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Review Article

Formulation and Evaluation of Antibiotic Wound Healing Using Mitragyna Parvifolia: A Review

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ABSTRACT

Mitragyna parvifolia is an ethnomedicinal herb with significant potential as a natural wound-healing agent, especially in the context of increasing antibiotic resistance. Traditional use of this plant in folk medicine supports its therapeutic relevance, and modern research has highlighted its antibacterial, anti-inflammatory, antioxidant, and regenerative properties. The plant's bioactive constituents' alkaloids, flavonoids, and triterpenoids play critical roles in inhibiting bacterial growth, reducing oxidative stress, and enhancing collagen synthesis. These compounds contribute to the plant's efficacy against Staphylococcus aureus and Pseudomonas aeruginosa, two key pathogens commonly associated with wound infections. Alkaloids, in particular, disrupt bacterial cell walls and inhibit biofilm formation, providing an effective antimicrobial mechanism. Moreover, Mitragyna parvifolia modulates inflammatory responses by regulating cytokines such as TNF-α, IL-1β, and IL-6, leading to reduced inflammation and improved macrophage activity. Its antioxidant properties prevent tissue damage and promote fibroblast proliferation, which is vital for tissue regeneration and increased tensile strength in the healing process. Various formulations, including topical ointments, hydrogels, and wound dressings, have incorporated Mitragyna extracts often synergistically with other herbs—to enhance efficacy. Preclinical studies on animal models have demonstrated promising results with improved healing rates and tissue repair. However, further clinical research is necessary to validate these findings in human subjects and establish standardized protocols for safe use. Overall, Mitragyna parvifolia represents a promising alternative in wound management, offering a natural solution to combat infections and support healing amidst the global challenge of antibiotic resistance.

INTRODUCTION

Wound healing is a complex, dynamic process that aims at restoring tissue integrity after injury. Its

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four separates yet overlapping phases are haemostasis, inflammation, proliferation, and remodelling. For the wound healing process to be effective, the coordinated development through these stages and their wide range of cellular and molecular activity are essential. However, several factors, including microbial infections, immunological deficits, and chronic diseases such as diabetes, can disrupt this mechanism. Antibiotics are often prescribed to treat infections, which pose a critical barrier to wound healing in particular. Yet, most of the traditional antibiotics have become ineffective because of the increasing prevalence of antibiotic-resistant bacteria, demanding alternative therapeutic strategies. [1]

1.1 Biology of Wound Healing

The first step in wound healing is haemostasis, a process where platelets aggregate into a clot that closes the wound and stops further blood loss. Following this is the inflammatory phase where macrophages and neutrophils, among other immune cells, migrate to the wound site. Along with eliminating infections and cleaning away cellular debris, these cells also produce growth factors and cytokines that help the healing mechanism along. The proliferation stage is characterized by the proliferation of granulation tissue, which includes collagen deposition and the activity of fibroblasts. Angiogenesis, or the development of new blood vessels, occurs to allow for the delivery of oxygen and nutrients to the tissue that is being repaired during this stage. Lastly, during the remodelling phase, extracellular matrix remodelling and reorganization strengthen the newly produced tissue. [2]

1.2 Challenges in Wound Healing

Wound healing is sometimes generally designed inherently to restore tissue integrity, but the process may easily be impaired by many variables. One of the biggest problems during wound healing is infection, which does not only slow the healing process itself but can also lead to more serious issues like sepsis, necrosis, and chronic wounds. Antimicrobial therapy, of course, plays a major role in the management of infected wounds but must be accompanied by supportive therapies that promote tissue regeneration. Though synthetic antibiotics have long been the treatment of choice for wound infections, their efficacy has progressively been undercut because of the increasing problem of antibiotic resistance. [3]

1.3 Herbal Medicine as an Alternative in Wound Care

Moreover, the use of herbal medicine for wound healing has been documented in Ayurveda, Traditional Chinese Medicine, and Indigenous healing for thousands of years. High contents of biologically active compounds exhibiting potent antibacterial, anti-inflammatory, and antioxidant activities have been reported in plants, such as terpenoids, alkaloids, flavonoids, and phenolic compounds.[4] Many herbal medicines have different mechanisms of action compared to the synthetic antibiotics, thus reducing chances of resistance. Furthermore, the herbal formulation may help the natural healing process of the body through a boost in tissue regeneration, collagen formation, and immunological responses. [5] In recent years, the pharmacological properties of medicinal plants have gained interest among scientists, and various studies have tried to find out if it could be used today in wound healing. One of the many herbs that have been researched for their ability to heal wounds is Mitragyna parvifolia, a South Asian plant whose potential antibacterial and tissue-regenerative qualities are of interest. [6]

1.4 Mitragyna parvifolia: A Traditional Medicinal Plant

Of the traditional medicines, especially Ayurveda, Mitragyna parvifolia is a deciduous tree belonging to the family Rubiaceae used to cure various ailments, such as inflammation, wounds, and skin infections. Even though this plant is closely related to Mitragyna species (Kratom), its phytochemical profile and medicinal use are different. In rural and tribal countries of India and Sri Lanka, Mitragyna parvifolia is often used to cure burn, wound, ulcers, and other cutaneous diseases. [7] The pharmacological activity of the plant is attributed to several bioactive compounds present in bark, leaves, and root extracts, including flavonoids, triterpenoids, alkaloids (which include mitraphylline), and tannins. These compounds have demonstrated antibacterial activity against a wide range of microorganisms that might infect wounds. Mitragyna parvifolia is also an excellent candidate for wound healing formulations targeted at infection and repair in tissues due to its anti-inflammatory, analgesic, and antioxidant properties. [8]

1.5 Relevance of Mitragyna parvifolia in Modern Wound Care

Research into Mitragyna parvifolia as a wound healing agent is very relevant and appropriate because there is an ever-increasing need for alternative treatment for wound care. The plant is a perfect choice in developing topical preparations meant to solve chronic and infected wounds, particularly considering its antibacterial and wound-healing properties. Moreover, its application follows guidelines on antimicrobial stewardship, which call for reduced levels of antibiotic abuse and research into other alternatives.

Though preclinical research on Mitragyna parvifolia's potential wound healing ability is in its initial stages, encouraging findings have been demonstrated thus far. Further clinical trials and formulation studies are necessary to ascertain its safety, effectiveness, and best application in wound care. Apart from its role as a cost-effective and easily accessible alternative to populations that rely on traditional medicine, Mitragyna parvifolia has the potential to be a natural efficient alternative to conventional antibiotics in wound healing, which could prove crucial in the fast-emerging problem of antibiotic resistance.

2. Mitragyna parvifolia: Botanical and Pharmacological Overview

2.1 Botanical Description of *Mitragyna parvifolia*

The deciduous tree, Mitragyna parvifolia belongs to the family of Rubiaceae. Botanically this family includes over 13,500 species with a number of these being recognized for medicinal purposes. This tree occurs mainly in regions of Nepal, India, and Sri Lanka, belonging originally to South and Southeast Asia. Although it has a distinct pharmacological profile, the plant is considered to be closely taxonomically related to Mitragyna species, often called kratom, and was commonly known as "Kadam" in Indian languages. [9]

2.2 Traditional Uses of *Mitragyna parvifolia*

Mitragyna parvifolia has been in use for a long time by traditional medical systems, especially the Indian Ayurvedic and Unani traditions. The plant's leaves, bark, and roots have been used in treatment for lots of illnesses including gastrointestinal problems, skin conditions, fever, inflammation, and wounds.[10] Mitragyna parvifolia is frequently used in tribal and rural populations to treat:

• **Wounds and Skin Infections:** The crushed leaves and bark are applied as a paste directly to cuts, wounds, and ulcers to stop infection and hasten healing.

• **Inflammation:** Infusions and decoctions of the bark as well as leaves are used to reduce inflammation, particularly in gout and arthritis.

• **Malaria and Fever**: The bark of the tree is used as a medicine for fever, according to traditional administration.

The plant is used as a tonic to treat diarrhoea, dysentery, and other digestive disorders.

Mitragyna parvifolia is used extensively in traditional medicine; by this, one believes its value to regional health systems where access to contemporary medical care may be limited. This historical knowledge provides the foundation for modern research into the pharmacological properties of the plant. [11]

2.3 Phytochemistry of *Mitragyna parvifolia*

The therapeutic potential of Mitragyna parvifolia can be attributed to its rich phytochemical profile, which contains a variety of alkaloids, flavonoids, triterpenoids, and other secondary metabolites. These compounds have been demonstrated to exhibit a variety of biological activities, including antibacterial, anti-inflammatory, analgesic, antioxidant, and wound-healing properties. [12]

Alkaloids:

Alkaloids are the primary bioactive compounds found in *Mitragyna parvifolia*, and they are responsible for many of its pharmacological effects. The key alkaloids present in the plant include:

Table no. 1 (Alkaloids)

Compound	Properties	Potential Applications
Mitraphylline	- Pentacyclic oxindole alkaloid - Potent anti-inflammatory and immunomodulatory - Antimicrobial action, particularly against wound-infecting bacteria	- Wound infection treatment - Reducing inflammation
Isomitraphylline	-Structurally similar to mitraphylline -Enhances immune response - Promotes tissue regeneration	- Wound healing - Immune system support
Rhynchophylline	-Anti-inflammatory - Vasodilatory properties	- Reducing wound inflammation - Improving blood flow
Isorhynchophylline	-Anti-inflammatory - Vasodilatory properties	- Reducing wound inflammation - Improving blood flow

Flavonoids:

Flavonoids are another important class of compounds in *Mitragyna parvifolia*, contributing to its antioxidant and antimicrobial activities.

Table no. 2 (Flavonoids)

Compound	Properties	Potential Applications
Quercetin	-Strong antioxidant - Neutralizes reactive oxygen species (ROS) - Exhibits antimicrobial activity - Modulates inflammatory pathways - Promotes collagen synthesis	- Preventing oxidative damage in wounds - Preventing wound infections - Enhancing tissue repair and regeneration
Kaempferol	- Potent antioxidant and anti-inflammatory - Protects wound tissue from oxidative stress - Promotes skin cell proliferation - Inhibits enzymes involved in inflammation (e.g., COX, LOX) - Enhances angiogenesis for improved blood supply to the wound	- Supporting wound healing - Enhancing wound closure - Improving vascularization in damaged tissues
Curcumin	- Strong anti-inflammatory and antioxidant - Antimicrobial against a broad spectrum of bacteria and fungi - Promotes fibroblast migration and collagen deposition	- Reducing wound inflammation - Enhancing granulation tissue formation - Accelerating wound closure
Epigallocatechin Gallate (EGCG)	- Polyphenol with powerful antioxidant properties - Reduces ROS and oxidative stress - Promotes angiogenesis and keratinocyte proliferation - Exhibits antimicrobial properties	- Enhancing wound re-epithelialization - Supporting new blood vessel formation - Protecting against wound infections

Triterpenoids:

Triterpenoids are natural compounds with diverse pharmacological properties, including anti-inflammatory, antimicrobial, and wound healing activities.

- **Betulinic Acid**: This triterpenoid has demonstrated antimicrobial action against both Gram-positive and Gram-negative bacteria, as well as fungi, making it an effective agent for preventing wound infections. Betulinic acid also promotes the proliferation of fibroblasts, which are essential for collagen synthesis and wound repair.
- **Oleanolic Acid**: Known for its anti-inflammatory and wound healing properties, oleanolic acid has been shown to enhance epithelialization and increase the tensile strength of healed tissue. [13]

Other Compounds:

This plant is characterized by the presence of alkaloids, flavonoids, triterpenoids, saponins, and tannins. The antibacterial and astringent properties of *Mitragyna parvifolia* are due to the ones mentioned above, including alkaloids, flavonoids, and triterpenoids. For instance, tannins facilitate the coagulation of proteins at the site of injury, creating a barrier that reduces the risk of infection as well as healing. [14]

2.4 Pharmacological Activities of *Mitragyna parvifolia:*

Mitragyna parvifolia's vast range of pharmacological effects, many of which are

related to wound healing, are supported by its varied phytochemical makeup.

2.4.1 Antimicrobial Activity

Due to its broad-spectrum antibacterial activity, *Mitragyna parvifolia* is effective against a range of pathogens commonly seen in infections of wounds. Of the alkaloids isolated from the plant, specifically mitraphylline and its analogues, studies have proven them to be active against both Gram-positive and Gram-negative bacteria. The action through disruption of the bacterial cell wall and possibly also through interference with vital metabolic processes essential to the survival of the bacteria is likely involved in the antibacterial action. [15]

The plant has demonstrated significant activity against:

- **Staphylococcus aureus**: A common pathogen in wound infections, including antibiotic-resistant strains like MRSA.
- **Pseudomonas aeruginosa**: A Gram-negative bacterium often involved in chronic wound infections and known for its antibiotic resistance.
- **Escherichia coli**: Another Gram-negative bacterium that can cause wound infections, especially in immunocompromised individuals.

In addition to its antibacterial properties, *Mitragyna parvifolia* has been shown to possess antifungal activity, making it useful in treating wounds complicated by fungal infections.

2.4.2 Anti-Inflammatory Effects

Because it leads to tissue damage as well as delayed repair, excessive or prolonged inflammation is one of the primary challenges to good wound healing. While its main mechanism to reduce inflammation occurs through its alkaloids that prevent the synthesis of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, *Mitragyna parvifolia* reduces inflammation at the wound site by regulating these cytokines, thus facilitating a faster healing process. Furthermore, these flavonoids and triterpenoids of the plant scavenge free radicals and reduce oxidative stress. They enhance the anti-inflammatory property of the plant to extend protective cover of the injured tissue. [16]

2.4.3 Antioxidant Properties

Since oxidative stress caused by reactive oxygen species can interrupt cell activity and delay tissue repair, the antioxidant properties of *Mitragyna parvifolia* are important for wound repair. Quercetin and kaempferol are two major flavonoids in the plant, which possess strong antioxidant properties; these molecules inhibit ROS, thus protecting cells against oxidative injury, and potentially accelerate the process of wound repair. [17]

2.4.4 Wound Healing and Collagen Synthesis

Due largely to its potential to activate collagen synthesis, the wound healing activity of *Mitragyna parvifolia* has been proven to be noteworthy. The skin's main structural protein, collagen, is basic for tissue regeneration and closure at a wound site. The growth factor of *Mitragyna parvifolia's* alkaloids and triterpenoids stimulates fibroblasts, the cells that synthesize collagen. This hastens the process of wound contraction and, therefore increases the tensile strength of the newly formed tissue. Preclinical studies in animal models have established that topical application of extracts from *Mitragyna parvifolia* considerably reduces healing time, enhances collagen synthesis, and

improves tissue quality at the newly formed site. [18]

3. Mechanism of Action of *Mitragyna parvifolia* in Wound Healing

Four stages are significant for tissue repair: haemostasis, inflammation, proliferation, and remodelling, intricately coordinated in the wound healing process. Herbal remedies, therefore, such as *Mitragyna parvifolia*, which can help with infections, inflammation, oxidative stress, and poor tissue regeneration, have attracted much interest regarding their usage to boost wound healing. It is assumed that the bioactive compounds like alkaloids, flavonoids, and triterpenoids present in this plant have been involved in multiple biological activities resulting in healing. The section below describes an exhaustive study of how *Mitragyna parvifolia* influences the process of wound healing. [19]

3.1 Antimicrobial Mechanism

Infection is one of the principal challenges to healing the wound, and it usually leads to a chronic wound or recovery delay.[24] Showing potent antibacterial activity, *Mitragyna parvifolia* is actively responsible against common causative agents of wound infections such as Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. The antimicrobial activities of the plant are mediated by many bioactive substances, particularly its alkaloids etc.[20]

3.2 Anti-Inflammatory Mechanism

Another important phase of wound healing is the inflammatory phase, where immune cells such as neutrophils and macrophages migrate to the wound site to eliminate bacteria and cell debris.[25] On the contrary, tissue damage and slowed healing can be caused by extreme or prolonged inflammation. *Mitragyna parvifolia's* anti-inflammatory properties help in modulating this response and ensure that the inflammatory phase is properly resolved.[21]

3.3 Antioxidant Mechanism[26]

During the inflammatory phase of wound healing, reactive oxygen species (ROS) are generated as a part of the immune response. ROS help eliminate pathogens but, at high concentrations, can cause oxidative stress and damage cellular lipids, proteins, and DNA. For chronic wounds, in which chronic inflammation maintains elevated levels of ROS, there is a particularly harmful effect of oxidative stress.[23]

3.4 Proliferation and Collagen Synthesis

With subsidence of inflammation, the proliferative phase of wound healing begins when there is the creation of new tissue and the synthesis of extracellular matrix components such as collagen. The main structural protein in skin tissue, collagen, is very important for scar formation, tensile strength, and wound closure.[22]

4. Formulation Strategies Involving *Mitragyna parvifolia* in Wound Healing

The objective of developing topical formulations with *Mitragyna parvifolia* is to effectively harness its medicinal properties for wound healing. The design of these formulations considers the bioactive constituents of the plant, stability, and delivery systems in order to maximize efficacy. This chapter discusses various formulation approaches ranging from extraction methods, dosage forms, and formulation bases among other factors that *enhance Mitragyna parvifolia's* therapeutic use. [27]

4.1 Extraction Methods

The techniques used to extract the bioactive chemicals from *Mitragyna parvifolia* have a significant impact on how well it works in formulations for wound healing. A number of extraction methods are frequently used:

4.1.1 Solvent Extraction

- Solvent extraction is a process where organic solvents such as ethanol, methanol, or even water are used to extract phytochemicals from the plant material. The selected solvent influences the yield and profile of the compounds extracted. Ethanol and methanol have been preferred because of their ability to extract polar as well as non-polar compounds, such as alkaloids, flavonoids, and triterpenoids.
- **Advantages**: High yield and comprehensive extraction of bioactive compounds.
- **Disadvantages**: Solvent residues may remain in the final formulation, potentially affecting safety and efficacy.

4.1.2 Cold Press Extraction

Cold press extraction is a mechanical method used to extract oils and other compounds without the use of heat. This technique is particularly useful for extracting lipophilic compounds from the leaves and seeds of *Mitragyna parvifolia*.

- **Advantages**: Retains sensitive compounds that may be degraded by heat.
- **Disadvantages**: May have lower yields compared to solvent extraction.

4.1.3 Steam Distillation

Steam distillation is primarily used to extract essential oils and volatile compounds from *Mitragyna parvifolia*. This method involves passing steam through plant material, allowing the volatile components to evaporate and be condensed back into liquid form.

- **Advantages**: Produces pure essential oils without chemical solvents.
- **Disadvantages**: Limited to volatile compounds and may not capture larger, non-volatile phytochemicals.

4.1.4 Supercritical Fluid Extraction (SFE)

Supercritical fluid extraction utilizes supercritical carbon dioxide (CO2) as a solvent to extract bioactive compounds. This method is gaining popularity due to its efficiency and environmental benefits. [28]

- **Advantages**: Produces high-quality extracts with minimal solvent residues and is environmentally friendly.
- **Disadvantages**: High setup costs and technical complexity.

4.2 Formulation Dosage Forms

The effectiveness of *Mitragyna parvifolia* in wound healing also depends on the formulation dosage forms. Various dosage forms can be developed to deliver its bioactive compounds effectively.

4.2.1 Topical Ointments and Creams

Ointments and creams are popular topical formulations for wound healing, as they provide a protective barrier and can enhance skin hydration.

- **Ointments**: Oil-based preparations that are effective for delivering lipophilic compounds from *Mitragyna parvifolia*. They are

occlusive, preventing moisture loss and facilitating healing.

- **Creams**: Emulsions of oil and water that allow for easy spread ability and absorption. Creams can incorporate both hydrophilic and lipophilic compounds from *Mitragyna parvifolia*. [29]

4.2.2 Gel Formulations

Hydrogel formulations containing *Mitragyna parvifolia* extracts provide a cooling and soothing effect, promoting comfort during the healing process. Gels can deliver high concentrations of bioactive compounds while allowing for moisture retention at the wound site.

- **Advantages**: Non-greasy, easily applied, and can be formulated to provide sustained release of bioactive compounds.

4.2.3 Wound Dressings

Incorporating *Mitragyna parvifolia* extracts into wound dressings, such as hydrocolloids or alginate dressings, can enhance their antimicrobial and healing properties. These dressings can provide a moist environment conducive to healing while delivering bioactive compounds directly to the wound site.

- **Advantages**: Provides both physical protection and therapeutic benefits. Controlled release of active compounds can be achieved over time.

4.3 Formulation Bases

The choice of formulation base is crucial for the stability, release profile, and skin compatibility of *Mitragyna parvifolia*-based preparations. Various bases can be used:

4.3.1 Lipophilic Bases

Lipophilic bases (e.g., petrolatum, beeswax) are suitable for ointments. They provide occlusion and enhance the residence time of the formulation on the skin.

- **Application**: Ideal for chronic or dry wounds requiring moisture retention and protection.

4.3.2 Water-Based Gels

Water-based gels are appropriate for incorporating hydrophilic extracts from *Mitragyna parvifolia*. These formulations provide cooling effects and facilitate easy absorption.

- **Application**: Suitable for acute wounds that require hydration and a soothing effect.

4.3.3 Emulsions

Emulsions (oil-in-water or water-in-oil) can effectively deliver both hydrophilic and lipophilic compounds. They enhance the bioavailability of the extracts while maintaining a pleasant texture for topical application. [30]

- **Application**: Suitable for a variety of wound types, providing flexibility in formulation.

4.4 Enhancing Formulation Efficacy

Several strategies can be employed to enhance the efficacy of *Mitragyna parvifolia* formulations:

4.4.1 Nanotechnology

Nanotechnology can be utilized to create Nano emulsions or Nano carriers for *Mitragyna parvifolia* extracts. These formulations enhance the stability and bioavailability of active compounds, allowing for deeper penetration into the skin.

- **Advantages**: Improved absorption, sustained release, and targeted delivery to the wound site.

4.4.2 Incorporation of Other Bioactive Agents

Combining *Mitragyna parvifolia* with other bioactive agents, such as honey, aloe vera, or antimicrobial peptides, can enhance the overall therapeutic effect of the formulation. These synergistic interactions can provide enhanced antimicrobial activity, promote healing, and reduce inflammation. [31]

4.4.3 PH Adjustment and Stabilization

Adjusting the pH of the formulation to match skin conditions can enhance the stability and effectiveness of *Mitragyna parvifolia* extracts. Maintaining an appropriate pH can also promote skin compatibility and minimize irritation.

4.4.4 Preservatives and Stabilizers

The inclusion of preservatives can extend the shelf life of the formulations, preventing microbial contamination. Additionally, stabilizers can be used to maintain the integrity of emulsions and prevent phase separation. [32]

5. Preclinical and Clinical Evaluation of *Mitragyna parvifolia* in Wound Healing

The preclinical and clinical evaluation of *Mitragyna parvifolia* in wound healing involves a series of rigorous studies to assess its safety, efficacy, and mechanism of action. These evaluations begin with in vitro and in vivo models before progressing to clinical trials. [33]

5.1 Preclinical Studies

5.1.1 in Vitro Studies

In vitro studies are the first step in understanding the wound healing potential of *Mitragyna parvifolia*. These studies focus on assessing:

- **Antimicrobial activity**: Extracts of *Mitragyna parvifolia* are tested against common wound pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* to evaluate its antimicrobial efficacy. Disc diffusion or minimum inhibitory concentration (MIC) assays are often employed.

- **Cytotoxicity**: The safety of extracts is tested on skin fibroblasts or keratinocytes to assess cytotoxicity and determine the maximum non-toxic concentration.

- **Cell Proliferation and Migration**: Using scratch assays, *Mitragyna parvifolia* extracts are tested for their ability to promote cell migration, a critical step in wound closure. [34]

5.1.2 in Vivo Studies

In vivo animal models, such as rats or mice, are employed to evaluate the wound healing efficacy of *Mitragyna parvifolia* in more complex biological systems.

- **Wound Healing Models**: Incisional or excisional wound models are commonly used. After creating wounds, *Mitragyna parvifolia*-based formulations are applied, and wound closure rates are compared with untreated controls or standard wound healing agents (e.g., silver sulfadiazine).

- **Histological Analysis**: Tissues from the wound site are examined microscopically to assess collagen deposition, re-epithelialization, and angiogenesis. The anti-inflammatory and antioxidant effects are also evaluated through biomarker analysis.

Preclinical studies often demonstrate that *Mitragyna parvifolia* accelerates wound healing, reduces inflammation, and enhances tissue regeneration, supporting its potential use in wound care products. [35]

5.2 Clinical Studies

Following successful preclinical studies, clinical trials are necessary to evaluate *Mitragyna parvifolia's* efficacy and safety in humans.[36]

5.2.1 Phase I: Safety and Tolerability

Phase I trials involve a small group of healthy volunteers to assess the safety, tolerability, and possible side effects of *Mitragyna parvifolia* formulations. The trial focuses on:

- **Dermal Irritation**: Testing for allergic reactions, irritation, or hypersensitivity.
- **Pharmacokinetics**: Evaluating how the formulation is absorbed, distributed, and metabolized when applied to human skin.

5.2.2 Phase II: Efficacy in Patients with Wounds

In Phase II trials, *Mitragyna parvifolia* formulations are tested on patients with specific wound types (e.g., diabetic ulcers, surgical wounds) to evaluate efficacy. Key endpoints include:

- **Rate of Wound Healing**: Measured by reduction in wound size, time to complete closure, and improved tissue regeneration.
- **Patient Comfort**: Pain reduction and improved mobility due to faster healing.
- **Infection Control**: Reduced incidence of infection and bacterial load at the wound site.

5.2.3 Phase III: Comparative Studies

In Phase III, larger, randomized controlled trials compare *Mitragyna parvifolia* with existing wound care treatments. The focus is on long-term safety, effectiveness, and patient outcomes in diverse populations.

5.3 Safety Profile

Throughout preclinical and clinical evaluations, the safety of *Mitragyna parvifolia* is consistently monitored. Studies generally show low toxicity, minimal allergic reactions, and excellent biocompatibility, making it a safe option for wound healing applications.[37]

6. Safety and Toxicity Considerations of *Mitragyna parvifolia* in Wound Healing

Although highly promising for therapeutic potential in the healing of wounds, adequate safety and toxicity studies are warranted to prevent misuse in clinical settings, causing harm to the patient. This section reviews the safety profile of *Mitragyna parvifolia* by focusing on toxicity concerns, side effects, and safety considerations in its use in wound care products.[38]

6.1 Preclinical Toxicity Studies

Preclinical studies form the foundation for understanding the toxicity profile of *Mitragyna parvifolia*. These studies include both in vitro and in vivo evaluations to assess cytotoxicity, dermal irritation, allergenic potential, and systemic toxicity.[39]

6.1.1 in Vitro Cytotoxicity Studies

Cytotoxicity testing is typically conducted on human skin cell lines such as keratinocytes and fibroblasts. The goal is to evaluate whether *Mitragyna parvifolia* extracts induce cell death or

impair normal cell functions at therapeutic concentrations.

- **Methods**: Common assays used include the MTT assay (to measure mitochondrial activity) and the LDH (lactate dehydrogenase) release assay (to measure membrane integrity).
- **Findings**: In most studies, *Mitragyna parvifolia* extracts exhibit low cytotoxicity at concentrations used for wound healing. However, at higher concentrations, there may be potential cytotoxic effects, emphasizing the importance of determining appropriate dosage ranges.

6.1.2 Dermal Irritation and Sensitization

As *Mitragyna parvifolia* is primarily used topically for wound healing, it's potential to cause skin irritation or sensitization must be assessed.

- **Irritation Testing**: Dermal irritation studies in animal models (e.g., rabbits or guinea pigs) are performed by applying the extract to intact and abraded skin, followed by observations for erythema, edema, and inflammation.
- **Sensitization Testing**: Sensitization tests, such as the local lymph node assay (LLNA), assess whether repeated exposure to *Mitragyna parvifolia* leads to allergic reactions.

6.1.3 Systemic Toxicity

Though *Mitragyna parvifolia* is typically applied topically, there is potential for systemic absorption, especially if the skin barrier is compromised by wounds. Animal studies evaluate the potential for systemic toxicity after prolonged use.

- **Oral Toxicity Studies**: Since some bioactive compounds in *Mitragyna parvifolia* might enter systemic circulation, oral toxicity studies in rodents are performed to determine the median lethal dose (LD50) and observe any systemic effects.
- **Acute and Chronic Toxicity**: Acute toxicity studies assess the immediate effects after a single high-dose application, while chronic toxicity studies examine the long-term effects of repeated exposure over weeks or months.

Findings: *Mitragyna parvifolia* generally exhibits low systemic toxicity. However, high doses or prolonged use could lead to gastrointestinal discomfort, liver enzyme elevation, or kidney function impairment in rare cases, underscoring the need for careful formulation to limit systemic exposure.

6.2 Clinical Safety Evaluations

Clinical safety evaluations focus on the real-world application of *Mitragyna parvifolia*-based formulations in humans, including potential side effects, interactions, and contraindications.

eg. Phase I trials involve a small cohort of healthy volunteers and patients with wounds, focusing on detecting any immediate adverse effects from topical application of *Mitragyna parvifolia*. These studies are critical for understanding skin reactions and systemic absorption in humans.

6.3 Safe Use and Regulatory Considerations

To ensure the safe use of *Mitragyna parvifolia* in wound healing formulations, several guidelines and considerations must be followed:

6.3.1 Dosage Control

Controlling the dose amount of *Mitragyna parvifolia* extracts in formulations is one of the major safety measures. Toxicity mainly comes from excessive use or applying overly concentrated products. Safe therapeutic dosage requirements are established during preclinical and early clinical trials and must be observed in commercial products. [40]

6.3.2 Product Labelling and Warnings

Clear product labelling is essential to inform users about potential risks, especially for individuals with known allergies to plant-based products. Labels should include warnings for:

- **Allergic Reactions**: Advising users to perform a patch test before full application.
- **Application on Large Wound Areas**: Cautioning against applying the product on large or deep wounds without medical supervision to avoid systemic absorption.

7. CONCLUSION:

Mitragyna parvifolia, a folk plant traditionally esteemed in Ayurvedic and folk medicine, is highly promising as a contemporary therapeutic agent for wound healing, particularly in response to increasing antibiotic resistance. Its highly diverse phytochemical composition involving powerful alkaloids, flavonoids, and triterpenoids attributes to a wide-ranging mode of action that targets some major issues in wound healing like microbial infection, inflammation, oxidative stress, and defective tissue regeneration. The antimicrobial activity of the plant against wound pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa, its capacity to modulate inflammatory cytokines, and its function in promoting collagen synthesis and tissue remodeling make it a potential natural substitute for traditional antibiotics. Topical formulations based on Mitragyna parvifolia extracts, from ointments and hydrogels to sophisticated nanocarriers, exhibit promising results in preclinical models, with enhanced healing and quality of tissue. But to bring this promise into clinical use, standardized extraction methods, optimized formulations, and extensive clinical trials are required to establish efficacy and safety in humans. With the global healthcare system looking for cost-effective and sustainable solutions to overcome the menace of antibiotic-resistant infections, Mitragyna parvifolia presents a science-based, affordable, and culturally acceptable solution for effective wound healing.

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