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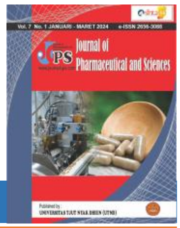

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Efficacy of *Mitragyna speciosa* (Kratom) Extract for Diabetic Ulcer Healing: A Literature Review

Efikasi Ekstrak *Mitragyna speciosa* (Kratom) terhadap Penyembuhan Ulkus Diabetik: Tinjauan Literatur

Edlin Edlin [a], Gusbakti Rusip [b*], Maya Sari Mutia [c], Yolanda Eliza Putri Lubis [d]

[a] *Doctoral Program, Faculty of Medicine, Universitas Prima Indonesia, Medan, Indonesia*
[b] *Department of Family Medicine, Faculty of Medicine, Universitas Prima Indonesia, Medan, Indonesia.*
[c] *Department of Histology, Faculty of Medicine, Universitas Prima Indonesia, Medan, Indonesia*
[d] *Department of Pharmacology, Faculty of Medicine, Universitas Prima Indonesia, Medan, Indonesia.*

**Corresponding author: gusbakti@unprimdn.ac.id*

Abstract

Diabetic ulcers, particularly diabetic foot ulcers (DFUs), are chronic complications of diabetes mellitus characterized by persistent inflammation, oxidative stress, impaired angiogenesis, increased infection risk, and delayed tissue remodeling. Botanically derived adjuncts have gained attention because their mixed phytochemical profiles may act on several wound-healing pathways simultaneously. *Mitragyna speciosa* (kratom) is an alkaloid-rich *Rubiaceae* plant with reported anti-inflammatory, antioxidant, antimicrobial, and pro-regenerative activities. This review aimed to evaluate the current evidence on the potential role of *Mitragyna speciosa* extract in diabetic ulcer healing, distinguish kratom-specific evidence from broader botanical context, and identify key knowledge gaps that must be addressed before clinical translation. Methods: A PRISMA-style systematic review was conducted using an internet search engine, which returned 521 records. Records were screened against predefined population, intervention, comparator, outcome, study-design, and attribution criteria. Eight sources met the eligibility criteria and were synthesized qualitatively. Results: No clinical trial, observational study, or in vivo diabetic-wound study directly compared kratom extract with standard wound care. Kratom-specific evidence was limited to in vitro and formulation studies. The available in vitro synthesis reported suppression of tumor necrosis factor-alpha, interleukin-6, cyclooxygenase-2, 5-lipoxygenase, nitric oxide, and reactive oxygen species, as well as stimulation of cell migration and angiogenesis. A topical spray film-forming kratom formulation has been developed, but efficacy data are not yet available. Broader systematic reviews indicate that botanical adjuncts may improve DFU healing outcomes, but these reviews did not include kratom. Current evidence supports biological plausibility but does not establish comparative effectiveness. Standardized kratom formulations require in vivo validation, dose-response assessment, safety evaluation, and adequately powered randomized clinical trials before any clinical recommendation can be made.

Keywords: ***Mitragyna speciosa; kratom; diabetic ulcer; wound healing; systematic literature review.***

Abstrak

Ulkus diabetik, khususnya ulkus kaki diabetik, merupakan komplikasi kronis diabetes melitus yang ditandai oleh inflamasi persisten, stres oksidatif, gangguan angiogenesis, peningkatan risiko infeksi, dan keterlambatan remodelling jaringan. Terapi adjuvan yang berasal dari bahan botani semakin mendapat perhatian karena profil fitokimianya yang kompleks dapat bekerja pada beberapa jalur penyembuhan luka secara bersamaan. *Mitragyna speciosa* (kratom) merupakan tanaman famili Rubiaceae yang kaya alkaloid dan dilaporkan memiliki aktivitas antiinflamasi, antioksidan, antimikroba, dan pro-regeneratif. Tinjauan literatur ini mengevaluasi bukti yang tersedia mengenai efektivitas ekstrak *M. speciosa* dibandingkan dengan perawatan luka standar dalam meningkatkan penyembuhan ulkus diabetik.Tinjauan sistematis bergaya PRISMA dilakukan melalui pencarian di internet, yang menghasilkan 521 rekam literatur. Rekam literatur disaring berdasarkan kriteria populasi, intervensi, pembanding, luaran, desain studi, dan atribusi yang telah ditetapkan sebelumnya. Delapan sumber memenuhi kriteria kelayakan dan disintesis secara kualitatif.Tidak ditemukan uji klinis, studi observasional, atau studi *in vivo* pada luka diabetik yang secara langsung membandingkan ekstrak kratom dengan perawatan luka standar. Bukti spesifik tentang kratom masih terbatas pada studi *in vitro* dan studi formulasi. Sintesis bukti *in vitro* yang tersedia melaporkan penekanan tumor necrosis factor-alpha, interleukin-6, cyclooxygenase-2, 5-lipoxygenase, nitric oxide, dan reactive oxygen species, disertai stimulasi migrasi sel dan angiogenesis. Formulasi kratom topikal berbentuk spray film-forming telah dikembangkan, tetapi data efikasinya belum tersedia. Tinjauan sistematis yang lebih luas menunjukkan bahwa adjuvan botani dapat meningkatkan luaran penyembuhan ulkus kaki diabetik, tetapi tinjauan tersebut tidak mencakup kratom. Bukti saat ini mendukung plausibilitas biologis, tetapi belum menetapkan efektivitas yang membandingkan. Formulasi kratom yang terstandar memerlukan validasi *in vivo*, penilaian hubungan dosis-respons, evaluasi keamanan, serta uji klinis acak dengan kekuatan sampel yang memadai sebelum rekomendasi klinis dapat diberikan.

Kata Kunci: ***Mitragyna speciosa; kratom; ulkus diabetik; penyembuhan luka; tinjauan literatur sistematis.***

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Introduction

Diabetic foot ulcers remain among the most serious complications of diabetes mellitus because they are associated with infection, hospitalization, amputation, recurrence, and mortality. A recent clinical review estimated that approximately 18.6 million people worldwide develop a diabetic foot ulcer each year [1]. Even after apparent wound closure, recurrence remains a major clinical challenge because neuropathy, abnormal plantar pressure, vascular compromise, and the need for continuous preventive care often persist [2]. The broader burden of chronic wounds further strengthens the need for improved therapies, as human wounds are associated with pain, disability, infection risk, healthcare expenditure, and loss of productivity [11].

The pathogenesis of diabetic foot ulcers is multifactorial and involves neuropathy, peripheral arterial disease, immune dysfunction, abnormal inflammatory signaling, infection, and impaired tissue repair. These mechanisms explain why diabetic foot ulcers cannot be managed adequately as purely local skin lesions. [4] At the cellular level, hyperglycemia and oxidative stress disrupt fibroblast function, keratinocyte migration, angiogenesis, extracellular matrix deposition, and immune cell activity, thereby prolonging inflammation and weakening the transition to the proliferative phase. [5] Normal wound repair proceeds through overlapping phases of hemostasis, inflammation, proliferation, and remodeling; when these cellular programs become dysregulated, the wound may persist as a chronic inflammatory lesion rather than progressing to closure. [6]

Current diabetic foot ulcer management is multidimensional and includes wound cleansing, debridement when indicated, infection control, vascular assessment, revascularisation when required, pressure off-loading, moisture balance, glycaemic optimization, and management of comorbidities. The IWGDF guideline emphasizes that interventions intended to enhance healing should be evaluated as additions to high-quality standard care. [8] Off-loading is particularly important for neuropathic plantar ulcers because persistent mechanical stress delays healing and promotes recurrence; therefore, adjunctive topical products should be assessed in studies in which off-loading is protocolized and applied consistently across groups. [9] Effective translation of wound-healing discoveries also requires alignment between biological mechanisms, reproducible experimental models, clinically meaningful endpoints, and safe delivery systems, especially for botanical products with complex and variable compositions. [7].

Medicinal plants have been explored as adjuncts to conventional diabetic wound care because they may provide anti-inflammatory, antimicrobial, antioxidant, or pro-regenerative effects. A systematic review of clinical studies reported that several medicinal-plant preparations improved wound-related outcomes in patients with diabetic foot ulcers. [3] Similarly, systematic reviews of topical herbal products suggest that botanical adjuncts may reduce wound area and support granulation when used alongside standard care. However, product heterogeneity limits direct comparison between individual plants. [12,13] Evidence from other plant candidates, such as *Momordica charantia*, also illustrates why species-specific evaluation is necessary, because wound-healing mechanisms observed in one plant cannot be transferred automatically to *Mitragyna speciosa* due to differences in phytochemistry, active constituents, and safety profile. [14]

Mitragyna speciosa (Korth.) Havil., commonly known as kratom, is an alkaloid-rich Rubiaceae plant that has attracted pharmaceutical interest due to its leaves containing numerous indole and oxindole alkaloids, particularly mitragynine and 7-hydroxymitragynine. [15,16] However, kratom pharmacology includes opioid-receptor-related activity, analgesic effects, stimulant-like effects at some doses, and clinically relevant safety concerns; therefore, wound-related development should not assume safety based only on traditional use. [17,18] Recent studies have examined *M. speciosa* ethanolic extract in relation to extraction efficiency, anti-inflammatory activity, cytotoxicity, and transdermal delivery. In contrast, kratom alkaloid extracts have shown dual COX-2 and 5-LOX inhibitory activity in LPS-stimulated RAW 264.7 macrophages. [19,20] Fermented kratom preparations have also shown antibacterial, antibiofilm, antioxidant, and anti-inflammatory activities, and kratom leaves and mitragynine have demonstrated alpha-glucosidase and pancreatic lipase inhibition, supporting broader diabetes-related interest. [21,22] Despite these mechanistic signals, kratom-specific evidence for diabetic ulcer healing remains limited and must be separated from general botanical evidence. This review, therefore, aimed to evaluate the effectiveness of *M. speciosa* extract compared with standard wound care for diabetic ulcer healing, distinguish direct from indirect evidence, and identify the translational steps required before clinical testing.

This study was conducted as a systematic literature review and organized according to a PRISMA-style structure covering identification, screening, eligibility assessment, and inclusion. PRISMA guidance was used to support transparent reporting of how records were identified, screened, and included. [23]. The review question was structured using population-intervention-comparator-outcome logic. The population comprised patients with diabetic ulcers or experimental and biological models relevant to diabetic ulcer healing. The intervention was *M. speciosa* extract, kratom-derived compounds, or kratom-containing formulations intended for wound treatment. The comparator was standard wound care, vehicle, placebo, or an equivalent control. Outcomes included wound closure, time to healing, wound-area reduction, epithelialization, granulation, vascularisation, infection-related outcomes, inflammatory and oxidative biomarkers, safety, and tolerability.

Method

Search Strategy and Databases

A structured literature search was conducted using two electronic databases, Google Scholar and Scopus, on 6 March 2026. The search aimed to identify studies evaluating *Mitragyna speciosa* (kratom) extract, kratom-derived compounds, or kratom-containing formulations in relation to diabetic ulcer healing, wound healing, inflammation, oxidative stress, antimicrobial activity, or wound-related formulation development. The search terms included: ("*Mitragyna speciosa*" OR "kratom" OR "kratom extract" OR "mitragynine" OR "7-hydroxymitragynine") AND ("diabetic ulcer" OR "diabetic foot ulcer" OR "diabetic wound" OR "chronic wound" OR "wound healing" OR "wound closure" OR "re-epithelialisation" OR "granulation" OR "angiogenesis") AND ("anti-inflammatory" OR "antioxidant" OR "antimicrobial" OR "topical formulation" OR "standard wound care"). In Scopus, searches were performed using title, abstract, and keyword fields where applicable. In Google Scholar, keyword combinations were searched manually because database-specific field tags are limited. Elicit was used as a supplementary AI-assisted tool to help organize retrieved records and identify potentially relevant literature. Still, the authors made final eligibility decisions based on predefined inclusion and exclusion criteria.

Table 1. Search strategy and keywords.

Concept	Representative keywords/terms
Intervention	"*Mitragyna speciosa*", "kratom", "kratom extract", "mitragynine", "7-hydroxymitragynine", "alkaloid extract"
Condition/population	"diabetic ulcer", "diabetic foot ulcer", "diabetic wound", "chronic wound", "diabetes mellitus"
Outcome	"wound healing", "wound closure", "re-epithelialization", "granulation", "angiogenesis", "wound-area reduction"
Comparator/context	"standard wound care", "topical herbal therapy", "medicinal plants", "anti-inflammatory", "adjunctive therapy"

Inclusion and Exclusion Criteria

Records were screened based on titles, abstracts, and or available full texts against predefined eligibility criteria. Screening considered population, intervention, outcomes, study design, and whether kratom-specific effects could be attributed independently from co-interventions. The criteria are presented in Table 2.

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Table 2. Inclusion and exclusion criteria.

Domain	Inclusion	Exclusion
Population	Diabetes mellitus with diabetic foot or other diabetic skin ulcers, or models directly relevant to diabetic wound healing	Non-diabetic populations or conditions unrelated to wound healing
Intervention	Topical or systemic *M. speciosa* / kratom extract, kratom-derived compounds, or kratom-containing wound formulations	Interventions not involving kratom, or kratom combined inseparably with other experimental treatments.
Outcomes	Wound-healing outcomes, including closure rate, time to healing, wound-area reduction, epithelialization, granulation, vascularisation, validated healing scales, relevant biomarkers, or safety	Studies without wound-healing outcomes, toxicity, or pharmacokinetics, only without wound relevance
Study design	Randomized controlled trials, controlled trials, systematic reviews, meta-analyses, well-designed observational studies, or mechanistically relevant experimental studies	Case reports, small case series, editorials, commentaries, or conference abstracts without full data
Attribution	The kratom effect can be isolated and attributed	Kratom effect not separable from co-interventions

Study Selection Process

The study-selection process was reported using a PRISMA-style flow diagram to improve transparency in the identification, screening, eligibility assessment, and inclusion of records. A total of 521 records were identified from Google Scholar and Scopus. The number of records retrieved from each database is presented separately in Figure 1. After title and abstract screening, 492 records were excluded because they did not meet the predefined population, intervention, outcome, study-design, or attribution criteria. The remaining 29 records were assessed for eligibility through full-text review or detailed bibliographic assessment. Of these, 21 records were excluded because they did not provide kratom-specific evidence, did not report diabetic ulcer or wound-healing outcomes, did not allow independent attribution of the intervention effect, or lacked sufficient methodological and outcome data. Finally, eight sources were included in the qualitative synthesis. Additionally, the attribution criterion required that the effect of *M. speciosa* could be independently assessed. Studies were included when kratom was evaluated as a single intervention, directly compared with a control condition, or reported with outcomes that could be clearly separated from co-interventions. Studies combining kratom with other active ingredients were excluded when the specific contribution of *M. speciosa* could not be determined. Titles, abstracts, and available full texts were screened according to the predefined eligibility criteria. Disagreements during screening were resolved through discussion and consensus among the authors.

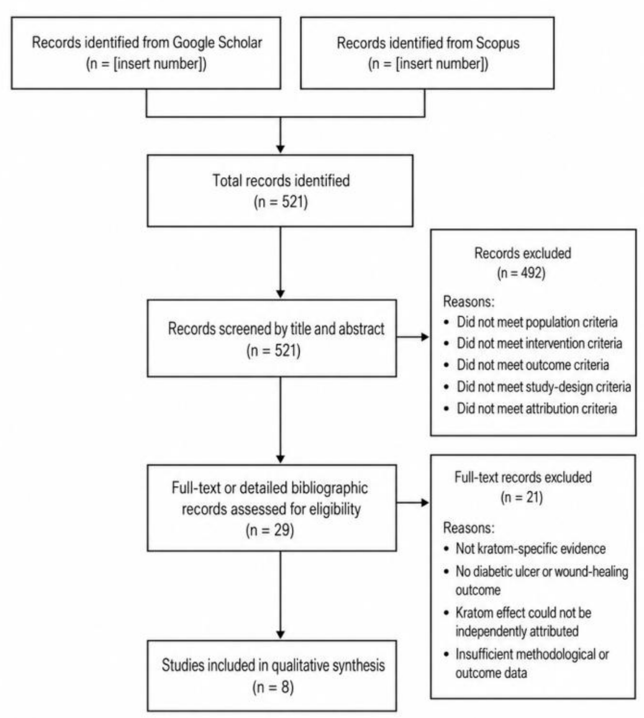

Figure 1. PRISMA flow diagram of study identification, screening, and inclusion.

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Data Extraction

Data were extracted using a structured framework. The extracted domains were study design and setting; participant or model characteristics; ulcer or wound characteristics, where applicable; kratom intervention details; comparator or standard-care details; wound-healing outcomes; mechanistic biomarkers; safety and tolerability; and methodological limitations. Unreported information was recorded as not reported rather than inferred.

Quality Assessment and Evidence Appraisal

Because the included sources were few and highly heterogeneous, a formal quantitative risk-of-bias assessment was not applied. The included evidence consisted of in vitro mechanistic studies, formulation research, pharmacological reviews, and contextual systematic reviews of botanical therapies; no clinical trial or in vivo diabetic wound study directly evaluating *M. speciosa* was identified. Therefore, the quality of the evidence was assessed using a narrative critical appraisal approach. Each source was evaluated based on study design, directness to the review question, availability of full text, intervention standardization, relevance of wound-healing outcomes, and methodological limitations. This approach allowed cautious interpretation of the available evidence while avoiding inappropriate pooling of heterogeneous study types.

The absence of a formal risk-of-bias assessment using tools such as ToxRTool for in vitro studies or AMSTAR-2 for systematic reviews should be considered a methodological limitation. Future updated reviews with a larger and more homogeneous evidence base should apply study-design-specific quality assessment tools.

Data Synthesis

A meta-analysis was not appropriate because the included sources differed in design, interventions, models, comparators, and outcomes. Findings were synthesized qualitatively and organized into two evidence categories: kratom-specific evidence, including in vitro mechanistic and formulation studies, and contextual evidence from systematic reviews of botanical adjuncts for DFUs. Direct evidence and indirect mechanistic evidence were interpreted separately throughout the synthesis. The most directly relevant kratom source was a systematic review of in vitro studies evaluating anti-inflammatory and wound-healing properties of *M. speciosa* in living cells. It was central to the synthesis because it reported kratom-specific mechanistic outcomes rather than general botanical effects. [25].

Preclinical Evidence for Kratom in Wound Healing

Kratom-specific evidence remained preclinical. The in vitro systematic review reported that *M. speciosa* extract suppressed nitric oxide, reactive oxygen species, TNF-alpha, IL-6, COX-2, and 5-LOX, while also stimulating cell migration, endothelial migration, and angiogenesis. [25] The same in vitro evidence indicated that crude extracts and alkaloid extracts may differ in cytotoxicity. Crude extracts appeared safer than alkaloid-rich extracts at higher concentrations, supporting the need for dose-finding and therapeutic window studies before animal or clinical use. [25] The available formulation study developed a topical spray film-forming system containing *M. speciosa* for diabetic wound application. However, the available report did not provide wound-closure outcomes, animal-model data, or clinical comparisons with standard care. [10] The kratom pharmacology review supported the ethnobotanical and phytochemical relevance of the plant, including traditional wound-related and diabetes-related uses. It did not provide quantitative diabetic ulcer outcomes or clinical evidence of wound healing. [15] Moreover, the primary kratom-specific evidence was derived from Hanafi et al. [25], which synthesized in vitro findings on the anti-inflammatory and wound-healing-related activities of *M. speciosa*. This source is relevant because it reported suppression of inflammatory mediators and oxidative stress markers, including TNF-alpha, IL-6, COX-2, 5-LOX, nitric oxide, and reactive oxygen species, as well as stimulation of cell migration, endothelial migration, and angiogenesis [25]. However, its evidence remains limited to cell-based models. It does not provide direct evidence from animal models of diabetic wounds or from clinical studies in patients with diabetic foot ulcers. Therefore, the findings should be interpreted as mechanistic support for biological plausibility rather than proof of therapeutic efficacy.

Novitasari et al. [10] reported the development of a topical spray film-forming system containing *M. speciosa* for potential diabetic wound application. This study is important from a pharmaceutical formulation perspective because it suggests that kratom extract can be incorporated into a topical delivery system [10]. However, it should be interpreted as a formulation feasibility study, not as evidence of efficacy. The study did

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not report wound closure, wound-area reduction, re-epithelialization, granulation, angiogenesis, animal-model outcomes, or clinical comparisons with standard wound care. Therefore, further pharmacological, safety, and efficacy studies are required before this formulation can be considered for clinical translation.

Contextual Evidence from Herbal Therapies for Diabetic Foot Ulcers

Evidence from other botanical therapies was included only to provide background context for plant-based adjunctive approaches in diabetic foot ulcer care. Systematic reviews have reported that several medicinal-plant preparations may improve wound-related outcomes, including wound-area reduction, epithelialization, granulation, and inflammatory markers, when used as adjuncts to standard care [3,12,13]. However, these reviews did not evaluate *M. speciosa* or kratom-derived formulations. Therefore, findings from non-kratom botanical products should not be interpreted as evidence of kratom efficacy. They only indicate that botanical adjuncts may be a relevant research area in diabetic wound care. Because *M. speciosa* has a distinct phytochemical profile, particularly its alkaloid-rich composition, evidence from other medicinal plants cannot be directly extrapolated to kratom-based diabetic ulcer treatment.

Diabetic Ulcer Characteristics and Safety

Detailed ulcer characteristics were largely unavailable in the kratom-specific sources. No included kratom source reported ulcer size, ulcer depth, duration, Wagner or University of Texas classification, infection status, peripheral arterial disease status, HbA1c, neuropathy severity, off-loading adherence, or prior treatment history in a diabetic ulcer population. Clinical safety data for kratom in diabetic ulcer treatment were not identified. Available in vitro evidence supports only a preliminary interpretation of cytotoxicity. It cannot define local tolerability, systemic absorption, safety with repeated application, or the risk of adverse events in patients with DFUs. [25] Broader kratom pharmacology literature raises safety and regulatory issues that remain relevant to topical development. These concerns do not prove that a topical wound formulation is unsafe, but they require that future studies include systematic safety monitoring. [17] Moreover, three themes emerged from the qualitative synthesis. First, kratom has mechanistic plausibility for wound healing because available in vitro studies show suppression of inflammatory and oxidative mediators and stimulation of migration and angiogenesis. [25] Second, the broader herbal therapy literature suggests that certain botanical adjuncts may improve DFU healing outcomes when added to standard care. This evidence is a supportive context, but it should not be interpreted as kratom-specific efficacy. [3] Third, there is a major translational gap between kratom's in vitro activity and clinical application. No identified study has tested kratom in a validated diabetic-wound animal model or in patients with DFUs. A detailed summary of the eight included sources is presented in Table 3. Full texts were available for four sources, while four sources were assessed using abstracts or bibliographic records because full texts were not accessible at the time of review. This represents a limitation because detailed methodology, intervention characteristics, and outcome reporting could not be fully evaluated for abstract-only sources. Therefore, findings from these sources were interpreted cautiously.

Table 3. Summary of main findings.

Theme	Key finding	Most relevant source
Anti-inflammatory mechanism	In vitro suppression of TNF-alpha, IL-6, COX-2, 5-LOX, nitric oxide, and reactive oxygen species.	Hanafi et al., 2025 [25]
Pro-regenerative mechanism	In vitro stimulation of cell migration, endothelial migration, and angiogenesis.	Hanafi et al., 2025 [25]
Formulation	A spray film-forming kratom system has been developed for diabetic wound application, but efficacy data are lacking.	Novitasari et al., 2025 [10]
Phytochemistry	Kratom leaves contain numerous alkaloids, especially mitragynine and 7-hydroxymitragynine.	Begum et al., 2025 [15]
Clinical herbal context	Medicinal-plant adjuncts have shown improvements in some DFU clinical outcomes, but kratom was not evaluated.	Ahmadian et al., 2021 [3]
Topical herbal context	Topical herbal therapy may reduce the DFU wound area and support granulation.	Djuma et al., 2024 [13]
Safety	Kratom-specific clinical safety data for diabetic ulcer treatment are unavailable.	Hanafi et al., 2025 [25]

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Interpretation of Major Findings

This review aimed to determine whether M. speciosa extract is more effective than standard wound care at promoting diabetic ulcer healing. The central finding is clear: no clinical trial, observational study, or in vivo diabetic-wound study has directly evaluated this comparison. The strongest kratom-specific signal is mechanistic rather than clinical. In vitro evidence shows anti-inflammatory and pro-regenerative effects that are biologically relevant to diabetic wound repair, but this level of evidence cannot establish comparative effectiveness in patients. [25] The formulation evidence indicates that kratom can be incorporated into a topical spray film-forming system. This is a useful step in pharmaceutical development, but formulation feasibility should not be interpreted as evidence of therapeutic efficacy. [10] The kratom pharmacology literature supports the relevance of mitragynine, 7-hydroxymitragynine, and other alkaloids as candidate bioactive constituents. However, the active compounds responsible for wound-related effects, as well as their dose-response relationships, remain insufficiently defined. [15] Absence of direct evidence should not be confused with evidence of ineffectiveness. The appropriate interpretation is that kratom remains a mechanistically plausible candidate that requires rigorous preclinical validation before clinical claims can be made. The interpretation of this review, therefore, prioritizes kratom-specific evidence. Broader botanical evidence was used only as contextual support and was not considered direct evidence for the effectiveness of *M. speciosa*. This distinction is important because each medicinal plant has different phytochemical constituents, pharmacological activities, safety concerns, and formulation challenges.

Phytochemical Complexity and Extract Standardization

Standardization is a major requirement for the development of *M. speciosa*-based wound formulations. Kratom leaves contain a complex phytochemical profile, particularly indole and oxindole alkaloids such as mitragynine and 7-hydroxymitragynine, together with other constituents that may influence biological activity and safety [15,16]. This complexity creates challenges for reproducibility because phytochemical composition may vary according to plant origin, growth conditions, harvest time, post-harvest handling, extraction solvent, extraction method, and formulation process.

This issue is important because crude extracts and alkaloid-rich fractions may not have the same biological activity or cytotoxicity profile. The available in vitro evidence suggests that crude extracts and alkaloid-rich extracts may differ in safety at higher concentrations [25]. Therefore, future studies should not only report biological activity but also provide detailed phytochemical and quality-control data.

Recommended standardization parameters include botanical authentication, voucher specimen deposition, extraction solvent, extraction yield, mitragynine and 7-hydroxymitragynine content, HPLC or LC-MS fingerprinting, batch-to-batch consistency, microbial quality testing, heavy metal testing, and stability evaluation of the final formulation. Without these parameters, comparison between studies will remain difficult, and translation into reproducible preclinical or clinical research will be limited.

Dose-Response Relationship and Therapeutic Window

The difference between crude extracts and alkaloid-rich extracts is important for determining the therapeutic window of *M. speciosa*-based wound formulations. The available in vitro evidence suggests that crude extracts and alkaloid-rich extracts may differ in cytotoxicity at higher concentrations [25]. This finding indicates that wound-healing-related activity should not be interpreted solely from a single effective concentration, but should be evaluated across a range of concentrations to balance biological activity and cellular safety.

A therapeutic window refers to the dose or concentration range within which the formulation produces desirable wound-healing effects while minimizing cytotoxicity. For *M. speciosa*, this window remains undefined. Crude extracts may contain multiple constituents that act synergistically, whereas alkaloid-rich fractions may contain higher concentrations of pharmacologically active compounds, which could increase cytotoxic or opioid-related safety concerns. Therefore, both preparations should be compared systematically.

Future dose-finding studies should evaluate crude extracts, alkaloid-rich fractions, and standardized formulations across multiple concentrations. These studies should assess anti-inflammatory activity, reduction in oxidative stress, fibroblast migration, keratinocyte migration, endothelial cell migration, angiogenesis, and cytotoxicity. After in vitro screening, selected doses should be validated in diabetic wound animal models using wound-area reduction, re-epithelialization, granulation tissue formation, angiogenesis, inflammatory biomarkers, oxidative stress markers, local tolerability, and systemic safety as key outcomes.

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Comparison with Previous Literature

The present findings are consistent with the broader clinical literature showing that medicinal plants may act as adjuncts in DFU care. However, those benefits were observed for other plant preparations, not for M. speciosa. [3] The topical-herbal review literature also supports the general concept that local botanical preparations may contribute to wound-area reduction and granulation. This context strengthens the rationale for studying kratom but does not provide direct evidence for kratom efficacy. [13] Compared with other wound-healing candidates, kratom remains at an earlier stage of evidence development. For example, Periplaneta americana preparations have advanced to a protocolized meta-analysis framework for chronic skin ulcers. [24] The contrast with *Momordica charantia* is also instructive, as that plant has a more extensive wound-healing review literature. Kratom now requires a similarly structured program of preclinical and clinical evaluation before it can be positioned as a diabetic wound adjunct. [14].

Mechanistic

A plausible mechanism can be proposed from the current kratom-specific evidence. Suppression of TNF-alpha, IL-6, COX-2, 5-LOX, nitric oxide, and reactive oxygen species could theoretically help reduce persistent inflammatory signaling in diabetic wounds. [25] The pro-regenerative component is equally important. Stimulation of fibroblast and endothelial cell migration, together with angiogenesis, aligns with the proliferative requirements of re-epithelialization, granulation tissue formation, and neovascularization. [25] Nevertheless, this mechanistic model remains hypothetical until validated in diabetic wound models and clinical studies. In vitro cell systems cannot reproduce wound perfusion, neuropathy, polymicrobial burden, systemic glycaemic control, off-loading, or repeated topical exposure in patients.

Additionally, Available in vitro evidence suggests that M. speciosa extract may suppress inflammatory mediators and oxidative stress markers, and promote cellular processes related to wound repair, including cell migration and angiogenesis. However, these findings should be interpreted only as evidence of biological plausibility at the cellular level. They do not establish therapeutic efficacy in diabetic ulcers, which are complex chronic wounds influenced by hyperglycemia, neuropathy, vascular impairment, infection risk, impaired angiogenesis, and delayed tissue remodeling. Therefore, the current evidence does not support clinical claims regarding the effectiveness of *M. speciosa* extract for diabetic ulcer healing. The translational gap between in vitro activity and clinical benefit remains substantial. Further validation in standardized diabetic wound animal models and well-designed clinical trials is required before any recommendation for clinical use can be made.

Research Gaps and Future Directions.

The most important gap is the absence of direct in vivo and clinical evidence. No included study tested kratom in a validated diabetic-wound animal model or compared a kratom formulation against standard care in patients with DFUs. A second gap is standardization. Future studies should define the plant source, authentication method, extraction solvent, extraction yield, marker compound content, microbial quality, formulation characteristics, and batch reproducibility before efficacy testing. A third gap is safety. Topical kratom development requires evidence on local irritation, sensitization, cytotoxicity, systemic absorption through compromised skin, repeated-dose exposure, and potential interactions with standard DFU therapies.

Table 4. Research gaps and future directions.

Research gap	Future direction
No in vivo evidence in diabetic-wound models	Conduct studies in validated diabetic-wound animal models before clinical testing.
No clinical trials in DFU patients	Design adequately powered randomized trials comparing standardized kratom formulations with placebo as adjuncts to protocolized standard care.
Lack of standardized extract and formulation	Standardize extraction, phytochemical characterization, marker compounds, microbial quality, and dosage form.
Uncharacterized dose-response and therapeutic window	Perform dose-finding studies comparing crude extracts and alkaloid-rich extracts.
Absent long-term and systemic safety data	Evaluate repeated topical exposure, local tolerability, systemic absorption, and adverse events.
Undefined kratom-specific healing endpoints	Use wound-area reduction, time to closure, re-epithelialization, granulation, vascularisation, infection outcomes, inflammatory biomarkers, and oxidative-stress markers.

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Regulatory, Safety, and Translational Considerations

Topical application of *M. speciosa* formulations to diabetic ulcers requires specific safety consideration. Diabetic ulcers are characterized by impaired skin integrity, persistent inflammation, increased risk of infection, and delayed tissue repair. These conditions may increase local penetration and possible systemic absorption of kratom alkaloids through damaged tissue. Therefore, the safety of topical kratom cannot be assumed from traditional use or from in vitro findings alone. Kratom contains pharmacologically active alkaloids, particularly mitragynine and 7-hydroxymitragynine, which have been associated with opioid-receptor-related activity and broader safety concerns [17,18]. Although topical delivery may reduce systemic exposure compared with oral administration, systemic absorption through compromised diabetic wounds has not been evaluated. This is important because repeated application may increase cumulative exposure, especially in large, chronic, infected, or poorly vascularised ulcers.

Potential interactions with medications commonly used in diabetic patients also remain unknown. These may include antidiabetic drugs, antihypertensive agents, anticoagulants, antibiotics, analgesics, and other wound-care treatments. At present, no study has evaluated whether topical kratom formulations influence glycaemic control, bleeding risk, infection control, local tissue irritation, hepatic or renal function, or opioid-related adverse effects. Therefore, the risk-benefit profile of kratom for diabetic ulcer healing remains undefined. Future studies should include local irritation and sensitization testing, repeated-dose topical safety evaluation, systemic absorption and pharmacokinetic assessment, liver and kidney function monitoring, blood glucose monitoring, respiratory and neurological observation, and systematic adverse event reporting. These safety data are required before kratom-based formulations can be considered for clinical testing in patients with diabetic ulcers.

Implications for Future Research

The immediate next step should be preclinical rather than clinical. Standardized kratom extracts should be evaluated in validated diabetic-wound animal models using vehicle controls and, where appropriate, active comparators. Outcomes should include wound-area reduction, time to closure, histological re-epithelialization, granulation-tissue quality, angiogenesis, bacterial burden, inflammatory biomarkers, oxidative-stress markers, and safety. Dose-finding studies should compare crude extracts and alkaloid-rich extracts, as these preparations may differ in both biological activity and cytotoxicity. The goal should be to identify a reproducible therapeutic window rather than to demonstrate activity at a single concentration. If preclinical efficacy and safety are demonstrated, the next step should be an adequately powered, blinded, randomized controlled trial in patients with DFUs. Such a trial should use a standardized kratom formulation as an adjunct to protocolized standard care, with concealed allocation, blinded outcome assessment, predefined ulcer-grade criteria, consistent off-loading, infection management, vascular assessment, and adverse-event monitoring.

Recommendations for Stakeholders

For clinicians, current evidence does not support the use of *M. speciosa* extract as a clinical treatment for diabetic ulcers. Standard diabetic wound care, including debridement, infection control, off-loading, vascular assessment, glycaemic control, and appropriate wound dressing, should remain the main therapeutic approach. For researchers, future studies should prioritize standardized kratom extracts or formulations, phytochemical characterization, dose-response evaluation, cytotoxicity testing, diabetic wound animal models, local and systemic safety assessment, and well-designed clinical trials. For regulatory agencies, kratom-based wound products require careful evaluation because *M. speciosa* contains pharmacologically active alkaloids and has potential safety concerns. Product quality, extract standardization, safety monitoring, and clinical evidence should be required before approval for therapeutic claims. For patients, kratom products should not be used as a substitute for standard diabetic ulcer care. Patients should consult healthcare professionals before using any kratom-based or herbal wound product, especially because clinical efficacy and safety in diabetic ulcers have not been established.

Conclusions and Future Directions

This systematic literature review indicates that the current evidence on *Mitragyna speciosa* extract for diabetic ulcer healing remains preliminary and insufficient to support a clinical recommendation. No clinical trial or observational study has directly compared kratom extract with standard wound care in patients with

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diabetic ulcers. The available evidence mainly consists of mechanistic, formulation, and early preclinical findings suggesting that kratom may have anti-inflammatory, antioxidant, antimicrobial, and pro-regenerative potential relevant to wound healing. However, biological plausibility does not establish therapeutic efficacy, especially because diabetic ulcers are complex chronic wounds influenced by hyperglycemia, neuropathy, vascular impairment, infection risk, impaired angiogenesis, and delayed tissue remodeling. Future studies should prioritize standardization of kratom extracts and formulations, phytochemical characterization, dose-response evaluation, local and systemic safety assessment, and validation in well-designed diabetic-wound animal models. If preclinical efficacy and safety are confirmed, adequately powered randomized clinical trials should be conducted to compare standardized kratom-based formulations with placebo or vehicle as adjuncts to protocolized standard wound care, using clinically meaningful endpoints such as wound-area reduction, time to closure, re-epithelialization, granulation, angiogenesis, infection control, inflammatory biomarkers, oxidative-stress markers, tolerability, and adverse events.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article. The authors also declare that there are no personal, financial, institutional, or other relationships that could be perceived as inappropriately influencing the representation, interpretation, or reporting of the findings presented in this review.

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