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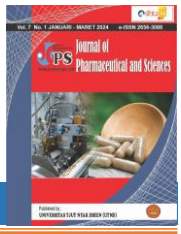

Etlingera elatior Fruit Extract and Diabetic Ulcer Healing: A Literature Review of Indirect Evidence and Research Gaps

Ekstrak Buah *Etlingera elatior* dan Penyembuhan Ulkus Diabetik: Tinjauan Literatur terhadap Bukti Tidak Langsung dan Kesenjangan Penelitian

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Abstract

Diabetic ulcers are major complications of diabetes mellitus and remain a significant clinical challenge due to impaired wound healing, persistent inflammation, oxidative stress, and increased susceptibility to infection. Natural products with antioxidant, anti-inflammatory, and antimicrobial properties have been increasingly investigated as complementary therapies for diabetic wound management. *Etlingera elatior* (torch ginger) is a tropical medicinal plant containing bioactive compounds with promising pharmacological activities. However, its potential role in diabetic ulcer treatment has not been systematically evaluated. This study aimed to assess available evidence regarding the potential effects of *E. elatior* fruit extract on diabetic ulcers in animal models through a literature review with a systematic search approach. Literature searches were conducted in Google Scholar and Scopus databases, followed by screening using predefined inclusion criteria related to animal studies, diabetic ulcer models, and E. elatior fruit extract intervention. The selection process followed the PRISMA framework. No study directly tested E. elatior fruit extract on diabetic ulcers in animal models. However, indirect evidence showed strong biological plausibility. Ethanol extract of E. elatior fruit demonstrated anti-hyperglycemic effects in diabetic rodents, with 400 mg/kgBW identified as the most effective dose for reducing plasma glucose and protecting pancreatic β-cells. Other studies reported significant reduction of hsCRP ($p < 0.05$), improvement in renal function, and antioxidant and antimicrobial activities. Major compounds included quercetin, vanillic acid, p-coumaric acid, and other phenolic and flavonoid compounds. These findings suggest potential therapeutic relevance, although direct in vivo diabetic wound studies are still required.

***Keywords*: Etlingera elatior; diabetic ulcer; wound healing; antioxidant activity; literature review; indirect evidence.**

Abstrak

Ulkus diabetik merupakan komplikasi utama diabetes melitus dan masih menjadi tantangan klinis yang signifikan karena terganggunya penyembuhan luka, inflamasi persisten, stres oksidatif, serta meningkatnya kerentanan terhadap infeksi. Produk alam yang memiliki sifat antioksidan, antiinflamasi, dan antimikroba semakin banyak diteliti sebagai terapi komplementer dalam penatalaksanaan luka diabetik. *Etlingera elatior* (kecombrang) merupakan tanaman obat tropis yang mengandung senyawa bioaktif dengan aktivitas farmakologis yang menjanjikan. Namun, potensi perannya dalam pengobatan ulkus diabetik belum dievaluasi secara sistematis. Penelitian ini bertujuan untuk menilai bukti yang tersedia mengenai potensi efek ekstrak buah *E. elatior* terhadap ulkus diabetik pada model hewan melalui tinjauan literatur sistematis. Pencarian literatur dilakukan pada basis data Google Scholar dan Scopus, kemudian dilanjutkan dengan penyaringan menggunakan kriteria inklusi yang telah ditetapkan, meliputi studi hewan, model ulkus diabetik, dan intervensi ekstrak buah *E. elatior*. Proses seleksi mengikuti kerangka PRISMA. Tidak ditemukan studi yang secara langsung menguji ekstrak buah *E. elatior* terhadap ulkus diabetik pada model hewan. Namun, bukti tidak langsung menunjukkan dasar biologis yang kuat. Ekstrak etanol buah *E. elatior* menunjukkan efek antihiperglikemik pada rodensia diabetik, dengan dosis 400 mg/kgBB diidentifikasi sebagai dosis paling efektif dalam menurunkan glukosa plasma dan melindungi sel β pankreas. Studi lain melaporkan penurunan bermakna kadar hsCRP ($p < 0,05$), perbaikan fungsi ginjal, serta aktivitas antioksidan dan antimikroba. Senyawa utama yang teridentifikasi meliputi kuersetin, asam vanilat, asam p-kumarat, serta senyawa fenolik dan flavonoid lainnya. Temuan ini menunjukkan potensi relevansi terapeutik, meskipun studi *in vivo* langsung pada model luka diabetik masih diperlukan.

***Kata Kunci*: Etlingera elatior; ulkus diabetik; penyembuhan luka; aktivitas antioksidan; tinjauan sistematis.**

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Introduction

Diabetic ulcers represent one of the most serious and disabling complications of diabetes mellitus and are a major cause of morbidity, hospitalization, reduced quality of life, and lower-limb amputation worldwide [1,2]. These ulcers commonly develop as a consequence of chronic hyperglycemia, peripheral neuropathy, peripheral arterial disease, immune dysfunction, and repeated minor trauma that is often unnoticed by patients. Once an ulcer develops, healing is frequently slow and incomplete because diabetes interferes with several biological processes required for normal tissue repair. In clinical practice, diabetic ulcers are difficult to manage because they are often accompanied by infection, tissue necrosis, poor vascular supply, and recurrent inflammation. Even with wound care, glycemic control, antibiotics, debridement, and pressure off-loading, many patients experience delayed healing or recurrence. Therefore, diabetic ulcers are not only a local wound problem but also a systemic manifestation of metabolic and vascular dysfunction.

Normal wound healing consists of overlapping phases, including hemostasis, inflammation, proliferation, and remodeling [6]. In diabetic conditions, these phases are disrupted by persistent hyperglycemia and chronic metabolic imbalance. Hyperglycemia impairs leukocyte function, reduces fibroblast activity, alters keratinocyte migration, and decreases collagen deposition. It also compromises angiogenesis, thereby limiting the formation of new blood vessels needed to deliver oxygen and nutrients to the wound area [3–5]. Prolonged inflammation is another important feature of diabetic wounds. Instead of progressing from the inflammatory phase to the proliferative phase, diabetic ulcers often remain trapped in a chronic inflammatory state. This leads to delayed granulation tissue formation, poor epithelialization, impaired extracellular matrix remodeling, and increased risk of secondary infection. These changes explain why diabetic wounds become chronic and treatment outcomes remain unsatisfactory, particularly in advanced cases [7].

The pathophysiology of diabetic ulcers involves a complex interaction between metabolic stress, vascular impairment, immune dysregulation, microbial colonization, and oxidative damage. Persistent hyperglycemia promotes the formation of advanced glycation end products and stimulates excessive production of reactive oxygen species (ROS), which damage lipids, proteins, nucleic acids, endothelial cells, and extracellular matrix components [8]. Oxidative stress also weakens cellular defense mechanisms and aggravates vascular dysfunction, thereby limiting tissue oxygenation. At the same time, diabetic ulcers are associated with increased inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein [9]. These mediators sustain inflammation, impair fibroblast proliferation, reduce collagen synthesis, and disturb the balance between matrix formation and degradation. In addition, insufficient angiogenesis and reduced growth factor activity limit neovascularization, oxygen supply, and nutrient delivery at the wound site [10]. Because diabetic ulcer healing is affected by multiple biological pathways, an ideal therapeutic agent should be able to simultaneously reduce oxidative stress, regulate inflammation, suppress microbial growth, improve metabolic status, and support tissue regeneration [11].

Natural products derived from medicinal plants have attracted increasing attention as potential complementary therapies for diabetic wound management [12]. This interest is based on the fact that many plants contain diverse secondary metabolites with multiple pharmacological actions. Unlike single-target synthetic drugs, plant extracts often contain complex mixtures of bioactive compounds that may act through several mechanisms at the same time. Flavonoids, phenolic acids, tannins, saponins, terpenoids, and alkaloids

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are among the major phytochemical groups associated with antioxidant, anti-inflammatory, antimicrobial, and wound-healing activities [13]. These properties are relevant for diabetic ulcers, where oxidative stress, persistent inflammation, infection susceptibility, and impaired tissue repair occur together. Antioxidant compounds may protect cells from ROS-induced damage, anti-inflammatory compounds may reduce excessive cytokine production, antimicrobial compounds may decrease wound contamination, and pro-healing compounds may support fibroblast activity, collagen deposition, epithelialization, and angiogenesis [14].

Etlingera elatior, commonly known as torch ginger, is a tropical medicinal plant widely distributed in Southeast Asia, including Indonesia. The plant is recognized for its culinary uses, especially in traditional foods, but various parts of *E. elatior* have also been used in traditional medicine. Its flowers, leaves, stems, rhizomes, and fruits have been reported to contain bioactive constituents that may contribute to health-related effects. Among these plant parts, the fruit has gained attention because it contains phenolic and flavonoid compounds with antioxidant and anti-inflammatory potential [15]. Pharmacological studies have reported that *E. elatior* fruit extract exhibits antioxidant, antimicrobial, and anti-inflammatory activities, which are mechanisms directly relevant to diabetic wound healing. The antioxidant activity may help counteract ROS accumulation in diabetic wounds, while anti-inflammatory effects may reduce prolonged inflammatory responses. In addition, antimicrobial activity may be useful because diabetic ulcers are highly susceptible to bacterial contamination and infection.

Experimental studies have also suggested that *E. elatior* fruit extract has antidiabetic potential. In diabetic animal models, the extract has been reported to reduce blood glucose levels, improve metabolic parameters, and protect pancreatic β-cells. These effects are important because poor glycemic control is one of the major factors that delays wound healing and increases ulcer recurrence. By improving glucose regulation, *E. elatior* fruit extract may indirectly support a more favorable wound-healing environment. Furthermore, the presence of compounds such as quercetin, vanillic acid, p-coumaric acid, and other phenolic constituents supports the biological plausibility of its use in diabetic complications. Quercetin and related phenolic compounds are recognized for their ability to scavenge free radicals, modulate inflammatory pathways, and protect tissues from oxidative injury. Such activities suggest multi-target benefits relevant to diabetic ulcer healing.

Despite these promising pharmacological properties, direct evidence regarding the effect of *E. elatior* fruit extract on diabetic ulcer healing remains limited. Existing studies have mainly focused on its antidiabetic, antioxidant, antimicrobial, anti-inflammatory, or organ-protective effects, rather than its direct application in diabetic wound models. Some studies have evaluated wound healing using other parts of *E. elatior* or related plant extracts, while others have examined diabetic complications without assessing wound closure, histopathology, angiogenesis, collagen deposition, or epithelialization. Therefore, a clear evidence gap remains. At present, it is still uncertain whether the biological activities observed in antidiabetic or anti-inflammatory studies can be translated into meaningful improvement in diabetic ulcer healing.

Based on this background, a literature review is needed to assess the available evidence and clarify the current state of knowledge regarding *E. elatior* fruit extract in relation to diabetic ulcers. Such a review is important to summarize existing findings and guide future experimental work. Therefore, this literature review with a systematic search approach aims to evaluate the available direct and indirect evidence regarding *E. elatior* fruit extract in relation to diabetic ulcer healing. This review also aims to identify research gaps related to extract preparation, dosage, route of administration, diabetic wound model selection, wound-healing outcomes, inflammatory markers, oxidative stress parameters, antimicrobial effects, histopathological changes, angiogenesis, and collagen formation.

Methods

Study Design

This study was conducted as a literature review with a systematic search approach. The PRISMA framework was used to guide the identification, screening, eligibility assessment, and reporting of the study selection process. However, this review was not prospectively registered in PROSPERO or the Open Science Framework, and a formal risk of bias assessment was not conducted. Therefore, the findings were interpreted as indirect evidence and research gap identification rather than as evidence of established therapeutic efficacy. [16]. The review was designed to identify, evaluate, and synthesize available experimental evidence regarding

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the potential therapeutic effects of *Etlingera elatior* fruit extract on diabetic ulcers in animal models. Because preliminary searching indicated that direct studies on E. elatior fruit extract in diabetic ulcer models were limited or unavailable, this review also considered indirect experimental evidence that was biologically relevant to diabetic wound healing. Such evidence included studies evaluating the antidiabetic, antioxidant, anti-inflammatory, antimicrobial, or wound-healing activities of E. elatior preparations, particularly when the reported mechanisms were related to the pathophysiology of diabetic ulcers. The review was therefore structured to clarify both the presence of direct evidence and the extent of supportive indirect evidence. However, this review was not prospectively registered in PROSPERO or the Open Science Framework. Therefore, the absence of protocol registration was acknowledged as a methodological limitation.

Literature Search Strategy

A literature search was conducted using two electronic databases, namely Google Scholar and Scopus. The search was performed to identify studies investigating *Etlingera elatior* fruit extract, diabetic ulcers, diabetic wounds, wound healing, and related experimental animal models. The search was limited to articles published between 2010 and 2025. Only articles written in English or Indonesian were considered eligible. The search strategy combined keywords related to the plant species, intervention, disease condition, biological activity, and experimental model. The main keywords included "*Etlingera elatior*", "torch ginger", "fruit extract", "diabetic ulcer", "diabetic wound", "wound healing", "animal model", "in vivo", "diabetes", "anti-inflammatory", "antioxidant", and "antimicrobial". Boolean operators such as "AND" and "OR" were used to improve the sensitivity and specificity of the search.

The following search string was used for Scopus: TITLE-ABS-KEY ("*Etlingera elatior*" OR "torch ginger") AND TITLE-ABS-KEY ("fruit extract" OR "ethanol extract") AND TITLE-ABS-KEY ("diabetic ulcer" OR "diabetic wound" OR "wound healing" OR "diabetes" OR "anti-inflammatory" OR "antioxidant" OR "antimicrobial") AND TITLE-ABS-KEY ("animal model" OR "in vivo" OR "experimental study").

For Google Scholar, the search was performed using simplified keyword combinations because of database-specific search limitations. The main Google Scholar search terms included: "*Etlingera elatior* fruit extract diabetic ulcer", "*Etlingera elatior* fruit extract wound healing", "*Etlingera elatior* fruit extract diabetes animal model", "torch ginger fruit extract antioxidant anti-inflammatory antimicrobial", and "*Etlingera elatior* diabetic animal model".

The search identified 359 records in total, consisting of 237 records from Google Scholar and 122 records from Scopus. A total of 87 duplicate records were removed, leaving 272 unique records for title and abstract screening. Manual citation tracking was not performed in the present review. Therefore, the absence of manual reference searching and the use of only two databases were acknowledged as methodological limitations.

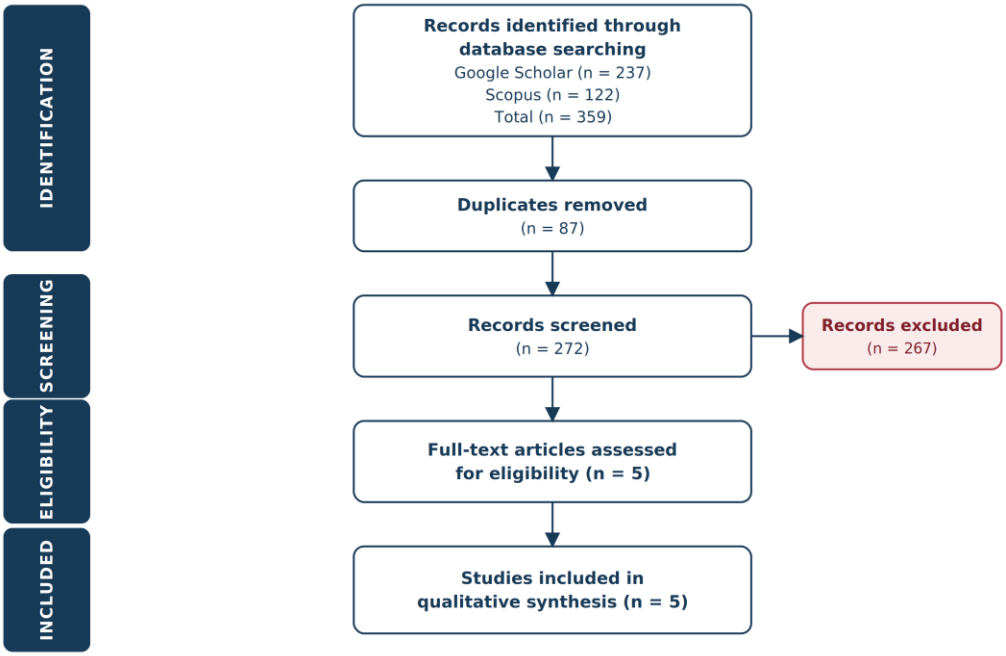

Figure 1. Prisma diagram

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Study Selection and Eligibility Criteria

The study selection process followed the PRISMA framework for identification, screening, eligibility assessment, and inclusion. To improve methodological clarity, the eligibility criteria were divided into two categories: direct evidence criteria and indirect evidence criteria. Moreover, the eligibility criteria were developed based on the PICO framework. The population included animal models of diabetes or diabetic ulcers. The intervention was *Etlingera elatior* fruit extract. The comparison included placebo, untreated control, vehicle control, or standard therapy. The outcomes included wound closure rate, wound area reduction, re-epithelialization, collagen deposition, angiogenesis, histopathological changes, inflammatory biomarkers, oxidative stress markers, and microbial-related outcomes.

Direct evidence was defined as experimental animal studies that fulfilled all of the following criteria: (1) used *Etlingera elatior* fruit extract as the intervention; (2) used diabetic animal models; (3) included diabetic ulcer or diabetic wound induction; and (4) reported wound-healing outcomes, such as wound closure rate, wound area reduction, healing time, re-epithelialization, granulation tissue formation, collagen deposition, angiogenesis, histopathological changes, inflammatory biomarkers, oxidative stress markers, or microbial-related outcomes.

Indirect evidence was defined as studies that did not fulfill all direct evidence criteria but were still biologically relevant to diabetic ulcer healing. These included: (1) studies evaluating *E. elatior* fruit extract in diabetic animal models without wound-healing outcomes; (2) studies evaluating *E. elatior* preparations in wound-healing models without diabetes; (3) studies evaluating antioxidant, anti-inflammatory, antimicrobial, antihyperglycemic, or tissue-protective activities of *E. elatior* preparations; and (4) diabetic wound-healing studies using other plant extracts, which were included only as methodological comparisons.

Studies were excluded if they were review articles, editorials, opinion papers, conference abstracts without sufficient data, purely in vitro studies without animal relevance, studies involving unrelated plant species without diabetic wound relevance, or studies that did not provide sufficient methodological or outcome information.

No study fulfilled all direct evidence criteria. Therefore, the final qualitative synthesis focused on indirect evidence and research gaps. Studies included as indirect evidence were not interpreted as proof of therapeutic efficacy of *E. elatior* fruit extract in diabetic ulcers, but rather as supportive evidence for biological plausibility and as a basis for identifying future research needs.

Table 1. Direct and Indirect Eligibility Criteria Used in the Review

Evidence Category	Eligibility Criteria	Interpretation in This Review
Direct evidence	Animal study using *Etlingera elatior* fruit extract; diabetic animal model; diabetic ulcer or diabetic wound induction; wound-healing outcomes reported.	Considered direct evidence for the effect of *E. elatior* fruit extract on diabetic ulcer healing. No included study fulfilled all these criteria.
Indirect evidence 1	*E. elatior* fruit extract used in diabetic animal models, but without ulcer or wound-healing outcomes.	Considered supportive evidence for antidiabetic, anti-inflammatory, antioxidant, or tissue-protective mechanisms.
Indirect evidence 2	*E. elatior* preparation used in wound-healing models, but not fruit extract and not diabetic animals.	Considered partial evidence for wound-healing potential of the plant species, but not direct evidence for fruit extract in diabetic ulcers.
Indirect evidence 3	Diabetic wound-healing studies using other plant extracts.	Used only as methodological comparison for future diabetic wound study design.
Excluded studies	Reviews, editorials, opinion papers, conference abstracts without sufficient data, unrelated plant studies, purely in vitro studies without animal relevance, or studies with insufficient methodological information.	Not included in the qualitative synthesis.

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Data Extraction

Data extraction was performed using a structured framework to ensure consistency and comparability across the included studies [18]. The extracted information covered several key domains. First, study characteristics were recorded, including author name, year of publication, study design, experimental model, number of groups, sample size, and duration of treatment. Second, animal model characteristics were collected, including animal species, strain, sex, age or body weight, method of diabetes induction, and method of ulcer induction or wound creation where available. For studies without diabetic ulcer models, the disease model or experimental condition was recorded to determine its relevance to the research question.

Third, details of the intervention were extracted, including the plant part used, extraction solvent, extraction method, extract concentration or standardization, dose, route of administration, treatment frequency, treatment duration, and vehicle or formulation used. Particular attention was given to studies using E. elatior fruit extract because this was the main intervention of interest. Fourth, outcome measures related to diabetic ulcer healing or its biological mechanisms were collected. These included wound closure, wound area reduction, healing time, histopathological findings, inflammatory markers such as hsCRP or cytokines, oxidative stress parameters, antimicrobial activity, angiogenesis-related markers, collagen formation, renal or metabolic parameters, and blood glucose levels.

Finally, mechanistic findings were extracted to evaluate the biological plausibility of E. elatior fruit extract for diabetic ulcer treatment. These included evidence of antihyperglycemic activity, pancreatic β-cell protection, antioxidant capacity, anti-inflammatory activity, antimicrobial activity, tissue protection, and possible involvement of phenolic or flavonoid compounds. Identified bioactive compounds, such as quercetin, vanillic acid, p-coumaric acid, and related phenolic constituents, were also recorded when available.

Data Synthesis

Due to heterogeneity in study designs, interventions, plant parts, disease models, treatment protocols, and outcome measurements, meta-analysis was not performed. Instead, the findings were synthesized qualitatively [19]. The included studies were grouped according to their relevance to the main research question. Direct evidence was defined as studies evaluating E. elatior fruit extract in diabetic ulcer animal models. Indirect evidence was defined as studies evaluating E. elatior fruit extract in diabetic animal models without ulcer outcomes, studies assessing E. elatior preparations in wound-healing models without diabetes, or studies reporting mechanisms relevant to diabetic wound repair.

The synthesis focused on determining whether the available evidence supports the potential therapeutic relevance of E. elatior fruit extract for diabetic ulcer healing. The main domains considered were glycemic control, inflammation, oxidative stress, antimicrobial activity, tissue protection, and wound-healing mechanisms. The results were summarized narratively to identify current evidence gaps and to guide future experimental studies using validated diabetic wound animal models.

Characteristics of Included Studies

The systematic search identified five studies with potential relevance to the therapeutic role of *Etlingera elatior* fruit extract in diabetic ulcer management. However, none of the included studies directly evaluated E. elatior fruit extract as an intervention for diabetic ulcers in animal models. Therefore, the available evidence should be interpreted as indirect or supportive evidence rather than direct experimental proof. The included studies were related to the review question through different aspects of diabetic ulcer pathophysiology, including glycemic control, inflammation, oxidative stress, antimicrobial activity, wound healing, and tissue repair.

The studies could be grouped into three categories based on their relevance to the research question. First, two studies investigated E. elatior fruit ethanol extract in diabetic animal models, but the outcomes were not diabetic ulcer or wound healing. These studies provided evidence on antidiabetic activity, pancreatic β-cell protection, reduction of systemic inflammation, and improvement of diabetic complications [20,21]. Second, one study evaluated E. elatior extract in a wound-healing model, but the extract was obtained from the stem or umbut rather than the fruit, and the model was not diabetic [22]. Third, two studies examined diabetic wound healing or diabetic complications using other plant extracts, namely Merremia mammosa and Manilkara zapota, rather than E. elatior [23,24]. These studies were included as indirect comparisons because they demonstrated relevant wound-healing mechanisms in diabetic animal models, such as improved tissue repair, angiogenesis, and metabolic protection.

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Imran et al. [20] investigated the radical scavenging and antidiabetic potential of E. elatior fruit ethanol extract. Although this study did not use a diabetic ulcer model, it is relevant because hyperglycemia is one of the major factors responsible for delayed wound healing in diabetes. The study reported that E. elatior fruit extract reduced plasma glucose levels, with 400 mg/kgBW identified as the most effective dose. In addition, the extract showed pancreatic β-cell protective effects, indicating that it may improve glucose regulation and reduce metabolic stress. These findings are important because adequate glycemic control is essential for successful diabetic wound healing. However, because wound closure, histopathology, angiogenesis, collagen formation, and inflammatory markers at the wound site were not evaluated, this study cannot provide direct evidence for diabetic ulcer healing.

Another study by Nurfadilah et al. [21] evaluated the effect of E. elatior fruit ethanol extract in a diabetic nephropathy model induced by streptozotocin–nicotinamide. The study reported improvement in diabetic-related parameters, including reduction of blood glucose, creatinine, albuminuria, and inflammatory marker hsCRP. This study is relevant because diabetic ulcers are strongly influenced by systemic inflammation, oxidative stress, and diabetic complications. The reduction of hsCRP suggests an anti-inflammatory effect, while improvement in renal function indicates possible tissue-protective activity. Nevertheless, the model focused on diabetic nephropathy rather than diabetic ulcers. Therefore, the findings support the biological plausibility of E. elatior fruit extract in diabetic complications but do not directly confirm its wound-healing efficacy.

Efendi et al. [22] investigated the wound-healing activity of torch ginger umbut extract in adult male mice. This study is partially relevant because it evaluated E. elatior in a wound-healing model. The extract reportedly accelerated wound repair, with optimal healing observed at a 10% concentration. However, the study used the umbut or stem part of the plant rather than the fruit, and the animals were not diabetic. This distinction is important because diabetic wounds have different biological characteristics compared with normal acute wounds. Diabetic wounds involve persistent inflammation, impaired angiogenesis, oxidative stress, delayed collagen deposition, and increased infection risk. Therefore, although the study supports the wound-healing potential of E. elatior, its findings cannot be directly extrapolated to E. elatior fruit extract in diabetic ulcer models.

Marchianti et al. [23] examined a gel formulation of Merremia mammosa in diabetic Wistar rats. Although this study did not use E. elatior, it was relevant because it used a diabetic wound model and assessed wound-healing outcomes in animals. The study provides useful methodological comparison for future research, particularly in relation to gel formulation, diabetic wound induction, and wound-healing assessment. However, because the intervention was a different plant extract, it cannot be considered direct evidence for E. elatior fruit extract.

Table 2. Structured Synthesis of the Included Studies

Study	Animal Model	Extract Type and Solvent	Dose and Route of Administration	Treatment Duration	Measured Parameters	Main Findings	Main Limitations
Imran et al. [20]	Experimental diabetic animals; species not clearly specified in the available report	*Etlingera elatior* fruit ethanol extract	200, 300, and 400 mg/kgBW; route not clearly described in the available report	Not clearly described in the available report	Plasma glucose level, radical scavenging activity, pancreatic histology, isolated bioactive compounds	The extract reduced plasma glucose levels, with 400 mg/kgBW reported as the most effective dose. Quercetin showed the strongest radical scavenging activity among the isolated compounds.	No diabetic ulcer model; no wound-healing endpoints; animal species and route of administration were not clearly described; limited information on extract standardization, randomization, blinding, and sample size calculation.

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Widyarini et al. [21]	Streptozotocin–nicotinamide-induced diabetic nephropathy model in white rats (*Rattus norvegicus*)	*Etlingera elatior* fruit ethanol extract using 96% ethanol	Dose and route were reported in the original study, but the review focused on diabetic nephropathy outcomes rather than wound-healing intervention	Treatment was conducted during pre-diabetic and diabetic periods	Blood glucose, creatinine, albuminuria, hsCRP, antioxidant activity, kidney histology	The extract reduced blood glucose, hsCRP, creatinine, and albuminuria, and improved kidney histological changes.	The model was diabetic nephropathy, not diabetic ulcer; no wound induction; no wound closure, angiogenesis, collagen deposition, or re-epithelialization outcomes.
Efendi et al. [22]	Non-diabetic adult male mice	Torch ginger umbut or stem extract	10% extract concentration; topical application to wound area	Healing was observed within 7–8 days	Wound-healing activity in mice	The 10% extract showed wound-healing activity in non-diabetic mice.	Used umbut or stem extract, not fruit extract; model was non-diabetic; limited quantitative wound-healing outcomes; findings cannot be directly extrapolated to diabetic ulcers.
Marchianti et al. [23]	Diabetic Wistar rats with wound model	*Merremia mammosa* gel formulation	Topical gel formulation	Not directly related to *E. elatior* intervention	Wound healing, VEGF expression, hydroxyproline level	The gel formulation accelerated diabetic wound healing and increased VEGF expression and hydroxyproline levels.	Used a different plant species, not *E. elatior*; included only as methodological comparison for diabetic wound study design.
Karle et al. [24]	Alloxan and STZ-NA-induced diabetic Wistar rats	*Manilkara zapota* fruit peel extract and fractions	Oral administration of extract/fractions	Not directly related to *E. elatior* intervention	Antidiabetic activity and diabetic complications	The extract improved diabetes-related parameters and complications.	Used a different plant species, not *E. elatior*; did not evaluate diabetic ulcer healing using *E. elatior* fruit extract.

Overall, no included study fulfilled all three core elements of the research question: (1) use of E. elatior fruit extract, (2) use of a diabetic animal model, and (3) evaluation of ulcer or wound healing as the primary outcome. The studies by Imran et al. [20] and Widyarini et al. [21] fulfilled the first and second elements because they investigated E. elatior fruit extract in diabetic models, but they did not assess wound-healing outcomes. The study by Efendi et al. [22] fulfilled the wound-healing and E. elatior elements, but it used stem extract rather than fruit extract and did not involve diabetic animals. Meanwhile, the studies by Marchianti et al. [23] provided useful comparative information on diabetic wound healing and antidiabetic plant-based therapy, but they used different plant species.

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These findings indicate that the current evidence base is fragmented. The pharmacological profile of E. elatior fruit extract suggests potential relevance to diabetic ulcer healing through antihyperglycemic, antioxidant, anti-inflammatory, and antimicrobial mechanisms. However, this potential remains unconfirmed because no study has directly tested E. elatior fruit extract in a validated diabetic wound model. Future studies should therefore combine E. elatior fruit extract with diabetic animal models and standardized wound-healing endpoints, such as wound closure percentage, healing time, re-epithelialization, collagen deposition, VEGF expression, inflammatory cytokines, oxidative stress markers, and histopathological evaluation.

Critical Appraisal of Included Studies

A critical appraisal of the included studies showed that the available evidence remains methodologically limited and highly indirect. None of the included studies fulfilled all core elements of the review question, namely the use of *Etlingera elatior* fruit extract, a validated diabetic ulcer animal model, and wound-healing outcomes. Therefore, the findings should be interpreted cautiously as supportive biological plausibility rather than direct evidence of therapeutic efficacy.

Table 3. Critical Appraisal of the Included Studies

Study	Strengths	Main Methodological Limitations	Implication for Interpretation
Imran et al. [20]	Evaluated *E. elatior* fruit ethanol extract; reported antidiabetic and radical scavenging activities; identified bioactive compounds such as quercetin, vanillic acid, p-coumaric acid, and p-hydroxybenzoic acid.	Animal species and some methodological details were not clearly described; no diabetic ulcer model; no wound-healing endpoints; limited information on randomization, blinding, sample size calculation, and extract standardization.	Supports antihyperglycemic and antioxidant potential, but cannot be interpreted as direct evidence for diabetic ulcer healing.
Widyarini et al. [21]	Used E. elatior fruit ethanol extract in a diabetic animal model; reported reduction in blood glucose, hsCRP, creatinine, and albuminuria; included histological kidney assessment.	Model was diabetic nephropathy, not diabetic ulcer; no wound creation; no wound closure, collagen deposition, angiogenesis, or re-epithelialization outcomes	Provides indirect evidence related to diabetic complications and inflammation, but does not confirm wound-healing efficacy.
Efendi et al. [22]	Evaluated wound-healing activity of E. elatior preparation; reported wound repair activity in mice.	Used umbut or stem extract, not fruit extract; model was non-diabetic; limited quantitative wound-healing parameters; no diabetic wound pathophysiology was represented.	Suggests wound-healing potential of E. elatior as a plant species, but cannot be directly extrapolated to fruit extract in diabetic ulcers.
Marchianti et al. [23]	Used diabetic wound model; evaluated relevant wound-healing parameters such as VEGF expression and hydroxyproline level.	Intervention was Merremia mammosa, not E. elatior; therefore, findings are not specific to E. elatior fruit extract.	Useful as a methodological comparison for future diabetic wound studies, but not evidence for E. elatior.
Karle et al. [24]	Evaluated antidiabetic effects and diabetic complications in animal models.	Used Manilkara zapota, not E. elatior; did not directly evaluate diabetic ulcer healing with E. elatior fruit extract.	Provides general comparison for antidiabetic plant research but does not support direct conclusions on E. elatior fruit extract.

Imran et al. [20] investigated the radical scavenging and antidiabetic potential of *E. elatior* fruit ethanol extract. The study is relevant because hyperglycemia and oxidative stress are important contributors to delayed diabetic wound healing. However, the study did not evaluate wound closure, wound area reduction, re-epithelialization, collagen deposition, angiogenesis, inflammatory cytokines, or histopathological changes

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in wound tissue. In addition, the animal species and several methodological details were not clearly described in the available report. Information on randomization, blinding, sample size calculation, and extract standardization was also limited. Therefore, this study supports only the antidiabetic and antioxidant potential of *E. elatior* fruit extract, but it cannot be used as direct evidence for diabetic ulcer healing.

Widyarini et al. [21] evaluated *E. elatior* fruit ethanol extract in a streptozotocin–nicotinamide-induced diabetic nephropathy model. This study provided useful evidence regarding antihyperglycemic, anti-inflammatory, antioxidant, and nephroprotective effects. However, the experimental model focused on diabetic nephropathy rather than diabetic ulcer or wound healing. Although the reduction of blood glucose and hsCRP is biologically relevant to diabetic wound repair, the study did not assess wound-related endpoints such as wound closure rate, granulation tissue formation, collagen deposition, angiogenesis, or re-epithelialization. Therefore, its relevance to diabetic ulcer healing remains indirect.

Efendi et al. [22] evaluated the wound-healing activity of torch ginger umbut or stem extract in non-diabetic mice. This study is partially relevant because it examined wound repair using *E. elatior*. However, the extract was prepared from the stem or umbut rather than the fruit, and the model did not involve diabetic animals. This is an important limitation because diabetic wounds differ from normal acute wounds in terms of prolonged inflammation, impaired angiogenesis, oxidative stress, delayed collagen deposition, and increased susceptibility to infection. Therefore, the findings cannot be directly extrapolated to *E. elatior* fruit extract in diabetic ulcer models.

Marchianti et al. [23] used a diabetic wound model and evaluated wound-healing outcomes, including angiogenesis and collagen-related parameters. However, the intervention was *Merremia mammosa* gel rather than *E. elatior* fruit extract. Thus, this study provides useful methodological reference for future diabetic wound studies but does not provide evidence for the efficacy of *E. elatior*.

Overall, the available studies were limited by indirectness, heterogeneity in plant parts and experimental models, incomplete reporting of randomization and blinding, limited information on sample size calculation, and insufficient extract standardization. These limitations reduce the strength of the conclusions and support the need for future studies using standardized *E. elatior* fruit extract in validated diabetic wound models.

Extract Preparation and Active Compounds

Among the five included studies, three investigated *Etlingera elatior* preparations and provided information on extract preparation, phytochemical constituents, and bioactive compounds [20–22]. Although these studies did not directly evaluate *E. elatior* fruit extract in diabetic ulcer models, they provide indirect mechanistic evidence relevant to diabetic wound pathophysiology. The available evidence indicates that *E. elatior* preparations contain phenolic and flavonoid compounds, which are commonly associated with antioxidant, anti-inflammatory, antimicrobial, and tissue-protective activities.

Widyarini et al. [21] evaluated *E. elatior* fruit ethanol extract in a streptozotocin–nicotinamide-induced diabetic nephropathy model. The extract was prepared using 96% ethanol and contained flavonoids, phenols, glycosides, saponins, tannins, steroids, terpenoids, and vanillic acid. The extract also showed antioxidant activity, with an IC_{50} value of 5.079 mg/L [21]. Although this study focused on diabetic nephropathy rather than diabetic ulcer healing, its findings are indirectly relevant because oxidative stress and systemic inflammation contribute to delayed wound repair in diabetic conditions.

Imran et al. [20] also investigated *E. elatior* fruit ethanol extract and reported radical scavenging and antidiabetic activities. Chromatographic separation identified quercetin, p-coumaric acid, vanillic acid, and p-hydroxybenzoic acid. Quercetin showed the strongest radical scavenging activity, followed by vanillic acid, p-hydroxybenzoic acid, p-coumaric acid, and crude extract [20]. However, the presence of these compounds should not be interpreted as direct evidence of diabetic ulcer healing activity, because the study did not assess wound closure, re-epithelialization, collagen deposition, angiogenesis, microbial burden, or inflammatory responses in diabetic wound tissue. Therefore, these findings only support biological plausibility and require further validation in diabetic ulcer models.

Efendi et al. [22] evaluated torch ginger umbut extract at 10% concentration in a non-diabetic wound-healing model. Although the study reported wound repair activity and identified phenols, polyphenols, flavonoids, and terpenoids, it used the stem or umbut rather than fruit extract and did not involve diabetic animals. Therefore, its findings cannot be directly generalized to *E. elatior* fruit extract in diabetic ulcer models.

Overall, phenolic and flavonoid compounds were consistently reported in *E. elatior* preparations [20–22]. However, most available evidence is based on ethanol extracts, and no included study compared ethanol

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with other solvents such as water, methanol, or acetone. Thus, future primary studies should compare extraction solvents, evaluate residual solvent safety, standardize the extract, and test oral or topical formulations in validated diabetic wound models.

Biological Mechanisms Relevant to Diabetic Ulcer Healing

Although none of the included studies directly evaluated diabetic ulcer healing endpoints using *Etlingera elatior* fruit extract, several biological mechanisms relevant to diabetic wound repair were reported across the available literature. These mechanisms include anti-inflammatory activity, antioxidant or radical scavenging activity, antimicrobial activity, anti-hyperglycemic effects, pancreatic β-cell protection, and tissue-protective effects. These findings are important because diabetic ulcer healing is not determined only by local wound closure, but also by systemic metabolic control, inflammatory regulation, oxidative stress reduction, microbial control, angiogenesis, collagen deposition, and tissue remodeling.

Widyarini et al. [21] evaluated *E. elatior* fruit ethanol extract in a streptozotocin–nicotinamide-induced diabetic nephropathy model and reported several findings relevant to diabetic wound pathophysiology. The extract significantly reduced hsCRP levels, indicating a systemic anti-inflammatory effect. This finding is biologically relevant because chronic inflammation is one of the major causes of delayed diabetic wound healing. Persistent elevation of inflammatory mediators may impair fibroblast proliferation, extracellular matrix formation, epithelialization, and collagen synthesis. Therefore, the reduction of hsCRP suggests that *E. elatior* fruit extract may have potential to modulate inflammatory responses in diabetic conditions, although this effect has not yet been confirmed in wound tissue.

The same study also reported antioxidant activity of *E. elatior* fruit ethanol extract, with an IC_{50} value of 5.079 mg/L for free radical scavenging activity [21]. Antioxidant activity is highly relevant to diabetic ulcer healing because hyperglycemia increases reactive oxygen species production and oxidative stress in wound tissues. Excessive oxidative stress may damage keratinocytes, fibroblasts, endothelial cells, and collagen matrix, thereby delaying wound contraction, re-epithelialization, angiogenesis, and remodeling. Therefore, the antioxidant properties of *E. elatior* fruit extract provide an important mechanistic basis for its potential use in diabetic wound management.

Imran et al. [20] also reported radical scavenging activity of *E. elatior* fruit ethanol extract and its isolated compounds. The study identified quercetin, vanillic acid, p-coumaric acid, and p-hydroxybenzoic acid as major aromatic compounds. Among these compounds, quercetin showed the strongest radical scavenging activity, followed by vanillic acid, p-hydroxybenzoic acid, p-coumaric acid, and the crude extract [20].

Efendi et al. [22] also noted antimicrobial activities associated with torch ginger extract. This mechanism is relevant because diabetic ulcers are highly susceptible to microbial colonization and infection. Infection can prolong inflammation, increase tissue destruction, delay granulation tissue formation, and increase the risk of severe complications. Therefore, antimicrobial activity may contribute to wound healing by reducing microbial burden and preventing infection-related delays in tissue repair. However, the available studies did not directly test antimicrobial effects in infected diabetic wounds.

Anti-hyperglycemic activity represents another important mechanism related to diabetic ulcer healing. Widyarini et al. [21] reported that *E. elatior* fruit ethanol extract significantly reduced blood glucose levels in diabetic animals. Similarly, Imran et al. [20] demonstrated that *E. elatior* fruit ethanol extract decreased plasma glucose levels at doses of 200, 300, and 400 mg/kgBW, with 400 mg/kgBW identified as the most effective dose. These findings are relevant because uncontrolled hyperglycemia delays wound healing through impaired leukocyte function, endothelial dysfunction, reduced angiogenesis, increased oxidative stress, and abnormal collagen metabolism. Therefore, improvement in glycemic status may indirectly support diabetic ulcer healing.

In addition to lowering blood glucose, Imran et al. [20] reported pancreatic β-cell protection based on histopathological evaluation. This finding suggests that *E. elatior* fruit extract may help preserve pancreatic structure and function under diabetic conditions. β-cell protection is relevant because preservation of insulin-producing cells may contribute to improved glucose homeostasis. Better glycemic control can create a more favorable biological environment for wound healing by reducing oxidative stress, inflammation, and vascular impairment. Nevertheless, this mechanism remains indirect because the study did not evaluate wound healing outcomes.

Widyarini et al. [21] also reported nephroprotective activity of *E. elatior* fruit extract in diabetic animals. The extract improved creatinine and albuminuria and reduced necrosis and inflammation in kidney histology. Although nephroprotection is not a direct wound-healing endpoint, it suggests tissue-protective and anti-

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inflammatory potential under diabetic conditions. This finding is relevant because diabetic complications often share common mechanisms, including oxidative stress, inflammation, endothelial dysfunction, and tissue damage. Therefore, the ability of *E. elatior* fruit extract to protect kidney tissue may support its broader pharmacological relevance in diabetes-related complications.

The most direct wound-healing markers, including angiogenesis and collagen synthesis, were reported by Marchianti et al. [23]. However, this study used *Merremia mammosa* gel formulation rather than *E. elatior* fruit extract. The study demonstrated increased vascular endothelial growth factor expression and hydroxyproline levels in diabetic wounds, indicating enhanced angiogenesis and collagen formation [23]. Although this evidence cannot be attributed to *E. elatior*, it provides an important methodological reference for future studies. Future investigations of *E. elatior* fruit extract in diabetic wound models should include similar endpoints, such as wound closure rate, VEGF expression, hydroxyproline content, collagen deposition, re-epithelialization, and histopathological scoring.

Table 3. Biological Mechanisms Relevant to Diabetic Ulcer Healing

Mechanism	Evidence Source	Key Findings
Anti-inflammatory activity	Widyarini et al. [21]	Significant reduction in hsCRP levels in diabetic animals, indicating systemic anti-inflammatory activity.
Antioxidant/radical scavenging activity	Widyarini et al. [21]	Demonstrated free radical scavenging activity with an IC_{50} value of 5.079 mg/L.
Antioxidant/radical scavenging activity	Imran et al. [20]	DPPH radical scavenging activity was demonstrated; quercetin showed the highest potency among isolated compounds.
Antioxidant/radical scavenging activity	Efendi et al. [22]	Antioxidant activity was associated with phenols, polyphenols, flavonoids, and terpenoids in torch ginger extract.
Antimicrobial activity	Efendi et al. [22]	Antimicrobial activity was noted for torch ginger extract.
Anti-hyperglycemic activity	Widyarini et al. [21]	Significant reduction in blood glucose was reported in diabetic animals treated with *E. elatior* fruit ethanol extract.
Anti-hyperglycemic activity	Imran et al. [20]	Plasma glucose decreased at 200, 300, and 400 mg/kgBW; 400 mg/kgBW was the most effective dose.
Pancreatic β-cell protection	Imran et al. [20]	Protective effect on pancreatic β-cells was confirmed by histopathological evaluation.
Nephroprotective activity	Widyarini et al. [21]	Improved creatinine and albuminuria; reduced necrosis and inflammation in kidney histology.
Angiogenesis and collagen synthesis	Marchianti et al. [23]	Increased VEGF expression and hydroxyproline levels in diabetic wounds, but the intervention was *Merremia mammosa*, not *E. elatior*.

Wound Healing and Glycemic Outcomes

Direct evidence for ulcer or wound healing using *E. elatior* fruit extract remains unavailable. Among the included studies, only Efendi et al. [22] evaluated the wound-healing activity of *E. elatior*, but the study used torch ginger umbut or stem extract rather than fruit extract and was conducted in non-diabetic mice. The study reported that 10% torch ginger umbut extract produced optimal wound healing within 7–8 days [22]. This finding suggests that *E. elatior* may contain bioactive compounds capable of supporting tissue repair. However, the absence of a diabetic model limits its applicability to diabetic ulcer healing. Diabetic wounds differ substantially from normal wounds because they are characterized by prolonged inflammation, impaired angiogenesis, reduced collagen deposition, delayed epithelialization, and increased infection risk.

The wound-healing study by Efendi et al. [22] also had several methodological limitations. It did not report detailed wound closure rates, wound area measurements, histopathological healing scores, inflammatory markers, angiogenesis markers, or re-epithelialization data. Therefore, while the study provides preliminary evidence of wound-healing activity, it does not provide sufficient mechanistic or quantitative data to confirm the therapeutic relevance of *E. elatior* for diabetic ulcer treatment.

For glycemic outcomes, two studies provided relevant evidence. Widyarini et al. [21] reported that *E. elatior* fruit ethanol extract reduced blood glucose levels and improved diabetic nephropathy-related parameters in diabetic animals. The extract also reduced creatinine and hsCRP, particularly when administered during pre-diabetic and diabetic periods. Imran et al. [20] found that *E. elatior* fruit ethanol

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extract at 400 mg/kgBW was the most effective dose for decreasing plasma glucose and protecting pancreatic β-cells. These glycemic effects are relevant because improved glucose control is an important prerequisite for diabetic wound healing. However, neither study evaluated wound healing directly.

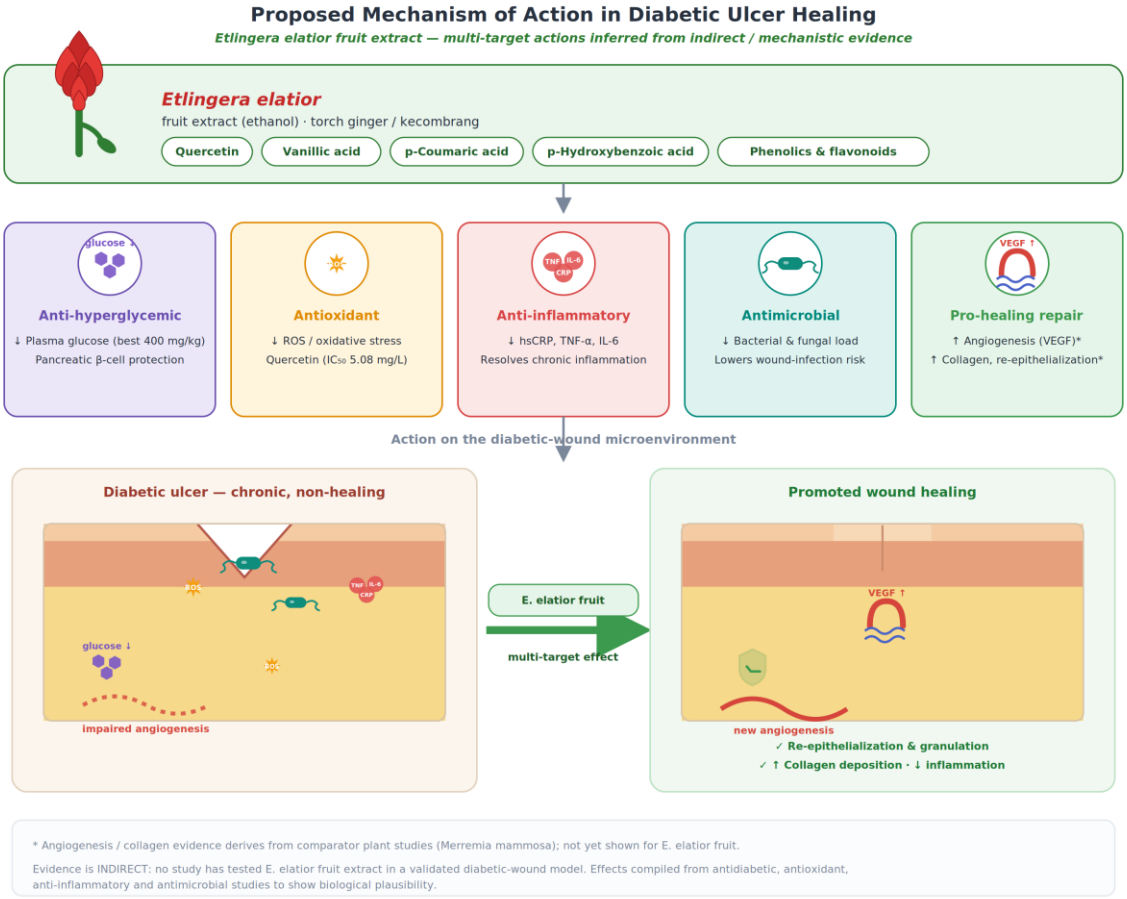

Figure 2. Potential mechanism of *Etlingera elatior* in Diabetic Ulcer Healing

Validity of Animal Models for Diabetic Ulcer Research

The animal models used in the included studies should be interpreted carefully. Widyarini et al. [21] used a streptozotocin–nicotinamide-induced diabetic nephropathy model. Although this model is relevant for evaluating diabetic complications, systemic inflammation, oxidative stress, and renal injury, it does not directly represent diabetic ulcer healing because no wound was induced and no wound-healing endpoints were assessed. Therefore, this study provides indirect mechanistic evidence rather than direct evidence for diabetic ulcer repair.

Imran et al. [20] evaluated the antidiabetic activity of *E. elatior* fruit extract, but the available report did not clearly describe the animal species and did not include a diabetic wound model. The study is useful for understanding antihyperglycemic and antioxidant effects, but it cannot validate the effect of *E. elatior* fruit extract on diabetic ulcer healing.

For future research, a more appropriate model would be streptozotocin-induced diabetic rodents combined with full-thickness excisional wounds. This model is more relevant because it represents both hyperglycemic conditions and measurable wound-healing outcomes, including wound closure, re-epithelialization, collagen deposition, angiogenesis, inflammatory response, oxidative stress, and histopathological repair. Therefore, future studies should directly test standardized *E. elatior* fruit extract in this validated diabetic wound model.

Synthesis

The central finding of this review is the absence of direct experimental evidence evaluating *E. elatior* fruit extract in diabetic ulcer animal models. The heterogeneity across the included studies does not reflect conflicting findings, but rather fragmented evidence across related yet non-overlapping research domains.

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Some studies examined *E. elatior* fruit extract in diabetic models without wound outcomes, one study examined *E. elatior* wound-healing activity in a non-diabetic model using the stem part, and another study investigated diabetic wound healing using a different plant extract. Therefore, the available evidence supports biological plausibility but does not confirm therapeutic efficacy.

Three lines of indirect evidence support the potential relevance of *E. elatior* fruit extract as a candidate for diabetic ulcer therapy. First, the extract demonstrated anti-hyperglycemic activity in diabetic animal models at doses of 200–400 mg/kgBW, with 400 mg/kgBW identified as the most effective dose [20]. This effect was accompanied by evidence of pancreatic β-cell protection [20] and reduction of systemic inflammation, including hsCRP [21]. Second, *E. elatior* preparations consistently demonstrated antioxidant and antimicrobial activities [20–22]. These mechanisms are relevant because oxidative stress and microbial infection are major barriers to diabetic wound repair. Third, *E. elatior* umbut extract showed wound-healing activity in non-diabetic mice at a 10% concentration [22]. However, the use of the stem part rather than fruit extract and the absence of diabetes limit the interpretation of this finding.

Several methodological limitations should be considered. The included studies varied in plant part used, extraction method, dose, animal model, and outcome parameters. Sample sizes were small in some studies, and detailed information regarding randomization, blinding, power calculation, and risk of bias was limited. In addition, direct wound-healing endpoints such as wound closure percentage, histopathological scoring, VEGF expression, hydroxyproline content, collagen deposition, re-epithelialization, and inflammatory cytokines in wound tissue were not evaluated using *E. elatior* fruit extract.

The literature gap is therefore specific and well-defined. Future studies should combine *E. elatior* fruit ethanol extract with validated diabetic wound models, such as streptozotocin-induced diabetic rodents with full-thickness excisional wounds. These studies should evaluate both topical and oral administration, including oral doses of 200–400 mg/kgBW and topical formulations based on standardized extract concentrations. Essential outcome parameters should include wound closure rate, healing time, histopathological score, collagen deposition, hydroxyproline content, VEGF expression, inflammatory cytokines, oxidative stress markers, microbial burden, and safety profile. Such studies are required to determine whether the pharmacological profile of *E. elatior* fruit extract can be translated into measurable therapeutic benefits for diabetic ulcer healing.

Dose–Response, Safety, and Research Gap Analysis

The structured synthesis indicates that the available evidence remains fragmented across different experimental models, plant parts, doses, routes of administration, and outcome parameters. A clear dose–response relationship for *E. elatior* fruit extract in diabetic ulcer healing cannot be established because no study has directly evaluated this extract in a diabetic wound model. The only dose-related evidence was reported by Imran et al. [20], in which *E. elatior* fruit ethanol extract at 200, 300, and 400 mg/kgBW reduced plasma glucose levels, with 400 mg/kgBW identified as the most effective dose. However, this finding reflects antihyperglycemic activity rather than wound-healing efficacy.

The safety and toxicity profile of *E. elatior* fruit extract also remains uncertain. No included study specifically assessed acute toxicity, chronic toxicity, LD50, NOAEL, local irritation, dermal toxicity, or long-term safety in the context of diabetic wound treatment. In addition, no study directly evaluated *E. elatior* fruit extract as a topical formulation for diabetic ulcers. Although topical preparations such as gels, creams, or ointments may be more relevant for open wounds, data on stability, dermal penetration, local irritation, extract standardization, and optimal concentration are still unavailable. The study by Marchianti et al. [23] using *Merremia mammosa* gel may serve only as a methodological comparison. Future studies should evaluate standardized *E. elatior* fruit extract in validated diabetic wound models and compare oral and topical administration.

Although several medicinal plants have been more extensively studied in diabetic wound models, the present review focused specifically on *E. elatior* fruit extract. Studies using other plant extracts, such as *Merremia mammosa* and *Manilkara zapota*, were included only as methodological comparisons and should not be interpreted as direct evidence for *E. elatior*. Future studies may compare standardized *E. elatior* fruit extract with other established wound-healing plant extracts to determine its relative advantages and limitations in diabetic ulcer models.

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Conclusions and Future Directions

This literature review found no direct experimental evidence evaluating *Etlingera elatior* fruit extract in diabetic ulcer animal models. The available studies only provide indirect evidence related to antihyperglycemic, antioxidant, anti-inflammatory, antimicrobial, and tissue-protective activities. Therefore, the potential role of *E. elatior* fruit extract in diabetic ulcer healing remains hypothetical.

Future studies should directly evaluate standardized *E. elatior* fruit extract in validated diabetic wound models, including assessment of wound closure, collagen deposition, angiogenesis, inflammatory markers, oxidative stress, microbial burden, dose–response relationship, and safety profile. Until such evidence is available, *E. elatior* fruit extract should be considered a candidate for further investigation rather than an established therapeutic agent for diabetic ulcer management.

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, analysis, interpretation, or reporting of the research findings.

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References

[1]. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. The New England Journal of Medicine 2017;376:2367-2375. https://doi.org/10.1056/NEJMra1615439.

[2]. Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic foot ulcers: a review. JAMA 2023;330:62-75. https://doi.org/10.1001/jama.2023.10578.

[3]. Negussie YM, Komicha MA, Abebe TW. Incidence and predictors of diabetic foot ulcer among patients with diabetes mellitus in a diabetic follow-up clinic in Central Ethiopia: a retrospective follow-up study. BMJ Open 2024;14:e085281. https://doi.org/10.1136/bmjopen-2024-085281.

[4]. Parveen K, Hussain MA, Anwar S, Elagib HM, Kausar MA. Comprehensive review on diabetic foot ulcers and neuropathy: treatment, prevention and management. World Journal of Diabetes 2025;16:100329. https://doi.org/10.4239/wjd.v16.i3.100329.

[5]. Rodrigues BT, Vangaveti VN, Malabu UH. Prevalence and risk factors of lower limb amputations in patients with diabetic foot ulcers: a systematic review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2022;16:102397. https://doi.org/10.1016/j.dsx.2022.102397.

[6]. Wondmeneh TG, Ebrahim OA. Systematic review and meta-analysis of diabetic foot ulcers and associated factors among adults in Ethiopia. Archives of Public Health 2025;83:309. https://doi.org/10.1186/s13690-025-01816-9.

[7]. Meloni M, Uccioli L, Andreadi A, Giurato L, Ruotolo V, Romano M, et al. Incidence and causes of major amputation in patients with diabetic foot ulcers: data from a retrospective study. Acta Diabetologica 2026;63:97-103. https://doi.org/10.1007/s00592-025-02577-1.

[8]. Aalaa M, Vahdani AM, Mohajeri Tehrani M, Mehrdad N, Zohdirad M, Sadati M, et al. Epidemiological insights into diabetic foot amputation and its correlates: a provincial study. Clinical Medicine Insights: Endocrinology and Diabetes 2024;17:11795514241227618. https://doi.org/10.1177/11795514241227618.

[9]. Chen L, Sun S, Gao Y, Ran X. Global mortality of diabetic foot ulcer: a systematic review and meta-analysis of observational studies. Diabetes, Obesity and Metabolism 2023;25:36-45. https://doi.org/10.1111/dom.14840.

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

[10]. Luo Y, Liu C, Li C, Jin M, Pi L, Jin Z. The incidence of lower extremity amputation and its associated risk factors in patients with diabetic foot ulcers: a meta-analysis. International Wound Journal 2024;21:e14931. https://doi.org/10.1111/iwj.14931.

[11]. Pitocco D, Spanu T, Di Leo M, Vitiello R, Rizzi A, Tartaglione L, et al. Diabetic foot infections: a comprehensive overview. European Review for Medical and Pharmacological Sciences 2019;23:26-37. https://doi.org/10.26355/eurrev_201904_17471.

[12]. Cedillo-Cortezano M, Martinez-Cuevas LR, Márquez López JA, Barrera López IL, Escutia-Perez S, Petricevich VL. Use of medicinal plants in the process of wound healing: a literature review. Pharmaceuticals 2024;17:303. https://doi.org/10.3390/ph17030303.

[13]. Daniel-Jambun D, Ong KS, Lim YY, Tan JBL, Lee WL, Muhamad A, et al. Antioxidant properties of Etlingera pubescens, an edible ginger plant endemic to Borneo. Food Bioscience 2018;25:44-51. https://doi.org/10.1016/j.fbio.2018.07.007.

[14]. Mutmainah M, Mayangsari Y, Santoso U, Chansuwan W, Sirinupong N. Phytochemical profile and antioxidant activity of torch ginger (*Etlingera elatior*) inflorescence extract after in vitro simulated digestion. Functional Foods in Health and Disease 2024;14:528-545. https://doi.org/10.31989/ffhd.v14i7.1382.

[15]. Sungthong B, Srichaikul B. Antioxidant activities, acute toxicity and chemical profiling of torch ginger (*Etlingera elatior* Jack.) inflorescent extract. Pharmacognosy Journal 2018;10:979-982. https://doi.org/10.5530/pj.2018.5.166.

[16]. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.

[17]. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. https://doi.org/10.1136/bmj.n160.

[18]. Kolaski K, Logan LR, Ioannidis JPA. Guidance to best tools and practices for systematic reviews. British Journal of Pharmacology 2024;181:180-210. https://doi.org/10.1111/bph.16100.

[19]. Snyder H. Literature review as a research methodology: an overview and guidelines. Journal of Business Research 2019;104:333-339. https://doi.org/10.1016/j.jbusres.2019.07.039.

[20]. Imran, Wahyuni, Fristiohady A, Leorita M, Malaka MH, Ilyas MY, et al. Radical scavenger and anti-diabetic potencies of *Etlingera elatior* fruits growing in South East Sulawesi-Indonesia. Research Journal of Pharmacy and Technology 2022;15:2141-2146. https://doi.org/10.52711/0974-360X.2022.00355.

[21]. Widyarini T, Indarto D, Soetrisno, Purwanto B. Can ethanol extract of *Etlingera elatior* fruit prevent inflammations on diabetic nephropathy mice models? Journal of Population Therapeutics and Clinical Pharmacology 2023;30:e138-e147. https://doi.org/10.47750/jptcp.2023.30.05.016.

[22]. Efendi MZ, Sumarmin R, Fadil MS. Bioactivity of torch ginger umbut extract (*Etlingera elatior*) against wound healing in mice (Mus musculus). Eksakta: Berkala Ilmiah Bidang MIPA 2020;21:124-130. https://doi.org/10.24036/eksakta/vol21-iss2/230.

[23]. Marchianti ACN, Sakinah EN, Elfiah U, Putri NKS, Wahyuliswari DI, Maulana M, et al. Gel formulations of Merremia mammosa (Lour.) accelerated wound healing of the wound in diabetic rats. Journal of Traditional and Complementary Medicine 2021;11:38-45. https://doi.org/10.1016/j.jtcme.2019.12.002.

[24]. Karle PP, Dhawale SC, Navghare VV. Amelioration of diabetes and its complications by Manilkara zapota (L.) P. Royen fruit peel extract and its fractions in alloxan and STZ-NA induced diabetes in Wistar rats. Journal of Diabetes and Metabolic Disorders 2022;21:1303-1314. https://doi.org/10.1007/s40200-022-01000-8.

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