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Topical Aloe Vera as an Adjunctive Therapy for Diabetic Foot Ulcers: A Systematic Review

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ABSTRACT

Diabetic foot ulcers (DFUs) remain a persistent clinical challenge due to impaired healing and high infection risk. This systematic review evaluates the potential benefit of topical Aloe vera as an adjunct to standard DFU care. A structured search of PubMed, ScienceDirect, ProQuest, and Google Scholar was conducted up to December 30, 2025, following PRISMA 2020 guidelines. Eight clinical studies (six randomized controlled trials/RCTs and two quasi-experimental studies), involving 402 patients, were included. Outcomes assessed included BWAT/BJWAT scores, granulation, epithelialization, and ulcer size. Across studies, Aloe vera was associated with improvements in wound healing parameters, particularly in mild-to-moderate, non-ischemic ulcers during early healing phases. Risk of bias assessment showed generally low to moderate concerns among RCTs, while non-randomized studies presented serious to critical risk of bias. Using GRADE, the certainty of evidence was low for wound scores and ulcer size reduction, and very low for granulation and healing outcomes, mainly due to risk of bias, inconsistency, and imprecision. Overall, Aloe vera may provide some benefit as a low-cost adjunctive therapy; however, the current evidence remains limited and should be interpreted with caution. Further well-designed, adequately powered trials with standardized outcomes are needed.

INTRODUCTION

Patients with diabetes mellitus are highly vulnerable to a range of chronic complications, including nephropathy, retinopathy, and neuropathy. Among the most severe of these is diabetic foot ulcers (DFUs) (Wang et al., 2022). DFUs are defined as tissue damage extending to at least the dermal layer in individuals with diabetes, and they are estimated to affect 19–34% of patients over their lifetime (McDermott et al., 2023). Globally, around 18.6 million new DFU cases occur each year, placing a substantial burden on morbidity, quality of life, and healthcare systems (Armstrong et al., 2023). If not managed appropriately, DFUs can progress to severe infection, gangrene, lower-limb amputation, and even death (Ndosi et al., 2018). The five-year mortality rate in patients with DFUs is reported to be approximately 30%, rising sharply following major amputation, with significant associated healthcare costs (Chia et al., 2025). In resource-limited settings, restricted access to advanced wound care further worsens patient outcomes (Ahn & He, 2026). Accelerating wound healing is therefore a critical priority to reduce both the clinical and economic burden of DFUs.

From a pathophysiological perspective, DFUs represent a complex condition arising from the interplay of neuropathy, ischemia, infection, and metabolic dysfunction (Dawi et al., 2025). Peripheral neuropathy leads to loss of protective sensation and increases the risk of repeated trauma, while peripheral arterial disease contributes to tissue hypoxia and impaired nutrient delivery (Parveen et al., 2025). Chronic hyperglycemia further drives persistent inflammation, oxidative stress, and endothelial dysfunction, all of which impair angiogenesis and immune responses (Dubský et al., 2025). In addition, dysfunction of fibroblasts and keratinocytes disrupts extracellular matrix formation and re-epithelialization, ultimately delaying wound healing (Hassan et al., 2025). Together, these factors create a hostile wound environment characterized by a high risk of infection and poor healing outcomes, even when appropriate treatment is provided (Armstrong et al., 2023).

Current DFU management relies on a comprehensive approach that includes debridement, infection control, off-loading, vascular optimization, glycemic control, and appropriate wound dressings (Everett & Mathioudakis, 2018). Despite this, healing is often prolonged and suboptimal, as standard therapies do not fully address chronic inflammation, impaired angiogenesis, oxidative stress, and high microbial burden in DFU wounds (R. Wang et al., 2025). Moreover, advanced wound care technologies, such as biomaterial-based therapies and specialized dressings, are frequently limited by cost and availability, particularly in low-resource

settings (Pinem et al., 2025). This highlights the need for adjunctive therapies that can complement, rather than replace, standard care. In this context, Aloe vera has gained attention as a topical agent used alongside conventional treatment to help improve the wound environment (Matei et al., 2025).

Aloe vera contains a range of bioactive compounds with anti-inflammatory, antioxidant, and antimicrobial properties. It has also been shown to promote fibroblast proliferation, collagen synthesis, and re-epithelialization, suggesting potential benefits in overcoming key barriers to DFU healing (Matei et al., 2025). Several clinical trials have reported that adding Aloe vera to standard wound care improves healing outcomes compared to standard care alone, including reductions in wound scores and faster tissue repair (Irani et al., 2023; Sandhiya et al., 2025). However, it is important to emphasize that Aloe vera should be considered an adjunctive therapy that supports healing, rather than a substitute for essential interventions such as debridement, off-loading, and infection control. Although there are indications that Aloe vera may be more affordable than some conventional agents in certain wound contexts, evidence regarding its cost-effectiveness remains limited and cannot yet be generalized to DFUs (Shahzad & Ahmed, 2013).

Despite its promising potential, the current body of evidence remains fragmented and heterogeneous. Some previous systematic reviews have evaluated Aloe vera across a broad range of wound types without specifically focusing on DFUs, limiting their clinical applicability to this population (Idrus et al., 2023; Hekmatpou et al., 2019). Conversely, systematic reviews focusing on DFUs often assess a wide range of herbal interventions without specifically examining the effectiveness of Aloe vera as a standalone therapy (Narzary et al., 2023). In addition, a systematic review protocol specifically targeting Aloe vera in DFUs has been published, but a comprehensive synthesis of results is not yet available (Jamiyanti et al., 2023). Variability in study design, intervention formulations, and reported outcomes further underscores the need for a more focused and rigorous evaluation of the evidence.

Based on these considerations, this study aims to systematically evaluate the effectiveness of topical Aloe vera as an adjunctive therapy in the healing of diabetic foot ulcers. The research question is formulated as follows: in patients with DFUs (Population), does the use of topical Aloe vera (Intervention), compared with standard care or other conventional interventions (Comparator), improve wound healing outcomes such as ulcer size reduction and wound closure (Outcomes)? By focusing on a clearly defined population, intervention, and clinically relevant outcomes, this review aims to provide a more targeted and practical synthesis of evidence for clinical application.

METHODS

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and completeness of reporting. All methodological steps followed the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions. An internal protocol was developed prior to study selection, covering the research question, eligibility criteria, search strategy, and plans for data extraction and analysis. Although the protocol was not registered in a public database such as PROSPERO, efforts were made to minimize selection and reporting bias by applying predefined criteria consistently throughout the review process.

Search Strategy

A comprehensive literature search was conducted across four electronic databases: PubMed, ScienceDirect, ProQuest, and Google Scholar, with the final search performed on December 30, 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms to maximize sensitivity and coverage. Keywords included variations of Aloe vera (e.g., Aloe, "Aloe vera", "Aloe barbadensis") combined with terms related to DFUs (e.g., "diabetic foot ulcer", "diabetic wound", "foot ulcer", and "diabetic feet"). The strategy was adapted for each database to account for differences in indexing systems and search interfaces, with systematic use of Boolean operators ("AND", "OR").

Database-specific filters were applied prior to exporting the search results, restricting studies to those published between 2015 and 2025 and to original research articles to enhance relevance. Additionally, manual screening of the reference lists of included studies was conducted to identify potentially missed articles. The detailed search strategy for each database is presented in Table 1.

Table 1. Literature search strategy used for study identification

Database	Search strategy	Records retrieved
PubMed	(("Aloe vera"[MeSH Terms] OR "Aloe barbadensis"[MeSH Terms] OR "Aloe gel" OR "Aloe extract") AND ("Diabetic Foot"[MeSH Terms] OR "Diabetic Foot Ulcer"[MeSH Terms] OR "Diabetic wound" OR "Foot ulcer"))	68
ScienceDirect	(("Aloe vera" OR "Aloe barbadensis" OR "Aloe gel" OR "Aloe extract") AND ("diabetic foot ulcer" OR "diabetic foot" OR "diabetic wound*" OR "foot ulcer" OR "chronic wound" OR "wound healing" OR "ulcer healing"))	1,197
ProQuest	(("Aloe vera" OR "Aloe barbadensis" OR "Aloe gel" OR "Aloe extract") AND ("diabetic foot ulcer" OR "diabetic wound" OR "foot ulcer" OR "ulcer healing"))	1,415
Google Scholar	(("Aloe vera" OR "Aloe barbadensis" OR "Aloe gel" OR "Aloe extract") AND ("diabetic foot ulcer" OR "diabetic foot" OR "diabetic wound" OR "foot ulcer")	796

Eligibility Criteria

Study eligibility was defined using a specifically operationalized PICOS framework. (1) The population included human patients with a clinical diagnosis of DFUs, with no restrictions on age, sex, ulcer size, ischemic status. or

severity; (2) The intervention consisted of topical Aloe vera, either as a single agent or in combination formulations, used as an adjunctive therapy; (3) Comparator groups included standard wound care, such as debridement, saline irrigation, conventional dressings, or topical placebo; (4) The primary outcomes were objective measures of wound healing, specifically ulcer size reduction and changes in wound scores. Secondary outcomes included time to wound closure, granulation tissue formation, epithelialization, and complete healing rates; (5) Eligible studies were interventional designs published between 2015 and 2025. Non-human studies, reviews, systematic reviews, meta-analyses, conference abstracts, commentaries, letters to the editor, case reports, clinical guidelines, and those lacking relevant clinical outcome data were excluded.

Study Selection

All retrieved records were exported and managed using Rayyan software for deduplication and screening. After removing duplicates, study selection was conducted in two stages: title and abstract screening, followed by full-text review. The selection process was performed using predefined inclusion and exclusion criteria. Studies meeting the initial criteria were advanced to full-text assessment. The study selection process is illustrated in a PRISMA flow diagram, detailing the number of records identified, screened, excluded, and the reasons for exclusion at each stage.

Data Extraction

Data were extracted using a standardized Microsoft Excel form and organized into three domains: study characteristics, intervention details, and outcomes. Study characteristics included author, year, design, sample size, age, DFU severity, ulcer size, infection, and glycemic status. Intervention data covered Aloe vera formulation, type of intervention, co-interventions, application protocol, frequency, duration, and comparator. Missing information was recorded as not reported (NR) to ensure consistency across studies. Outcome data included primary measures such as wound score changes, ulcer size reduction, and time to wound closure, as well as secondary outcomes like granulation tissue formation, epithelialization, tissue characteristics, and adverse events. Key comparative results between intervention and control groups and the direction of effect were also extracted. All data were cross-checked to maintain accuracy and alignment with the predefined extraction tables.

Quality Assessment

The methodological quality of the included studies was evaluated through a structured risk of bias assessment. RCTs were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, while non-randomized studies were appraised using the ROBINS-I tool. Each study was examined across key domains, including the randomization process, deviations from intended interventions, completeness of outcome data, outcome measurement, and selective reporting. Based on these domains, studies were categorized as having low, moderate, or high risk of bias, and these judgments were taken into account when interpreting the findings.

In addition to study-level assessment, the overall certainty of evidence for each primary outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. This assessment considered five domains: risk of bias, inconsistency, indirectness, imprecision, and potential publication bias. The certainty of evidence was then classified as high, moderate, low, or very low, providing a broader context for understanding the strength and reliability of the synthesized results.

Data Synthesis

A narrative synthesis was conducted due to heterogeneity in study designs, variations in Aloe vera formulations, and differences in reported outcomes, which precluded meta-analysis. The synthesis was structured using two complementary approaches: by outcome domain and by intervention type. Within each category, findings were analyzed to identify patterns in the direction and consistency of effects across studies, particularly for key wound healing parameters such as wound score reduction, ulcer size change, and time to wound closure. Differences in comparator type, wound severity, and co-interventions were also considered to contextualize variability in results. This approach enabled a more nuanced interpretation of trends, including areas of consistent benefit, mixed findings, and uncertainty, while taking into account methodological quality and certainty of evidence.

RESULTS OF STUDY

Results of the Literature Search

The systematic search identified 3,476 records from PubMed (n = 68), Google Scholar (n = 796), ScienceDirect (n = 1,197), and ProQuest (n = 1,415). Prior to screening, 463 duplicate records and 1,561 records flagged as ineligible by database filters (including publication year, study design, and article type restricted to academic journal articles) were removed, leaving 1,452 records for title and abstract screening. Of these, 1,406 records were excluded, and 46 articles were sought for full-text retrieval. Twelve reports could not be retrieved, resulting in 34 full-text articles assessed for eligibility. A total of 26 studies were excluded due to inappropriate intervention (n = 7), wrong patient population (n = 10; including non-DFU populations [n = 6] and non-human studies [n = 4]), or insufficient outcome data (n = 9). Finally, eight studies met the inclusion criteria and were included in the qualitative synthesis (Figure 1).

Characteristics of Included Studies

Eight clinical studies involving a total of 402 patients with DFUs were included, with sample sizes ranging from 17 to 66. The majority were RCTs, including several double-blind designs, while two employed quasi-experimental approaches. Participants were predominantly middle-aged to older adults, although one study included a broader age range (18–80 years). Ulcer severity varied substantially, from superficial grade 1 lesions to Wagner grade II–III ulcers and moderate-to-severe wounds requiring debridement. Key clinical variables were inconsistently reported across studies; infection status ranged from non-infected to moderately infected wounds, while glycemic control varied from well-controlled HbA1c levels (<6–7%) to hyperglycemia or was not reported. Ulcer size was also variably described, reflecting considerable heterogeneity in baseline wound characteristics (Table 2).

Characteristics and Types of Interventions

All included studies evaluated Aloe vera as an adjunct to standard wound care rather than as monotherapy. Interventions were broadly categorized into Aloe-only formulations (gel or dressing) and combination therapies (e.g., Aloe with honey or Plantago major). Most studies used topical Aloe gel applied once daily, although some applied it twice daily or every two days. Application methods varied from simple topical use to post-debridement protocols. Co-interventions were consistently present, including saline irrigation, dressings, debridement, antibiotics, and off-loading. Treatment duration ranged from 8 days to 8 weeks. Control groups received standard care, saline dressings, or placebo. Overall, variability in formulations, protocols, and co-interventions reflects the complexity of isolating Aloe vera's specific effect.

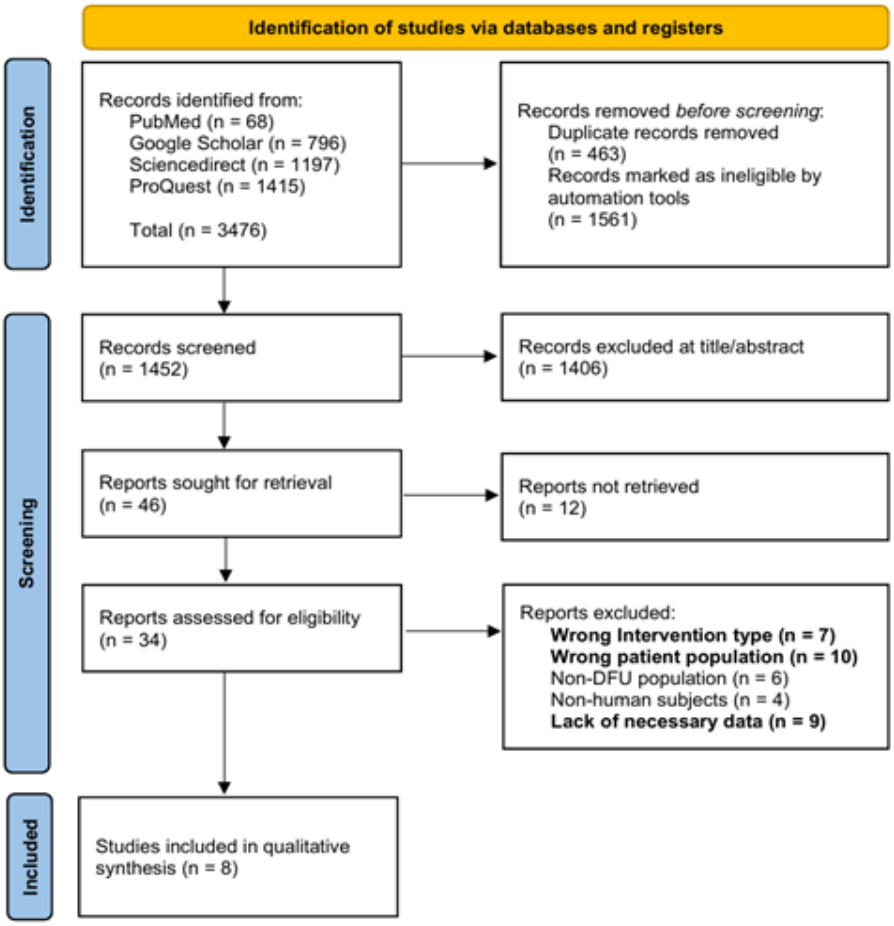

Figure 1. PRISMA flow diagram for identification of relevant studies.

Table 2. Baseline Characteristics of Included Studies

Study	Design	N	Age (years)	DFU Severity	Ulcer Size	Infection Status	Glycemic Status
Aqsa et al., 2019	RCT	60	46.3 vs 47.4	Wagner I–II	NR	Infected	HbA1c <6
Irani et al., 2023	Double-blind RCT	66	57.7 ± 11.6 vs 56.2 ± 9.5	Grade 1 (superficial)	<10 cm²	Non-infected	HbA1c <7
Muslim et al., 2025	RCT (3-arm pilot)	60	18–80	Wagner II–III	NR	NR	NR
Sandhiya et al., 2025	Parallel RCT	60	50.9 ± 9.3 vs 55.1 ± 13.6	Moderate–severe (debridement)	NR	Likely infected	CBG ~260 mg/dL
Daphne & Prince, 2019	Quasi-experimental	60	NR	Mild–moderate	NR	NR	NR
Malini et al., 2022	Quasi-experimental	17	53.3 vs 50.6	BWAT stage 2–4	NR	NR	NR
Bahar et al., 2015	Double-blind RCT	39	56.3 ± 10.2	Non-infected, non-ischemic	0.5–4 cm²	Non-infected	HbA1c measured
Najafian et al., 2019	Double-blind RCT	40	61.5 ± 8.0 vs 57.0 ± 8.4	Wagner 1–2 (neuropathic)	≤2 cm²	Moderate infection	HbA1c <10%

Notes. DFU = diabetic foot ulcer. Wagner = Wagner ulcer classification system. BWAT/BJWAT = Bates–Jensen Wound Assessment Tool. NR = not reported.

Table 3. Characteristics of Aloe vera Interventions

Study	Aloe Formulation	Intervention Type	Co-interventions	Application Protocol	Frequency	Duration	Comparator
Aqsa et al., 2019	Aloe dressing	Dressing	Standard wound care	Dressing applied topically with routine care	Daily	8 days	Saline dressing
Irani et al., 2023	Aloe gel	Topical gel	Saline wash + sterile dressing	Thin layer applied, followed by dressing and saline wash	Daily	3 weeks	Standard care
Muslim et al., 2025	Aloe gel	Topical gel	Standard wound care	Applied with dressing	Daily	21 days	Saline; Hepar sulph
Sandhiya et al., 2025	100% Aloe vera	Topical gel	Debridement + IV antibiotics + povidone iodine	Applied after debridement	Daily	28 days	Standard care
Daphne & Prince, 2019	Aloe gel	Topical gel	Routine care (unspecified)	Applied topically	Daily	10 days	Routine care
Malini et al., 2022	Aloe gel	Topical gel	Standard nursing care	Applied by nurse	Every 2 days	3 weeks	NaCl 0.9%
Bahar et al., 2015	Aloe (50%) + honey (25%)	Combination gel	Debridement + offloading + saline	Applied with dressing	2× daily	8 weeks	Placebo gel
Najafian et al., 2019	Aloe + Plantago major	Combination gel	Antibiotics + debridement + dressing	5-mm layer applied	2× daily	4 weeks	Placebo gel + standard care

Notes. All groups received background DFU management including debridement, saline irrigation, sterile dressings, infection control, and off-loading as indicated. Plantavera is a herbal gel containing 5% Aloe vera and 5% Plantago major. CMC = Carboxymethyl cellulose

Table 4. Wound-Healing Outcomes and Main Effects of Aloe vera

Study	Primary Outcome	Secondary Outcome	Key Result
Aqsa et al., 2019	–	Granulation tissue formation	100% vs 53.3% (p<0.001); strong early improvement with Aloe across subgroups.
Irani et al., 2023	Wound score (BWAT)	–	Both groups improved (17.1→32.8 vs 18.5→31.4); significant time effect but no overall group difference (p=0.352), suggesting comparable healing.
Muslim et al., 2025	Ulcer size reduction	Time to wound closure	Greater reduction with Aloe (2.5 ± 1.0 vs 1.2 ± 0.8 cm², p<0.01); also improved vs saline Faster closure with Aloe (28 ± 3.5 vs 35 ± 4.3 days, p<0.01).
Sandhiya et al., 2025	Wound score (BWAT)	Tissue characteristics (granulation, epithelialization)	Greater reduction in Aloe group (42→19 vs 43→25); ≥22-point improvement in 13 vs 1 patients (p=0.0029).
Daphne & Prince, 2019	Wound score (BWAT)	Adverse events	Significant reduction (35→21 vs control 33); MD=12, p<0.05, favoring Aloe.
Malini et al., 2022	Wound score (BJWAT)	Tissue characteristics (granulation, epithelialization)	Greater improvement in Aloe group (45.6→32.3 vs 42.9→39.7); p=0.001 vs 0.013. Greater improvement in tissue regeneration parameters in Aloe group.
Bahar et al., 2015	Ulcer size reduction	_	Higher healing proportion (95.5% vs 78.6%) but not statistically significant (p=0.11).
Najafian et al., 2019	Ulcer score + surface area	Adverse events	Significant reduction in total score (p<0.001) and surface (p=0.039), but not depth. No adverse effects reported.

Notes. BWAT = Bates–Jensen Wound Assessment Tool. BJWAT = Bates–Jensen Wound Assessment Tool (brief version). Wound area is reported as cm² unless otherwise stated. p-values refer to between-group comparisons.

Table 5. GRADE assessment of the certainty of evidence.

Outcome	Population (I/C)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty
Wound score (BWAT/BJWAT)	203 / 162	Serious	Serious	Serious	Serious	Undetected	⊗⊗◯◯ Low
Ulcer size reduction	99 / 79	Some concerns	Serious	Not serious	Serious	Undetected	⊗⊗◯◯ Low
Granulation / healing	100 / 78	Serious	Serious	Serious	Serious	Suspected	⊗◯◯◯ Very Low

Main Outcomes

Primary Outcome

For primary outcomes, most studies assessed objective wound healing using validated scoring systems (BWAT/BJWAT) and ulcer size reduction. Overall, Aloe vera was associated with greater improvements in wound scores in several studies, including Sandhiya et al. (42→19 vs 43→25; p=0.0029), Daphne & Prince (35→21 vs 33; p<0.05), and Malini et al. (45.6→32.3 vs 42.9→39.7; p=0.001 vs 0.013). Najafian et al. also reported significant reductions in total ulcer score and surface area (p<0.001; p=0.039). However, Irani et al. found comparable improvements between groups (p=0.352). For size-based outcomes, Muslim et al. demonstrated greater ulcer reduction with Aloe (2.5 vs 1.2 cm^2; p<0.01), while Bahar et al. reported higher healing rates (95.5% vs 78.6%) without statistical significance.

Secondary Outcome

For secondary outcomes, findings were more limited but generally supported a beneficial role of Aloe vera. Aqsa et al. reported markedly higher early granulation tissue formation (100% vs 53.3%; p<0.001). Muslim et al. also observed faster wound closure (28 vs 35 days; p<0.01). Improvements in tissue characteristics, including granulation and epithelialization, were noted in studies such as Malini et al. and Sandhiya et al., indicating enhanced tissue regeneration. In contrast, combination therapy studies showed less consistent effects, with partial improvements limited to specific domains. Importantly, no adverse effects were reported in studies that assessed safety, suggesting a favorable tolerability profile (Table 4).

Data Synthesis

Overall, Aloe vera–based interventions demonstrated a generally favorable effect on wound healing outcomes, although the magnitude and consistency of these effects varied across clinical contexts and outcome domains. For score-based outcomes (BWAT/BJWAT), most studies reported greater reductions in wound severity in the Aloe groups, accompanied by improvements in tissue characteristics such as granulation and epithelialization. However, this pattern was not universal, as at least one randomized controlled trial showed comparable improvements between intervention and control groups, indicating a substantial contribution from standard wound care.

For size-based outcomes and clinical endpoints, findings also tended to favor Aloe vera, particularly when compared with basic care such as saline dressings, with evidence of greater ulcer size reduction and shorter time to wound closure. Nevertheless, these benefits appeared less consistent in more complex clinical scenarios, including moderate-to-severe ulcers, infected wounds, or settings involving intensive co-interventions such as debridement and antibiotic therapy. This suggests that the observed effects are influenced not only by the intervention itself but also by underlying wound characteristics and concurrent treatments.

When further stratified by intervention type, Aloe-only formulations demonstrated relatively more consistent improvements in early wound healing parameters, including reductions in wound scores and ulcer size, as well as enhanced granulation and epithelialization in several studies. However, these effects were not uniformly observed across all trials, reinforcing the influence of clinical heterogeneity and standard care practices. In contrast, studies evaluating Aloe-containing combination therapies (e.g., Aloe with honey or Plantago major) showed more variable results, with some improvements observed but inconsistent statistical significance across outcomes. Importantly, due to the presence of additional bioactive components, these effects cannot be attributed specifically to Aloe vera alone, thereby limiting causal interpretation.

Risk of Bias Assessment

The methodological quality of the included studies showed considerable variation. Among the RCTs, most were judged to have either low risk of bias or some concerns, reflecting generally acceptable study conduct, although several domains such as deviations from intended interventions and outcome measurement were not consistently robust. A smaller proportion of trials were rated as high risk of bias, mainly due to issues related to lack of blinding, incomplete outcome data, or selective reporting. These limitations may have influenced the reliability of the observed treatment effects (Figure 2).

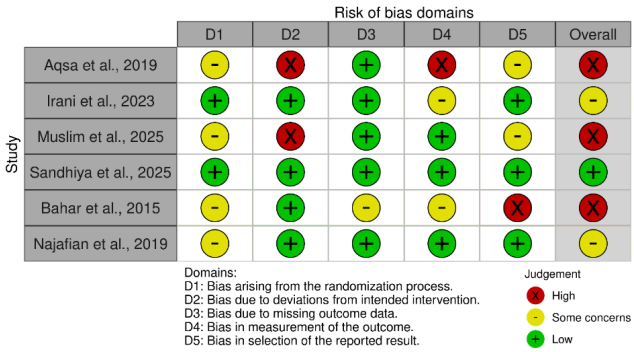

Figure 2. Traffic light plot of risk of bias using the RoB 2 tool across included studies.

In contrast, the non-randomized studies demonstrated more substantial methodological weaknesses. One study was assessed as having a critical risk of bias, primarily driven by serious confounding and deviations from intended interventions, while the other was judged to have a serious overall risk of bias. These findings indicate that results from non-randomized designs should be interpreted with greater caution, as they are more vulnerable to systematic errors (Figure 3).

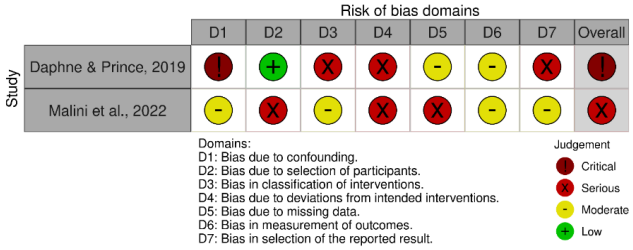

Figure 3. Traffic light plot of ROBINS-I tools risk-of-bias across included studies.

Certainty of Evidence

The certainty of evidence, assessed using the GRADE approach, was generally low across most outcomes (Table 5). Both wound score–based outcomes and ulcer size reduction

were downgraded due to concerns regarding risk of bias, inconsistency, and imprecision, despite a general trend favoring Aloe vera. In contrast, clinical endpoints such as granulation and healing rates were rated as very low certainty, mainly due to heterogeneous outcome definitions and inconsistent results. Overall, these findings suggest that while Aloe vera shows potential benefit, the current evidence remains limited and should be interpreted cautiously.

DISCUSSION

Overall, the available clinical evidence indicates that topical Aloe vera, when used as an adjunctive therapy, is associated with improvements in several wound healing parameters among patients with DFU, particularly when compared with basic care such as saline dressings or routine wound management. Most included studies, encompassing both RCTs and quasi-experimental designs, consistently reported improvements in wound assessment scores (BWAT/BJWAT), along with enhanced granulation, epithelialization, and reductions in wound size (Aqsa et al., 2019; Muslim et al., 2025; Daphne & Prince, 2019; Malini et al., 2022; Najafian et al., 2019). Some RCTs further demonstrated greater improvements in wound scores and faster healing progression in the Aloe vera groups compared with controls (Sandhiya et al., 2025), whereas others showed favorable trends without reaching statistical significance (Bahar et al., 2015). However, these findings were not entirely consistent, as highlighted by Irani et al. (2023), where both intervention and control groups improved without significant differences, particularly in superficial and non-ischemic ulcers.

The interpretation of these findings requires caution, as most reported outcomes represent surrogate indicators of wound quality rather than definitive clinical endpoints. The majority of studies had relatively short follow-up durations, typically ranging from 8 to 21 days (Aqsa et al., 2019; Irani et al., 2023; Muslim et al., 2025; Daphne & Prince, 2019; Malini et al., 2022), with only a few extending to 28 days or up to 8 weeks (Bahar et al., 2015; Sandhiya et al., 2025; Najafian et al., 2019). These timeframes predominantly capture the inflammatory and proliferative phases of wound healing rather than the remodeling phase, which requires longer durations for collagen maturation and restoration of tensile strength (El Ayadi et al., 2020). Consequently, the observed benefits likely reflect early healing responses, such as granulation and epithelialization, rather than sustained or complete wound closure (Mo et al., 2022). Although improvements in BWAT/BJWAT scores suggest enhanced wound bed characteristics, their clinical significance remains uncertain due to the absence of established minimal clinically important differences in DFU populations, limiting their direct translation into patient-centered outcomes.

The findings of this review are broadly consistent with previous literature. A systematic review by Hekmatpou et al. (2019) reported beneficial effects of Aloe vera across various wound types, although the overall quality of evidence was limited. Conversely, Dat et al. (2012) concluded that high-quality evidence remains insufficient to support definitive clinical effectiveness. In burn wound populations, meta-analyses by Huang et al. (2024) and Levin et al. (2022) demonstrated accelerated healing with Aloe vera, yet differences in pathophysiology limit direct extrapolation to DFU. Compared with acute burn injuries, DFU is a more complex condition influenced by chronic metabolic and vascular impairments, which likely contributes to the greater heterogeneity and less consistent outcomes observed in this review.

The variability in treatment response observed across studies can be explained by the complex interaction between systemic patient factors, local wound characteristics, and concurrent treatments (Guo & DiPietro, 2010). Poor glycemic control, for instance, is associated with increased oxidative stress, macrophage dysfunction, and prolonged inflammation, all of which impair progression to the proliferative phase (Xiang et al., 2018). Although Aloe vera possesses anti-inflammatory and antioxidant properties that may improve the local wound microenvironment, these effects are unlikely to fully compensate for underlying systemic impairments (Zeng et al., 2020). In addition, deeper or infected ulcers are characterized by increased inflammatory burden, elevated protease activity such as matrix metalloproteinases (MMPs), and impaired tissue perfusion, which may further limit the effectiveness of local therapies (Q. Wang et al., 2025).

This complexity is further compounded by variations in co-interventions across studies, including debridement, infection control, systemic antibiotics, and off-loading strategies. Several trials implemented these standard measures alongside Aloe vera, such as debridement with systemic antibiotics and antiseptic care (Sandhiya et al., 2025), off-loading and wound preparation (Bahar et al., 2015), and antibiotic therapy with routine dressing protocols (Najafian et al., 2019; Irani et al., 2023). These interventions independently influence wound healing outcomes, making it difficult to isolate the specific contribution of Aloe vera (Nahak et al., 2025). Therefore, the observed heterogeneity likely reflects the combined effects of local therapies, systemic conditions, and overall wound care strategies rather than the isolated efficacy of Aloe vera alone (Boulton et al., 2022).

Importantly, additional variability arises from differences in intervention composition across studies. Combination therapies (e.g., Aloe with honey or Plantago major) introduce multiple bioactive agents with overlapping antimicrobial, anti-inflammatory, and pro-healing properties, which may act synergistically, redundantly, or even competitively depending on formulation and clinical context (Bahar et al., 2015; Najafian et al., 2019). This complexity increases variability in treatment response and obscures the specific contribution of Aloe vera. In contrast, Aloe-only formulations provide a more direct and biologically coherent intervention, primarily targeting early wound healing processes such as inflammation modulation and fibroblast activation (Aqsa et al., 2019; Irani et al., 2023; Muslim et al., 2025; Daphne & Prince, 2019; Malini et al., 2022; Sandhiya et al., 2025). As a result, although their effects are generally modest, they appear more consistent across studies. These differences highlight that variability in outcomes is not solely due to patient or wound characteristics, but also reflects underlying differences in intervention complexity and mechanistic interactions.

From a biological perspective, the observed clinical effects are supported by mechanisms that directly target key disruptions in DFU wound healing. Normal wound repair involves coordinated phases of hemostasis, inflammation, proliferation, and remodeling (Matei et al., 2025), yet this process is often dysregulated in DFU due to prolonged inflammation and impaired progression to later stages (Bai et al., 2023). Bioactive components of Aloe vera, particularly polysaccharides such as glucomannan and acemannan, have been shown to stimulate fibroblast proliferation, enhance collagen synthesis, and regulate extracellular matrix turnover through modulation of MMP activity (Rahman et al., 2017).

Furthermore, upregulation of vascular endothelial growth factor (VEGF) promotes angiogenesis and cellular migration, both of which are essential for tissue repair during the proliferative phase (Irani et al., 2023).

In addition to these structural effects, Aloe vera exerts antioxidant, anti-inflammatory, and antimicrobial activities that contribute to improving the wound microenvironment. Compounds such as flavonoids, vitamins C and E, and phenolic substances help reduce oxidative stress and chronic inflammation, thereby facilitating the transition from the inflammatory to the proliferative phase (Abid et al., 2025; Massoud et al., 2023; Sánchez et al., 2020). Its antimicrobial properties may also reduce microbial burden in mildly contaminated wounds and limit early biofilm formation (Abid et al., 2025; Martin et al., 2025). These mechanisms collectively support the biological plausibility of Aloe vera in enhancing early wound healing processes, although their effectiveness remains contingent on adequate systemic conditions (Hekmatpou et al., 2019).

From a clinical perspective, Aloe vera should be positioned as an adjunctive rather than a primary therapy in DFU management. Nearly all included studies administered Aloe vera alongside standard care, suggesting that its observed benefits are likely additive rather than independent (Hofmann et al., 2023; Seneviratne et al., 2024). Its use appears most appropriate in mild to moderate, non-ischemic DFU, where tissue perfusion is relatively preserved (Shafaie et al., 2020; Wernick et al., 2025). In contrast, in ulcers complicated by severe ischemia or infection, its therapeutic contribution is likely limited due to the dominant influence of systemic and vascular factors (Mohammad Zadeh et al., 2019). Therefore, its role should be interpreted within the context of comprehensive DFU management rather than as a standalone therapeutic intervention.

Nevertheless, the overall certainty of evidence remains low to very low based on GRADE assessment. This is primarily driven by small sample sizes, heterogeneity in study design, and risks of bias related to inadequate randomization and blinding (Hróbjartsson et al., 2014; Gan, 2025). The inclusion of quasi-experimental studies further raises concerns regarding underpowering and the stability of effect estimates (Daphne & Prince, 2019; Malini et al., 2022). Substantial clinical heterogeneity in ulcer severity, infection status, and glycemic control introduces additional confounding. Moreover, most outcomes were based on wound scoring systems such as BWAT/BJWAT, which, although useful for assessing tissue characteristics, remain subjective and may not fully capture clinically meaningful endpoints such as complete wound closure or amputation risk (Bates-Jensen et al., 2019).

Finally, the possibility of publication bias should be considered. Most included studies were small in scale and conducted within limited geographic regions, with a tendency to report positive findings. The absence of formal assessments, such as funnel plot analysis, limits objective evaluation of this bias. In addition, small-study effects may contribute to overestimation of treatment effects. Therefore, the apparent consistency of favorable findings should be interpreted cautiously, considering the potential distortion introduced by publication bias.

CONCLUSIONS AND RECOMMENDATION

Based on the available evidence, topical Aloe vera may be considered as an adjunctive therapy in DFU management, particularly for improving early wound healing parameters such as granulation, epithelialization, and wound scores, with more consistent effects observed in mild to moderate, non-ischemic ulcers. However, the overall certainty of evidence is low, limited by small sample sizes, short follow-up, heterogeneity in study design and clinical characteristics, and reliance on surrogate outcomes, and therefore Aloe vera should not replace standard care. Therefore, further well-designed RCTs with standardized Aloe vera formulations, longer follow-up periods, and the inclusion of clinically meaningful outcomes such as complete wound closure, amputation rates, recurrence, and long-term safety, with systematic reporting of adverse events are required to establish its definitive clinical role.

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DECLARATION

Ethics approval and consent to participate

Not applicable. This study is a systematic review of published literature and did not involve direct participation of human subjects or animals.

Consent for publication

Not applicable. No individual person's data, images, or identifiable information are included in this article.

Availability of data and materials

All data analyzed in this study are derived from publicly available published articles and are included in this manuscript and its referenced sources.

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Artificial intelligence–assisted tools were used for language refinement and formatting support, but not for data extraction, analysis, interpretation, or scientific decision-making.

Authors' contributions

Syafiq Maulana conceived the study design, developed the methodology, conducted the literature search, performed data curation, formal analysis, investigation, software preparation, visualization, and managed project administration.

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Syafiq Maulana completed his Bachelor of Medicine (S.Ked) at Universitas Islam Negeri Maulana Malik Ibrahim Malang and is currently undertaking the medical professional program at the same institution. His research interests include molecular medicine, tropical medicine, and clinical biomarkers for the diagnosis of a wide range of diseases.

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