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ORIGINAL ARTICLE

The Role Of *Mitragyna speciosa* (Korth) As An Anti-Inflammatory Agent In Wound Healing In Living Cells

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ABSTRACT

Background: Wound is a condition in which the integrity of body tissue is disrupted, leading to the activation of a complex biological process known as wound healing. This process aims to restore the protective skin barrier, prevent infection, and minimize fluid loss. It involves sequential phases of hemostasis, inflammation, proliferation, and remodeling. While inflammation is essential for initiating repair, prolonged or excessive inflammation may delay the healing process. *Mitragyna speciosa* (Korth) is a medicinal plant traditionally used in various cultures and has been reported to exhibit multiple pharmacological properties, including anti-inflammatory, antioxidant, antibacterial, analgesic, and wound-healing activities.

Methods: The present systematic review was conducted to identify and synthesize scientific evidence regarding the potential of *Mitragyna speciosa* extract as a therapeutic agent in wound healing through anti-inflammatory and other biological pathways. Literature searches were performed in ScienceDirect, PubMed, MDPI, DOAJ, and Google Scholar following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results :A total of 1,176 studies were screened, and five experimental studies fulfilled the inclusion criteria. The findings consistently demonstrated that *Mitragyna speciosa* extract suppressed pro-inflammatory mediators such as nitric oxide, reactive oxygen species, tumor necrosis factor-alpha, interleukin-6, and enzymatic pathways including cyclooxygenase-2 and 5-lipoxygenase. In addition, the extract stimulated cell migration, endothelial migration, and angiogenesis, thereby supporting tissue regeneration. Toxicity profiles suggest that the extract is safe at effective concentrations, although responses remain dose-dependent.

Conclusions: Overall, *Mitragyna speciosa* shows promise as a plant-based therapeutic option for wound healing. Nevertheless, current evidence is limited and largely derived from in vitro studies, indicating the need for more extensive in vivo and clinical investigations.

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Introduction

Wounds represent a pathological condition characterized by the loss or damage of body tissues, which may result from trauma, burns, temperature changes, chemicals, electrical injury, or animal bites (Sjamsuhidajat et al., 2017). The wound healing process is a highly coordinated physiological response that aims to restore skin barrier function and prevent infection and fluid loss. Delayed healing can result in severe complications such as chronic wounds, which are difficult to manage and may ultimately lead to amputation (Mills et al., 2020). Similarly, open wounds particularly burns are prone to bacterial invasion, with increased risks of infection and sepsis (Lestari et al., 2023). Wound healing progresses through four overlapping but distinct phases: hemostasis, inflammation, proliferation, and remodeling (Sjamsuhidajat et al., 2017; Zakaria et al., 2023). Factors such as diabetes, obesity, vascular disease, ischemia, aging, and genetic predispositions exacerbate impaired healing and are strongly associated with chronic wound pathology (Huelsboemer et al., 2024; Zhao et al., 2016).

Current wound care strategies range from conventional approaches to advanced therapies. The global market for advanced wound care is projected to reach USD 18.7 billion by 2027, with an estimated compound annual growth rate (CAGR) of 6.6% between 2020 and 2027 (Zakaria et al., 2023). Conventional treatments include the use of anti-inflammatory drugs such as corticosteroids and NSAIDs, which may alleviate inflammation but are associated with adverse gastrointestinal and cardiovascular effects (Agrawal et al., 2024). Systemic and prolonged use of these agents is therefore discouraged. Topical antibiotics have been used to deliver higher drug concentrations directly to the wound site, reducing microbial infections. However, excessive use contributes to antibiotic resistance, delays hypersensitivity responses, and may trigger secondary infections (Goyal et al., 2024). Chronic wound management often requires local debridement, irrigation, and sometimes reconstructive surgery, yet persistent inflammation continues to serve as a major barrier to complete healing (Huelsboemer et al., 2024).

Medicinal plants have historically served as the foundation of modern pharmacology, offering affordable, effective, and holistic therapeutic options with immunomodulatory potential (Goyal et al., 2024). Plant-derived therapies are advantageous due to their abundant availability, low production costs, and reduced risk of microbial resistance compared to single-compound drugs (Zakaria et al., 2023). One such promising plant is *Mitragyna speciosa* (Korth). (*M. speciosa*), commonly referred to as kratom. Native to Southeast Asia, particularly Indonesia, Malaysia, and Thailand, kratom has been traditionally employed to manage fever, diabetes, diarrhea, pain, wound healing, and withdrawal symptoms (Rahmawati et al., 2024). It has also been reported to enhance energy, act as a mild stimulant, induce euphoria, and contribute to chronic pain management (Tuntiyasawasdikul et al., 2024). Despite its growing popularity, *M. speciosa* has not received approval from the U.S. Food and Drug Administration (FDA) due to concerns regarding potential misuse. Nonetheless, recent reports indicate relatively low abuse potential, with increasing medical and recreational interest observed in the United States and Europe (Rahmawati et al., 2024).

Phytochemical analyses of *M. speciosa* have identified over 40 alkaloids, with mitragynine (66%) as the dominant constituent, followed by paynantheine (8.6%), speciogynine (6.6%), 7-hydroxymitragynine (2%), and speciociliatine (0.8%) (Ahmad et al., 2022). These compounds exhibit diverse pharmacological activities, including analgesic, antinociceptive, antidiarrheal, antioxidant, antibacterial, and anti-inflammatory effects (Salim et al., 2022; Tohar et al., 2019; Tuntiyasawasdikul et al., 2024). Since inflammation is a critical yet potentially detrimental phase of wound healing, prolonged or excessive inflammatory responses can impair tissue repair (Huelsboemer et al., 2024). Compounds derived from kratom may therefore serve as modulators of inflammatory pathways, promoting effective healing (Tohar et al., 2019). This study aims to provide a comprehensive analysis of the anti-inflammatory role of *M. speciosa* in wound healing, supported by experimental evidence. The findings are expected to enhance mechanistic understanding and support the development of safe, effective, and sustainable plant-based wound care therapies.

Methods

Data Sources

A systematic literature review was conducted to identify, collect, and analyze relevant information for this study. The research was designed to address the question of whether *Mitragyna speciosa* (Korth) extract exerts anti-inflammatory effects and accelerates wound healing. The PICO framework (Population, Intervention, Comparison,

and Outcome) was applied, focusing on the anti-inflammatory activity and wound healing effects of *M. speciosa* leaf extract in living cells. The search strategy was implemented using PubMed, ScienceDirect, MDPI, DOAJ, and Google Scholar databases, covering publications between June 2016 and June 2025. Search keywords included: On ScienceDirect: ("*Mitragyna speciosa*" OR kratom OR mitragynine) AND ("anti-inflammatory" OR "anti-inflammation") AND ("wound healing" OR "wound closure") AND ("in vivo" OR "in vitro"); ("*Mitragyna speciosa*" OR kratom OR mitragynine) AND ("anti-inflammatory" OR "anti-inflammation") AND ("wound healing" OR "wound closure"); *Mitragyna speciosa*. kratom. inflammatory. wound healing. wound closure; *Mitragyna speciosa*. Anti-Inflammatory Agents. Wound Healing. Macrophage; (kratom OR "*Mitragyna speciosa*") AND ("anti-inflammatory" OR "wound healing") AND ("animal" OR "cell" OR "model"); ("*Mitragyna speciosa* extract" OR kratom) AND ("wound closure rate" OR "granulation tissue" OR "re-epithelialization" OR "collagen fiber") AND ("mice" OR "keratinocyte"); and several variations including terms related to extracellular matrix, fibroblasts, COX-2 inhibition, TNF-alpha suppression, and IL-6 regulation. On PubMed: (kratom OR "*Mitragyna speciosa*") AND ("wound healing" AND "anti-inflammatory"); ("Mitragyna"[Mesh] OR "*Mitragyna speciosa*"[Supplementary Concept] OR kratom OR mitragynine) AND ("Anti-Inflammatory Agents"[Mesh] OR "TNF-alpha"[Mesh] OR "IL-6"[Mesh]) AND ("Wound Healing"[Mesh] OR "Collagen"[Mesh] OR "Extracellular Matrix"[Mesh]) AND ("Models, Animal"[Mesh] OR "Cells, Cultured"[Mesh]); along with terms such as proliferation, macrophage, and fibroblast. On MDPI: "*Mitragyna speciosa*. Inflammatory"; "*Mitragyna speciosa*. M2". On DOAJ: "*Mitragyna speciosa*. Inflammatory". On Google Scholar: "*Mitragyna speciosa* (Korth) wound healing inflammation -review".

Study Selection Process

The screening and analysis process involved four independent reviewers (ESAFH, MASJ, KNJR, RAP) following PRISMA guidelines. The initial step included filtering based on publication date (2016–2025) and article type (original research). Duplicate studies were then removed, followed by screening according to inclusion and exclusion criteria. The inclusion criteria were: (1) national or international articles evaluating the anti-inflammatory properties of *M. speciosa* and its relevance to wound healing, either directly through in vivo wound healing studies or indirectly through in vitro anti-inflammatory mechanisms; (2) publications in English or Indonesian; and (3) experimental studies. Exclusion criteria included: (1) articles not addressing *M. speciosa* as an anti-inflammatory agent in wound healing; (2) reviews, editorials, expert opinions, letters to the editor, and single case reports; (3) literature reviews; and (4) studies without available full-text. The screening process was facilitated using Rayyan software.

Data Extraction and Risk of Bias Assesment

To ensure the validity and reliability of the evidence included in this review, methodological quality was assessed for all studies selected. This evaluation aimed to identify potential sources of bias that could affect study outcomes. Risk of bias assessment was conducted systematically using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental Studies. The evaluation process was supported by a large language model (LLM, Gemini) and subsequently reviewed comprehensively by the lead investigator (ESAFH).

Data Synthesis

Due to significant heterogeneity across the extracted studies—including differences in study design (in vitro across various cell lines and in vivo animal models), extraction methods of *M. speciosa*, concentrations used, and outcome measures—a narrative synthesis approach was adopted. The synthesis was conducted thematically, grouping studies according to predefined themes aligned with the review objectives: (1) anti-inflammatory effects through the suppression of inflammatory mediators; (2) potential in wound healing; and (3) safety profile and cytotoxicity. Relevant findings for each theme were summarized and discussed descriptively to highlight patterns, similarities, and differences across studies. The results were presented narratively and supported with a table of study characteristics, including title, year, authors, objectives, samples, instruments, methods, and findings.

Result

Study Selection The initial search identified 1,176 records across the databases ScienceDirect, PubMed, DOAJ, MDPI, and Google Scholar. Four databases (excluding Google Scholar) underwent preliminary filtering to exclude articles published outside the period June 2016–June 2025 and non-research articles, resulting in 95 eligible records. After removing duplicates, 44 articles remained. Subsequent title and abstract screening excluded studies not relevant to the research focus, leaving 8

articles. The eligibility assessment was then applied, whereby articles that met the inclusion criteria were retained and those fulfilling exclusion criteria were removed. Ultimately, 4 studies from these databases were included. The search in Google Scholar followed a slightly different approach due to the platform's limited filtering functions. A total of 599 records were retrieved. After excluding articles published outside 2016–2025, 417 remained.

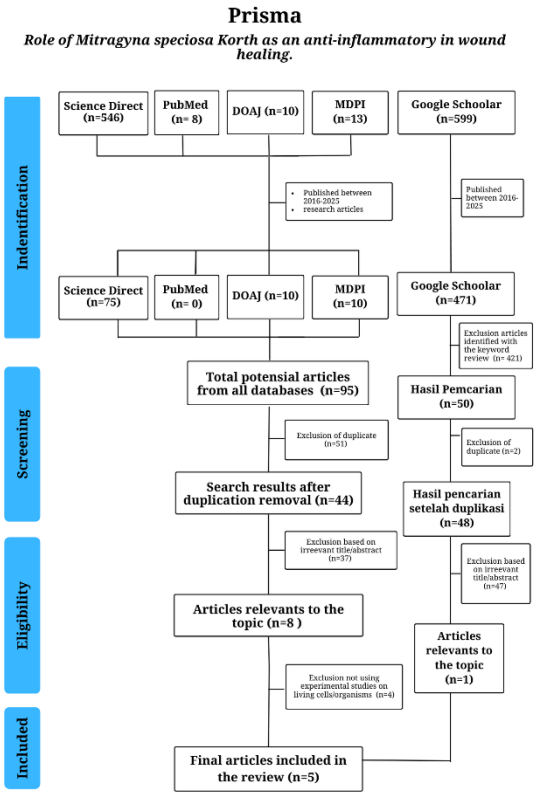

Figure 1. PRISMA Flow Chart

To refine the process and avoid review articles (which were part of the exclusion criteria), the keyword "review" was excluded, yielding 50 records. Duplicate removal reduced this number to 48. Title and abstract screening further excluded irrelevant studies, leaving 1 article. The eligibility assessment confirmed that this study met the inclusion criteria. In total, 5 articles from all databases were included in the final analysis. All five studies included were published between 2016 and 2025 and specifically evaluated the anti-inflammatory effects of *Mitragyna speciosa* in the context of wound healing. Data extraction from these articles covered title, authors, objectives, methodology/instruments, and results, which are summarized in a supplementary table.

Sudy Characteristic

All five included studies were published between 2016 and 2025 and evaluated the anti-inflammatory effects of *M. speciosa* in the context of wound healing. Data extraction involved collection of study title, authors, objectives, methodology/instruments, and main findings. These details were summarized in a table (see Appendix).

Risk of Bias Assesment

The methodological quality and risk of bias of the five included studies were assessed using the Joanna Briggs Institute (JBI) Checklist for Quasi-Experimental Studies, with the assistance of a Large Language Model (LLM, Gemini). Results indicated variable levels of bias across the studies, but none demonstrated a high risk of bias. Most studies exhibited strong methodological quality in fundamental domains. All clearly defined cause-and-effect relationships and employed appropriate negative controls. Consistency of treatment across groups was also well reported, minimizing performance bias. However, weaknesses were noted in domains with unclear identification, particularly affecting outcome measurement reliability. Studies by Tohar et al. (2019), Tuntiyawasdikul et al. (2024), and Rahmawati et al. (2024) consistently fulfilled most JBI criteria, with transparent reporting, appropriate controls, and robust data analysis. The study by Salim et al. (2022) demonstrated a moderate risk of bias. While most JBI criteria were satisfied, unclear blinding in outcome assessment introduced potential bias. Similarly, Zakaria et al. (2023) showed a moderate risk of bias, primarily due to methodological subjectivity in the scratch assay. This included manual scratch creation, visual boundary determination, semi-manual use of ImageJ, and the absence of blinding procedures. Despite these limitations, no study exhibited high risk of bias. The overall low-to-moderate risk supports the inclusion of all five studies in this systematic review.

Result Synthesis

1. **Anti-inflammatory Effects Through Suppression of Inflammatory Mediators**

Inflammation is a physiological process of the body in response to harmful stimuli such as infection, injury, and irritants. It functions to clear damaged tissue, combat infection, and initiate healing. However, when prolonged, inflammation may impede the wound healing process (Xu et al., 2021). Extracts of *M. speciosa* have been shown to exert anti-inflammatory effects by suppressing inflammatory mediators through various pathways (Rahmawati et al., 2024; Salim et al., 2022; Tohar et al., 2019; Tuntiyawasdikul et al., 2024; Zakaria et al., 2023). Four of the reviewed studies reported evidence of anti-inflammatory activity through suppression of inflammatory mediators.

The study by Rahmawati et al. (2024) employed RAW 264.7 macrophage cells treated for 1 hour with two types of extracts: crude extract (25, 50, and 100 ppm) and alkaloid extract (6.25, 12.5, and 25 ppm). Cells were subsequently induced with 1 µg/mL lipopolysaccharide (LPS) to trigger inflammation and incubated for 24 hours. Regarding oxidative stress, a significant reduction in reactive oxygen species (ROS) was observed. The strongest reduction occurred at 25 ppm of the alkaloid extract, showing a 64% decrease, followed by the crude extract at 100 ppm with a 50% decrease. Both extracts also reduced nitric oxide (NO) production, with maximum inhibition at 7–8 nM for 100 ppm crude extract and 25 ppm alkaloid extract. The extracts demonstrated a reduction in pro-inflammatory cytokines (TNF-α and IL-6). TNF-α inhibition was observed at concentrations ≥12.5 ppm for the alkaloid extract and ≥50 ppm for the crude extract, whereas IL-6 inhibition was most effective at 100 ppm crude extract and 25 ppm alkaloid extract. Interestingly, not all concentrations exhibited inhibitory effects; TNF-α increased at 25 ppm crude extract, while IL-6 increased at 25 ppm alkaloid extract. COX-2 and 5-LOX pathways were also affected. COX-2 was inhibited by an average of 33.46% across all alkaloid concentrations, while crude extract showed inhibition only at 25 ppm. 5-LOX inhibition was observed at ≤12.5 ppm alkaloid extract (35.06%), with no inhibition observed for crude extract (Rahmawati et al., 2024).

Inhibition of NO production was also demonstrated in the study by Tohar et al. (2019), which utilized *M. speciosa* extracts obtained through Supercritical Fluid Extraction (SFE). Extraction occurred in two steps: the first using pure CO2, and the second with CO2 plus ethanol. Fifteen different extracts were tested on RAW 264.7 macrophages inflamed by interferon-γ (IFN-γ) and LPS. Six extracts showed moderate inhibition (51–64%), while nine demonstrated weak inhibition (16–48%). The most potent extract, labeled M5S1, was obtained using step 1 (100% CO2) at 3000 psi and 60°C, with an inhibition rate of 60.08 ± 10.02% and cell viability of 91.98 ± 5.58%. M5S1 contained the highest concentration of palmitic acid (34.90%), a known phospholipase A2 inhibitor with anti-inflammatory properties, although other compounds in the extract may also contribute (Tohar et al., 2019). Anti-inflammatory activity was further investigated by Tuntiyawasdikul et al. (2024), who evaluated NO inhibition and inflammatory gene expression. RAW 264.7 macrophages were cultured in 96-well plates for NO assays and 12-well plates for gene expression assays at a density of 1.5 × 10^5 cells. Cells were treated with varying concentrations of *M. speciosa* extract (10–300 µg/mL) and aminoguanidine (10–100 µg/mL) as a positive control for NO assays, while indomethacin was used as a positive control for gene expression assays. Cells were stimulated with LPS (50 µg/mL). Results demonstrated a dose-dependent reduction in NO production, with an IC50 of 147.79 ± 8.97 compared to 35.83 ± 3.33 for the positive control. Significant dose-dependent suppression of mRNA expression was also observed for pro-inflammatory genes (iNOS, COX-2, IL-1β, and IL-6), with IC50 values of 182.71 ± 11.31 for iNOS, 275.82 ± 34.07 for COX-2, 286.29 ± 21.99 for IL-6, and 289.60 ± 43.51 for IL-1β. By contrast, positive control IC50 values were 45.37 ± 8.0 for iNOS, 53.59 ± 6.40 for COX-2, 41.29 ± 1.68 for IL-6, and 53.24 ± 3.24 for IL-1β. These findings provide evidence of the anti-inflammatory effects of *M. speciosa* at the transcriptional level (Tuntiyawasdikul et al., 2024). Inflammatory gene expression plays a critical role in wound healing, with pro-inflammatory cytokines regulating gene expression to facilitate tissue repair and remodeling (Mahmoud et al., 2024). Salim et al. (2022) investigated the anti-inflammatory effects of *M. speciosa* using a carrageenan-induced paw edema model in mice. Animals were divided into a control group, a carrageenan-only group, and treatment groups receiving oral *M. speciosa* extract at doses of 75 mg/kg, 150 mg/kg, and 200 mg/kg. Results demonstrated reduced paw swelling at all doses, measured with a plethysmometer at 0, 1, 2, and 4 hours post-carrageenan injection. Histological examination showed restoration of skin thickness approaching normal, particularly at 150 mg/kg and 200 mg/kg. Oral administration of *M. speciosa* extract produced significant anti-inflammatory effects, including reduced vascular permeability, thereby limiting edema formation. The extract effectively suppressed early-phase edema by inhibiting synthesis, release, or activity of hyperalgesic mediators (Salim et al., 2022). Strong antioxidant activity of *M. speciosa* extracts was also highlighted in this study. Antioxidant capacity was evaluated using three assays: ABTS radical scavenging, Ferric Reducing Antioxidant Power (FRAP), and total phenolic content (TPC) via Folin-Ciocalteu reagent. Both crude and alkaloid extracts demonstrated strong ABTS radical scavenging, with 94% inhibition at 1000 ppm, indicating high antioxidant activity. In FRAP and TPC assays, crude extract was approximately 20 times more effective in reducing ferric ions compared to the alkaloid extract. TPC analysis

confirmed significantly higher total phenolic content in the crude extract (7224 ± 46.4 mg GAE g−1) (Rahmawati et al., 2024). Antioxidants contribute to both anti-inflammatory and wound healing processes, as excessive ROS production or impaired detoxification leads to inflammation and oxidative stress-induced cellular damage—major factors delaying wound healing (Chaniad Id et al., 2020).

2. Potential for Wound Healing

Wound healing is closely associated with the inflammatory process, as wound repair consists of four overlapping phases, one of which is inflammation (Sjamsuhidajat et al., 2017; Zakaria et al., 2023). The study by Zakaria et al. (2020) demonstrated that the mechanism of wound healing extends beyond anti-inflammatory activity. The wound healing potential was attributed to two mechanisms: enhanced cell migration and the promotion of angiogenesis. Stimulation of cell migration was assessed by creating artificial wounds in fibroblast and HUVEC monolayer cultures, followed by treatment with various extract fractions (methanol crude extract, dichloromethane fraction, and ethyl acetate fraction) at concentrations of 1.56 µg/mL, 3.13 µg/mL, and 6.25 µg/mL. The extracts were evaluated for their ability to stimulate fibroblast and endothelial cell migration to close the artificial wound. Results indicated that all extracts contributed to accelerated cell migration compared to the control. Notably, the ethyl acetate and dichloromethane fractions exhibited the most rapid migration activity in fibroblasts, achieving 71.22–70.85% closure at 3.13 µg/mL. The ethyl acetate fraction also demonstrated the fastest closure in HUVEC cells. These findings provide evidence that *M. speciosa* extract can enhance wound healing processes (Zakaria et al., 2023). Angiogenesis plays a critical role in wound healing, as it ensures an adequate blood supply to the wound site and promotes tissue regeneration and repair (Nazarnezhad et al., 2022). The study by Zakaria et al. (2020) further evaluated the angiogenic potential of *M. speciosa* extract in HUVECs. Cells were cultured on a tissue-mimicking matrix (Matrigel®) and treated with varying extract concentrations (1.56, 3.13, and 6.25 µg/mL). The angiogenesis assay demonstrated significant stimulation of tube formation compared with the control group. Among the fractions, the ethyl acetate fraction was most effective, producing the greatest total branching length across all tested concentrations, with values of 9014.33, 7750, and 10,986 pixels, respectively. Chemical analysis (LC-MS/MS) identified multiple bioactive compounds within the extracts. The ethyl acetate fraction contained the highest diversity of compounds, including flavonoids, phenols, and fatty acids, all of which are known to exert therapeutic effects such as anti-inflammatory, antioxidant, and antibacterial activities—properties that collectively support wound healing (Zakaria et al., 2023).

3. Safety Profile and Cytotoxicity

Overall, the five analyzed studies demonstrated that *M. speciosa* extracts exhibit a favorable safety profile at effective concentrations. In several assays, cytotoxicity testing was essential to confirm that the observed reduction in nitric oxide (NO) production reflected anti-inflammatory effects rather than cell death (Tohar et al., 2019). Determining a safe concentration range for cells is also important for evaluating the therapeutic potential of the extract. Zakaria et al. (2023) conducted cytotoxicity testing using 3T3 fibroblasts and HUVEC endothelial cells seeded in 96-well plates at a density of 1×10^4 cells/well. Extracts were tested at concentrations of 1.56, 3.13, 6.25, 12.5, 25, and 100 µg/mL. The crude ethanol extract, hexane fraction, and ethyl acetate fraction all demonstrated safety profiles with cell viability ranging between 50–150%. In contrast, the dichloromethane fraction exhibited slight cytotoxicity at higher concentrations (75.418 ± 5.286 µg/mL). In HUVEC cells, the hexane fraction was found to be the most cytotoxic, with a notably low IC_{50} value of 21.323 ± 7.766 µg/mL. Extracts are generally considered non-toxic when their IC_{50} values exceed 30 µg/mL (Zakaria et al., 2023). Rahmawati et al. (2024) also evaluated cytotoxicity using the MTT assay in RAW 264.7 macrophages. Cells were treated with either crude extract (25, 50, 100, and 200 ppm) or alkaloid extract at equivalent concentrations. The results revealed that the crude extract was safe and non-toxic to RAW 264.7 cells, with viability ranging from 91–100% across all tested concentrations, even at the highest dose. Conversely, the alkaloid extract exhibited concentration-dependent cytotoxicity. At 25 ppm, viability remained safe at 100%, but decreased to 46% at 50 ppm, 10% at 100 ppm, and reached complete cell death at 200 ppm. These findings suggest that the crude extract is considerably safer across a wider dose range compared to the alkaloid extract (Rahmawati et al., 2024).

Cytotoxicity testing was also conducted by Tohar et al. (2019) using RAW 264.7 macrophages with the MTT assay, involving 15 treatment groups and one control group. Cell viability was reported as a percentage, calculated by comparing the absorbance of treated cells with untreated controls.

For NO inhibition to be considered valid, cell viability was required to remain above 85%. Results showed that 9 of the 15 groups maintained viability above this threshold, while the remainder fell below (Tohar et al., 2019). Further cytotoxicity evaluation was performed by Tuntiyawasdikul et al. (2024), who applied the MTT assay across four skin-relevant cell lines: human fibroblasts (CRL-2522), human keratinocytes (HaCaT), mouse melanoma cells (B16F10), and murine macrophages (RAW 264.7). Cells were cultured in 96-well plates and treated with five extract concentrations, up to 2.5 mg/mL. Viability was measured spectrophotometrically at 570 nm. The IC_{50} values obtained were: keratinocytes (1.29 ± 0.03 mg/mL), macrophages (1.40 ± 0.03 mg/mL), melanocytes (1.99 ± 0.06 mg/mL), and fibroblasts (2.46 ± 0.18 mg/mL). These results indicate a favorable safety profile, as IC_{50} values exceeding 1 mg/mL are generally considered non-toxic (Tuntiyawasdikul et al., 2024).

Discussion

This systematic review synthesizes evidence from five experimental studies aimed at evaluating the role of *Mitragyna speciosa* (Korth) as an anti-inflammatory agent in the context of wound healing. Overall, the findings provide strong scientific support for the traditional use of this plant. Extracts of *M. speciosa* consistently suppress multiple inflammatory markers. Collectively, the analyzed studies demonstrate a reduction in the production of ROS, NO, and pro-inflammatory cytokines such as TNF-α and IL-6, as well as the inhibition of enzymatic pathways mediated by COX-2 and 5-LOX. However, it is important to note that inflammation is a critical component of the wound healing process, serving to cleanse wounds and combat pathogens. Prolonged inflammation, on the other hand, may hinder wound repair (Xu et al., 2021). The anti-inflammatory effects of *M. speciosa* are associated with its bioactive compounds. According to Tohar et al. (2020), extraction using Supercritical Fluid Extraction identified fraction M5S1 as the most potent extract, containing palmitic acid as the major compound (34.90%). Other compounds, such as tocopherol, were also shown to contribute to its anti-inflammatory effects (Tohar et al., 2019). *M. speciosa* exhibits multifactorial activity, reflecting the synergistic interaction of various bioactive compounds, including flavonoids, phenols, and fatty acids, in addition to its well-known alkaloids. Beyond anti-inflammatory activity, this review also highlights direct evidence of wound-healing potential. Zakaria et al. (2023) reported that extracts specifically accelerated fibroblast and endothelial (HUVEC) cell migration and promoted angiogenesis. Such effects are crucial, as cell migration plays an essential role in wound closure, while angiogenesis ensures adequate nutrient and oxygen supply for tissue regeneration (Voza et al., 2024; Wang et al., 2024; Zakaria et al., 2023).

This systematic review is not without methodological limitations. The primary limitation lies in the reliance on narrative synthesis, due to substantial heterogeneity in study designs, interventions, and outcomes, which precluded quantitative meta-analysis. Consequently, conclusions were drawn qualitatively and did not provide a pooled systemic effect. The implications of these findings span clinical practice, policy, and future research. Clinically, it is still premature to recommend the broad use of *M. speciosa*. Nonetheless, the present findings offer a robust scientific foundation for the development of plant-derived therapeutic agents. From a policy perspective, *M. speciosa* and its main alkaloids, mitragynine and 7-OH mitragynine, are not yet approved by the FDA (Rahmawati et al., 2024). Current regulatory restrictions are largely based on concerns regarding the potential misuse of kratom, as higher doses may produce opioid-like effects and associated adverse outcomes. Therefore, a balanced regulatory framework is essential to facilitate research into its therapeutic compounds while tightly controlling its use (Davidson et al., 2021; Demick et al., 2020). Findings suggesting that crude extracts are safer than pure alkaloid fractions at higher concentrations may also provide important insights for regulatory bodies (Tohar et al., 2019).

Several critical directions are identified for future research. The foremost priority is to advance *in vivo* studies using clinically relevant wound models, such as excision, incision, or burn wounds in animals, to validate *in vitro* findings and assess all phases of wound healing. Standardization of extraction protocols and formulation is also necessary to ensure consistency and reproducibility of results. Further studies should focus on isolating and identifying the most active compounds responsible for anti-inflammatory and pro-regenerative effects, as well as clarifying the underlying molecular signaling pathways. Long-term toxicity evaluations, systemic safety studies, and comparative analyses examining the efficacy of *M. speciosa* extracts against standard wound care agents are essential steps before progressing to human clinical trials.

Conclusion

Mitragyna speciosa (Korth) is a plant long recognized in traditional medicine for its broad therapeutic effects, particularly in wound healing. Based on the systematic review conducted, this plant demonstrates clinically proven effects in regulating the suppression of inflammation, including modulation of NO, ROS, TNF-α, IL-6, and the enzymatic pathways of COX-2 and 5-LOX. Moreover, *M. speciosa* actively promotes the healing process by stimulating fibroblast and endothelial cell migration as well as angiogenesis, indicating its potential as a future therapeutic option for wound healing. Current wound-healing therapies commonly involve corticosteroids and NSAIDs, which are associated with various side effects, including cardiovascular and gastrointestinal complications, while excessive use of antibiotics has also led to resistance. Plant-based therapies such as *M. speciosa* are therefore expected to offer benefits by reducing adverse effects compared to conventional treatments. However, its utilization faces regulatory challenges due to the potential for misuse, leading to psychotropic effects and other harmful side effects. Thus, stronger scientific evidence is required to support its therapeutic claims. Controlled and evidence-based management of this plant may optimize its benefits and provide significant clinical advantages, although further research remains necessary before its application in humans. The findings of this study are expected to serve as a foundation for future research in developing plant-based therapies, particularly for wound healing.

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Ethics statement: This study is a systematic review that synthesizes data from previously published studies. As no new experiments involving human participants or animals were conducted, ethical approval and informed consent were not required. All data analyzed were obtained from publicly available sources in accordance with ethical publishing standards.

Conflict of Interest

No conflict of interest in this study

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