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Review Article

Wound Healing Potential of *Ehretia laevis* Roxb.: A Comprehensive Review of Phytochemical, Preclinical, and Clinical Studies

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ABSTRACT

Ehretia laevis Roxb., a medicinal tree from the Boraginaceae family, has been a cornerstone of traditional medicine across Asia for treating a multitude of ailments, particularly those involving inflammation and tissue damage. This review synthesizes and critically evaluates current scientific evidence on the wound-healing potential of *Ehretia laevis* Roxb., a traditionally used medicinal plant whose modern pharmacological validation remains limited. By integrating preclinical and emerging clinical data, the review aims to bridge traditional ethno-medicinal knowledge with contemporary biomedical science while outlining strategies for developing standardized phytopharmaceutical to address challenges such as chronic wounds and antimicrobial resistance. A comprehensive literature search across major scientific databases identified *in vitro, in vivo*, toxicological, and preliminary clinical studies relevant to wound repair, antimicrobial activity, and phytochemistry. Thematically analysed data revealed that *E. laevis* possesses multifaceted wound-healing abilities driven by pentacyclic triterpenoids, flavonoids, and phenolic acids, which contribute to its antimicrobial, anti-inflammatory, and antioxidant effects. Its therapeutic efficacy is notably solvent-dependent: less polar extracts enhance healing in clean excision wounds, whereas highly polar extracts perform exceptionally well in complex burn injuries and may even surpass standard treatments. Preliminary clinical observations also indicate the effectiveness of traditional leaf preparations in infected wounds without requiring adjunct antibiotics.
Overall, the evidence positions *E. laevis* as a promising phyto-antibiotic candidate for modern topical formulations. However, concerns regarding hepatotoxicity in non-polar extracts underscore the need to prioritize safer polar fractions. Future progress will depend on developing standardized, safe extracts, conducting large-scale clinical trials, and performing detailed mechanistic studies focusing on key regulators of wound repair such as VEGF and TGF-β.

Keywords: *Ehretia laevis*, Wound healing, Antimicrobial, Phytochemistry.

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INTRODUCTION

Wound healing is an intricate and dynamically coordinated biological process aimed at restoring the structural and functional integrity of damaged tissue. This process is conventionally demarcated into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling (Velnar *et al.*, 2009). The initial hemostasis phase involves immediate vasoconstriction and platelet aggregation, forming a fibrin clot. This is succeeded by the inflammatory phase, crucial for clearing microbial contaminants and cellular debris via the infiltration of neutrophils and macrophages (Guo & DiPietro, 2010).

However, the inflammatory phase must be precisely regulated. If it becomes prolonged or excessive, often due to infection, poor nutritional status, or underlying systemic diseases, it directly impedes the transition to the proliferative phase, resulting in chronic, non-healing wounds (Martin & Nunan, 2015). Such chronic wounds pose a major clinical and socioeconomic

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challenge (Frykberg & Banks, 2015). Adding complexity to wound management is the increasing global prevalence of multidrug-resistant pathogens, which has rendered many conventional synthetic antibiotics significantly less effective. Consequently, there is an urgent and critical need to identify and scientifically validate alternative therapeutic agents capable of offering a holistic, multi-target approach to wound care. Natural products, particularly medicinal plants, frequently contain a complex mixture of bioactive compounds that can modulate inflammation, combat microbial invaders, and stimulate tissue regeneration simultaneously, a multifaceted strategy often superior to single-target synthetic drugs (Kumar *et al.*, 2007; Jiang *et al.*, 2025).

Ethnobotanical Significance of *E. laevis* and Scientific Impetus

Ehretia laevis Roxb. is a medium-sized deciduous tree of the Boraginaceae family, distributed widely across tropical and subtropical regions of Asia, Africa, and Australia (Council of Scientific and Industrial Research, 2002; Jiang *et al.*, 2025). It holds a long-standing place in traditional medicinal systems such as *Ayurveda* and *Siddha*, where various plant parts are used to treat respiratory, gastrointestinal, and reproductive ailments (Kirtikar & Basu, 2005). Notably, it's most consistent and culturally widespread application is in managing skin-related conditions including cuts, burns, ulcers, wounds, and minor fractures typically through the topical application of a leaf paste (Jyothirmai *et al.*, 2014). This enduring ethnomedicinal practice suggests genuine therapeutic potential for tissue repair and provides strong justification for modern pharmacological investigation. However, despite this robust traditional foundation, scientific validation of its wound-healing properties remains fragmented (Kumar *et al.*, 2007).

This review aims to systematically collate, critically evaluate, and synthesize the available scientific evidence regarding the wound healing activity of *E. laevis*. The objectives are to evaluate existing evidence on the plant's therapeutic activity, clarify its phytochemical profile and mechanisms, compare its preclinical efficacy with standard treatments, assess its solvent-dependent safety, and identify research gaps to guide future standardization and clinical translation.

METHODOLOGY

Search Strategy and Data Sources

The primary literature search was executed across major, peer-reviewed biomedical and scientific databases, including PubMed (MEDLINE), Scopus, Web of Science, and Google Scholar. The search strategy was constructed using a combination of the three key concepts of this review: the plant, the therapeutic outcome, and the mechanism. Here is a very short version: Boolean operators were used to combine plant-related terms ("*Ehretia laevis*," "*Khandu Chakka*," "*Ajan Vruksha*") with keywords for wound healing, antimicrobial activity, anti-inflammatory action, and phytochemistry, using synonyms and truncation to capture all relevant literature.

Data Extraction and Synthesis

Data extracted from each study included plant parts used, extraction solvents, test concentrations, animal models, efficacy measures (such as MIC values and wound contraction), and toxicological findings. These data were then analyzed thematically to identify consistent effects, link specific compounds to biological activities, and highlight contradictions, particularly those related to solvent-dependent variations in efficacy and safety.

Botanical Identity and Traditional Application

Ehretia laevis Roxb. is classified under the Boraginaceae. It is characterized as a small to medium-sized deciduous tree commonly found thriving in tropical and subtropical Asian environments, including India, Pakistan, and China (Council of Scientific and Industrial Research, 2002). The plant is known by numerous vernacular names, such as "*Khandu Chakka*" and "*Ajan Vruksha*" in parts of India (Sakharkar & Alexander, 2023).

The traditional utilization of *E. laevis* is highly consistent across geographical regions, focusing heavily on topical application for the management of tissue damage. Various parts of the plant, especially the leaves and bark, have been historically prepared into pastes for treating skin cuts, ulcers, burns, and even minor fractures. This long-standing and widespread application for localized tissue damage strongly substantiates the hypothesis that the plant possesses genuine intrinsic therapeutic bioactivity, thereby providing a robust foundation for modern scientific exploration (Kirtikar & Basu, 2005).

Phytochemical Profile and Correlation to Wound Healing Mechanisms

Major Phytochemical Classes in E. laevis

The therapeutic efficacy of *E. laevis* is attributed to a diverse matrix of secondary metabolites distributed across its leaves, fruit, roots, and bark. Phytochemical investigations reveal the presence of pentacyclic triterpenoids, phenolic acids, flavonoids, alkaloids, saponins, and steroids, with their concentration and composition varying according to the plant part and the polarity of the extraction solvent (Jiang *et al.*, 2025). This diversity of secondary metabolites is a common feature of medicinal plants in the Boraginaceae family, many of which are recognized for their wound-healing properties (Hussain *et al.*, 2018). Alongside these compounds, the plant contains essential minerals like zinc and copper, which serve as crucial enzymatic cofactors in cell proliferation and collagen synthesis, highlighting its capacity to support multiple phases of tissue repair (Khobragade *et al.*, 2017).

Specific Bioactive Compounds and their Role in Healing Phases

The bioactive compounds identified in *E. laevis* collectively support its strong anti-inflammatory, antimicrobial, and wound-healing activities by acting through multiple complementary mechanisms (Jiang *et al.*, 2025). Pentacyclic triterpenoids such as betulinic acid and botulin predominantly found in the fruit help modulate inflammation and accelerate dermal repair, with betulin specifically promoting keratinocyte differentiation essential for re-epithelialization. Lupeol, present in the leaves, adds further anti-inflammatory and antioxidant support during the proliferative phase of healing. Flavonoids and phenolic compounds, including quercetin, kaempferol, gallic acid, and tannic acid, contribute significant antimicrobial, antioxidant, and anti-inflammatory activities (Li *et al.*, 2010). Gallic and tannic acids also provide astringent effects that aid wound contraction and help prevent microbial colonization.

Together, these phytochemicals enable *E. laevis* to function as a comprehensive "wound-environment modulator," supporting all major stages of healing from controlling inflammation and infection to reducing oxidative stress and promoting tissue reconstruction. This multi-target, synergistic profile highlights the therapeutic advantage of the plant's natural compound matrix over conventional single-target synthetic agents (Kumar *et al.*, 2007; Shukla & Kaur, 2018). The relationships between key phytochemicals and their established roles in wound healing are explained in Table 1 (Jiang *et al.*, 2025; Khobragade *et al.*, 2017).

Pharmacological Mechanisms of Action (*In vitro* and *In vivo* Fundamentals)

The therapeutic strength of *E. laevis* is derived from the synergistic interplay of three major pharmacological activities that collectively manage the complex pathophysiology of an injured site.

Anti-inflammatory Properties: Modulation of the Initial Healing Cascade

The initial inflammatory response is obligatory for wound debridement and defense against infection, but when it becomes dysregulated or prolonged, it prevents the timely progression to the tissue repair phases. The ability of *E. laevis* to modulate this phase is a key component of its efficacy. *In vivo* assays, specifically the carrageenan-induced rat paw edema model, have confirmed that polar extracts (methanol, aqueous) significantly reduce acute inflammation (Jyothirmai *et al.*, 2016).

This anti-inflammatory action is primarily attributed to the high content of triterpenoids and flavonoids. Such compounds are widely documented to inhibit key pro-inflammatory enzymes like Cyclooxygenase-2 (COX-2) and scavenge free radicals, thereby modulating the inflammatory cascade (Calixto *et al.*, 2003). By effectively dampening excessive inflammation, *E. laevis* creates a more favorable microenvironment for tissue regeneration (Sharma *et al.*, 2021).

Table 1: Bioactive Phytochemicals of *Ehretia laevis* and their Pharmacological Relevance to Wound Healing.

Sl. No.	Phytochemical	Plant Part Found	Reported Pharmacological Activity	Specific Relevance to Wound Healing
1.	Betulinic Acid & Betulin	Fruit	Anti-inflammatory, Antimicrobial	Reduces inflammation; promotes skin cell differentiation and acceleration.
2.	Lupeol	Leaves	Anti-inflammatory, Antioxidant	Modulates inflammation and protects new tissue from oxidative damage.
3.	Quercetin & Kaempferol	Leaves, Fruit	Antioxidant, Anti-inflammatory	Protects fibroblasts/keratinocytes from oxidative stress; inhibits wound pathogens.
4.	Gallic & Tannic Acid	Leaves, Bark	Antimicrobial, Astringent	Inhibits microbial growth and promotes early wound contraction.
5.	Zinc (Zn)	Stem bark	Enzymatic co-factor	Essential for cell proliferation and collagenase activity (Remodelling phase).
6.	Copper (Cu)	Stem bark	Enzymatic co-factor	Required for lysyl oxidase, critical for collagen cross-linking.
7.	Oleanolic Acid	Stem bark, Root	Antimicrobial, Anti-inflammatory	Prevents bacterial colonization and controls excessive inflammation.
8.	Rutin	Leaves	Antimicrobial, Immunity enhancer	Prevents infection and supports systemic immune response to injury.
9.	Phytol	Fruit, Bark	Antioxidant, Immunity enhancer	Mitigates oxidative stress and supports immune-mediated repair.

Antimicrobial Efficacy: Addressing Wound Pathogens

Bacterial colonization and subsequent infection represent the single most frequent cause of delayed or non-healing wounds. *E. laevis* demonstrates broad-spectrum efficacy, providing a robust defense against a range of clinically significant Gram-positive organisms, such as Staphylococcus aureus and Bacillus subtilis, as well as Gram-negative bacteria, including Escherichia coli and Pseudomonas aeruginosa (Bangre *et al.*, 2025). Quantitative Minimum Inhibitory Concentration (MIC) studies provide further detail regarding this activity. Investigations comparing different solvent extracts indicate that efficacy varies depending on the pathogen. For example, an isopropanol extract proved most effective against *S. aureus* (MIC 1.0 mL), whereas an acetone extract showed the highest potency against *E. coli* (MIC 1.25 mL). This differential targeting based on extract type suggests that the selection of the extraction solvent for future standardized pharmaceutical preparations should not only consider overall wound healing but also be specialized based on the target pathogen profile expected in the clinical application (e.g., focusing on extracts most potent against common nosocomial infections like *P. aeruginosa* or *S. aureus*) (Murarkar *et al.*, 2018). The quantitative data supporting these antimicrobial claims is presented below. A consolidated summary of these *in vitro* antimicrobial findings is presented in Table 2 (Singh *et al.*, 2021; Rushikesh *et al.*, 2018).

Antioxidant Activity and Mitigation of Oxidative Stress

The complex biochemical environment of a healing wound often involves the excessive generation of Reactive Oxygen Species (ROS), which can lead to oxidative stress. This oxidative damage can injure critical newly formed cells, such as fibroblasts and keratinocytes, thereby severely impairing the efficiency of the proliferative phase. *E. laevis* possesses strong antioxidant properties, largely conferred by its high concentrations of phenolic acids and flavonoids. *In vitro* assays confirm that methanolic and hydro alcoholic extracts exhibit high radical scavenging capabilities (Sharma *et al.*, 2023). This potent antioxidant capacity is particularly relevant when considering the plant's performance in complex, high-stress wound environments, such as burns.

Translational Efficacy: Preclinical and Clinical Validation

Comparative Analysis of Efficacy in Preclinical Animal Models

Preclinical studies utilizing animal models provide essential evidence by evaluating the plant's efficacy within a complex biological system, offering crucial insights into its translational potential. Studies have compared the activity of *E. laevis* extracts in two distinct wound models: excision (simulating clean, acute injuries) and burn wounds (simulating complex, high-inflammation injuries) (Harne *et al.*, 2021; Thakre *et al.*, 2024b).

Findings from Excision Wound Models (Low-Inflammation Healing)

In studies utilizing Wistar rats with excision wounds, a 5% ointment derived from the chloroform fraction of *E. laevis* leaves demonstrated rapid healing. The key finding was a near-maximal 95.41% wound contraction rate, which was comparable to the positive control, Povidone-Iodine (96.35%). In contrast, other fractions, such as the aqueous fraction, showed substantially lower efficacy (68.36% contraction). This result strongly suggests that the less polar chloroform solvent concentrates the compounds (likely lipophilic triterpenoids) most effective at driving mechanical wound contraction and stimulating re-epithelialization in clean, relatively non-inflamed wounds (Harne *et al.*, 2021).

Performance in Burn Wound Models (High-Inflammation Healing)

A different comparative study utilizing albino rabbits with third-degree burn wounds yielded a contrasting and critical finding. In this high-inflammation model, the highly polar aqueous extract ointment proved superior, achieving 42.41% wound contraction, an outcome that significantly surpassed

Table 2: Summary of *in vitro* Antimicrobial Activity of *E. laevis* Extracts.

Sl. No.	Extract Type	Microorganism	Concentration (µg/mL)	Zone of Inhibition (mm)
1.	Methanolic	*E. coli*	1000	24.43
2.	Methanolic	*S. aureus*	1000	21.6
3.	Methanolic	*P. aeruginosa*	1000	25.1
4.	Methanolic	*B. subtilis*	1000	25.4
5.	Aqueous	*E. coli*	1000	17
6.	Aqueous	*S. aureus*	1000	23
7.	Ethanolic	*E. coli*	1000	Nil
8.	Ethanolic	*S. aureus*	1000	20
9.	Crude	*E. coli*	1000	16
10	Crude	*S. aureus*	1000	23

the contraction rate observed with the clinical standard, Silver Sulfadiazine (38.08%). Meanwhile, the less polar chloroform extract, which was superior in the excision model, performed poorly in the burn model. This contradiction highlights a fundamental principle: the plant's efficacy is critically dependent on the wound's underlying pathophysiology. This phenomenon is termed the Solvent-Dependent Mechanism Shift. For clean excision wounds, the priority is contraction, driven best by the less polar fraction's compounds. For highly inflamed burn wounds, the primary need is robust anti-inflammatory action and antioxidant protection against massive tissue damage. The polar aqueous extract, rich in highly soluble polyphenols, is uniquely equipped to manage this oxidative stress and inflammation, proving therapeutically superior to the standard antimicrobial treatment in this specific context. This mandates the adoption of a wound-specific therapeutic strategy when developing phytopharmaceutical formulations from *E. laevis* (Thakre *et al.*, 2024b).

Preclinical Wound Healing Studies on *E. laevis* Comparing Efficacy across Different Extraction Solvents are explained in Table 3.

Preliminary Clinical Evaluation and Phyto-Antibiotic Potential

Clinical evidence supporting the use of *E. laevis* remains preliminary, derived primarily from a single interventional study involving 34 human patients with diverse wound types (fresh, chronic, infected, and non-infected). Patients were treated with the traditional fresh leaf paste applied daily without concurrent antibiotic or antiseptic use. The key finding of the clinical assessment was the maintenance of healing efficacy across all wound categories. Statistical analysis indicated that healing time was not significantly influenced by wound chronicity or, crucially, infection status ($p = 0.375$). Wounds that were initially infected healed as effectively as non-infected wounds. This result carries profound clinical implications: it strongly suggests that the intrinsic antimicrobial properties of the *E. laevis* paste are clinically effective in managing wound pathogens without the need for synthetic antibiotics. If this efficacy is replicated in subsequent large-scale trials, *E. laevis* could be successfully developed as a valuable topical phyto-antibiotic, providing a sustainable alternative therapeutic agent vital for mitigating the accelerating public health crisis of antimicrobial resistance in wound care settings (Thakre *et al.*, 2024a).

Safety Profile and Formulation Constraints

Evaluating the safety profile is as critical as establishing efficacy, and the toxicological data for *E. laevis* reveals a complex picture where safety is inextricably linked to the extraction solvent utilized. This dependency on polarity represents the paramount constraint on its future pharmaceutical development (Perveen *et al.*, 2016). The traditional use of a fresh leaf paste is not practical for widespread clinical use due to issues of standardization, stability, and dosing. Research is needed to develop modern, stable, and clinically applicable formulations, such as standardized ointments, creams, hydrogels, or bioactive dressings. The development of a tincture-based ointment, as proposed in one research protocol, is a promising step in this direction (Itankar *et al.*, 2025).

Acute and Sub-Acute Toxicological Studies

Generally, acute oral toxicity studies conducted according to established guidelines have demonstrated the relative safety of the polar extracts. The crude and methanolic extracts were found to be safe in mice at doses up to 2000 mg/kg, indicating a low potential for immediate acute toxicity with oral administration of these polar preparations (Jyothirmai *et al.*, 2014).

Furthermore, these polar extracts have shown beneficial effects on hepatic function. Studies on paracetamol-induced hepatotoxicity in rats demonstrated that the Aqueous Fraction (AFEL) significantly mitigates liver damage by attenuating oxidative stress and inflammation. This hepatoprotective effect is widely attributed to the high concentration of polyphenolic compounds, such as rutin, quercetin, and kaempferol, found in the polar fractions (Singh *et al.*, 2024).

Table 3: Synopsis of Preclinical Wound Healing Studies on *E. laevis*.

Sl. No.	Study Reference	Animal Model	Wound Type	*E. laevis* Preparation	Comparator	Key Efficacy Outcome (Contraction %)
1.	Harne *et al.*, (2021)	Wistar Rats	Excision Wound	5% Chloroform Fraction Ointment	Povidone-Iodine	95.41% (Comparable to standard)
2.	Harne *et al.*, (2021)	Wistar Rats	Excision Wound	5% Aqueous Fraction Ointment	Povidone-Iodine	68.36% (Slightly better than control)
3.	Thakre *et al.*, (2024b)	Albino Rabbits	3rd Degree Burn	Aqueous Extract Ointment	Silver Sulfadiazine	42.41% (11.37% more effective than standard)
4.	Thakre *et al.*, (2024b)	Albino Rabbits	3rd Degree Burn	Chloroform Extract Ointment	Silver Sulfadiazine	34.6% (Less effective than standard)

The Paradox of Solvent-Dependent Safety: Hepatoprotection vs. Hepatotoxicity

The safe profile of polar extracts stands in stark contrast to the toxicity observed with non-polar preparations. This is the Safety Paradox of *E. laevis*. A sub-acute toxicity study involving the non-polar n-hexane leaf extract demonstrated dose-dependent hepatotoxicity in mice. While the acute median Lethal Dose (LD_{50}) was high (>4000 mg/kg), repeated daily dosing over 15 days resulted in significant elevation of liver enzymes (ALT and AST) and bilirubin. Subsequent liver histology confirmed cellular aggregation, vacuolation, and mild to moderate necrosis at higher doses (1000–4000mg/kg). This duality implies that the non-polar extraction process concentrates hazardous, lipophilic compounds, whereas the polar extraction process concentrates protective, hydrophilic compounds. For regulatory approval and safe clinical use, this finding imposes a crucial constraint: future commercial and standardized formulations must strictly mandate the use of only highly polar solvents (e.g., aqueous or hydro alcoholic). This requirement overrides the occasional higher efficacy observed with non-polar fractions in specific preclinical models, emphasizing that safety must be the determining factor in formulation development (Perveen *et al.*, 2016).

CONCLUSION AND FUTURE DIRECTIONS

Ehretia laevis Roxb. shows strong wound healing potential due to its anti-inflammatory, antioxidant, and antimicrobial activities. Its therapeutic effectiveness varies with extraction methods and wound type polar extracts are more effective in burn wound management, while non-polar extracts enhance contraction in excision wounds. However, non-polar extracts carry a risk of hepatotoxicity, whereas polar extracts demonstrate a safer profile, emphasizing the need for careful and standardized formulation.

Despite promising findings, key research gaps remain. Clinical evidence is still limited, and the molecular mechanisms driving *E. laevis*'s wound healing effects are not yet fully understood. Future research should focus on developing safe, standardized formulations particularly those based on polar extracts, alongside mechanistic studies to identify active compounds and clarify their roles in inflammation control, angiogenesis, and collagen formation. Well-designed, large-scale clinical trials are also essential to validate its efficacy in chronic and non-healing wounds compared with current treatments. Addressing these gaps will be critical for advancing *E. laevis* from preclinical promise to a reliable therapeutic option in wound care.

ABBREVIATIONS

***E. laevis*:** *Ehretia laevis* Roxb.; **ROS:** Reactive Oxygen Species; **MIC:** Minimum Inhibitory Concentration; **VEGF:** Vascular Endothelial Growth Factor; **TGF-β:** Transforming Growth Factor Beta; **COX-2:** Cyclooxygenase-2; **Zn:** Zinc; **Cu:** Copper; **AFEL:** Aqueous Fraction of Ehretia laevis; **LD_{50}:** Median Lethal Dose; **ALT:** Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **MEDLINE:** Medical Literature Analysis and Retrieval System Online.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

The authors confirm that AI tools, including ChatGPT, were used for language refinement. All content, interpretations, and conclusions presented in this review are the authors' own, and the use of AI did not influence the scientific accuracy or integrity of the work.

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