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The role of low-level laser therapy as a complementary approach in promoting wound healing among patients with diabetic foot ulcers: A systematic review

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Abstract

Background: A common and complicated side effect of diabetes is diabetic foot ulcers (DFUs), which frequently lead to chronic wounds that are challenging to heal. Another technique that has gained interest is low-level laser therapy (LLLT), which speeds up the healing of diabetic foot ulcers. The purpose of this systematic review is to evaluate how well LLLT aids in the healing of diabetic foot ulcers that are chronic.
Purpose: To assess the effects of low-level laser therapy on the healing of diabetic foot ulcers, particularly with regard to ulcer size reduction, pain relief, and overall wound healing.
Method: A comprehensive search for English-language full-text studies published between 2015 and 2024 was conducted across a number of databases, including PubMed, ScienceDirect, and Google Scholar. Randomized controlled trials that assessed the impact of LLLT on diabetic foot ulcers are required for inclusion. Measurements of wound size, ulcer healing progress, and pain reduction were used to analyze the results.
Results: The analysis includes seven studies that consistently showed benefits from using LLLT. Significant decreases in ulcer size, better tissue repair, and when comparing the treated groups to the control groups, pain relief was seen. Although different laser parameters, such as wavelengths and dosages, were reported in the research, all of them shown positive outcomes in terms of speeding up wound healing and lowering pain levels related to diabetic foot ulcers.
Conclusion: Low-level laser therapy is a useful supplementary technique for promoting the healing of diabetic foot ulcers. Patients with chronic diabetic foot ulcers benefit from LLLT by experiencing less pain, faster wound healing, and an overall higher quality of life. To ascertain the optimal laser parameters and assess the long-term efficacy of LLLT in the management of diabetic wounds, more extensive research is necessary.

Keywords: Diabetic Foot Ulcers; Low-level Laser Therapy; Pain Levels; Wound Healing.

INTRODUCTION

Diabetic foot ulcers (DFUs) represent one of the most prevalent and severe complications associated with diabetes mellitus (Wang, Yuan, Xu, & Yu, 2022). These ulcers typically result from peripheral arterial disease, neuropathy, and sustained hyperglycemia—factors that collectively hinder the normal wound healing process (Yang, Rong, & Wu, 2022). DFUs markedly elevate the risk of infections, lower-limb amputations, and mortality, imposing a significant strain on global healthcare systems (Raja, Maturana, Kayali, Khouzam, & Efeovbokhan, 2023). Despite ongoing advancements in diabetes care, the development of effective therapeutic approaches to enhance wound healing remains a considerable challenge, thereby highlighting the need for alternative and innovative treatment modalities (Wijaya, Budiyanto, & Astuti, 2019).

Low-level laser therapy (LLLT), also referred to as photobiomodulation, has emerged as a promising non-invasive intervention aimed at accelerating

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wound healing (Rashidi, Yadollahpour, & Mirzaiyan, 2015). This technique involves the application of low-intensity laser light to target tissues, thereby stimulating cellular responses and facilitating tissue repair (Júnior, Vieira, Andrade, & Aarestrup, 2007). LLLT is believed to support the healing process by enhancing blood flow, reducing inflammation, promoting cellular proliferation, and increasing mitochondrial activity (Hopkins, McLoda, Seegmiller, & Baxter, 2004). These physiological effects are particularly beneficial in the context of chronic wounds, such as DFUs, which are characterized by prolonged healing times (Andrade, Clark, & Ferreira, 2014).

A growing body of research has investigated the efficacy of LLLT in wound management, reporting favorable outcomes including enhanced tissue regeneration, reduced inflammatory response, and accelerated wound closure (Seyyedi, Taram, Heydari, & Valizadeh, 2022). Nonetheless, discrepancies in laser parameters, treatment protocols, and study designs have led to a heterogeneous body of evidence (Abesi & Derikvand, 2023). This variability underscores the necessity for a rigorous and systematic review to synthesize existing findings and provide a clearer understanding of LLLT's therapeutic potential in the management of diabetic foot ulcers (Lucas, Stanborough, Freeman, & De Haan, 2000).

RESEARCH METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of the ScienceDirect, Google Scholar, and PubMed databases was conducted for full-text, English-language research articles published between 2015 and 2024. The search utilized specific keywords, including "low-level laser therapy," "wound healing," "diabetic foot ulcers," "LLLT," and "RCT."

The inclusion criteria were determined using the PICO framework: Population = patients with diabetic foot ulcers; Intervention = low-level laser therapy (LLLT); Comparison = standard wound care or other control interventions; Outcome = improvement in wound healing. An overview of the included studies and extracted data is presented in Table 1.

Search results yielded 54 articles from ScienceDirect, 21 from PubMed, and 5,523 from Google Scholar. Following the screening of titles and abstracts, 5,565 studies were excluded due to irrelevance or failure to meet the inclusion criteria. Of the 15 full-text articles assessed for eligibility, eight were excluded because of methodological flaws or incomplete data. Ultimately, seven studies were selected for inclusion in the review.

Among the reviewed studies, two focused on the efficacy of LLLT in promoting wound healing in patients with diabetic foot ulcers. Two additional studies investigated the therapy's effects on enhancing microcirculation and tissue regeneration. One study explored the role of LLLT in reducing inflammation in chronic wounds, while another examined the synergistic effect of combining LLLT with standard wound care in accelerating the healing process.

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RESEARCH RESULTS

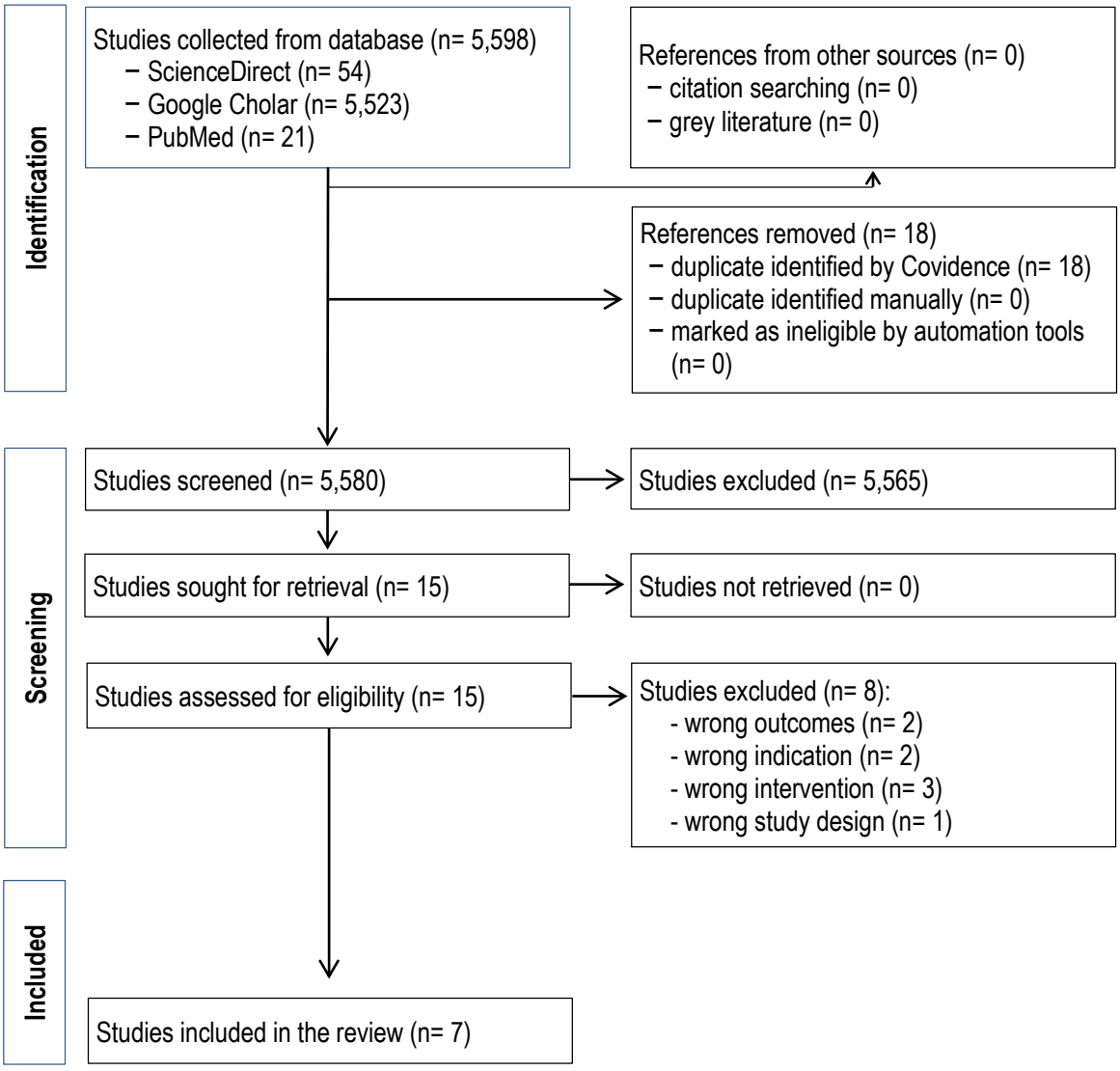

Figure 1. PRISMA flow diagram

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Table 1. Summary of the Articles' Review

(Author,Year) (Country)	Purpose	Method	Results
(Feitosa et al, 2015). (Brazil)	To evaluate the effects of the low-level laser therapy applying Laser on the tissue repair in ulcer carriers due to diabetes.	Sixteen type II diabetic patients, ulcer carriers in the lower limbs, participated in the research from which eight were in the control group and eight were submitted to the low-level laser therapy with a pulsed wave form, visible ray, wavelength of 632.8 nm, 30 mW peak power, (Laser -HTM). The application time was of 80 ($4J/cm^{2)}$ seconds. The application was punctual without contact (approximately 1mm of distance), the pen being held in a perpendicular position related to the wound, in equidistant points. There were 12 appointments, of which three were done weekly in alternated days. Photograph records and an application of the brief inventory of pain were done before and after 30 days of follow-up.	There was a significant decrease in the size of the wound when compared to the control group ($p<0.05$). The pain was also reported as having an intense improvement in the treated group.
(Priyadarshini et al, 2018) (India)	To study the role of low-level laser therapy on diabetic ulcers, i.e. Reduction in size of the ulcer, faster wound healing, control of infection, cost effectiveness and if secondary procedures like split skin grafting can be avoided.	A total of 100 patients with Diabetic foot ulcer fitting the inclusion criteria was included in the study and they were randomly categorized into control and study group. Patients in the study group received treatment with LLLT. Ulcer bed with edge was irradiated locally with red light (660nm), about $4-8J/cm^2$ for 20 minutes was delivered for 15 days on daily basis. Conventional dressing was preferred for covering after irradiation and controls were treated with conventional therapy alone which includes dressings with Betadine or wet with saline, Course of antibiotic treatment and sloughs removed whenever needed. The size, grade and culture status of the ulcer was assessed on Day 1 and day 15. Duration of stay in hospital was noted to assess cost effectiveness.	In LLLT group, after completing 15 days treatment complete wound healing was achieved in 66.6% of grade-1 ulcers and 4.4% of grade-2 ulcers and 96.6% of grade-2 ulcers improved to grade-1. In contrary only 3.4% of grade-2 ulcers improved to Grade 1 and a majority of ulcers remained as such. Reduction in Mean area of ulcer at day-15 was statistically significant in LLLT group (13.74 ± 11.88 to $3.97\pm5.41cm^2$ and $P<0.001$) whereas reduction of mean

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(Author,Year) (Country)	Purpose	Method	Results
			ulcer area among controls was statistically not significant (19.09±15.03cm2 to 18.80±17.70cm^2 and P=0.859). Mean total cost of the treatment was less compared to conventional treatment group. (2264.3±140 Vs 3588.4±68 Rs).
(Santos et al., 2018) (Brazil)	To analyze the efficacy of the therapeutic use of low-level laser therapy (LLLT) on the tissue repair process of chronic wounds in patients with diabetic feet through the analysis of Pressure Ulcer Scale for Healing (PUSH) scales, pain and the measurement done using the Image software.	This clinical trial was carried out with 18 patients 30–59 years of age, who had chronic wounds on their foot due to complications of diabetes mellitus. The patients were randomly allocated in two different groups of equal numbers: Control and Laser Groups. The LLLT equipment used in the research has a wavelength of 660 nm, 30 mW power, continuous mode emission, 6 J/cm^2 dosimetry, 48/48 h in a 4-week period. Measurement and the aspect of wounds were noted in the PUSH scale and the pain was evaluated weekly. The Mann–Whitney U nonparametric test was used to compare groups.	The Laser Group presented a significant increase of the tissue repair index when compared with the Control Group, with a significant statistical difference ($p < 0.013$). There was no significant difference between the groups in all the weeks using the PUSH scale.
(Wadee et al., 2022) (Egypt)	To compare the effectiveness of LLLT versus HBOT on the healing of chronic DFU.	Seventy-five patients with chronic diabetic ulcers aged ranging from 40–65 years were recruited and assigned randomly into three groups. HBOT group received 100% pure oxygen 2.5 ATA delivered for 60 min per session for 30 sessions (5 sessions per week for 6 successive weeks). LLLT group received GaAlAs diode laser producing a total power output of 1440 mW with following wavelengths: 5 × 850 nm (200 mW), 12 × 670 nm (10 mW),8 × 880 nm (25 mW), and 8 × 950 nm (15 mW); the	Within group comparisons demonstrated a statistically significant decrease in USA and ulcer volume in both HBOT and LLLT groups (p-value = 0.0001 in all measurements). The multiple comparisons between groups for USA, there was insignificant difference between HBOT and LLLT

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(Author,Year) (Country)	Purpose	Method	Results
		energy density (fluency) was adjusted for 4 J/cm^2 with a pulse frequency of 10 kHz. Each session lasted 8 min every two days. The control group received conventional wound care only (wound cleansing twice daily using saline or similar dressing). Both LLLT and HBOT groups received conventional wound care in addition to their program. Measurements for ulcer surface area (USA; transparency method) and ulcer volume (volumetric method) were performed before starting the study and in the second, fourth, and sixth-weeks post-treatment.	groups after 2-, 4-, and 6-weeks (p-value = 0.48, 0.813, and 0.629, respectively), while for ulcer volume, there was a statistically significant difference in favor of the LLLT group only after 2- and 4-weeks (p = 0.037 and 0.042, respectively) while an insignificant difference after 6-weeks (p-value = 0.911).
(Cardoso et al., 2021) (Brazil)	To determine the dose response and efficacy of low-level laser therapy on diabetic foot ulcer healing: A randomized controlled trial protocol.	This randomized, double-blind, controlled trial will be conducted at the Physical Therapy University Clinic. Eighty volunteers will be randomized into four groups. The control group will receive placebo LLLT + conventional treatment. The three active groups will receive 10 (G10), 8 (G8), or 4 J/cm^2 (G4) of GaAs 904 nm LLLT plus conventional treatment twice a week for 20 sessions. Conventional treatment involves cleaning and dressing the ulcers.	This trial can potentially provide important information and assist in clinical decision-making regarding DFU treatment with LLLT.
(Kajagar et al., 2012) (India)	To determine mean percentage reduction of wound area in study and control groups.	A total of 68 patients with Type 2 DM having Meggitt-Wagner Grade I foot ulcers of atleast more than 4 weeks duration, less than 6 × 6 cm^2 with negative culture were studied. Patients were randomized into two groups of 34 each. Patients in study group received LLLT with conventional therapy and those in control group were treated with conventional therapy alone. Healing or percentage reduction in ulcer area over a period of 15 days after commencement of treatment was recorded. *Statistical Analysis*: Unpaired Student *T* Test and Mann Whitney *U* test.	Mean age of the patients was 50.94 years in control group and 54.35 years in study group (p = 0.065). There was no significant difference between control and study group with respect to mean FBS and HbA1c levels (p > 0.05), suggesting no biochemical differences between two groups. Initial ulcer area was 2608.03 mm^2 in study group and

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(Author,Year) (Country)	Purpose	Method	Results
			2747.17 mm^2 in control group ($p = 0.361$). Final ulcer area was 1564.79 mm^2 in study group and 2424.75 mm^2 in control group ($p = 0.361$). Percentage ulcer area reduction was 40.24 ± 6.30 mm^2 in study group and 11.87 ± 4.28 mm^2 in control group ($p < 0.001$, $Z = 7.08$). Low Level Laser Therapy is beneficial as an adjunct to conventional therapy in the treatment of diabetic foot ulcers (DFU).
(Torkaman et al., 2024) (Iran)	To investigate the impact of photobiomodulation (PBM) using a Ga-As laser on the release of serum hypoxia-inducible factor 1-α (HIF-1α), vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor-2, and nitric oxide (NO) in diabetic patients with DFUs.	In this double-blind RCT, a total of 30 patients with grade II DFUs were enrolled. The patients were randomly divided into two groups: the PBM ($n = 15$) and the placebo ($n = 15$). In the PBM group, a Ga-As laser (904 nm, 2 J/cm^2, 90 W) was given for 3 days/week for 4 weeks (11 sessions). In the placebo group, the power was turned off. Both groups received similar standard wound care. Before and after interventions, the levels of serum HIF-1α, VEGF, NO, and sVEGFR-2 were measured. In addition, the percentage decrease in the wound surface area (%DWSA) was measured.	Following the intervention, the results revealed that the PBM group had significantly lower levels of VEGF than the placebo group ($p = 0.005$). The %DWSA was significantly higher in the PBM group compared to the placebo group ($p = 0.003$). Moreover, VEGF showed a significant negative correlation with %DWSA ($p < 0.001$).

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DISCUSSION

Numerous studies have shown how effective low level laser therapy (LLLT) is in reducing pain and accelerating the healing process of people with diabetic foot ulcers. These results are supported by a comprehensive analysis of several studies, including randomized controlled trials (RCTs) and experimental designs, which consistently show that LLLT accelerates healing and reduces ulcer size and discomfort. LLLT significantly reduced ulcer size and accelerated healing, with better results in terms of ulcer volume reduction compared to hyperbaric oxygen therapy (Wadee, Fahmy, & El-Deen, 2021); Priyadarshini, Babu, & Thariq, 2018).

A reduction in the size and severity of their wounds, with LLLT resulting in faster healing and shorter hospitalization time (Feitosa, Carvalho, Feitosa, Coelho, Oliveira, & Arisawa, 2015). The results of these studies suggest that LLLT can be used to treat diabetic foot ulcers, with significant benefits for wound healing and pain control. Analyses evaluating the impact of LLLT on serum vitamin D levels, magnesium levels, and improved tissue repair further corroborated these findings, demonstrating the multiple therapeutic benefits of this therapy. In addition, the integration of LLLT with conventional care practices reinforces its effectiveness, especially in improving healing rates and reducing ulcer severity (Feitosa et al., 2015; Kajagar, Godhi, Pandit, & Khatri, 2012; Cardoso, Dos Santos, da Rocha, & Hazime, 2021)

Type of Complementary Intervention Therapy

"Low-level laser therapy is one of the most popular complementary therapies for diabetic foot ulcers" (Huang, Chen, Xiong, Huang, & Liu, 2021). This non-invasive method stimulates cellular mechanisms that promote healing by using light with a certain wavelength (Argenis, Aguilar, & Najar, 2022). The efficacy of LLLT in decreasing ulcer size, improving tissue repair, and reducing pain has been shown in numerous research. LLLT has been demonstrated in a number of randomized controlled trials to dramatically decrease ulcer size and speed up the healing process, frequently producing superior outcomes than other therapies such hyperbaric oxygen therapy (Mokmeli, Daemi, Ayatollahzadeh, Ayatollahzadeh, & Hajizadeh, 2010). Combining LLLT with standard care has been particularly beneficial in promoting faster healing (Srilestari, Nareswari, Simadibrata, & Tarigan, 2017).

LLLT has been shown to considerably lower pain levels as a result of its beneficial effects on wound healing (Argenis et al., 2022). Studies have reported substantial decreases in pain, as measured using tools like the Visual Analog Scale (VAS) (Mokmeli et al., 2010). This decrease in pain is ascribed to the therapy's effects on inflammation reduction and nerve regeneration, both of which are critical for the treatment of diabetic neuropathy (Srilestari et al., 2017). LLLT helps foot ulcers physically heal by increasing circulation and promoting tissue regeneration, which also improves the patient's general comfort and quality of life (Beckmann, Meyer-Hamme, & Schröder, 2014).

LLLT provides many advantages than just pain relief and wound healing (Huang et al., 2021). According to certain research, it can raise serum levels of vitamin D and magnesium, both of which are necessary for the healing of skin and wounds (Carvalho, Feitosa, Coelho, Rebêlo, Castro, Sousa, & Arisawa, 2016). Additionally, LLLT has been shown to enhance tissue healing, particularly in wounds that are chronic (Elmer, 2019). These combined biological, biochemical, and clinical effects underscore the versatility and the capability of LLLT to serve as a supplementary therapy for diabetic foot ulcers, providing a holistic approach to care that addresses multiple aspects of wound recovery and patient well-being.

Measurement of Pain Levels

When treating diabetic foot ulcers, pain is a major concern. Several studies have used a variety of pain measurement instruments to evaluate the efficacy of complementary therapies, including LLLT. A commonly used technique for assessing pain levels is the VAS, which measures pain intensity on a scale from 0 (no pain) to 10 (highest discomfort). VAS was used in the analyzed trials to assess pain levels both before and after LLLT treatment. The results of this study consistently show a significant decrease in pain intensity after applying LLLT, indicating that this therapy is useful in reducing diabetic foot ulcer discomfort.

To quantify pain and neuropathy symptoms in patients undergoing LLLT, additional instruments

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such as the "Numeric Pain Rating Scale (NPRS)" and the "Michigan Neuropathy Screening Instrument (MNSI)" have been used in addition to the VAS. These tools are beneficial for capturing more detailed aspects of pain, including its intensity, frequency, and impact on daily activities (Wang, Huang, Deng, Zhao, Deng, Liu, & Cheng, 2022). For example, one study showed that after receiving LLLT, patients experienced a reduction in both the VPT (Vibration Perception Threshold) and NPRS scores, suggesting improved neuropathic pain and sensory function (Lin, Li, Lin, Tang, & Li, 2021). This pain reduction is crucial for enhancing patient comfort and promoting faster recovery in those suffering from diabetic neuropathy and related complications (Bashiri, 2013).

A favorable therapeutic consequence that improves the patients' quality of life is the notable decrease in pain that occurs after LLLT treatment. Since pain alleviation can result in increased mobility, decreased discomfort, and improved psychological well-being, it is crucial for the management of chronic disorders like diabetic foot ulcers (Alpiah & Alfiyani, 2023). Patients may find that using LLLT in their treatment plans reduces their need for pharmaceutical painkillers, which can have negative side effects and aren't always successful in managing neuropathic pain. Consequently, LLLT as a supplemental intervention offers a viable, non-invasive method of treating diabetic foot ulcer patients' pain (Hendra, Nugraha, Wahyuni, Ayu, & Saraswati, 2019).

CONCLUSION

According to the studies reviewed, this treatment has continuously shown remarkable pain relief, better tissue regeneration, and a dramatic reduction in ulcer size. Moreover, its effectiveness has been confirmed in various clinical settings, which demonstrates its potential as a trustworthy instrument in the comprehensive treatment of diabetic foot disorders. In addition, it was found that LLLT increased serum levels of essential minerals including magnesium and vitamin D and promoted the healing process by increasing angiogenesis and reducing ulcer volume.

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