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Research Article

# Effectiveness and Tolerability of Topical Curcumin for Management of Diabetic Foot Ulcer: A Pilot Clinical Study

**Milind Ruke[1], Iffat[1], Arun Maurya[1], Avinash Bhise[1], Jyolsna Agnes Jose[2, *], Kesavalu Purushothaman[2]**

[1]Department of Podiatry, Advance Diabetic Foot and Wound Clinic, Mumbai, India

[2]Department of Innovation, Stabicon Life Sciences Pvt. Ltd, Bangalore, India

## Abstract

Background: Diabetic foot ulcers (DFUs) affect 9.1 to 26.1 million individuals globally each year, with 15-25% of those with diabetes mellitus (DM) experiencing them during their lives. DFUs are a major cause of amputations, accounting for 85% of such cases in diabetic patients. Curcumin, a compound from Curcuma longa, shows potential in wound healing through mechanisms such as inhibiting the NLRP3 inflammasome pathway, promoting autophagy, and regulating microRNA expression. This study evaluated the efficacy and safety of C3-DiagardTM Cream in treating DFUs. Methods: This open-label, prospective clinical study assessed the efficacy and safety of C3-DiagardTM cream, containing 0.05mg of Harida (Curcuma longa) extract, in treating and preventing DFUs. The cream was applied twice daily for 12 weeks. Key outcomes were assessed through wound size reduction, pain (VAS score), and any adverse reactions during the treatment. Results: Fifty DM patients (36 males, 14 females; mean age 57.58±12.67 years) were enrolled. Among the patients, 75% (38 individuals) showed a wound healing response between 70% and 99%. The average wound size decreased significantly from 6.63 $cm^2$ at baseline to 1.83 $cm^2$ after 12 weeks, with a mean reduction of 4.8 $cm^2$ ($p < 0.05$). Pain levels, measured by VAS score, significantly dropped from an average of 8 to 3 ($p < 0.05$). No adverse reactions were reported, highlighting the cream's safety. Conclusion: C3-DiagardTM cream is effective in reducing the size of diabetic foot ulcers and alleviating pain, with a favourable safety profile. This study supports the clinical use of C3-DiagardTM as a well-tolerated treatment option for patients with DFUs.

## Keywords

Diabetic Foot Ulcer, Curcumin, Wound Healing, Curcuma Longa

## 1. Introduction

The global annual incidence of diabetic foot ulcers (DFUs) ranges between 9.1 to 26.1 million cases. Approximately 15 to 25% of individuals with diabetes mellitus (DM) experience the development of DFU at some point in their lives. This complication holds significant clinical importance as it stands as a primary cause of amputations in diabetic patients, with 85% of amputations being directly associated with DFUs.

The impact of DFUs extends beyond the immediate physical consequences, affecting both the quality of life and life expectancy of affected individuals. Notably, DFU patients face a

*Corresponding author: Jyolsna.A@Lyruslife.com (Jyolsna Agnes Jose)

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2.5-fold higher risk of mortality at 5 years compared to diabetes patients who do not develop foot ulcers [1]. DFUs represent a prevalent complication in individuals with poorly controlled DM. The development of these ulcers is often attributed to factors such as inadequate glycemic control, underlying neuropathy, peripheral vascular disease, and suboptimal foot care, all of which contribute to the increased risk of complications such as osteomyelitis and lower extremity amputations. The occurrence of DFUs is frequently localized to areas of the foot subjected to repetitive trauma and pressure sensations. The progression of a diabetic ulcer typically unfolds in three stages—initially, a callus forms, a consequence of neuropathy. Motor neuropathy induces physical deformities in the foot, while sensory neuropathy results in a loss of sensation, leading to ongoing trauma. Additionally, autonomic neuropathy contributes to skin dryness. Subsequently, the callus undergoes frequent trauma, leading to subcutaneous hemorrhage. Eventually, the callus erodes, transforming into an ulcer. It is crucial to address the underlying factors contributing to the development of DFUs, including optimizing glycemic control, managing neuropathy, and promoting proper foot care practices. Early intervention and comprehensive care can mitigate the risk of complications, including osteomyelitis and the need for lower extremity amputations [2].

This underscores the severity of DFUs as a critical medical concern, emphasizing the need for effective prevention, early detection, and comprehensive management strategies to improve outcomes for individuals with diabetes [1]. The incidence of DFUs is expected to rise annually alongside the increasing number of newly diagnosed diabetics. The etiology of DFUs is diverse, involving multiple factors. Common underlying causes include inadequate glycemic control, the presence of calluses, foot deformities, improper foot care, ill-fitting footwear, peripheral neuropathy, compromised circulation, dry skin, among others.

Neuropathy, a common complication affecting approximately 60% of individuals with diabetes, is a significant precursor to the development of foot ulcers. The risk of foot ulcers is further heightened in individuals with flat feet, as this anatomical condition leads to disproportionate stress across the foot, resulting in tissue inflammation in high-risk areas. Early identification and optimal treatment of foot ulcers play a crucial role in determining prognosis. Unfortunately, delays in care can have severe consequences, potentially culminating in the need for foot amputation.

The progression of DFUs is multifaceted, involving factors such as diabetic peripheral arterial disease, peripheral neuropathy, and foot malformations. The treatment of DFUs primarily focuses on symptomatic management, encompassing debridement, appropriate antibiotic therapy, and strategies to promote wound healing. However, the therapeutic outcomes are often suboptimal, and the prognosis remains a significant clinical challenge.

Given the limitations in current treatments, there is an urgent need to explore and develop drugs to address the complexities of DFUs. It is noteworthy that a majority (60–80%) of foot ulcers do heal with proper management. However, 10–15% of ulcers may persist, and 5–24% can progress to the point of requiring limb amputation within 6–18 months after the initial evaluation. This underscores the critical importance of early intervention and the ongoing quest for more effective therapeutic options to improve outcomes for individuals with DFUs [3].

Curcumin, derived from the rhizome of Curcuma longa, is an antioxidant polyphenol known for its anti-inflammatory properties. Numerous studies have documented the topical application of curcumin as a practice for promoting wound healing [4]. Curcumin, a polyphenol derived from Curcuma longa, commonly known as turmeric, and belonging to the ginger family, is characterized by its rhizomes that produce a vibrant yellow dye. The vital bioactive constituents of turmeric are phenolic curcuminoids, with curcumin (diferuloylmethane) being the most significant. In various wound models, curcumin has demonstrated the ability to reduce the secretion of cytokines, thereby promoting wound healing. Additionally, it serves as an effective antioxidant and radioprotective agent. Notably, curcumin has been shown to inhibit tumor necrosis factor (TNF) by diminishing its effects in fibroblast lytic assays. The anti-inflammatory properties of curcumin are attributed to its capacity for free radical scavenging activity [5].

Curcumin exerts diverse biological activities through its interactions with various molecules and cellular targets. It regulates gene expression by influencing epigenetic modifications, including DNA methylation, histone modification, and microRNA expression. This multifaceted regulation affects numerous pathways and contributes to the wide range of biological effects attributed to curcumin. In the context of diabetic nephropathy, curcumin has demonstrated efficacy by inhibiting the NLRP3 inflammasome pathway. Additionally, curcumin promotes autophagy, mitigating renal tubular epithelial cell apoptosis induced by advanced glycation end products. Studies have revealed that curcumin's pharmacological actions include the inhibition of miR-133b, leading to the restoration of estimated glomerular filtration rate and acceleration of wound healing impaired by diabetes. Similarly, curcumin has been shown to decrease the expression of miR-138, contributing to enhanced wound healing. Additionally, the suppression of miR-152-3p has been associated with the inhibition of apoptosis promotion of fibroblast proliferation and migration, ultimately expediting the wound healing process in DFUs [6]. The current study aimed to assess the efficacy and safety of C3-DiagardTM Cream in the treatment of DFUs.

## 2. Methodology

### 2.1. Study Design

This study is an open-label prospective clinical study designed to evaluate the efficacy and safety of C3-DiagardTM

cream in the treatment and prevention of DFUs. The study protocol was approved by Suraksha Ethics Committee (Mumbai). All patients gave informed consent including for photographs of their wounds.

## 2.2. Study Drug

During the study, the enrolled patients were treated with a product that contained Harida (Curcuma longa) extract 0.05 mg. The cream was applied 1 cc per 5 cm2 ulcer size twice daily for 3 months.

## 2.3. Participants

The inclusion criteria encompassed both male and female individuals aged 20 to 80 years, inclusive, diagnosed with either Type 1 or Type 2 diabetes and undergoing therapy for glycemic control utilizing available diabetes drugs, including insulin. Participants having a glycosylated hemoglobin (HbA1c) ≤ 12%. Additionally, they needed to exhibit at least one DFU meeting specific criteria: a full-thickness ulcer of UTWCS Grade I-A or II-A, ulcer size (area) > 2 cm 2 and ≤ 10 cm2 post-debridement at the time of enrolment, the ulcer located on or below the malleoli, the ulcer present for > 4 weeks at the time of enrolment, and a minimum 3 cm margin between the qualifying Target Ulcer and any other ulcers on the specified foot post-debridement. Furthermore, participants must not have had an active infection by clinical inspection, as defined by IDSA/IWGDF criteria.

Exclusion criteria comprised pregnant or lactating women, individuals with a body mass index (BMI) exceeding 35 kg/m$^2$, wounds requiring imminent surgical intervention (including revascularization or plastic surgery), and the presence of any clinically significant medical condition (s) in the medical history during the screening period that, according to the investigator's opinion, could interfere with wound healing. Patients currently receiving or scheduled to receive specific medications or therapies within 30 days of the enrollment visit, which could potentially interfere with wound healing during the study, were also excluded. Ulcers with exposed bone or associated with osteomyelitis, the presence of necrosis, purulence, or sinus tracts that could not be removed by debridement, as well as current sepsis, were additional exclusion criteria.

## 2.4. Outcome Measures

The primary outcome was the percentage of wound contraction using the Walker and Mason formula. Linear wound healing, which calculates the average distance the wound has healed from the initial wound edge to the centre of the wound, incidence of complete healing of the target ulcer measured to ensure the target ulcer area, such as length, width, and depth changed. The secondary outcome included visual analogue scale (VAS) score for pain, Treatment-Emergent Adverse Event (TEAE).

## 2.5. Statistical Analysis

The biostatistician analyzed the data using a finalized statistical analysis plan (SAP). All statistical analyses were performed using R Software. Data were summarized using descriptive statistics for continuous endpoints, including the number of subjects, mean, standard deviation, minimum, median, and maximum, while categorical endpoints were summarized with frequency and percentage. In this study, the changeover at different time points were compared using paired t test.

# 3. Results

The present study encompassed 50 patients diagnosed with DM, comprising of 36 males and 14 females. The mean age of the patients was 57.58 ±12.67 years. The majority (37.5%) of patients were taking metformin and insulin injections. All patients consistently applied C3-DiagardTM cream over the entire 12-week treatment duration.

In relation to the wound healing percentage, 75% (38) of patients exhibited a range of responses ranging from 70% to 99% (Figure 1). The average wound size at the start of the treatment was 6.63 cm, and 1.83 cm at the end of the treatment with a mean wound size reduction of 4.8 cm ($p < 0.05$) (Figure 2). There was significant reduction in the average VAS score for pain from 8 to 3 ($p < 0.05$) (Figure 3).

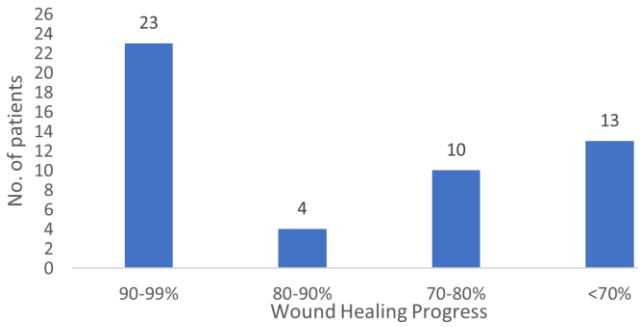


***Figure 1.*** *Wound Healing Progress at the End of Treatment.*

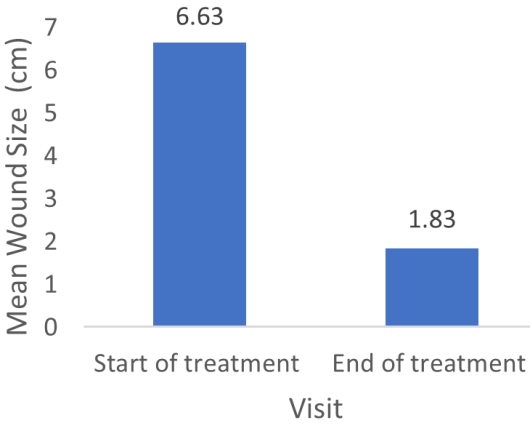


***Figure 2.*** *Wound Size Reduction Over Time.*

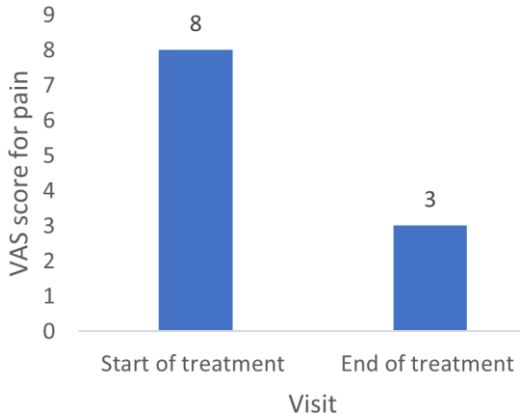


***Figure 3.*** *Reduction of VAS score for pain over time.*

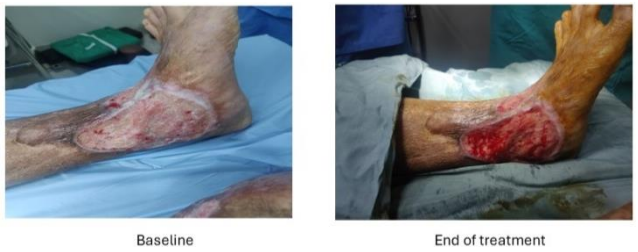


***Figure 4.*** *45-year-old male patient with initial wound size of 8cm on day 0 experienced 96% wound healing at end of treatment.*


***Figure 5.*** *54-year-old female patient with initial wound size of 5cm on day 0 experienced 95% wound healing at end of treatment.*

## 4. Discussion

The development of DFUs is a prevalent complication among individuals with diabetes, affecting approximately 25% of them over their lifetime [7]. These ulcers can lead to severe complications, including infections, amputations, and reduced quality of life [8]. C3-DiagardTM cream has been proposed as a treatment for DFUs due to its ability to promote wound healing and reduce inflammation. The study by Jiang et al. reflected that in diabetic patients with foot wounds, strict blood sugar control reduces the chance of amputation [9]. Peripheral vascular disease and reduced blood flow further exacerbate the status of DFUs. The current approach to managing DFUs involves a comprehensive strategy encompassing blood sugar control, infection eradication, promotion of ulcer healing, and relief of high pressure. C3-DiagardTM cream has been suggested as a potential treatment for DFUs due to its wound healing and anti-inflammatory properties.

The demographic profile of our study reflects participants with an average age ranging from 50 to 60 years, with a gender distribution of 70% males and 30% females (36 males and 14 females). In a trial conducted by Agharazi et al., application of curcumin ointment lead to a significant reduction in the size of diabetic ulcers at five weeks [10]. The findings of our study are similar to those of previous studies, which confirmed the safety and efficacy of C3-DiagardTM cream, formulated with harida extract, in promoting the healing of DFUs. The cream contributed to wound healing by reducing the average wound size by 4.8 cm, oxidative stress, suppressing inflammatory activities, and facilitating the proliferation and remodelling stages. The average VAS score for pain also reduced from 8 to 3. Notably, curcumin, a key component of C3-DiagardTM, has been associated with fibroblast infiltration into the wound site, accelerating the overall process of wound healing [11]. Moreover, our observations revealed that more than 90% healing was achieved for 23 (46%) patients in our study, with noticeable changes in the length, width, and depth of the ulcers. No major side effects were reported. C3-DiagardTM cream demonstrated good tolerability in all patients.

Despite its single-center focus and smaller sample size, the study holds valuable insights, providing a focused and detailed examination of the intervention's effectiveness. While acknowledging these limitations, the findings contribute significantly to the understanding of the targeted population, offering a foundation for future research and potential applications in similar settings.

## 5. Conclusion

Use of C3-DiagardTM cream led to a significant reduction in the size of diabetic ulcers and reduced pain. This study concludes that C3-DiagardTM is clinically effective in the management of diabetic foot ulcer. The absence of adverse reactions underscores the safety profile of C3-DiagardTM cream, making it a well-tolerated option for patients with diabetic ulcers.

## Abbreviations

| | |
|---|---|
| DFU | Diabetic Foot Ulcers |
| DM | Diabetes Mellitus |
| HbA1c | Glycosylated Hemoglobin |
| SAP | Statistical Analysis Plan |
| TEAE | Treatment-Emergent Adverse Event |
| TNF | Tumor Necrosis Factor |
| VAS | Visual Analogue Scale |

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## Author Contributions

**Milind Ruke:** Conceptualization, Data curation, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing

**Iffat:** Data curation, Investigation, Writing – review & editing

**Arun Maurya:** Data curation, Investigation, Writing – review & editing

**Avinash Bhise:** Writing – review & editing

**Jyolsna Agnes Jose:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing

**Kesavalu Purushothaman:** Conceptualization, Methodology, Writing – review & editing

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## Conflicts of Interest

The authors declare no conflicts of interest.

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