A systematic review of efficacy on larva debridement in diabetic foot ulcers

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Abstract

Larva therapy, also known as maggot therapy, biodebridement, or maggot debridement therapy, involved the application of live fly larva to a patient's wound for debridement, disinfection, and wound healing. Despite its wide application in diabetic foot ulcers, the efficacy of this intervention remains uncertain. This review aimed to examine the benefits of larva therapy in diabetic foot ulcers by conducting systematic review. This systematic review sought relevant articles using MeSH-based keywords in databases such as Scopus, PubMed, Science Direct, and ProQuest. The inclusion criteria for the articles were as follows: population - patients with diabetic foot ulcers, intervention - the use of debridement or therapeutic application of maggot therapy with *Lucilia sericata*, comparison - none, outcome - the results of articles demonstrating the effectiveness of using *Lucilia sericata* maggot therapy on diabetic foot ulcers. Article quality assessment was conducted using the Joanna Briggs Institute guidelines. Descriptive analysis was performed with a narrative approach, considering articles published from 2018 to 2023. Based on the literature search, 237 articles were found with matching keywords from Scopus (103), PubMed (77), Science Direct (14), and ProQuest (43). After screening for inclusion and exclusion criteria, 11 articles were identified for inclusion in this review. These 11 articles indicate that larva therapy can be an effective method in treating diabetic foot ulcers, especially when used correctly and tailored to each patient's condition and needs. Green bottle fly larva, *Lucilia sericata*, produce proteolytic enzymes that can assist in wound healing. Larva therapy is effective when combined with other procedures. In clinical practice, it is highly recommended that nurses provide an individualized approach and assess potential side effects.

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Introduction

Diabetes Mellitus (DM) is one of the non-communicable diseases that remains a global concern.[1,2] DM occurs when elevated blood glucose levels result from the pancreas' inability to produce adequate insulin,[3] known as hyperglycaemia, where the body cannot produce enough insulin or utilize insulin effectively.[4] According to data from The International Diabetes Federation (IDF), in 2019, there were approximately 463 million people aged 20-79 years worldwide who had diabetes.[5] The World Health Organization (WHO) also reports an 8.5% increase in the prevalence of DM in the adult population, with 422 million people worldwide suffering from DM.[6] In Southeast Asia, the prevalence reached 10,1 %,[7] primarily in middle and low-income countries.[8]

Globally, DM is estimated to affect 9% of the population.[9] It is projected that by 2030, DM will rank as the 7th leading cause of death worldwide.[10] One of the long-term complications of Diabetes Mellitus is Diabetic Foot Ulcer (DFU). The frequency of DFU occurrence is especially high in individuals with type 2 diabetes for more than ten years, with 60% experiencing disability to the point of leg amputation.[11,12] DFU currently have a high incidence, affecting 85% of DM patients.[13] According to a past review, one in every 20 hospitalized DM patients has a diabetic foot ulcer.[14] Every 20 seconds, a lower limb is lost due to DM.[15] Diabetic foot ulcers are characterized by the presence of infection, ulceration, and damage to the foot tissue.[16] Chronic foot ulcers are a common complication in DM patients, leading to a high rate of hospitalization and amputations.[17] Approximately 15% of DM patients will develop foot ulcers at some point in their lives,[18] and among them, 14-24% will require amputations, making foot ulcers a significant predictor of future amputations.[19]. This requires proper collaboration between individuals with diabetes and related health workers.[20] Therefore, interventions aimed at preventing the

progression of diabetic ulcers are necessary.

Debridement is generally defined as the "process of removing all non-healing materials from the wound".[15] Several methods are currently applied in the management of diabetic ulcers, including surgery, conventional dressings, larva therapy, enzyme preparations, polysaccharide beads, and hydrogels.[21] For years, larva therapy has been promoted to have more benefits in regeneration by removing necrotic tissue.[22] Nevertheless, the detailed benefits of this issue have not been determined. Therefore, the Society for Vascular Surgery[23] commissioned this evidence synthesis report to evaluate the quality of evidence supporting existing debridement methods and to estimate their relative benefits.

Larva therapy, also known as maggot therapy, biodebridement, or maggot debridement therapy, involves the application of live fly larva, including "medical-grade" maggots,[24] to a patient's wound to achieve debridement, disinfection, and ultimately wound healing.[17] Larva therapy uses newly hatched and sterilized larva from the common green bottle fly, *Phaenicia (Lucilia) sericata*, which is a type of myiasis or ectoparasitic infestation in living or necrotic tissue induced by artificially raising fly larva to high levels[25] controlled clinical conditions.[19] This type of larva therapy appears to offer more benefits than non-biodebridement interventions.

The beneficial effects of larva therapy were first documented in the year 1557. The introduction and widespread use of antibiotics in the 1940s had an impact on the gradual increase in general treatments.[24] In recent years, with the increasing incidence of drug resistance, there has been renewed interest in using maggots in the management of chronic wounds,[15] especially in treating wounds infected with Methicillin-Resistant Staphylococcus Aureus (MRSA) or bacteria resistant to some types of antibiotics, such as amoxicillin and penicillin, and other drug-resistant pathogens.[26] The current evidence supporting larva therapy for chronically infected lesions comes from several small clinical trials.[27] This systematic review aimed to examine the benefits of larva therapy in diabetic foot ulcers.

Materials and Methods

Study design

This study is a systematic literature review conducted to address the research question, which examines empirical evidence on larva therapy for diabetic foot ulcers. The study was conducted systematically using the PRISMA literature review approach without conducting a meta-analysis on quantitative data.

Search strategy

The search was conducted on four databases: Scopus, Science Direct, PubMed, and ProQuest. Keywords were based on MeSH terms, such as [("Debridement" OR "surgical debridement") AND ("Diabetic foot") AND ("Larva" OR "maggot therapy")].

Eligibility criteria

All search results are organized in Mendeley Desktop and reviewed to determine whether they meet the inclusion criteria. Results that are identical or not identical to the research paper are discarded. In this systematic review, the inclusion criteria used are patients with diabetic foot ulcers undergoing debridement or therapeutic use of maggot therapy with *Lucilia sericata*; comparisons include standard care; article outcomes indicate the effectiveness of *Lucilia sericata* maggot therapy on diabetic foot ulcers; included study designs are Case Reports, True Experimental Research Designs, Randomized Clinical Trials, Publication Years 2018-2023, and the language used is English.

Study selection

Article selection was checked using the following criteria: the last 5 years, language used (English), keyword suitability, abstract, full text, study type, and article duplication. Initially, 237 studies were obtained from the database search. The duplicates were then removed, and the titles and abstracts of the articles were screened. Articles were considered relevant for review if they met the criteria. The remaining studies were reduced to only 11 empirical publications. Title and abstract screening was then used to evaluate how well the article content matched the research topic.

Risk of bias

All search results were organized in Mendeley Desktop and reviewed to determine whether they met the inclusion criteria. Results identical or not identical to the research papers were discarded. The quality assessment of the articles and bias risk was independently performed by the research team using the Joanna Briggs Institute (JBI) critical appraisal tool (Table 1).

Data extraction

The articles that were read in full were then organized and explored based on the author's name, publication year, sample age, study design, sample size, wound size, number of larva, intervention program, session frequency and duration, and findings (Table 2 and 3). All of these steps were carefully recorded and reported following the 2020 PRISMA flow diagram[28] (Figure 1).

The search results yielded 237 articles, which were then screened and adjusted based on a full-text assessment, resulting in 11 articles. The flowchart for this study is as follows.

The Joanna Briggs Institute (JBI) critical appraisal checklist was used to analyze and mitigate bias risks for each article in this study. If a research article scored a minimum of 50% on the critical appraisal criteria, as agreed upon by the researchers, it was included in the inclusion criteria. The analysis is descriptive, using a narrative approach based on predefined themes.[29]

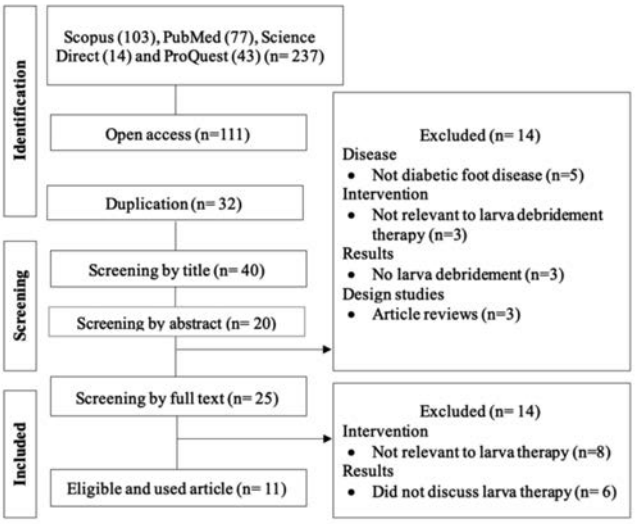

Figure 1. PRISMA flow diagram of the article selection process.

Results

Study characteristics

Based on the systematic review conducted, the reviewed articles had the following study characteristics: Case Report Studies (n=5), True Experimental Research Design (n=5), and a Randomized Clinical Trial (RCT) research design (n=1). The research was carried out in Iran (Parizad *et al*., 2022; Choobianzali *et al*., 2022; Hajimohammadi *et al*., 2021; Parizad *et al*., 2021; Jafari *et al*., 2022; Siavash *et al*., 2021), Mexico (Fonseca-Munoz *et al*., 2020), Poland (Szczepanowski *et al*., 2022), and Turkey (EGRIBEL *et al*., 2022). The studies included in this systematic review came from research conducted in various countries worldwide, and all studies used the same type of fly, namely *Lucilia sericata*. A total of 270 samples participated in the therapy with *Lucilia sericata* larva. Based on the review results, it is evident that larva therapy using maggots can improve the healing of diabetic foot ulcers.

Outcomes

These eleven articles discussed larva therapy as a method that can be used to treat diabetic foot ulcers. Larva therapy not only removes necrotic tissue debris from patients with fasciitis (inflammation of the tissue beneath the foot extending from the heel to the toes)[41] but also disinfects the wound, minimizes tissue loss, and promotes granulation tissue growth.[34] Larva consume dead tissue and thus effectively break down this tissue.[42] The saliva of these larva can digest dead wound tissue efficiently and can also eliminate microorganisms at the wound infection site.[43] If diabetic foot ulcers are left untreated, severe conditions such as septicemia can threaten patients, and even death.[44]

Based on the case study results in the research by Parizad *et al*. (2022),[30] Choobianzali *et al*. (2022),[31] Hajimohammadi *et al*. (2021),[32] Parizad *et al*. (2021),[33] and Fonseca-Munoz *et al*. (2020),[34] it is known that interventions were carried out on wounds in the lower extremities, each with varying wound sizes. The studies utilized *Lucilia sericata* larva in combination with surgical debridement,[30,32,33] mechanical debridement, as well as normal saline,[31] Negative Pressure Wound Therapy (NPWT), and silver foam dressing.[33] In a study conducted by Fonseca-Muñoz *et al*. (2020), therapy was not administered to wounds on the patients' feet but to wounds on the scrotum of two patients undergoing larva therapy. In the research by Szczepanowski *et al*. (2022),[35] Jafari *et al*. (2022),[36] Siavash *et al*. (2021),[37] Dehghan *et al*. (2020),[38] and EGRIBEL *et al*. (2022).[39] True Experimental Research Design was employed, featuring a control group not receiving *Lucilia sericata* larva. The Session Frequency & Duration in each study was set at 48 to 72 hours. Nezakati *et al*.'s (2020)[40] Randomized Clinical Trial design demonstrated significantly higher wound healing and reduction of necrotic tissue in the intervention group.

The synthesis of research findings indicates that combining surgical debridement and larva therapy is a safe and effective strategy for enhancing the healing of diabetic foot ulcers. This approach not only demonstrates affordability but also proves highly effective in treating challenging diabetic foot ulcers, preventing leg amputation, and addressing cases unresponsive to conventional therapy. Larva therapy, especially when using *Lucilia sericata* larva, emerges as a valuable method for wound cleaning, effectively removing necrotic tissue, minimizing tissue loss, and promoting granulation tissue growth. Moreover, the research suggests that larva therapy is effective for atypical diabetic foot ulcers that do not respond well to standard treatments, highlighting its potential as an alternative or supplementary method alongside traditional approaches such as sharp debridement, antibiotic therapy, and modern dressings. These findings collectively emphasize the therapeutic benefits of larva therapy in accelerating wound healing and reducing the size of diabetic foot ulcers, making it a simple yet impactful intervention for biofilm formation in wound care.

Discussion

This review aims to examine the benefits of larva therapy in diabetic foot ulcers. According to the Food and Drug Administration (FDA), larva therapy is highly effective in treating non-healing wounds and open wounds with dead tissue.[32] Larva therapy reduces the number of surgical procedures that would otherwise be required and produces favorable outcomes.[34]

Wound healing process

Green bottle fly larva, *Lucilia sericata*, release proteolytic enzymes that aid in wound healing.[45,46] These enzymes assist in breaking down necrotic (dead) tissue in wounds[47] by digesting necrotic tissue, cleansing the wound of harmful substances, and promoting healthy tissue formation.[26] The enzymes produced by *Lucilia sericata* larva have proteolytic properties, meaning they

Table 1. Critical appraisal results for included studies using the JBI Critical Appraisal Checklist.

No	Author (year)	Design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
1.	Parizad *et al.* (2022)[30]	Case report study	Y	Y	Y	Y	Y	N	N	Y	N/A	N/A	N/A	N/A	N/A	6/8
2.	Choobianzali *et al.* (2022) [31]	Case report study	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	N/A	N/A	8/8
3.	Hajimohammadi *et al.* (2021) [32]	Case report study	Y	Y	Y	Y	Y	Y	N	Y	N/A	N/A	N/A	N/A	N/A	7/8
4.	Parizad *et al.* (2021) [33]	Case report study	Y	Y	Y	Y	Y	Y	N	Y	N/A	N/A	N/A	N/A	N/A	7/8
5.	Fonseca-Munoz *et al.* (2020)[34]	Case report study	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	N/A	N/A	8/8
6.	Szczepanowski *et al.* (2022)[35]	True Experimental Research Design	Y	Y	N	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	N/A	8/9
7.	Jafari *et al.* (2022)[36]	True Experimental Research Design	Y	Y	N	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	N/A	8/9
8.	Siavash *et al.* (2021)[37]	True Experimental Research Design	Y	Y	N	Y	Y	N	Y	Y	Y	N/A	N/A	N/A	N/A	7/9
9.	Dehghan *et al.* (2020)[38]	True Experimental Research Design	Y	Y	N	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	N/A	8/9
10.	EGRIBEL *et al.* (2022)[39]	True Experimental Research Design	Y	Y	N	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	N/A	8/9
11.	Nezakati *et al.* (2020) [0]	Randomized Clinical Trial	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	11/13

No	Title Authors	Country setting	Age of participants	Sample size	Wound area	Numbers of larva used	Intervention program	Session frequency and duration	Findings
1.	Surgical debridement and maggot debridement therapy (MDT) bring the light of hope to patients with diabetic foot ulcers (DFUs): A case report.[30]	Iran	72 years of age.	1	1×1 cm left foot	Not mentioned	DFU is treated and managed surgical debridement and maggot debridement therapy.	10 sessions of Maggot Debridement Therapy (MDT) were performed (one therapy session every 48 hours). every 48 hours).	This case report suggests that using surgical debridement and MDT is a safe and effective approach to facilitate DFU healing.
2.	Reviving hope by using of maggot debridement therapy in patients with diabetic foot ulcer: A case report study.[31]	Iran	51 years of age.	1	2×2 cm right foot	Not mentioned	Maggot debridement, mechanical debridement as well as normal saline.	After 10 sessions (one session every 48 hours) maggot debridement therapy (MDT)	This case report reveals that maggot therapy is an affordable and highly potent drug Treatment methods to improve DFU healing.
3.	Saving diabetic foot ulcers from amputation by surgical debridement and maggot therapy: A case repor.[32]	Iran	72 years of age	1	6×5 and 3×3 on the heel and the sole of the right foot.	Not mentioned	Surgical debridement and maggot debridement.	In all, 10 MDT sessions were conducted (one session every 48 hours)	This case report study shows that the combined use of surgical debridement and MDT is a safe and effective approach to improve DFU healing and prevent leg amputation.
4.	Surgical debridement, maggot therapy, negative pressure wound therapy, and silver foam dressing revive hope for patients with diabetic foot ulcer: A case report.[33]	Iran	63 years of age	1	4×6, 6×8, and 6×3 On three sites of the left external ankle in the form of two deep, the sole as a superficial ulcer and the left heel as a deep skin groove.	Not mentioned	Surgical debridement, maggot therapy, Negative Pressure Wound Therapy (NPWT), and silver foam dressing.	10 sessions conducted once in 48 hours	Based on the clinical results of this case report study, the wound care team can use the combination the therapy applied in this case report is to treat refractory DFU.
5.	Clinical study of Maggot therapy for Fournier's gangrene.[34]	Mexico	32- 59 years of age	2	Scrotum over the previous 15 days.	300 and 500 larva	Maggot debridement	3-8 sessions conducted once 48 hours	Maggot therapy not only effectively removes impurities of necrotic tissue of patients with fasciitis, but also disinfects wounds, minimizes tissue loss, and promotes granulation tissue growth.
6.	Microbiological effects in patients with leg ulcers and diabetic foot treated with *Lucilia sericata* larva.[35]	Poland	63-67 years of age	80	Not mentioned	Not mentioned	Maggot debridement	10 sessions conducted once in 48 hours	Wound cleaning with the use of L sericata larva is highly recommended in situations where necrosis has penetrated deep into the tissues.
7.	Lucillia Sericata larva therapy in the treatment of diabetic chronic Wounds.[36]	Iran	45-65 years of age	40	38,5 cm	Not mentioned	Maggot debridement	10 sessions conducted once in 48 hours	Larva therapy is effective in healing diabetic wounds. The size of the wound after the treatment of the larva is smaller than ever before.
8.	Efficacy of Maggot Debridement Therapy on Refractory Atypical Diabetic Foot Ulcers: An Open-Label Study.[37]	Iran	38-75 years of age	42	Not mentioned	10-15 larva	Maggot debridement	For 48 to 72 hours. MDT repeated 5 times	Our findings show that MDT is effective treatment for inadequate atypical DFU responsive to conventional therapies.
9.	A New Approach to Maggot Therapy for Healing of Diabetic Foot Ulcers.[38]	Iran	37-55 years of age	27	Not mentioned	Not mentioned	Maggots therapy added routine treatment as a complementary therapy.	Once in 48 hours	Maggot therapy other routine methods for DFU healing and indicates that this type of therapy can be added for conventional treatment approaches such a sharp debridement, antibiotic therapy and modern dressings to achieve a satisfactory result.
10.	Exploring the Effects of *Lucilia sericata* Larva on Biofilm-forming Bacteria in Wounds.[39]	Turkey	28-37 years of age	30	Not mentioned	Not mentioned	Therapy of maggots with sterile *Lucilia sericata.*	Once in 48 hours	Therapy with the larva of L. sericata, a simple and effective method, can accelerate the healing of biofilm formation wound.
11.	Effects of *Lucilia sericata* Maggot Therapy in Chronic Wound Treatment: A Randomized Clinical Trial.[40]	Iran	45-66 years of age	45	Not mentioned	Not mentioned	Therapy of maggots with sterile *Lucilia sericata.*	Larva should usually be removed within 48-72 hours after prescription	Our results show the larva of *L. sericata* Therapy can significantly increase the rate of wound healing.

Table 3. Larva debridement in diabetic foot ulcers.

No	Study	DFU Indicators	Types of Larva
1.	Case report study	Diabetes mellitus	*Lucilia sericata*
2.	Case report study	Diabetes mellitus	*Lucilia sericata*
3.	Case report study	Diabetes mellitus	*Lucilia sericata*
4.	Case report study	Diabetes mellitus	*Lucilia sericata*
5.	Case report study	Diabetes mellitus	*Lucilia sericata*
6.	True experimental research design	Diabetes mellitus	*Lucilia sericata*
7.	True experimental research design	Diabetes mellitus	*Lucilia sericata*
8.	True experimental research design	Diabetes mellitus	*Lucilia sericata*
9.	True experimental research design	Diabetes mellitus	*Lucilia sericata*
10.	True experimental research design	Diabetes mellitus	*Lucilia sericata*
11.	Randomized clinical trial	Diabetes mellitus	*Lucilia sericata*

can break peptide bonds in proteins and necrotic tissue.[48] This is one of the main ways larva accelerate wound healing.[26] These enzymes also have antibacterial properties that can help minimize the risk of infection in wounds.[49] Proteolytic enzymes are crucial for various biological processes, including food digestion, the regulation of enzyme and protein activities, tissue regeneration during wound healing, and the elimination of pathogens such as bacteria and viruses.[50]

Larva therapy administration procedure

In the eleven articles, it was found that the age of patients undergoing larva therapy ranged from 28 to 75 years. Additionally, the average patient's family had a history of Diabetes and hypertension and their associated treatments. The condition of the wound area in each patient varied, depending on the severity or the patient's condition, which also influenced the frequency and duration of the larva therapy itself. When providing larva therapy, the average time needed for a patient to undergo larva treatment was 10 sessions (one session every 48 to 72 hours). During each session, patients were asked about their tolerance or ability to undergo larva therapy. If the answer was "yes," the intervention continued, but if the answer was "no," the intervention was stopped. Overall, the wound healing process through larva therapy varied for each patient, depending on the size and depth of the wound.

Based on the systematic review above, some articles suggest that a combination of larva therapy with surgical debridement,[30-33] silver dressings, and Negative Pressure Wound Therapy (NPWT) is highly effective in treating refractory diabetic foot ulcers.[33] Furthermore, Hajimohammadi *et al.* in Parizad *et al.* (2022) reported that combining surgical debridement and larva therapy is a safe and effective strategy for treating diabetic foot ulcers and preventing amputations.[32] Choobianzali *et al*. in Parizad *et al*. (2022) reported that larva therapy is an affordable and highly effective treatment approach for improving the healing of diabetic foot ulcers.[31] However, Soares *et al.* (2009) stated that the use of larva therapy in diabetic foot ulcers, compared to hydrogel, provided limited health benefits, longer healing times, and slightly higher additional costs than using hydrogel.[51]

Effects of larva therapy on patients

Larva therapy can have side effects such as itching and the sensation of something crawling on the skin. Regarding the stimulation of the nervous system due to larva distension, some patients may experience varying levels of pain, which can be alleviated by timely larva removal or the use of medications.

Psychological effects, such as anxiety, are another result of larva therapy,[52] mainly due to the placement of larva to clean diabetic foot ulcers. Patients unfamiliar with this procedure may initially feel fear and anxiety. Therefore, as a nurse, preventive measures can be taken to minimize patient anxiety, such as providing clear explanations about the procedure, showing empathy towards the anxiety experienced by the patient, offering patients the choice to observe the larva therapy procedure, providing psychological preparation for what the patient will experience during the therapy process, administering anesthesia for pain relief where possible, and involving additional support, such as family or close friends, with the patient. It is essential to remember that every patient undergoing larva therapy by a nurse requires a different approach, and professionalism is always required to help patients cope with their anxiety regarding larva therapy.

Limitations of the study

This study has several limitations. It's based on just two patients with scrotal wounds undergoing larva therapy, which limits its generalizability, statistical power, and the ability to draw causal conclusions. There is no control group, which further impacts the study's validity. Patient heterogeneity introduces confounding variables that can affect the results. Self-reported data may introduce bias, and the study does not address the long-term sustainability of the therapy. The lack of specific FDA citations affects the study's credibility. Furthermore, the study is focused on the benefits and administration of larva therapy, excluding complications, adverse effects, and alternative treatments. Inconsistent treatment durations and limited comparisons with other strategies hinder the evaluation of relative advantages and disadvantages.

Conclusions

This unique therapy has the potential to accelerate healing by breaking down necrotic tissue and promoting healthy tissue formation. The study highlights variations in patient response and suggests that the cost-effectiveness of larva therapy may vary. It also emphasizes the importance of addressing patient discomfort and anxiety. Green bottle fly larva, *Lucilia sericata*, produce proteolytic enzymes that can assist in wound healing. Larva therapy is

effective when combined with other procedures. However, nurses should understand the potential side effects and patient anxiety, providing a professional and individualized approach. With proper care, larva therapy can help in healing diabetic foot ulcers. Overall, the findings suggest that larva therapy has promise in wound management, but further research and individualized patient care are essential for its success. Future researchers can contribute to a deeper understanding of larva therapy's potential in wound management and improve the quality of care for patients with non-healing wounds.

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