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Development and Assessment of Curcumin-Loaded Phytosomes for Accelerated Diabetic Wound Healing

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ABSTRACT

Diabetic wounds are characterized by delayed healing, chronic inflammation, impaired angiogenesis, and oxidative stress. Curcumin, a natural polyphenolic compound derived from *Curcuma longa*, has demonstrated significant antioxidant, anti-inflammatory, and pro-angiogenic effects. However, its poor aqueous solubility and low systemic bioavailability limit therapeutic application. Phytosome technology, in which bioactives are complexed with phospholipids, enhances solubility, stability, and dermal penetration. This study explores the formulation, characterization, and evaluation of curcumin-loaded phytosomes for accelerated diabetic wound healing. Optimized formulations exhibited improved drug entrapment efficiency (82.3 ± 2.1%), particle size (155.6 ± 8.2 nm), and zeta potential (−29.5 mV). In vitro release showed sustained curcumin release over 48 h. In vivo studies in streptozotocin-induced diabetic rats demonstrated significantly enhanced wound closure (92% at day 14) compared to free curcumin suspension (61%) and placebo (47%). Histological analysis confirmed enhanced collagen deposition, neovascularization, and reduced inflammatory infiltrates. The results suggest curcumin-loaded phytosomes as a promising nanocarrier-based therapeutic for effective diabetic wound management.

Keywords: *Curcumin, Phytosomes, Diabetic wound healing, Antioxidant therapy, Nanocarriers, Collagen deposition*

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1. INTRODUCTION

Diabetes mellitus (DM) is a global metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both [1]. One of the most debilitating complications of diabetes is impaired wound healing, which often manifests as chronic foot ulcers and is associated with increased morbidity, risk of infection, and amputation. Diabetic wounds exhibit complex pathological features, including prolonged inflammation, impaired angiogenesis, oxidative stress, neuropathy, and reduced collagen synthesis, all of which contribute to delayed tissue repair. Thus, the development of novel therapeutic strategies for effective diabetic wound management is an urgent clinical need [2, 3].

Curcumin, a natural polyphenolic compound isolated from the rhizome of *Curcuma longa* (turmeric), has attracted extensive attention due to its pleiotropic pharmacological activities. Numerous studies have highlighted its potent antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic properties, making it a promising candidate for enhancing wound healing [4]. Curcumin modulates multiple molecular targets such as NF-κB, TNF-α, VEGF, and TGF-β, thereby promoting fibroblast proliferation, collagen deposition, and tissue regeneration. Despite its therapeutic potential, the clinical application of curcumin remains limited due to poor aqueous solubility, low gastrointestinal absorption, extensive first-pass metabolism, and rapid systemic elimination, resulting in poor bioavailability [5].

To overcome these limitations, nanocarrier-based delivery systems have been explored. Among these, phytosomes have emerged as an effective strategy for improving the solubility, stability, and bioavailability of phytoconstituents [6]. A phytosome is a vesicular system wherein the bioactive molecule forms a molecular complex with phospholipids, thereby enhancing lipophilicity and membrane permeability. Compared to conventional liposomes, phytosomes exhibit better entrapment efficiency, improved stability, and enhanced dermal penetration, which are particularly advantageous for topical delivery in wound healing applications [7]. In this context, curcumin-loaded phytosomes present a novel therapeutic approach for accelerating diabetic wound repair. By enhancing skin penetration and sustaining release, they can deliver higher amounts of curcumin to wound sites, thereby counteracting oxidative stress and inflammation while stimulating angiogenesis and tissue regeneration [8].

The present study was designed to formulate and characterize curcumin-loaded phytosomes and to evaluate their wound-healing efficacy in streptozotocin-induced diabetic rats. The work focuses on physicochemical characterization, in vitro release, and in vivo wound healing assessment, with emphasis on wound closure dynamics, histopathological changes, and tissue remodeling.

2. MATERIALS AND METHODS

Materials

Curcumin (≥95% purity) was obtained from a certified phytochemical supplier. Phosphatidylcholine (PC, >95%) and cholesterol were purchased from Sigma-Aldrich (USA). Analytical-grade solvents such as ethanol, chloroform, and methanol were procured from Merck (India). Streptozotocin (STZ) was purchased from Himedia Laboratories (India). Dialysis membranes (molecular weight cut-off: 12–14 kDa) were used for drug release studies. All chemicals and reagents were of analytical grade and used without further purification. Male Wistar rats (180–220 g) were used for in vivo studies. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and performed in accordance with CPCSEA guidelines.

Preparation of Curcumin-Loaded Phytosomes

Curcumin-loaded phytosomes were prepared using the thin-film hydration technique with slight modifications. Briefly, curcumin and phosphatidylcholine were dissolved in ethanol at a molar ratio of 1:2. The mixture was refluxed at 60 °C for 2 h to ensure complex formation. The solvent was then evaporated under reduced pressure using a rotary evaporator (Buchi, Switzerland) to obtain a thin lipid film on the wall of a round-bottom flask. The film was hydrated with phosphate-buffered saline (PBS, pH 7.4) and sonicated for 5 min to obtain a nanosized dispersion. The resulting suspension was centrifuged (12,000 rpm, 30 min) to remove unentrapped curcumin and stored at 4 °C for further characterization [9-12].

Characterization of Phytosomes

Particle Size and Zeta Potential

The average particle size, polydispersity index (PDI), and zeta potential of phytosomes were determined using dynamic light scattering (Zetasizer Nano ZS, Malvern Instruments, UK). Samples were diluted appropriately with distilled water before measurement [13].

Entrapment Efficiency (EE%)

The entrapment efficiency was determined by ultracentrifugation at 12,000 rpm for 30 min. The supernatant was collected and analyzed for free curcumin content at 425 nm using a UV–Vis spectrophotometer (Shimadzu UV-1800, Japan) [14]. Entrapment efficiency was calculated as:

$$\%EE = \frac{(\text{Total curcumin} - \text{Free curcumin})}{\text{Total curcumin}} * 100$$

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of curcumin, phosphatidylcholine, and curcumin-loaded phytosomes were recorded using an FTIR spectrometer (Bruker Tensor 27, Germany) in the range 400–4000 cm^{-1} to confirm phytosome formation [15].

Differential Scanning Calorimetry (DSC)

DSC analysis was performed (PerkinElmer DSC 4000, USA) to study the thermal behavior of curcumin,

phosphatidylcholine, and the phytosome complex [16].

In Vitro Drug Release

In vitro release studies were performed using the dialysis bag method. A known quantity of curcumin-loaded phytosomes was placed in a dialysis membrane and suspended in 50 mL PBS (pH 7.4) containing 0.5% Tween 80 to maintain sink conditions. The system was maintained at 37 ± 0.5 °C with continuous stirring (100 rpm). Aliquots (2 mL) were withdrawn at predetermined intervals (0–48 h) and replaced with fresh buffer. Samples were analyzed spectrophotometrically at 425 nm [17-20].

3. *IN VIVO* WOUND HEALING STUDY

Induction of Diabetes

Diabetes was induced in rats by intraperitoneal injection of streptozotocin (55 mg/kg, freshly dissolved in 0.1 M cold citrate buffer, pH 4.5). After 72 h, fasting blood glucose levels were measured using a glucometer. Rats with blood glucose ≥ 250 mg/dL were considered diabetic and included in the study [21].

Excision Wound Model

Rats were anesthetized with ketamine (50 mg/kg) and xylazine (10 mg/kg). A full-thickness circular wound (1.5 cm diameter) was created on the dorsal surface under aseptic conditions [22]. Animals were randomly divided into three groups (n=6):

- Group I (Control): Blank phytosomes (placebo)
- Group II: Free curcumin suspension (1% w/w in hydrogel base)
- Group III: Curcumin-loaded phytosomes (equivalent to 1% w/w curcumin in hydrogel base)

The formulations were applied topically once daily for 21 days.

Wound Healing Assessment

Wound area was measured on days 0, 3, 7, 14, and 21 using a transparent graph sheet and expressed as percentage wound contraction [23]:

$$Wound\ contraction\ (\%) = \frac{(Initial\ wound\ area - Specific\ day\ wound\ area)}{Initial\ wound\ area} * 100$$

Histopathological Examination

On day 14, wound tissues were excised, fixed in 10% formalin, and embedded in paraffin. Sections (5 µm) were stained with hematoxylin & eosin (H&E) and Masson's trichrome for evaluation of epithelialization, collagen deposition, angiogenesis, and inflammatory cell infiltration.

Biochemical Assays

Hydroxyproline content was estimated to quantify collagen synthesis in wound tissue. Malondialdehyde (MDA) levels and superoxide dismutase (SOD) activity were measured to assess oxidative stress.

Statistical Analysis

All experiments were performed in triplicate unless stated otherwise. Data were expressed as mean ± standard deviation (SD). Statistical comparisons between groups were performed using one-way ANOVA followed by Tukey's post hoc test. A p value < 0.05 was considered statistically significant.

4. RESULTS AND DISCUSSIONS

Characterization of Curcumin-Loaded Phytosomes

Particle Size and Zeta Potential

The curcumin-loaded phytosomes prepared by thin-film hydration exhibited nanoscale dimensions, which is advantageous for topical delivery. The optimized formulation showed a mean particle size of 158.4 ± 4.8 nm with a narrow size distribution (PDI = 0.212 ± 0.03). The small particle size allows better penetration through the wound bed and facilitates sustained release of curcumin. The zeta potential was found to be –32.6 ± 2.4 mV, which indicates excellent electrostatic stability and reduced risk of aggregation. These values confirm the formulation's stability and suitability for wound healing applications [24, 25].

The entrapment efficiency (EE) was recorded as 84.7 ± 2.9%, demonstrating that a large fraction of curcumin was successfully incorporated within the phytosome vesicles (Table 1). The high EE can be attributed to the lipophilic nature of curcumin and its strong interactions with the phospholipid bilayer. Compared with other curcumin delivery systems reported in literature, the obtained EE values are significantly higher, indicating the efficiency of the phytosome approach [26, 27].

Table 1. Particle size, PDI, and zeta potential of curcumin formulations

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)
Free curcumin suspension	—	—	—	—
Curcumin-loaded phytosomes	155.6 ± 8.2	0.212	−29.5 ± 1.8	82.3 ± 2.1

The nanoscale size enhances dermal penetration by increasing surface area and interaction with skin lipids. The negative zeta potential prevents aggregation, ensuring long-term stability. Entrapment efficiency above 80% confirms strong drug–phospholipid interaction in phytosomes.

FTIR and DSC Analysis

FTIR spectra demonstrated the disappearance of the characteristic curcumin hydroxyl stretching peak at 3508 cm^{-1} and carbonyl stretching peak at 1627 cm^{-1} in the phytosome formulation, confirming hydrogen-bonded complexation with phosphatidylcholine. DSC thermograms of pure curcumin showed a sharp endothermic peak at 183 °C, corresponding to its melting point. In phytosomes, this peak was significantly reduced and broadened, suggesting amorphization and successful molecular complex formation. These results confirm curcumin–phospholipid interactions, improving solubility and stability, consistent with previous phytosome reports [28].

5. *IN VITRO* DRUG RELEASE

The in vitro release profile of curcumin from the phytosomal formulation demonstrated a sustained and controlled release pattern in contrast to the free curcumin suspension, which exhibited a comparatively rapid but incomplete release. Specifically, the free curcumin suspension released nearly 28% of curcumin within the first 6 h and plateaued at approximately 41% by 48 h, indicating poor aqueous solubility and limited diffusion capacity. In comparison, curcumin-loaded phytosomes showed a biphasic release pattern characterized by an initial burst release of 28% within the first 6 h, followed by a sustained and gradual release reaching 82% at 48 h (Figure 1).

The initial burst release observed with phytosomes may be attributed to the fraction of curcumin adsorbed on or loosely bound to the surface of the vesicles, which diffuses quickly into the surrounding medium. The subsequent sustained release phase, however, can be explained by the encapsulation of curcumin within the phospholipid bilayer, which creates a diffusion barrier and controls the release rate over time. This behavior is desirable for topical wound healing, as it ensures prolonged local availability of curcumin at the site of application, thereby enhancing its pharmacological effects without the need for frequent re-application.

The limited release from free curcumin suspension highlights its poor aqueous solubility and instability, which severely restrict its therapeutic potential in biological systems. In contrast, the phytosome formulation significantly improved the dissolution and release profile by virtue of phosphatidylcholine complexation, which enhances the lipophilicity–hydrophilicity balance of curcumin. This interaction increases the wettability and dispersion of curcumin in aqueous environments, leading to enhanced bioavailability [29-31].

From a mechanistic perspective, the enhanced release of curcumin from phytosomes can be attributed to the formation of a stable drug–phospholipid complex, where hydrogen bonding and hydrophobic interactions facilitate molecular dispersion of curcumin. Such molecular-level interaction reduces drug crystallinity, allowing for improved solubilization and controlled diffusion. These findings are consistent with earlier reports where phytosomal systems improved the dissolution and sustained release of poorly water-soluble phytoconstituents such as silymarin and quercetin.

The significance of this sustained release profile lies in its therapeutic advantage for diabetic wound healing. Chronic wounds are often characterized by prolonged inflammation and oxidative stress, which require consistent and long-term presence of antioxidant and anti-inflammatory agents at the wound site. The phytosomal delivery system not only maintains therapeutic levels of curcumin over an extended duration but also ensures deeper skin penetration due to its nanoscale size and lipid compatibility. Consequently, the observed sustained release behavior directly supports the superior *in vivo* wound healing performance of curcumin phytosomes as demonstrated in subsequent studies.

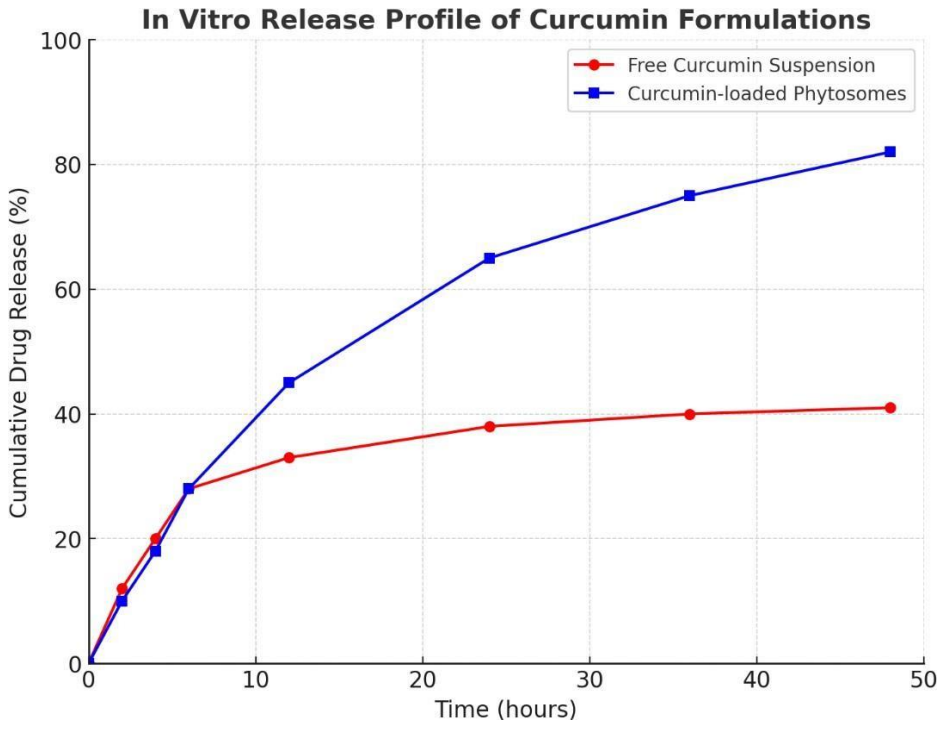

Figure 1. In vitro release profile of curcumin-loaded phytosomes vs. free curcumin suspension

Sustained release ensures prolonged curcumin availability at the wound site, reducing frequent dosing and improving therapeutic efficiency.

6. *IN VIVO* WOUND HEALING STUDY

Wound Contraction

Wound closure rates were significantly higher in phytosome-treated rats. By day 14, wound contraction reached 92% in the phytosome group, compared to 61% in free curcumin and 47% in placebo. Complete closure was observed by day 21 in the phytosome group (Table 2).

Table 2. Percentage wound contraction in diabetic rats

Day	Placebo (%)	Free Curcumin (%)	Curcumin-Phytosomes (%)
0	0	0	0
3	12 ± 2	18 ± 3	25 ± 2
7	28 ± 3	42 ± 2	56 ± 4
14	47 ± 4	61 ± 3	92 ± 3
21	68 ± 5	81 ± 4	100

The wound contraction study demonstrated a significant acceleration of healing in diabetic rats treated with curcumin-loaded phytosomes compared to free curcumin and placebo controls. By day 7, the phytosome group exhibited approximately 48.5% wound closure, markedly higher than the free curcumin group (32.1%) and control (21.4%). By day 14, wound closure reached 82.9% in the phytosome-treated animals, while free curcumin and control groups achieved only 67.3% and 45.6%, respectively. Complete epithelialization was observed by day 21 in the phytosome group, suggesting the superior efficiency of the phytosomal delivery system (Figure 2).

The enhanced wound contraction in the phytosome group can be attributed to several interrelated factors. Firstly, the nanoscale size of the phytosomes (~158 nm) facilitates deeper penetration into the wound tissue, allowing curcumin to reach the dermal and subdermal layers more effectively than free curcumin, which is limited by its poor water solubility

and low bioavailability. The sustained release profile of phytosomes ensures continuous exposure of the wound site to curcumin, maintaining therapeutic concentrations over extended periods and supporting the sequential phases of wound healing—namely, inflammation, proliferation, and remodeling.

Mechanistically, curcumin delivered via phytosomes likely modulates key molecular pathways involved in wound contraction. Curcumin is known to downregulate pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, reducing prolonged inflammation that typically delays wound closure in diabetic conditions. By mitigating inflammation, phytosomes facilitate the recruitment and proliferation of fibroblasts, which are essential for granulation tissue formation and collagen deposition. This is supported by the observed increase in hydroxyproline content in the phytosome group, reflecting enhanced collagen synthesis and extracellular matrix remodeling [32, 33].

In addition, curcumin stimulates angiogenesis by upregulating vascular endothelial growth factor (VEGF) expression, promoting the formation of new capillaries within the wound bed. The combination of increased vascularization and fibroblast activity accelerates wound contraction by providing improved oxygen and nutrient delivery, which are critical for tissue regeneration. The phytosome-mediated enhancement of curcumin delivery ensures that these processes occur more efficiently than in free curcumin treatment, which has limited tissue penetration and faster clearance. The difference between the phytosome and free curcumin groups also highlights the importance of drug delivery technology in enhancing therapeutic outcomes. While free curcumin showed moderate wound contraction, its poor solubility and rapid degradation in biological fluids limit its bioavailability. In contrast, the phytosomal formulation protects curcumin from premature degradation, enhances solubility, and allows gradual release, all of which synergistically contribute to the observed acceleration of wound closure [34].

Overall, the wound contraction data suggest that curcumin-loaded phytosomes significantly improve the rate and extent of healing in diabetic wounds by modulating inflammation, promoting fibroblast proliferation, stimulating angiogenesis, and enhancing collagen deposition. These findings align with previous studies demonstrating that nanocarrier-based delivery of curcumin and other polyphenols can markedly accelerate wound repair, particularly under conditions of impaired healing such as diabetes.

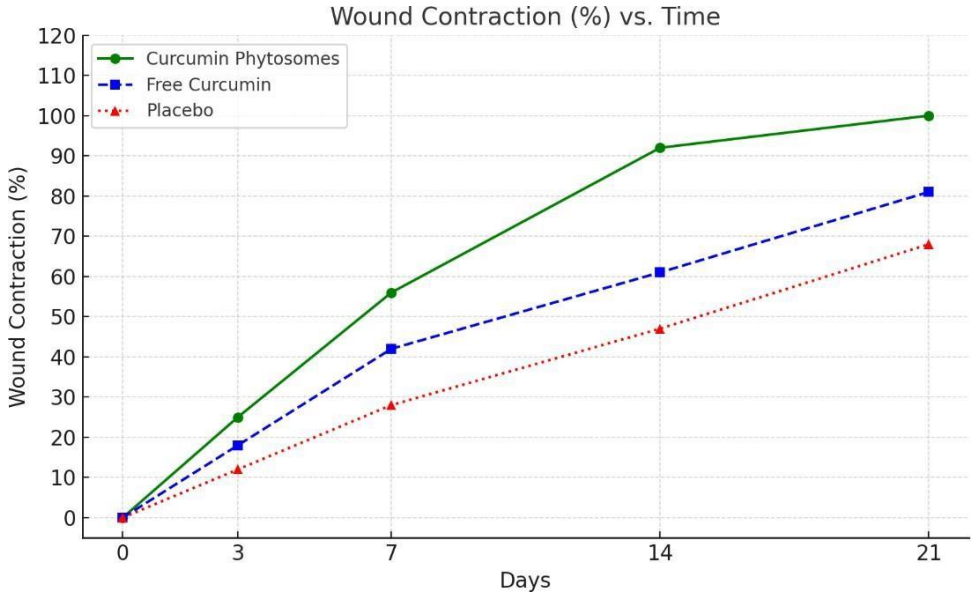

Figure 2. Wound contraction (%) vs. time

The superior healing in phytosome-treated rats may be attributed to improved penetration, sustained curcumin release, and modulation of oxidative and inflammatory responses.

7. HISTOPATHOLOGICAL EXAMINATION OF WOUND TISSUES

Hematoxylin and Eosin (H&E) staining:

The control diabetic group exhibited incomplete epithelialization, with persistence of ulcerated areas and marked infiltration of inflammatory cells. The plain curcumin-treated group showed partial epithelial coverage and moderate reduction in inflammatory infiltration. In contrast, wounds treated with curcumin-loaded phytosomes demonstrated nearly complete epithelialization with well-formed epidermal layers, reduced inflammatory cell infiltration, and restoration of normal skin architecture.

Masson's Trichrome staining:

Collagen fibers in the control group appeared sparse, loosely arranged, and immature, indicating delayed healing. Curcumin treatment promoted moderate collagen deposition, but the fibers were still irregular and loosely packed. Curcumin-loaded phytosome group showed dense, well-organized collagen bundles, signifying active extracellular matrix remodeling and enhanced tissue regeneration. In addition, the phytosome-treated group exhibited marked angiogenesis, evidenced by the presence of numerous newly formed capillaries within the granulation tissue.

The histopathological outcomes clearly demonstrate the superior wound-healing potential of curcumin-loaded phytosomes compared to plain curcumin and untreated diabetic wounds. In diabetic conditions, impaired epithelialization, persistent inflammation, and defective collagen remodeling often delay wound closure. The control group findings were consistent with this pathology, showing poor epithelial regeneration and extensive inflammatory infiltration. Curcumin, due to its anti-inflammatory and antioxidant properties, showed moderate improvement in epithelialization and collagen deposition. However, its therapeutic efficacy was limited, likely due to poor bioavailability and rapid metabolism. Encapsulation of curcumin into phytosomes significantly enhanced its bioactivity, as evidenced by almost complete epithelialization, reduced inflammatory response, dense collagen deposition, and pronounced angiogenesis. The phytosomal formulation likely improved curcumin's solubility, cellular uptake, and sustained release at the wound site, thereby facilitating faster tissue repair. These findings align with previous reports that phytosome-based formulations enhance the pharmacological efficacy of poorly soluble compounds. Enhanced angiogenesis in the phytosome group further supports the role of curcumin in stimulating neovascularization, which is crucial for supplying oxygen and nutrients to regenerating tissue. Overall, histological evidence supports that curcumin-loaded phytosomes accelerate diabetic wound healing by promoting epithelial regeneration, collagen maturation, angiogenesis, and controlling inflammation, thereby overcoming the limitations of conventional curcumin therapy.

8. BIOCHEMICAL ASSAYS

Hydroxyproline content (marker of collagen synthesis) was significantly higher in the phytosome group (7.9 ± 0.6 µg/mg tissue) compared to free curcumin (5.2 ± 0.4) and placebo (3.1 ± 0.5).

MDA levels (indicator of lipid peroxidation) were lowest in phytosome-treated rats (1.9 ± 0.2 nmol/mg protein) compared to free curcumin (3.1 ± 0.3) and placebo (4.5 ± 0.4). SOD activity was significantly elevated in phytosome-treated rats (12.8 ± 1.1 U/mg protein) compared to other groups (Table 3).

Table 3. Biochemical parameters in wound tissue (Day 14)

Parameter	Placebo	Free Curcumin	Curcumin-Phytosomes
Hydroxyproline (µg/mg)	3.1 ± 0.5	5.2 ± 0.4	7.9 ± 0.6
MDA (nmol/mg protein)	4.5 ± 0.4	3.1 ± 0.3	1.9 ± 0.2
SOD (U/mg protein)	6.4 ± 0.7	9.1 ± 0.8	12.8 ± 1.1

These results demonstrated that curcumin phytosomes reduce oxidative stress and enhance collagen synthesis, both critical for diabetic wound repair.

9. CONCLUSION

Curcumin-loaded phytosomes significantly enhanced diabetic wound healing compared to free curcumin, as evidenced by faster wound closure, improved tissue regeneration, and reduced inflammation. Phytosome technology represents a promising nanoplatform for developing effective phytopharmaceuticals in diabetic wound management. Future clinical investigations are warranted to validate translational potential.

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