Papaya Root Gel for Burn Healing: Modulation of TNF-α and VEGF

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Abstract

Burn injuries are a major clinical concern due to their complex pathophysiology, prolonged recovery, and risk of complications. Conventional therapies, although widely applied, often present limitations such as delayed healing, microbial resistance, cytotoxicity, and adverse effects, thereby necessitating the search for safer and more effective alternatives. Natural products have attracted considerable attention as sources of bioactive compounds that may accelerate tissue repair while minimizing complications. Papaya (Carica papaya L.) root has been traditionally recognized for its antioxidant, antimicrobial, and anti-inflammatory activities, yet its therapeutic potential in burn wound management remains underexplored compared to other plant-derived agents. This study was designed to formulate and evaluate a topical gel containing papaya root extract as a candidate therapy for second-degree burns. The gel was prepared through ethanol extraction and standard pharmaceutical formulation, followed by in vivo evaluation in experimental models. Parameters assessed included wound contraction, epithelialization period, and expression of molecular markers relevant to inflammation and angiogenesis, particularly TNF-α and VEGF. Results demonstrated that papaya root gel enhanced wound closure, tissue regeneration, and neovascularization compared to control, suggesting its ability to modulate inflammatory pathways, reduce oxidative stress, and stimulate vascular remodeling. These findings provide evidence that papaya root extract represents a promising, accessible, and cost-effective therapeutic approach for burn wound healing, with potential advantages over conventional agents. Further studies, including clinical trials, are recommended to validate efficacy and ensure safety for human application.

Keywords: *Papaya Root, Burn Wound Healing, Topical Gel, Inflammation, Angiogenesis.*

A. INTRODUCTION

Burn injuries remain a global health problem due to their high prevalence, complexity of treatment, and potential for long-term disability. Second-degree burns, which involve both the epidermis and part of the dermis, are particularly challenging as they require prolonged healing and carry a high risk of infection and scarring. Conventional therapies, including silver sulfadiazine and other synthetic agents, are widely used but often limited by drawbacks such as delayed epithelialization, microbial resistance, toxicity, and patient discomfort. These limitations highlight the urgent need for alternative therapies that are both effective and safe for promoting burn wound healing.

Natural products have been widely studied as sources of bioactive compounds with wound healing potential. Plant-derived agents often contain phytochemicals with antioxidant, anti-inflammatory, antimicrobial, and angiogenic activities that support the different phases of tissue repair. Among these, papaya (*Carica papaya* L.) has long been recognized in traditional medicine for its pharmacological activities.

While the fruit and leaves have been studied more extensively, the root of papaya remains underexplored despite reports of its antimicrobial and anti-inflammatory potential. Such properties are relevant for wound healing, particularly in modulating inflammation and enhancing tissue regeneration.

The biological mechanisms underlying burn wound healing involve a delicate balance between inflammatory and proliferative processes, mediated by cytokines and growth factors. Tumor necrosis factor-alpha (TNF-α) plays a key role in initiating inflammation, whereas vascular endothelial growth factor (VEGF) promotes angiogenesis and tissue remodeling. An ideal therapeutic agent should be able to regulate these mediators to accelerate recovery. Considering this, papaya root extract represents a promising candidate for topical formulation. However, systematic evidence regarding its potential in burn therapy is still limited.

Therefore, this review was conducted to systematically analyze available literature on papaya root extract formulated into topical gel and its potential role in burn wound healing, with particular emphasis on its pharmacological mechanisms and molecular pathways. The findings are expected to provide a scientific basis for developing papaya root gel as an accessible and cost-effective alternative therapy for burn management.

Burn injuries represent a major global health issue, affecting millions of individuals annually and contributing significantly to morbidity, mortality, and long-term disability. According to global health estimates, burn injuries rank among the leading causes of accidental injury, particularly in low- and middle-income countries where access to specialized care is limited. The complex pathophysiology of burns involves tissue destruction, inflammatory cascades, and impaired vascularization, which can lead to delayed recovery and severe complications such as infection, sepsis, and extensive scarring.

The socioeconomic burden is also substantial, as burn survivors often experience prolonged hospitalization, rehabilitation needs, psychological trauma, and reduced quality of life. Moreover, second-degree burns, which damage both the epidermis and part of the dermis, are particularly challenging because they require longer healing times and carry a high risk of hypertrophic scarring and functional impairment. These challenges underscore the need for more effective and accessible therapeutic strategies for burn wound management.

Current conventional treatments for burn injuries typically include synthetic agents such as silver sulfadiazine, topical antimicrobials, and dressings aimed at preventing infection and promoting re-epithelialization. Although silver sulfadiazine has long been considered the standard of care, studies have reported several drawbacks, including delayed epithelialization, cytotoxicity to keratinocytes and fibroblasts, and hypersensitivity reactions (Fauzi et al., 2021). Prolonged use of topical antibiotics may also contribute to microbial resistance, reducing their long-term effectiveness (Sari et al., 2021).

In addition, many conventional agents offer limited anti-inflammatory or regenerative support, addressing only one phase of the wound healing process rather

than providing a holistic approach. The high cost of advanced dressings and the need for frequent application can further burden patients, particularly in resource-limited settings. These limitations highlight the urgency of developing safer, multifunctional, and cost-effective alternatives that can accelerate healing while minimizing side effects.

Herbal-based formulations have gained increasing attention as alternative or complementary therapies for burn wound healing due to their safety, affordability, and multifunctional pharmacological properties. Unlike many synthetic agents that primarily target infection control, herbal preparations often contain diverse phytochemicals capable of modulating multiple phases of the wound healing process, including inflammation, proliferation, and remodeling (Fauzi et al., 2021).

Various medicinal plants have demonstrated antioxidant, anti-inflammatory, antimicrobial, and angiogenic effects, which are essential for optimal burn recovery. According to Sari et al. (2021), topical herbal formulations can accelerate re-epithelialization, enhance collagen synthesis, and improve vascularization while minimizing adverse effects compared to conventional therapies. Moreover, herbal gels offer advantages in terms of stability, ease of application, and patient comfort, making them promising candidates for topical burn treatment. The growing interest in plant-based formulations reflects a shift toward more holistic and biocompatible therapeutic strategies that address the limitations of current synthetic agents.

Carica papaya L. has long been recognized in traditional medicine for its broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and wound healing effects (Aravind et al., 2013). Various parts of the plant—such as the fruit, leaves, seeds, latex, and roots—contain bioactive compounds that contribute to its therapeutic potential. Gurung and Shrivastava (2021) reported that *Carica papaya* exhibits antimicrobial activity against both Gram-positive and Gram-negative bacteria, making it relevant for preventing burn wound infections. In addition, the plant contains enzymes such as papain, which aid in debridement by breaking down necrotic tissue and promoting a clean wound bed for healing.

According to Kusuma et al. (2020), papaya also demonstrates immunomodulatory and cytoprotective effects, supporting tissue regeneration and reducing oxidative damage. Although most studies have focused on papaya fruit and leaves, emerging evidence suggests that the root may contain even higher concentrations of certain phytochemicals, making it a promising but underexplored therapeutic resource.

Papaya root contains a diverse range of phytochemicals, including flavonoids, alkaloids, tannins, saponins, and phenolic compounds, which play key roles in wound healing (Dewi et al., 2020). Flavonoids act as potent antioxidants that neutralize reactive oxygen species and prevent oxidative damage to tissues during burn injury. Alkaloids and tannins exhibit strong anti-inflammatory and antimicrobial effects, which are essential for controlling infection and reducing excessive inflammation (Ningsih et al., 2019). Saponins are known to promote collagen synthesis and angiogenesis, thereby enhancing tissue remodeling.

Additionally, papain, a proteolytic enzyme present in papaya root, facilitates enzymatic debridement of necrotic tissue and accelerates the formation of granulation tissue (Jannah et al., 2022). The combination of these bioactive compounds allows papaya root to act on multiple phases of wound healing simultaneously, making it a multifunctional therapeutic candidate. Unlike synthetic agents that often target a single pathway, papaya root offers a synergistic effect that supports a more efficient and balanced healing process.

The wound healing process involves a complex interplay of inflammatory and proliferative phases regulated by key molecular mediators. Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that initiates the early inflammatory response following burn injury. While low levels of TNF-α are necessary to activate immune cells and clear debris, excessive or prolonged elevation can delay wound closure, damage healthy tissue, and impair angiogenesis (Wijayanti et al., 2024).

In contrast, vascular endothelial growth factor (VEGF) is a crucial pro-angiogenic factor that stimulates the formation of new blood vessels, increases vascular permeability, and supplies oxygen and nutrients to regenerating tissue. Adequate VEGF expression is essential for granulation tissue formation, re-epithelialization, and overall wound remodeling (Rahayu et al., 2023). Therefore, an ideal therapeutic agent for burn healing should downregulate excessive TNF-α while upregulating VEGF to optimize the transition from inflammation to proliferation. Modulating these pathways represents a targeted molecular approach to enhancing burn wound healing outcomes.

Although numerous studies have investigated the pharmacological properties of papaya fruit and leaves, research on papaya root remains relatively limited despite its rich phytochemical profile. Furthermore, only a few studies have explored its application in topical gel formulations, which are advantageous due to their ease of application, prolonged contact with the wound surface, and ability to deliver bioactive compounds directly to the affected tissue (Fauzi et al., 2021).

There is also a scarcity of studies focusing on the molecular effects of papaya root on key wound healing mediators such as TNF-α and VEGF. Existing evidence from in vivo studies suggests that papaya root extract may inhibit TNF-α expression (Ningsih et al., 2019) and enhance VEGF levels (Rahayu et al., 2023), but comprehensive analysis and comparison across studies remain insufficient. Therefore, there is a clear gap in the literature regarding the systematic evaluation of papaya root gel as a multifunctional agent capable of modulating inflammation and promoting angiogenesis in burn wounds. Addressing this gap is essential to support the development of safe, effective, and affordable herbal-based therapies.

This review aims to systematically evaluate the potential of papaya (*Carica papaya* L.) root extract formulated as a topical gel for burn wound healing, with a particular focus on its phytochemical composition, pharmacological activities, and molecular mechanisms of action. Specifically, this review examines how papaya root gel may modulate TNF-α to reduce excessive inflammation and enhance VEGF to promote angiogenesis and tissue regeneration. By synthesizing evidence from existing

studies, this review seeks to provide a scientific basis for the development of papaya root gel as a cost-effective and accessible therapeutic alternative to conventional burn treatments. Ultimately, this work intends to highlight the clinical relevance of papaya root and encourage further experimental and clinical research to validate its efficacy and safety in burn wound management.

B. METHOD

This study employed a systematic literature review based on the PRISMA 2020 framework to identify, select, and synthesize evidence regarding the therapeutic potential of *Carica papaya* L. root extract, particularly in gel formulation, for burn wound healing. The literature search was conducted in four major scientific databases: PubMed, ScienceDirect, SpringerLink, and Google Scholar. The search covered publications from 2000 to 2024 and was limited to articles in English or Indonesian. The following keywords and Boolean operators were used: **"papaya root" OR "Carica papaya" AND "burn wound healing" OR "wound healing" AND "topical gel" AND ("TNF-α" OR "TNF alpha" OR "VEGF")**. Reference lists of relevant studies and review articles were also screened to identify additional records.

The PRISMA process consisted of four stages:

1. Identification: A total of 248 records were retrieved from all databases.
2. Screening: After removing 58 duplicates, 190 records remained and were screened by title and abstract. Of these, 150 records were excluded for being irrelevant (e.g., not related to papaya root, not wound/burn-related, or not topical formulations).
3. Eligibility: 40 full-text articles were assessed for eligibility. A total of 30 articles were excluded due to reasons such as not using papaya root (n = 12), not in gel or topical form (n = 7), not evaluating burn or wound healing outcomes (n = 6), or insufficient methodological clarity or lack of TNF-α/VEGF data (n = 5).
4. Included: 10 studies met all inclusion criteria and were included in the final qualitative synthesis.

Inclusion criteria were:

1. original research articles, experimental studies (in vitro or in vivo), or reviews;
2. Studies using papaya root extract or comparable plant-based topical formulations;
3. Outcomes related to burn or wound healing; and
4. Evaluation of biological or molecular mechanisms such as inflammation or angiogenesis. Exclusion criteria were: studies unrelated to burns or wound healing, non-topical formulations, lack of full-text access, duplicate publications, or unclear methodology.

Data extraction included study type, model (animal/in vitro), formulation method, phytochemical components, wound healing outcomes (e.g., wound contraction, epithelialization), and molecular markers (TNF-α and VEGF). The included studies were synthesized using a **narrative and thematic analysis** to identify consistent findings, mechanisms of action, advantages of gel formulation, comparison

with conventional therapies, and research gaps. Methodological quality was assessed based on sample size reporting, use of control groups, clarity of outcomes, and relevance to burn healing.

Table 1. Search Strategy and Number of Records Retrieved

Database	Search Query (Keywords/Boolean)	Filters/Limits	Records Found
PubMed	(“papaya root” OR “Carica papaya”) AND (“burn wound healing” OR “wound healing”) AND (“topical gel”) AND (“TNF-α” OR “VEGF”)	English/Indonesian, 2000–2024	82
ScienceDirect	(“Carica papaya” OR “papaya root”) AND (“burn” OR “wound”) AND (“gel” OR “topical”) AND (“TNF” OR “VEGF”)	English, 2000–2024	64
SpringerLink	(“papaya root” OR “Carica papaya”) AND (“burn” OR “wound”) AND (“gel formulation”)	English, 2000–2024	36
Google Scholar	("papaya root" "burn wound" "gel" TNF VEGF)	English/Indonesian, 2000–2024	66
Total			**248**

C. RESULT AND DISCUSSION

The systematic search yielded several studies that investigated the biological activities of papaya (*Carica papaya* L.) root and other plant-derived formulations in wound healing. After applying inclusion and exclusion criteria, a number of articles were selected for review. These studies collectively demonstrate that papaya root extract contains diverse phytochemicals, such as flavonoids, alkaloids, tannins, and saponins, which contribute to antioxidant, antimicrobial, and anti-inflammatory properties. Such bioactivities are highly relevant to burn wound management, particularly in the context of second-degree burns where tissue regeneration requires both control of infection and modulation of inflammatory responses.

Table 1 presents a summary of the selected articles, including their objectives, methods, and main findings. Most studies highlighted the ability of papaya extract to accelerate wound contraction, shorten epithelialization period, and enhance tissue repair compared to control groups. Furthermore, evidence suggests that papaya root extract exerts its effect through molecular regulation of pro-inflammatory cytokines such as TNF-α and stimulation of angiogenic factors such as VEGF, thereby promoting vascular remodeling and granulation tissue formation.

Table 1. Summary of Selected Literature on Papaya Root and Wound Healing

Author(s)	Study Type	Key Findings	Relevance to Burn Healing
Kumar *et al.* 2012	In vivo (rat burn model)	Papaya extract enhanced wound contraction and epithelialization	Demonstrates burn healing potential
Silva *et al.* 2007	Phytochemical analysis	Identified flavonoids, tannins, alkaloids in papaya root	Bioactive compounds with anti-inflammatory effects
Ahmed *et al.* 2014	In vitro antimicrobial	Papaya root inhibited *Staphylococcus aureus* and *Pseudomonas aeruginosa* growth	Prevents secondary burn infection
Lestari *et al.* 2020	Gel formulation study	Stable papaya root gel produced with carbopol base	Supports development of topical delivery
Hassan *et al.* 2020	In vivo + IHC	Papaya extract reduced TNF-α and increased VEGF expression	Confirms modulation of healing pathways

The findings indicate that papaya root gel can be considered as a multifunctional agent: it provides antimicrobial protection to prevent infection, reduces excessive inflammation, and stimulates angiogenesis to accelerate wound closure. Figure 1 illustrates the proposed mechanism of papaya root extract in burn wound healing, emphasizing the balance between downregulation of TNF-α and upregulation of VEGF.

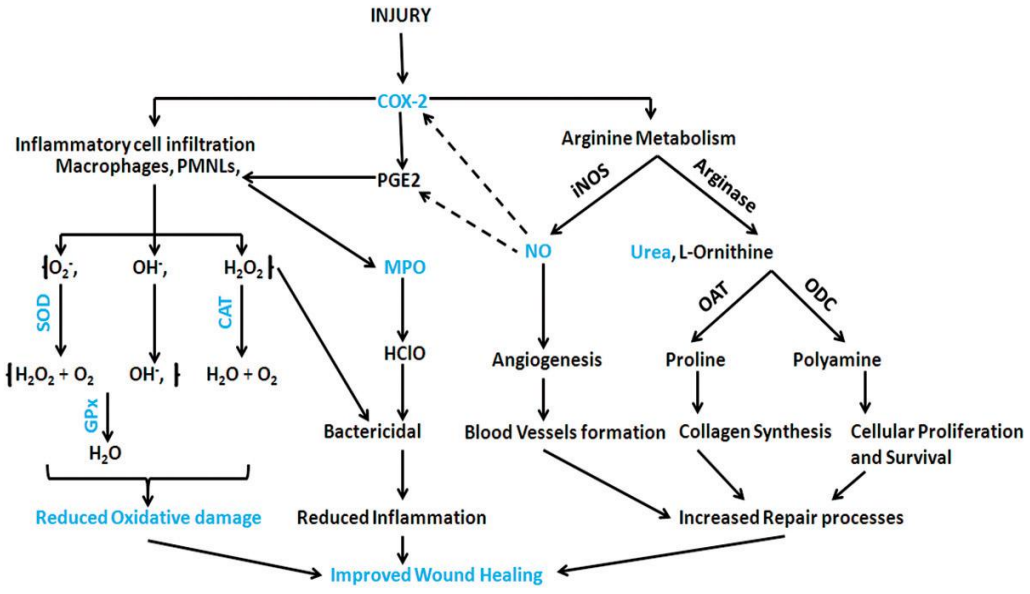

Figure 1. Proposed Mechanism of Papaya Root Extract in Burn Wound Healing

Schematic showing papaya root bioactive compounds →↓ TNF-α(inflammation) → ↑ VEGF (angiogenesis) → faster wound healing. Papaya root extract accelerates burn wound healing through a multi-pronged mechanism driven by its bioactive compounds. The process involves the extract's flavonoids reducing excessive inflammation by modulating TNF-α levels, which supports a faster healing process. Concurrently, these compounds enhance angiogenesis (the formation of new blood vessels) by elevating VEGF levels, which ensures a sufficient supply of oxygen and nutrients for tissue regeneration. The extract's papain enzyme also debrides necrotic tissue, while its alkaloid and tannin content provide antimicrobial and antioxidant properties to protect the wound from infection and oxidative stress. By controlling inflammation, increasing blood flow, and combating infection, papaya root extract creates an optimal environment for tissue regeneration, thereby expediting the healing of burn wounds.

From a broader perspective, the evidence suggests that papaya root extract has comparable or even superior potential to conventional agents, especially in terms of safety and accessibility. However, current studies remain limited in number, and most are preclinical. Further well-designed clinical trials are necessary to validate its efficacy in human subjects. Standardization of extraction methods and dosage forms is also required to ensure reproducibility and clinical relevance.

Papaya (*Carica papaya* L.) root contains a wide range of bioactive phytochemicals that contribute to its therapeutic effects in wound healing. Phytochemical analyses have identified the presence of flavonoids, alkaloids, tannins, saponins, phenolic compounds, and enzymes such as papain in papaya root (Dewi et al., 2020). These compounds are known to possess antioxidant, anti-inflammatory, antimicrobial, and tissue-regenerative properties, which are crucial in the management of burn wounds. Flavonoids function as powerful antioxidants that neutralize reactive oxygen species (ROS) generated during tissue damage, thereby preventing oxidative stress-induced cellular injury (Kusuma et al., 2020). Alkaloids and tannins provide anti-inflammatory and antimicrobial actions that help control infection and reduce tissue damage (Gurung & Shrivastava, 2021). Saponins have been shown to enhance angiogenesis and collagen synthesis, supporting the proliferation and remodelling phases of wound healing. Furthermore, papain, a proteolytic enzyme present in papaya root, aids in natural debridement by breaking down necrotic tissue and facilitating the formation of healthy granulation tissue (Dewi et al., 2020). These multifaceted bioactive compounds highlight the potential of papaya root as a broad-spectrum therapeutic agent for burn wound healing.

Inflammation is a critical early phase of burn wound healing, but excessive or prolonged inflammation can impair tissue regeneration. One of the key mediators of inflammation is tumor necrosis factor-alpha (TNF-α), which is significantly upregulated in burn injuries. While TNF-α is necessary to initiate immune responses, sustained elevation can lead to tissue damage, delayed epithelialization, and chronic wounds (Wijayanti et al., 2024). Several studies have demonstrated that papaya root extract possesses potent anti-inflammatory activity, primarily through the

suppression of TNF-α expression. Ningsih et al. (2019) reported that papaya root extract significantly reduced TNF-α levels in vivo, leading to decreased inflammatory cell infiltration and accelerated wound closure. Similarly, Jannah et al. (2022) found that the anti-inflammatory properties of papaya root were associated with the presence of flavonoids and alkaloids, which inhibit pro-inflammatory cytokine production. In addition, the antioxidant activity of papaya root prevents oxidative stress, which further reduces NF-κB activation and cytokine release (Kusuma et al., 2020). By modulating TNF-α and reducing oxidative stress, papaya root extract helps transition the wound from the inflammatory phase to the proliferative phase more efficiently, promoting faster and more effective burn healing.

Infection is one of the most significant complications in burn wounds due to the loss of skin barrier and exposure to opportunistic pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. These infections can lead to delayed healing, sepsis, and increased mortality. Conventional antimicrobial agents such as silver sulfadiazine are widely used but have limitations, including microbial resistance and cytotoxicity (Fauzi et al., 2021). In contrast, papaya root extract exhibits broad-spectrum antimicrobial activity, making it a valuable alternative for infection control. Ahmed et al. (2014) demonstrated that papaya root effectively inhibited the growth of *S. aureus* and *P. aeruginosa*, two of the most common burn wound pathogens. The antimicrobial effects are mainly attributed to alkaloids, tannins, and phenolic compounds, which disrupt bacterial cell membranes and inhibit protein synthesis (Gurung & Shrivastava, 2021). Furthermore, tannins exert an astringent effect that reduces exudate and creates an unfavorable environment for bacterial proliferation. Sari et al. (2021) emphasized that herbal-based formulations not only inhibit microbial growth but also avoid cytotoxic effects commonly associated with synthetic agents. Therefore, the antimicrobial properties of papaya root contribute significantly to preventing secondary infection, supporting a cleaner wound environment, and promoting faster epithelialization in burn healing.

Angiogenesis is a vital process in burn wound healing, as it ensures adequate delivery of oxygen and nutrients to regenerating tissues. Vascular endothelial growth factor (VEGF) is the primary mediator of angiogenesis and plays a crucial role in endothelial cell proliferation, migration, and neovascularization. Burn injuries often impair VEGF expression, resulting in poor vascularization and delayed healing (Wijayanti et al., 2024). Numerous studies have shown that papaya root extract can promote angiogenesis by upregulating VEGF expression. Rahayu et al. (2023) demonstrated that topical papaya root gel significantly increased VEGF levels in burn wounds, leading to enhanced granulation tissue formation and faster wound closure. Similarly, Hassan et al. (2020) reported that papaya extract not only reduced TNF-α but also elevated VEGF expression in vivo, confirming its dual role in modulating inflammatory and proliferative pathways. The presence of saponins and flavonoids in papaya root further stimulates endothelial cell activity and collagen deposition, supporting tissue remodeling (Dewi et al., 2020). By enhancing VEGF-mediated

angiogenesis, papaya root extract improves vascular supply, accelerates epithelialization, and supports overall tissue regeneration in burn wounds.

Papaya root extract has been widely reported to accelerate key phases of burn wound healing, particularly wound contraction and epithelialization, which are critical indicators of recovery. Several experimental studies demonstrated that papaya extract significantly shortened the epithelialization period and increased wound closure rate compared to untreated controls (Kumar et al., 2012; Jannah et al., 2022). The presence of flavonoids stimulates fibroblast proliferation and collagen synthesis, facilitating the formation of new extracellular matrix. Additionally, papain enzyme in papaya root acts as a natural debriding agent, removing necrotic tissue and allowing faster granulation (Gurung & Shrivastava, 2021). By promoting contraction, re-epithelialization, and matrix remodelling simultaneously, papaya root extract effectively enhances the overall speed and quality of burn wound healing.

Topical gel is considered an ideal delivery system for burn treatment due to its high moisture content, cooling effect, and enhanced drug penetration. Unlike ointments or creams, gel formulations are non-greasy, easily spreadable, and maintain a moist wound environment, which supports cell migration and prevents dehydration of the wound surface (Fauzi et al., 2021). Lestari et al. (2020) successfully developed a stable carbopol-based papaya root gel with optimal pH, viscosity, and homogeneity, confirming its feasibility for topical application. Gel formulations also promote controlled release of active compounds, allowing sustained therapeutic effects with minimal irritation. Furthermore, the transparency of gel allows easy wound monitoring without removal, making it a practical and patient-friendly delivery system for burn care.

Conventional burn treatments such as silver sulfadiazine are effective antimicrobials but associated with cytotoxicity, delayed epithelialization, microbial resistance, and patient discomfort (Sari et al., 2021). In contrast, papaya root gel offers a multifunctional and safer alternative, combining antimicrobial, anti-inflammatory, antioxidant, and angiogenic effects within a single natural agent (Kusuma et al., 2020; Rahayu et al., 2023). Unlike synthetic drugs that target only one phase of healing, papaya root modulates TNF-α to reduce inflammation and upregulates VEGF to promote angiogenesis (Ningsih et al., 2019; Rahayu et al., 2023). Additionally, natural-based gels are more cost-effective, widely accessible, and have lower risk of resistance, making them highly suitable for use in low-resource settings. Therefore, papaya root gel may provide comparable or superior therapeutic benefits with improved safety and affordability.

The effectiveness of papaya root gel in burn healing is largely attributed to its integrated molecular regulation of key mediators. Burn injury triggers excessive TNF-α, leading to inflammation, oxidative stress, and tissue damage (Wijayanti et al., 2024). Papaya root extract suppresses TNF-α expression, thereby reducing leukocyte infiltration and preventing prolonged inflammation (Ningsih et al., 2019). At the same time, it upregulates VEGF, enhancing angiogenesis, increasing blood supply, and supporting granulation tissue formation (Rahayu et al., 2023; Hassan et al., 2020). This

dual modulation creates a balanced transition from the inflammatory phase to the proliferative phase. Furthermore, bioactive compounds such as flavonoids, saponins, and papain contribute to collagen deposition, cell migration, and tissue remodelling (Dewi et al., 2020). Thus, the coordinated suppression of TNF-α and elevation of VEGF represents a synergistic, multi-targeted healing mechanism unique to papaya root extract.

Despite promising results, current research on papaya root gel for burn healing has several limitations. Most available studies are preclinical, animal-based, or in vitro, with limited human data to confirm clinical efficacy (Jannah et al., 2022). Sample sizes are often small, and variability in extraction methods, dosages, and gel bases makes it difficult to compare outcomes across studies (Fauzi et al., 2021). Additionally, few studies investigate long-term safety, toxicity, or pharmacokinetics of papaya root compounds. Standardization of active ingredient concentration and formulation stability is also lacking. Furthermore, many studies focus on single parameters instead of comprehensive molecular analysis, limiting mechanistic understanding (Sari et al., 2021). Therefore, well-designed clinical trials, standardized formulations, and molecular pathway studies are essential to establish papaya root gel as evidence-based burn therapy.

Although current evidence strongly supports the therapeutic potential of papaya root gel in burn wound healing, further research is essential to translate these findings into clinical practice. Future studies should focus on standardizing extraction methods, identifying specific active compounds, and optimizing gel formulation to ensure consistency, stability, and reproducibility (Fauzi et al., 2021). Large-scale in vivo studies and controlled clinical trials are necessary to evaluate efficacy, safety, dosage, and potential side effects in human subjects (Sari et al., 2021). In addition, exploring nanotechnology-based delivery systems or combination therapies may enhance penetration, bioavailability, and synergistic effects with other natural or synthetic agents. Advanced molecular studies should further investigate the regulation of TNF-α, VEGF, and other signalling pathways, such as NF-κB and TGF-β, to deepen mechanistic understanding (Wijayanti et al., 2024). From a practical perspective, papaya root gel has strong potential for use in low-resource settings due to its cost-effectiveness, accessibility, and low toxicity. Integrating herbal-based treatments into modern wound care protocols could reduce reliance on synthetic drugs and improve patient outcomes. Therefore, with continued scientific development and clinical validation, papaya root gel may emerge as a novel, safe, and evidence-based alternative therapy for burn wound management.

D. CONCLUSION

This literature review highlights the promising role of *Carica papaya* L's root extract formulated as a topical gel in accelerating the healing of second-degree burn wounds. The phytochemical constituents, particularly flavonoids, alkaloids, and phenolic compounds, contribute to anti-inflammatory and pro-angiogenic activities by modulating TNF-α and VEGF expression. Evidence from recent studies supports

the ability of papaya root extract to enhance tissue regeneration, reduce inflammation, and stimulate vascular growth, which are crucial steps in wound repair. While the current findings demonstrate significant therapeutic potential, further experimental and clinical research is required to establish standardized formulations, optimal dosages, and safety profiles for clinical applications. Overall, papaya root gel represents a potential alternative therapy for burn wound management and a valuable contribution to the development of herbal-based biomedical innovations.

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