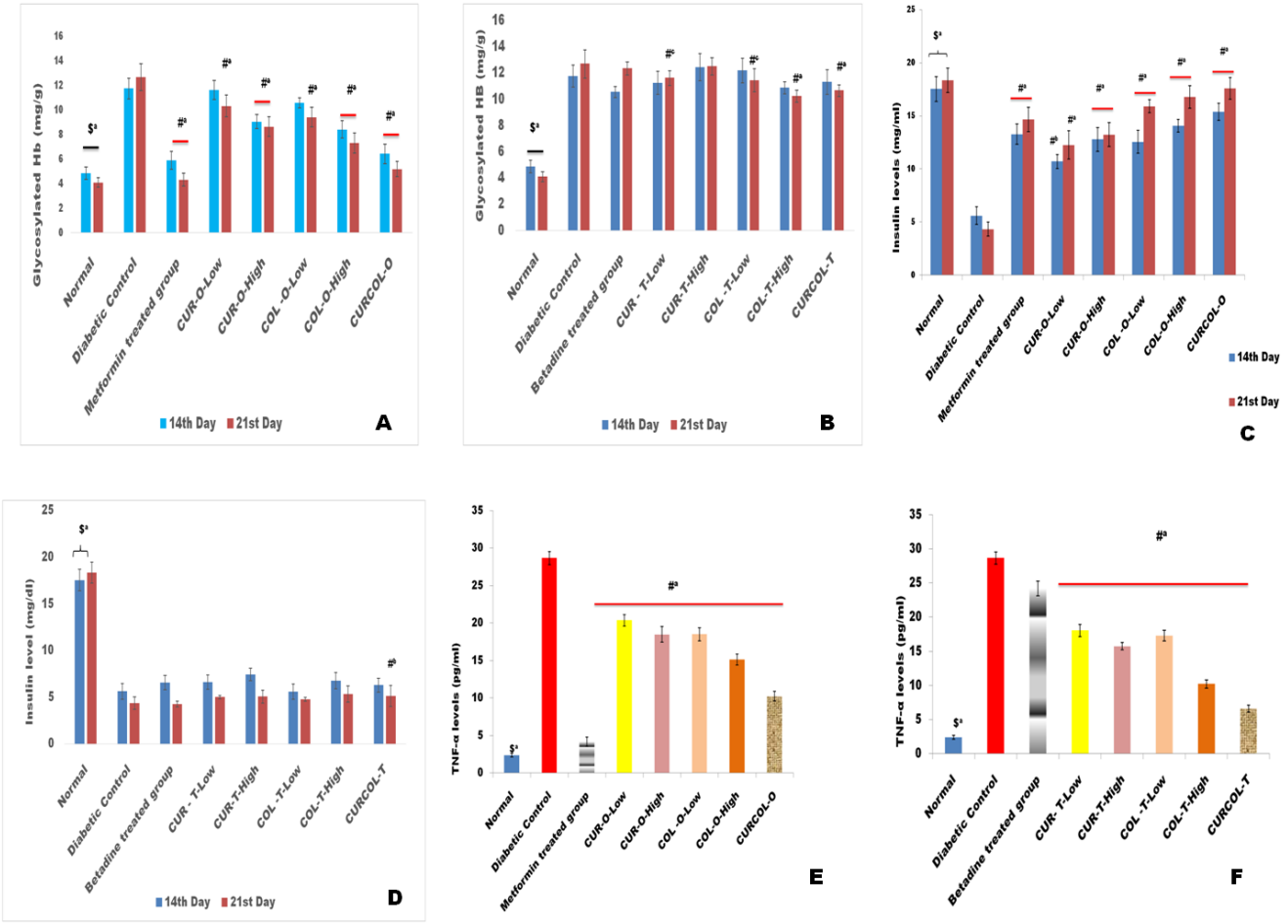

Figure 5: Effect of colostrum and curcumin individually and in combination on biochemical parameters (Figures 5A to 5F). A one-way ANOVA and the Tukey-Kramer multiple comparisons test were used to statistically analyze the data. For each group (*n*=6), the values are Mean±SEM, and a *p* value of less than 0.05 was deemed significant. $ Normal vs. positive group, # Positive control vs. all treatment groups. *p* values of a <0.001, b <0.01, and c <0.05.

like DFUs. Liposomes efficiently encapsulate and protect bioactive substances, whereas hydrogels create a moist and biocompatible environment that promotes wound healing.[61] Liposome-loaded hydrogels combine the benefits of both systems to improve drug stability, prolong localized release, and improve tissue penetration. This dual-delivery platform not only solves the limitations of traditional topical therapies, such as quick clearance and limited drug retention, but also opens the door to site-specific, controlled, and sequential delivery of therapeutic agents. The usage of liposome-loaded hydrogel in wound healing is also reported.[39] Thus, the purpose of the liposomal hydrogel formulation developed in this study was to co-deliver colostrum and curcumin for improved topical therapeutic potential. It has been described that the liposomes prepared by phosphatidylcholine and cholesterol in a 7:3 molar ratio can provide structural stability and biocompatibility.[62] This, in turn, can provide effective encapsulation of the hydrophobic curcumin and the bioactive colostrum components. In order to ensure its even distribution throughout the lipid bilayer, curcumin was successfully dissolved using a chloroform: methanol (2:1, v/v) mixture during lipid film preparation. The resultant nanosized liposomes were incorporated into a hydrogel matrix based on carbopol, which offered a pH-adjustable, mucoadhesive, and biocompatible composition appropriate for topical administration. Furthermore, the hydrogel method allowed for the controlled release of encapsulated bioactives while simultaneously improving liposome retention on the skin's surface.

The physicochemical characterization of the developed liposomal formulations revealed promising capabilities for topical administration applications. The small particle sizes, particularly for individual liposomal systems, indicate a larger surface area, which may encourage greater penetration and skin contact. Because of co-encapsulation, dual-loaded liposomes may be slightly larger, indicating increased structural complexity. Zeta potential levels greater than -30 mV were observed in all formulations, indicating high electrostatic stability.[63] The higher entrapment efficiencies demonstrated here attest to the liposomal system's ability to efficiently load both curcumin and colostrum.

Making liposome dispersions more viscous is often accomplished by mixing them with a hydrogel. Because of their semi-solid

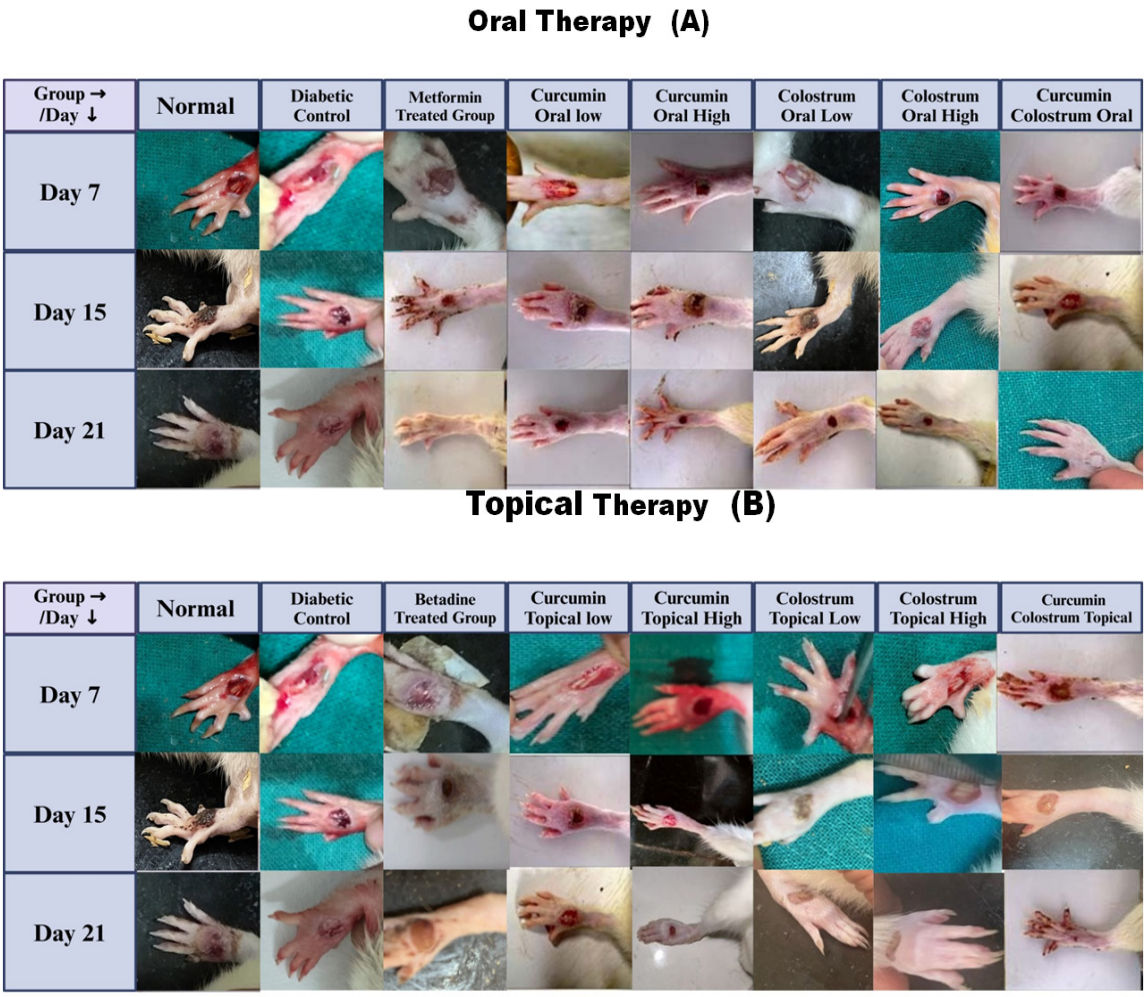

Figure 6: Oral (Figure A) and topical (Figure B) effects of colostrum and curcumin individually and in combination on wound contractions.

form, liposomal hydrogels can be applied topically, prolonging the release of the drugs from liposomes and preserving the liposome's original size during storage. The key formulation characteristics of gel, including pH, spreadability, and viscosity, play critical roles in ensuring therapeutic efficacy, stability, and patient compliance. The observed pH values of all formulations were within the physiologically acceptable range, ensuring skin compatibility,[64] especially in DFUs, where the skin barrier is generally compromised. Moreover, the observed pH can preserve the structural integrity of liposomes and reduce the degradation of these bioactives. Additionally, the strength and efficacy of a gel composition are influenced by rheological characteristics like viscosity and spreadability, which are intimately related to one another.[65] The spreading value noticed here indicates good spreading behaviour of liposomal formulations and the values were comparable to the control, indicating the addition of liposomal gel did not considerably affect the spreading. Moreover, similar results were reported in an earlier study.[66] The observed viscosity signifies that the formulations can effectively hold the liposomes, are optimal for topical application, and can provide adequate retention in the application site to exert the therapeutic effect.

The balance of incoming and exiting glucose regulates glucose homeostasis in the bloodstream.[67] Insulin normally inhibits and enhances the removal of glucose from peripheral tissues; but, in a diabetic state, glucose production rises and its appearance in the blood surpasses its disappearance, leading to hyperglycemia. In healthy settings, reactive oxygen species help regulate some intracellular signaling pathways and fight microbial invasion.[68] However, in diabetic individuals, excessive blood glucose causes oxidative stress, which halts wound healing in an uncontrolled period of inflammation. However, oxidative stress brought on by high blood sugar in diabetics prevents wound healing during an uncontrolled inflammatory phase.

One of the main causes of delayed wound healing in diabetes is hyperglycemia, which has an impact on oxidative balance, vascular function, and immunological response. In our trials, the combination of colostrum and curcumin, particularly at higher dosages, resulted in significant decreases in blood glucose levels both orally and topically, with the oral high-dose group demonstrating the greatest efficacy by day 21. This is consistent with recent results suggesting curcumin's hypoglycemic potential and colostrum's immunomodulating characteristics. Interestingly, topical treatments produced significant glucose-lowering effects, implying either systemic absorption or local effects altering peripheral insulin sensitivity and inflammation.

Body weight maintenance, a surrogate indication of general health and metabolic improvement in diabetic animals, showed significant improvement in treated groups. Animals treated with liposome-based colostrum and curcumin, particularly in combination, demonstrated statistically significant increases in body weight, which correlated with improved glycemic management and decreased systemic stress.

The antioxidant enzyme study demonstrates the therapeutic effectiveness of the developed formulations. Diabetics generally promote oxidative stress, as seen by elevated MDA levels and reduced endogenous antioxidant enzymes, including SOD, CAT, and GSH. The data observed here revealed that oral and topical therapies efficiently restored these oxidative imbalances, with liposomal mixtures of colostrum and curcumin restoring antioxidant levels to almost normal levels. This antioxidant increase is critical because oxidative damage significantly inhibits cellular repair processes in chronic wounds. Consistent with the antioxidant findings, various groups had strong anti-inflammatory benefits. HbA1c levels were dramatically improved in the oral treatment groups, especially with the combination formulation. TNF-α was significantly reduced in treated groups. Western blot analysis revealed that the formulations effectively reduce

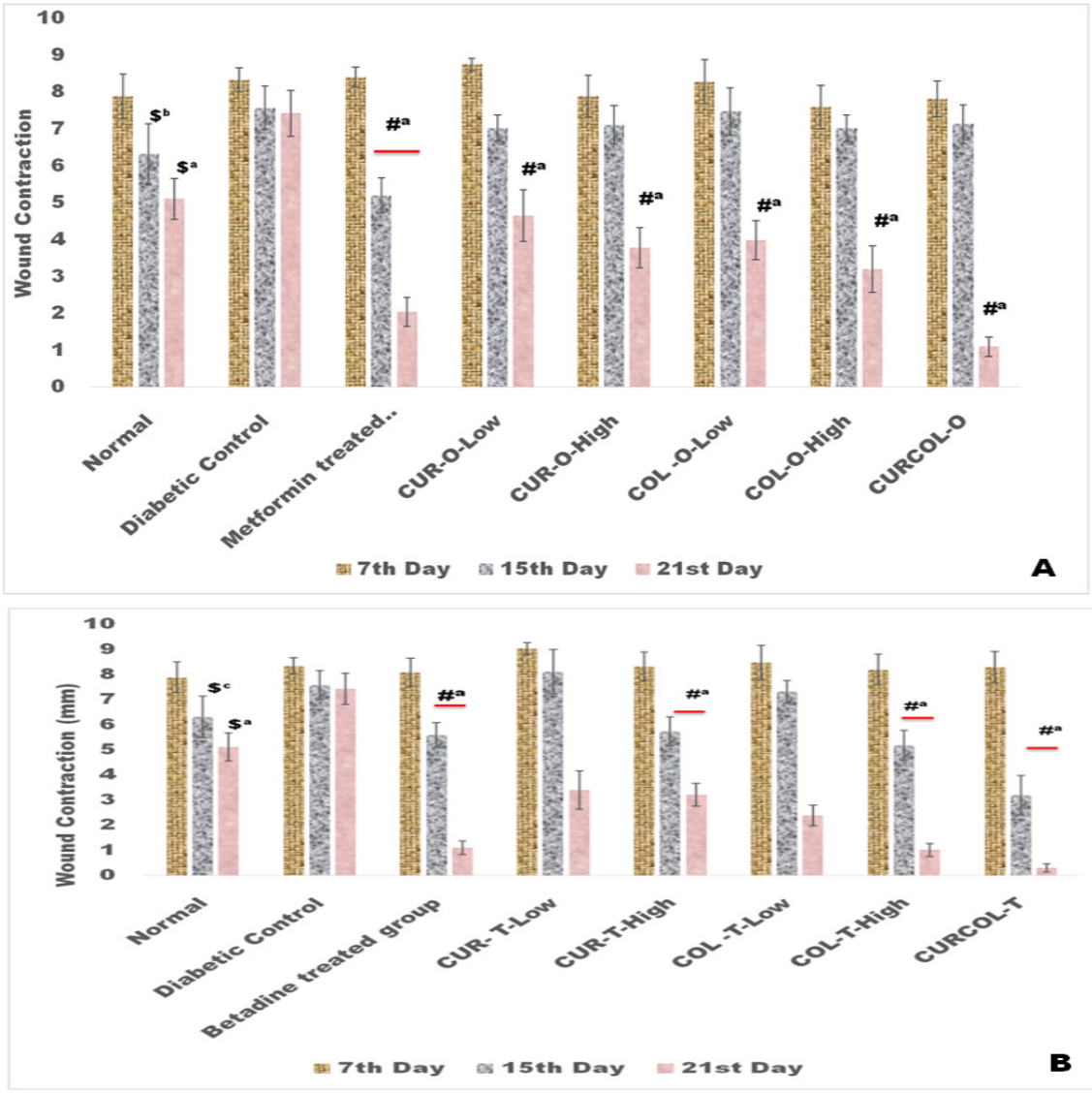

Figure 7: Representative photographic pictures of wound closures in various oral (Figure A) and topical (Figure B) treated groups on the 7th, 15th, and 21st day.

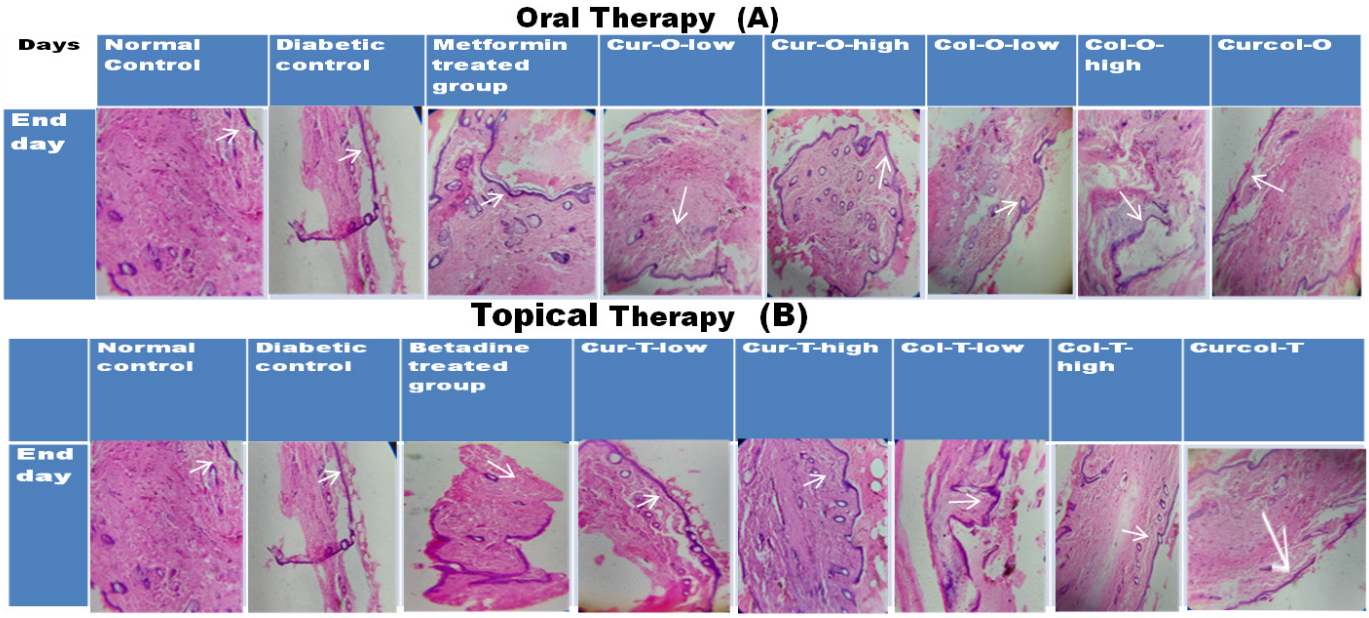

Figure 8: Representative photograph of rat foot ulcer tissue at the end of the experiment after being treated with different formulations, oral (Figure 8A) and topical (Figure 8B).

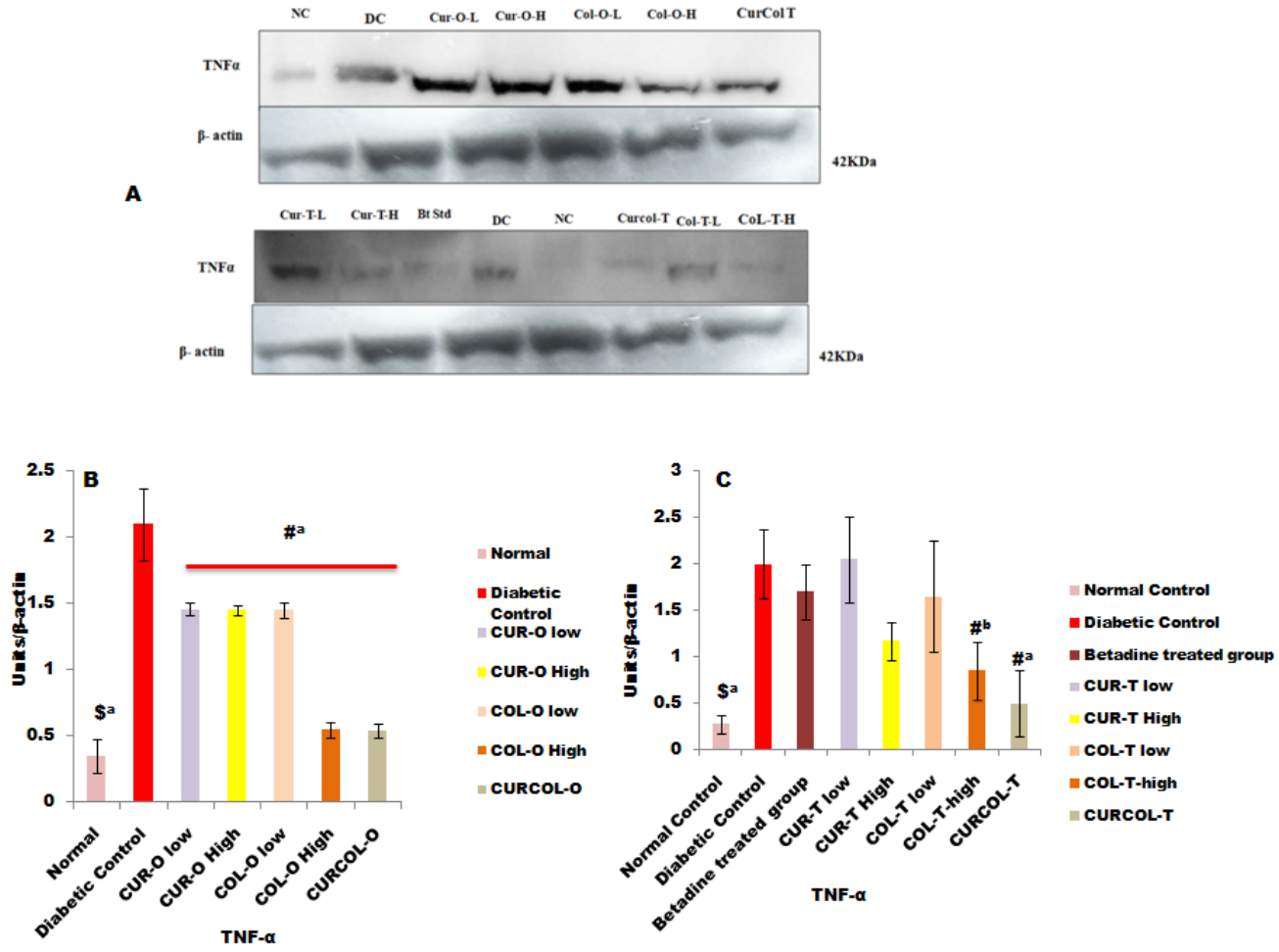

Figure 9: Western blot analysis of TNF-α in various treated groups.

TNF-α protein expression in ulcer tissues, supporting their anti-inflammatory properties both locally and systemically.

The data on wound contraction clearly demonstrate the potential of liposomal hydrogel's clinical usefulness. In all oral and topical application experiments, the combined treatment resulted in faster wound closure, which was most noticeable on the 21st and 27th days. The histological investigation supported these findings, revealing increased fibroblast activity, collagen deposition, and re-epithelialization in treated groups. The accelerated tissue regeneration observed in the combined therapy group is consistent with the increased biochemical and molecular parameters, confirming the developed formulation's superior wound healing capacity.

Colostrum is a magic product that contains various components such as fats, proteins, peptides, nucleotides, and less lactose. It is used as a traditional food and has been reported to have various pharmacological activities like anti-diabetic, anti-inflammatory, anti-microbial, and immune modulators.[69] The potential of colostrum in chronic non-healing wounds,[70] as well as in deep wound dressing[71] is reported. Curcumin is also a lipophilic polyphenol that has anti-diabetic, anti-inflammatory, anti-aging, and anti-cancer activity by various multifarious targets. Curcumin has been shown to improve wound healing capabilities.[72,73] The probable mechanism of active molecules of curcumin can accelerate wound closure, improve collagen deposition, and reduce inflammatory markers like TNF-α. They may increase the activity of antioxidant enzymes at the wound site and enhance angiogenesis. Though individually colostrum and curcumin demonstrated wound healing efficacy, our results confirmed the positive association in wound healing activity in DFUs.

CONCLUSION

The *in vivo* study findings demonstrated the diverse therapeutic potential of developed liposome-based formulations containing colostrum and curcumin in the treatment of DFUs. Both oral and topical administration of these agents, individually or in combination, showed significant improvements in glycemic control, oxidative stress regulation, inflammation reduction, and wound healing progression. Indeed, the combination of colostrum and curcumin liposomes provides a synergistic therapeutic strategy. These findings demonstrate the potential of colostrum and curcumin-loaded liposomes as a novel and emerging drug delivery technology for the oral/topical treatment of DFUs, necessitating additional clinical research.

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ABBREVIATIONS

CAT: Catalase; **DFU:** Diabetic Foot Ulcers; **GPx:** Glutathione peroxidase; **GSH:** Glutathione; **MDA:** Malondialdehyde; **PDGF:** Platelet-derived growth factor; **PDI:** Polydispersity index; **SEM:** Standard Error Mean; **SOD:** Superoxide dismutase; **STZ:** Streptozotocin; **TGF-β:** Transforming growth factor-beta.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CREDIT AUTHORSHIP STATEMENT

Conceptualization, IC, SG; Data Curation, IS, IZ; Formal Analysis, SB, ABN; Writing-Original Draft, IC; Writing-Review and Editing, ABN, SG. All authors have contributed significantly to the work, have read, and approved the final manuscript for publication.

SUMMARY

- Diabetic foot ulcers are prevalent in the diabetes population.
- Curcumin and colostrum liposome-based formulation was treated as oral and topical drug therapy on rats.
- Hypoglycemic and antioxidant effect was noticed at the end of the intervals.
- Inflammatory marker TNF-α of wound tissue was found to decrease.
- The wound healing effect showed effective improvement.
- The dual combination of colostrum with curcumin showed a synergistic effect.

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