



NARRATIVE REVIEW: POTENTIAL OF TERMINALIA CATAPPA LEAF EXTRACT AS A NATURAL AGENT FOR BURN WOUND HEALING

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ABSTRACT

Burn injuries induce oxidative stress, inflammation, and collagen degradation, impairing skin regeneration. *Terminalia catappa* L. (ketapang) has potential as a healing agent due to its rich bioactive compounds, including flavonoids, tannins, saponins, triterpenoids, and phytosterols. This narrative review aims to evaluate the wound-healing potential of *Terminalia catappa* L. extract based on preclinical evidence and its underlying pharmacological mechanisms. This structured narrative review aims to evaluate the wound healing potential of *Terminalia catappa* L. extract based on preclinical evidence and its underlying pharmacological mechanisms. Relevant scientific literature (2014–2023) was sourced from ScienceDirect, PubMed, ResearchGate, and Google Scholar, and analyzed using a qualitative thematic narrative synthesis. The major phytoconstituents of ketapang—including punicalagin, ellagic acid, gallic acid, luteolin, kaempferol, betulinic acid, and β -sitosterol—act synergistically to suppress oxidative stress via ROS scavenging and modulate inflammation by inhibiting NF- κ B, MAPK, COX-2, iNOS, and pro-inflammatory cytokines (IL-6, IL-1 β , TNF- α). Additionally, the extract supports extracellular matrix regeneration by enhancing fibroblast proliferation and collagen deposition. Preclinical evidence demonstrates that ketapang extract accelerates wound contraction, re-epithelialization, and granulation tissue formation. In a second-degree burn model, a 25% methanolic ketapang leaf extract ointment provided optimal collagen density compared to 50% and 100% concentrations. In conclusion, ketapang extract shows promising potential for development into an effective topical preparation for burn wound healing.

Keywords: anti-inflammatory; antioxidant; burn wound; herbal medicine; *terminalia catappa* L.; *terminalia catappa* leaf extract

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INTRODUCTION

Burn injury is a type of tissue trauma caused by exposure to thermal sources, chemicals, radiation, electricity, or friction. This condition may affect individuals regardless of age or environmental background. Fundamentally, burn injury occurs due to the transfer of thermal energy to body tissues, resulting in cellular and structural tissue damage (Jeschke et al., 2020). Burn management must be tailored to the etiology and severity of the injury, as each type of burn elicits distinct physiological and pathophysiological responses, including inflammatory reactions, fluid loss, and electrolyte imbalance. In general, burns are classified according to the depth and extent of tissue involvement. Burns affecting only the outermost layer of the skin (epidermis) are categorized as superficial or first-degree burns. When tissue damage extends into the dermis, the injury is classified as a second-degree burn, which is further subdivided into superficial partial-thickness (grade 2A) and deep partial-thickness (grade 2B) burns. Third-degree or full-thickness burns occur when the entire dermal layer is destroyed, whereas fourth-degree burns represent the most severe form of injury, characterized by necrosis extending into deeper underlying tissues (Jeschke et al., 2020).

In the advancement of modern pharmaceutical formulations, the utilization of naturally derived active compounds has gained increasing attention due to their favorable biocompatibility, relatively

low toxicity, and diverse pharmacological activities. One plant with considerable potential for development as a therapeutic agent for burn wound management is *Terminalia catappa* L., commonly known as ketapang in Indonesia. *Terminalia catappa* is a tropical plant widely distributed throughout Asian regions. The tree can grow up to approximately 35 meters in height and is characterized by an erect, symmetrical canopy with horizontally spreading branches. Its leaves are dark green, glossy, and slightly coarse in texture, measuring approximately 15–25 cm in length and 10–14 cm in width. The abaxial leaf surface is covered with fine trichomes, while the leaf margins are entire, and the adaxial surface appears smooth. This species is monoecious, bearing both male and bisexual flowers on the same plant, with inflorescences arranged in spike-like clusters arising from the leaf axils (Zan, 2019). *Terminalia catappa* L. has long been recognized as a medicinal plant utilized in traditional medicine. This plant contains various secondary metabolites with potential therapeutic effects in promoting wound healing (Sine, 2016). *Terminalia catappa* leaves are rich in bioactive secondary metabolites that act synergistically, including phenolic compounds, tannins, saponins, phytosterols, and flavonoids, which exhibit antifungal, antibacterial, and anti-inflammatory activities. Flavonoids, phenolic compounds, and saponins function as antioxidants by scavenging free radicals, thereby suppressing inflammatory processes and minimizing tissue damage. In addition, flavonoids and saponins have been reported to inhibit metalloproteinase enzyme activity, thereby preventing collagen degradation and promoting more effective collagen synthesis. Tannins contribute to the stabilization of collagen fibers while exerting antibacterial effects that help prevent wound-site infections, whereas phytosterols play a role in reducing inflammation and supporting cellular regeneration processes (Ramadhian et al., 2017).

Although numerous studies have reported the pharmacological activities of *Terminalia catappa* leaf extract, particularly its antioxidant, anti-inflammatory, and antimicrobial properties, the available evidence remains scattered across various publications. Furthermore, the treatment of burns continues to present significant clinical challenges due to the risk of infection, prolonged inflammation, delayed tissue regeneration, and limitations associated with some conventional therapies. Therefore, a comprehensive review of the current scientific evidence regarding the potential of *Terminalia catappa* leaf extract for burn wound healing is needed. This review aims to summarize and critically evaluate existing findings on the phytochemicals, pharmacological mechanisms, and healing activities of *Terminalia catappa* leaf extract, thereby providing a scientific basis for its future development as a natural therapeutic agent for burn wound treatment.

METHOD

This study was conducted as a narrative review of previous research investigating the potential of *Terminalia catappa* leaves for burn wound healing. Relevant scientific literature published between 2014 and 2023 was collected from ScienceDirect, PubMed, ResearchGate, and Google Scholar. From the obtained literature, selected original studies were qualitatively evaluated and synthesized through thematic narrative analysis to map the extract's synergistic effects on oxidative stress, inflammation, and extracellular matrix regeneration. The keywords used in the literature search included anti-inflammatory, antioxidant, burn wound, herbal medicine, *Terminalia catappa* L., *Terminalia catappa* leaf extract.

RESULT

This literature review search and screening process successfully identified relevant articles evaluating the phytoconstituents, pharmacological mechanisms, and preclinical efficacy of *Terminalia catappa* L., which are synthesized in the tables below.

Phytoconstituents and Skin-Related Activities

Terminalia catappa L. possesses considerable dermatological potential due to its diverse bioactive constituents, including tannins, flavonoids, phenolic acids, triterpenoids, saponins, and phytosterols. These compounds exhibit multicomponent and multitarget mechanisms of

action, enabling *Terminalia catappa* to simultaneously modulate various cutaneous pathological processes, such as inflammation, oxidative stress, and pigmentation disorders (Table 1).

Table 1.

Bioactive Compounds of *Terminalia catappa* and Their Skin-Related Pharmacological Activities

Compound	Phytochemical Class	Skin-Related Activities	Mechanism of Action	Reference
Punicalagin	Tanin (ellagitannin)	Antioxidant, anti-inflammatory, anti-aging	Scavenge ROS; ↓MAPK/AP-1 → ↓MMP-1,-3; ↓COX-2	(Mininel et al., 2014)
Ellagic acid	Phenolic acid	Antioxidant, anti-inflammatory, anti-aging, antipigmentation	Neutralization of ROS; inhibition of NF-κB; ↓tyrosinase	(Abiodun et al., 2016)
Luteolin	Flavonoid	Antioxidant, anti-inflammatory	Inhibition of COX 2/iNOS; ↓sitokin; ROS scavenging	(Hung et al., 2022)
Kaempferol	Flavonoid	Antioxidant, inflammatory	↓NF-κB; suppression of MMP activity	(Hung et al., 2022)
Gallic acid	Phenolic acid	Antioxidant, inflammatory, depigmenting	Scavenge ROS; ↓IL-6,TNF; tyrosinase inhibition	(Abiodun et al., 2016)
Betulinic acid	Triterpenoid	Anti-inflammatory, wound healing	Inhibition of NF-κB/JNK; ↑collagen, ↓nitric oxide	(Pertuit et al., 2015)
β-Sitosterol	Phytosterol	Antioxidant, anti-inflammatory, wound healing	Modulation of NF-κB/TLR; ↓cytokines inflammatory	(Hung et al., 2022)

Preclinical Efficacy Evidence

Preclinical evidence from multiple *in vivo* models consistently demonstrates the efficacy and safety profile of *Terminalia catappa* L. extracts in accelerating tissue regeneration, as summarized Table 2.

Table 2.

Summary of Preclinical Evidence of *Terminalia catappa* in Dermatology

Experimental Model	Intervention	Dosage/Concentration	Outcomes	Reference
Excision wound model in Wistar rats	Topical ointment containing methanolic stem bark extract of <i>Terminalia catappa</i>	10% extract ointment applied daily for 18 days	Increased wound contraction up to 97.4% on day 18; reduced epithelialization period; complete epithelialization observed on day 16; enhanced granulation tissue area, with effects significantly greater than the control group and slightly higher than the comparison group	(Khan et al., 2014)
Incision wound model in mice (<i>Mus musculus</i>)	Topical ointment containing ethanol extract of green and brown <i>T. catappa</i> leaves	Ethanol leaf extract concentrations of 20%, 40%, and 60% (b/v), administered once daily until day 16	Increased wound closure in all extract-treated groups; GL20 and BL40 achieved complete wound closure on day 12; BL20 achieved complete wound closure on day 13; GL20 was recommended as the most effective concentration	(Nugroho et al., 2019)
Excision wound model in mice (<i>Mus musculus</i>)	Ointment formulations containing ethanol extract of	Ointments formulated with green leaf extract, brown leaf extract, and ethanol extract, each at	Enhanced wound closure, particularly in the GLW group; highest DNA and wound area values observed in GLE (0.849	(Agung Nugroho et al., 2019)

	green and brown <i>T. catappa</i> leaves	60% concentration	µg/mL) and GLW (0.852 µg/mL); increased hydroxyproline levels in all treatment groups; enhanced collagen synthesis and fibroblast proliferation	
Second-degree burn wound model in white rats (<i>Rattus norvegicus</i>)	Topical ointment containing methanolic <i>T. catappa</i> leaf extract	Extract ointments at 25%, 50%, and 100%; positive control using Bioplacenton®	Increased collagen fiber density, particularly at the 25% concentration; P1 25% = 90.32%, P2 50% = 86.77%, P3 100% = 83.36%; 25% concentration demonstrated the most optimal collagenesis effect, whereas the 100% concentration tended to be less effective	(Yulianto et al., 2020)
Physiological safety model in mice (<i>Mus musculus</i>)	Oral administration of <i>Terminalia catappa</i> seed oil	Acute toxicity test for 72 h: 544.5; 5,445; 10,890; 16,335; and 21,780 mg/kg BW. Follow-up study: 544.5 mg/kg and 5,445 mg/kg BW for 14 and 28 days	No mortality observed; hematological parameters remained within physiological ranges; AST, ALT, and creatinine levels increased dose-dependently; no evidence of inflammation, degeneration, necrosis, or pathological changes in heart and kidney tissues	(Nguy et al., 2023)
Prenatal toxicity model in pregnant rats	Oral aqueous extract of <i>Terminalia catappa</i>	100, 200, and 400 mg/kg BW administered daily for 21 consecutive days	Oral LD50 estimated at >2000–5000 mg/kg; increased ALP at 100 mg/kg; elevated AST and ALT at 200 mg/kg; increased albumin at 400 mg/kg; renal tubular necrosis and hepatic necrosis observed; reduced uterine contractions indicating a tocolytic effect	(Abdullahi et al., 2023)

DISCUSSION

Phytoconstituents and Mechanism of *Terminalia catappa* L. in Dermatology

Several compounds that have been identified include luteolin, gallic acid, kaempferol, and their derivatives. Other phenolic compounds, such as punicalagin, punicalin, ellagic acid, and gallic acid, have also been detected in the leaf and twig extracts of *Terminalia catappa* L. (Hung et al., 2022). In dermatology, the primary mechanisms of action of *Terminalia catappa* L. involve antioxidant, anti-inflammatory, anti-aging, depigmenting, and wound-healing activities. Compounds such as punicalagin, ellagic acid, and gallic acid are capable of scavenging free radicals or reactive oxygen species (ROS). This mechanism is particularly important because excessive ROS production can damage cellular membranes, skin proteins, and collagen, thereby accelerating skin aging processes. Recent studies have demonstrated that *Terminalia catappa* extracts are capable of reducing ROS, nitric oxide (NO), inducible nitric oxide synthase (iNOS), as well as pro-inflammatory cytokines such as IL-6 and IL-1β (Paik et al., 2024).

During the early phase of skin injury, such as burn wounds or ultraviolet (UV) exposure, a significant surge in reactive oxygen species (ROS) occurs. Phenolic compounds belonging to the ellagitannin group, including punicalagin and punicalin, together with ellagic acid, function as highly efficient radical scavengers. This mechanism is crucial for preventing lipid peroxidation of cellular membranes and protecting collagen structures as well as extracellular proteins from oxidative degradation. Enhancement of the endogenous antioxidant defense system is also mediated by kaempferol through activation of the Nrf2 (Nuclear factor erythroid 2-related factor 2) signaling

pathway, which subsequently induces the expression of protective antioxidant enzymes within keratinocytes. (Abiodun et al., 2016; Mininel et al., 2014)

The anti-inflammatory effects of *Terminalia catappa* L. extract extend beyond merely alleviating erythema, as the extract actively modulates intracellular signal transduction pathways. The flavonoids luteolin and kaempferol specifically inhibit the transcriptional activity of NF- κ B (Nuclear Factor-kappa B) (Figure 1) and the MAPK (Mitogen-Activated Protein Kinase) signaling pathway. This inhibition subsequently suppresses the expression of pro-inflammatory enzymes, including COX-2 and iNOS, while also reducing the secretion of pro-inflammatory cytokines such as IL-6, IL-1 β , and TNF- α . (Chen et al., 2021; Hung et al., 2022).

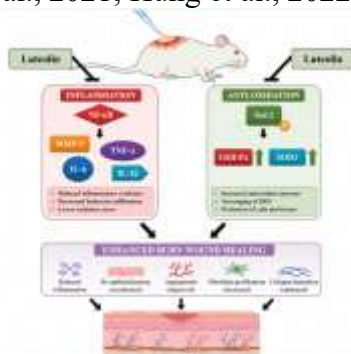


Figure 1. A schematic representation of the mechanism of action of luteolin in STZ-induced impaired wound healing in mice (Chen et al., 2021). Luteolin enhances the healing of diabetic wounds by inhibiting inflammation and increasing antioxidant capacity. This mechanism is associated with a reduction in the expression of NF- κ B-mediated MMP-9, IL-6, TNF- α , and IL-1 β , as well as an increase in the expression of Nrf-2-mediated GSH-Px and SOD1.

Simultaneously, betulinic acid and β -sitosterol contribute to the wound-healing process through modulation of inflammatory responses and promotion of tissue regeneration. Betulinic acid has been reported to enhance the proliferation and viability of human dermal fibroblasts, which are essential for extracellular matrix formation and collagen deposition during wound repair. Furthermore, β -sitosterol has demonstrated significant therapeutic benefits in burn wound management by promoting rapid eschar separation, early granulation tissue formation, and accelerated wound closure while maintaining a moist wound environment. These biological activities support the progression of burn wounds from the inflammatory phase to the proliferative phase, thereby facilitating tissue regeneration and improving healing outcomes. In addition, polyphenolic constituents such as punicalagin may contribute to extracellular matrix remodeling and tissue repair through their antioxidant and anti-inflammatory properties. Collectively, the synergistic actions of these bioactive compounds highlight the potential of *Terminalia catappa* leaf extract as a natural therapeutic agent for burn wound healing (Odama et al., 2023; Wei & Sakr, 2025)

To achieve optimal aesthetic regeneration outcomes, ellagic acid and gallic acid may contribute to the prevention of post-inflammatory hyperpigmentation (PIH) following burn wound healing through their anti-melanogenic activities. Ellagic acid has been shown to suppress melanogenesis by reducing tyrosinase activity and inhibiting cAMP-mediated CREB and MITF signaling pathways, resulting in decreased melanin production in melanocytes. In addition, its antioxidant properties help attenuate oxidative stress, which is known to stimulate melanogenesis during the wound-healing process. Gallic acid has also demonstrated anti-melanogenic effects by reducing tyrosinase activity and downregulating melanogenesis-related proteins, including microphthalmia-associated transcription factor (MITF), tyrosinase, and tyrosinase-related protein-1 (TRP-1). Collectively, these mechanisms may help minimize excessive melanin deposition after tissue repair, thereby promoting a more uniform restoration of normal skin pigmentation and reducing the risk of post-inflammatory hyperpigmentation (Su et al., 2013; Yang et al., 2021).

Preclinical Evidence

Terminalia catappa L. extract demonstrates significant dermatological efficacy in accelerating tissue regeneration. Extracts derived from the leaves and stem bark of this plant have consistently been reported to enhance wound contraction rates, accelerate re-epithelialization, and optimize granulation tissue formation.

Dynamics of Excision and Incision Wound Healing

Preclinical evidence demonstrates that topical intervention using *Terminalia catappa* L. extract significantly accelerates the wound resolution phase. In a Wistar rat model, topical application of a 10% methanolic stem bark extract ointment achieved 97.4% wound contraction by day 18, surpassing the efficacy of the control group and demonstrating comparable activity to povidone-iodine treatment. This effect was supported by a progressive reduction in wound area and accelerated complete epithelialization within a 17-day period. Similar findings were observed in mouse (*Mus musculus*) models, in which ethanol leaf extracts (green and brown leaves) at concentrations ranging from 20% to 40% achieved complete wound closure earlier (days 12–13) compared with the control group (Khan et al., 2014; Nugroho et al., 2019).

Histobiochemical Profile and Tissue Regeneration

The regenerative activity of *Terminalia catappa* L. has been confirmed through both molecular and histological parameters. Ethanol and aqueous extracts derived from green *Terminalia catappa* leaves significantly increased total DNA levels in newly formed wound tissue, reaching values of 0.849 µg/mL and 0.852 µg/mL, respectively. This increase in DNA density serves as a strong indicator of intensive cellular proliferation. Furthermore, elevated hydroxyproline levels indicate active stimulation of collagen synthesis and fibroblast proliferation. In a second-degree burn wound model, a 25% extract concentration produced the highest collagen fiber density (90.32%), suggesting that low to moderate doses are more effective in modulating extracellular matrix deposition compared with higher concentrations (100%) (Agung Nugroho et al., 2019; Yulianto et al., 2020).

Evaluation of Physiological Safety and Toxicity

Acute and subchronic toxicity studies have provided a comprehensive overview of the safety profile of *Terminalia catappa*. Oral administration of *Terminalia catappa* seed oil in mice at doses up to 21,780 mg/kg body weight did not result in mortality or pathological alterations in hepatic and renal tissues. In contrast, reductions in liver enzyme markers (AST/ALT) and creatinine levels were observed, suggesting potential hepatoprotective and renoprotective effects under certain conditions (Nguy et al., 2023). However, particular caution is required regarding the use of aqueous leaf extracts during pregnancy. Evidence from studies in pregnant rats demonstrated that administration at a dose of 400 mg/kg body weight induced elevated liver enzyme levels, renal tubular necrosis, and tocolytic effects involving uterine contractions. These findings indicate the presence of safety threshold limitations in subjects with specific physiological conditions (Abdullahi et al., 2023).

CONCLUSION

Terminalia catappa L. extract possesses considerable potential as a wound-healing agent due to its rich content of bioactive compounds, including flavonoids, tannins, phenolic compounds, saponins, triterpenoids, and phytosterols. These constituents exhibit antioxidant, anti-inflammatory, antibacterial, and tissue-regenerative activities. Preclinical evidence has demonstrated that *Terminalia catappa* extract can accelerate wound contraction, enhance re-epithelialization, stimulate fibroblast proliferation, and increase collagen deposition. Therefore, *Terminalia catappa* extract shows promising potential for development as a topical active ingredient for burn wound healing. Nevertheless, the currently available evidence remains limited to the preclinical stage. Further studies are required to establish extract standardization, optimal therapeutic dosage, topical safety, and clinical efficacy in humans.

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