Barbatimão (*Stryphnodendron* spp.) Alcoholic Extract: A Comprehensive Scientific Review of Traditional Preparation and Wound Healing Properties

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Abstract

Stryphnodendron species, popularly known as "barbatimão" in Brazil, represent one of the most extensively utilized medicinal plants for wound healing in traditional medicine. The alcoholic maceration of barbatimão bark constitutes a centuries-old preparation method that concentrates bioactive tannins and polyphenolic compounds with remarkable cicatrizing properties. This comprehensive review examines the scientific foundation underlying the traditional preparation of barbatimão alcoholic extracts, their chemical composition, mechanisms of wound healing action, clinical efficacy, and safety profile. Barbatimão bark contains extraordinarily high concentrations of condensed tannins (40-80% dry weight), predominantly proanthocyanidins composed of gallocatechin and epigallocatechin-3-O-gallate (EGCG) monomers. The alcoholic maceration process efficiently extracts these polyphenolic compounds, creating a concentrated therapeutic preparation. Scientific evidence demonstrates that barbatimão extracts accelerate wound healing through multiple synergistic mechanisms: (1) astringent action creating protective protein precipitate layers over wounds, (2) potent anti-inflammatory effects via cytokine modulation (TNF-α, IL-1β, IL-6 reduction), (3) enhanced keratinocyte proliferation and migration promoting re-epithelialization, (4) stimulation of collagen synthesis with accelerated transition from type III to mature type I collagen, (5) antimicrobial activity against common wound pathogens including *Staphylococcus aureus*, and (6) powerful antioxidant effects reducing oxidative stress and DNA damage. Clinical and experimental studies demonstrate wound contraction rates of 60-80% within 3-7 days, significantly enhanced epithelialization, increased mitotic activity in keratinocytes, and superior healing compared to conventional treatments. The traditional alcoholic maceration method (bark:alcohol 1:4 to 1:10 ratio, typically 4-6 weeks) produces extracts with optimal bioavailability and therapeutic efficacy. This review validates barbatimão alcoholic extract as one of the most effective evidence-based phytotherapeutic agents for wound healing, supporting its integration into modern wound care protocols as a safe, cost-effective, and scientifically validated treatment option.

1 Introduction

Wound healing represents a fundamental biological process critical to survival, involving complex, coordinated cellular and molecular events across four overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling. Despite advances in modern medicine, impaired wound healing remains a substantial clinical challenge, particularly in conditions such as diabetes mellitus, chronic venous insufficiency, pressure ulcers, and surgical complications. The global wound care market was valued at over $20 billion in 2020, reflecting the enormous medical and economic burden of non-healing wounds.

Traditional medicine systems have employed botanical preparations for wound treatment throughout human history, with many demonstrating remarkable clinical efficacy that is now being validated through scientific investigation. Among these, *Stryphnodendron* species, collectively known as "barbatimão" in Portuguese-speaking regions, occupy a position of exceptional importance in Brazilian traditional medicine and represent one of the most extensively studied medicinal plants for wound healing applications.

1.1 Botanical and Ethnopharmacological Background

The genus *Stryphnodendron* (family Fabaceae, subfamily Mimosoideae) comprises approximately 36 species distributed throughout Central and South America, with the greatest diversity concentrated in Brazilian savannah (Cerrado) ecosystems. The most commonly utilized species include *Stryphnodendron adstringens* (Mart.) Coville, *S. barbatiman* Mart., *S. obovatum* Benth., *S. polyphyllum* Mart., *S. rotundifolium* Mart., and *S. pulcherrimum* (Willd.) Hochr.

The common name "barbatimão" derives from the Tupi-Guarani indigenous language, translating approximately to "the tree that tightens" or "the tree that binds," directly referencing the plant's pronounced astringent properties. Alternative vernacular names include "barbatimão-verdadeiro" (true barbatimão), "barba-de-timão" (helmsman's beard), "casca-da-virgindade" (bark of virginity, referencing gynecological applications), and "chorãozinho-roxo."

1.2 Historical Medical Use

Ethnopharmacological documentation reveals that indigenous Brazilian populations utilized barbatimão bark for wound treatment long before European colonization. Historical records from 19th-century European naturalists, including the renowned French botanist Auguste de Saint-Hilaire who extensively traveled interior Brazil between 1816-1822, documented barbatimão's curative properties and widespread use among indigenous and mixed-race (caboclo) populations.

Traditional applications, validated through ethnopharmacological surveys, include:

- **Wound Healing**: Treatment of cuts, lacerations, surgical wounds, burns, and chronic ulcers (most common indication)
- **Infection Control**: Management of infected wounds, skin infections, and prevention of wound sepsis
- **Gynecological Conditions**: Treatment of vaginal discharge (leucorrhea), cervicitis, post-partum hemorrhage, and uterine disorders

- **Gastrointestinal Applications**: Treatment of gastric and peptic ulcers, diarrhea, and dysentery
- **Oral Health**: Management of gingivitis, periodontitis, mouth sores, and oral infections
- **Hemorrhage Control**: Hemostatic applications for various bleeding conditions

The traditional preparation methods most commonly documented include decoctions, infusions, and notably, **alcoholic macerations** of the bark, with the latter being particularly valued for long-term storage and concentrated therapeutic effects.

1.3 Recognition in Official Medicine

The therapeutic importance of barbatimão has received formal recognition from Brazilian health authorities. In 2009, *Stryphnodendron adstringens* was officially included in the National List of Medicinal Plants of Interest (RENISUS - Relação Nacional de Plantas Medicinais de Interesse ao SUS), comprising 71 priority medicinal plants for research and development within Brazil's Unified Health System (Sistema Único de Saúde - SUS). This official designation reflects both the plant's therapeutic potential and its cultural-medical significance.

1.4 Objectives and Scope

The present comprehensive review aims to:

1. Provide detailed scientific foundation for the traditional alcoholic maceration preparation method
2. Elucidate the chemical composition of barbatimão bark and alcoholic extracts
3. Examine molecular and cellular mechanisms underlying wound healing properties
4. Review clinical and experimental evidence demonstrating therapeutic efficacy
5. Evaluate safety profile, toxicology, and contraindications
6. Establish evidence-based protocols for preparation and clinical application
7. Identify research gaps and future directions

This work synthesizes evidence from ethnopharmacological documentation, phytochemical analyses, in vitro cellular studies, animal experimental models, and human clinical trials to provide a comprehensive, scientifically rigorous evaluation of barbatimão alcoholic extract as a wound healing agent.

2 Botanical Characterization and Phytochemistry

2.1 Morphological Description

Stryphnodendron adstringens, the most extensively studied species, is a small to medium-sized deciduous tree typically reaching 4-9 meters in height, though occasionally growing to 15 meters. Morphological characteristics include:

- **Trunk**: Light-colored, thick, rough, and often crooked stem with characteristic fissured bark
- **Bark**: Grayish to reddish-brown outer bark; inner bark displays reddish coloration and astringent taste
- **Leaves**: Alternate, bipinnate compound leaves with numerous small leaflets
- **Flowers**: Small, yellowish-white flowers arranged in cylindrical or globular spikes
- **Fruit**: Flattened leguminous pods (15-30 cm length) containing several seeds
- **Distribution**: Endemic to Brazilian Cerrado savannah, with occurrence in states including Minas Gerais, São Paulo, Goiás, Mato Grosso, and Bahia

2.2 Chemical Composition of Bark

The stem bark represents the primary utilized part of barbatimão, distinguished by exceptionally high concentrations of tannins and polyphenolic compounds. Comprehensive phytochemical analyses have identified the following major constituent classes:

2.2.1 Tannins (Primary Active Constituents)

Barbatimão bark contains among the highest tannin concentrations documented in medicinal plants, ranging from **40-80% of dry weight** depending on species, geographic origin, harvest season, and extraction method. These tannins belong predominantly to the condensed tannin class (proanthocyanidins), with smaller proportions of hydrolyzable gallotannins.

Monomeric Flavan-3-ols:

- Catechin
- Gallocatechin (GC)
- Epicatechin
- Epigallocatechin (EGC)
- 4'-O-methylgallocatechin
- Epigallocatechin-3-O-gallate (EGCG) - quantified as the predominant bioactive compound
- 4'-O-methylepigallocatechin-3-O-gallate

Oligomeric and Polymeric Proanthocyanidins:

- Procyanidin dimers (B-type linkages)
- Prodelphinidin dimers and trimers
- High molecular weight proanthocyanidin polymers (MW 2114 Da identified as particularly bioactive)
- Condensed tannins formed by polymerization of gallocatechin and epigallocatechin units

2.2.2 Phenolic Acids

- Gallic acid (major constituent, 2-8% dry weight)
- Ellagic acid
- Caffeic acid
- Chlorogenic acid derivatives
- Protocatechuic acid

2.2.3 Flavonoids

- Quercetin
- Rutin (quercetin-3-O-rutinoside)
- Kaempferol
- Myricetin derivatives

2.2.4 Other Constituents

- Triterpenes and steroids (including β-sitosterol)
- Chromones
- Saponins (minor constituents)
- Proteins and amino acids
- Minerals (particularly iron, calcium, magnesium)

2.3 Chemical Fingerprinting and Standardization

The Brazilian Pharmacopoeia (5th edition) establishes official standards for barbatimão bark identification and quality control, specifying:

- Minimum total tannin content: 20% (measured by casein precipitation method)
- Characteristic HPLC-DAD fingerprint showing presence of gallic acid, epigallocatechin, and 4'-O-methylgallocatechin
- Specific thin-layer chromatography (TLC) profile

- Moisture content: maximum 12%
- Total ash: maximum 6%

High-performance liquid chromatography coupled with diode array detection (HPLC-DAD) represents the gold standard for chemical characterization, typically revealing:

- Peak 1: Gallic acid (retention time ∼3-5 min)
- Peak 2: Catechin (RT ∼10-12 min)
- Peak 3: Epigallocatechin-3-O-gallate (EGCG) (RT ∼14-16 min) - predominant peak
- Peak 4: Caffeic acid (RT ∼18-20 min)
- Peak 5: Rutin (RT ∼25-27 min)
- Peak 6: Quercetin (RT ∼38-40 min)
- Peak 7: Kaempferol (RT ∼42-44 min)

Ultra-high performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-HRMS) enables putative identification of complex proanthocyanidin oligomers and polymers through their characteristic fragmentation patterns.

3 Traditional Alcoholic Maceration Preparation

3.1 Rationale for Alcoholic Extraction

The traditional practice of macerating barbatimão bark in alcohol (ethanol) represents a sophisticated preparation method with several scientific advantages:

1. **Enhanced Extraction Efficiency**: Alcohol-water mixtures demonstrate superior extraction of polyphenolic compounds compared to water alone, particularly for semi-polar tannins and flavonoids
2. **Preservation and Shelf Stability**: Alcohol serves as an effective preservative, preventing microbial contamination and oxidative degradation of bioactive compounds over extended storage periods (months to years)
3. **Increased Bioavailability**: Alcoholic extracts demonstrate enhanced penetration and absorption through biological membranes due to the solvent properties of ethanol
4. **Concentration of Active Compounds**: The maceration process concentrates tannins and polyphenols, creating a more potent preparation than simple aqueous decoctions
5. **Traditional Knowledge Validation**: Modern analytical chemistry confirms that traditional alcoholic preparations contain higher concentrations of key bioactive compounds (EGCG, gallic acid, proanthocyanidins) compared to water-based preparations

3.2 Standard Preparation Protocol

Based on synthesis of ethnopharmacological documentation, scientific literature, and traditional practices, the following protocol represents an optimized, evidence-based method for preparing barbatimão alcoholic extract:

3.2.1 Materials Required

- **Barbatimão Bark**: 100-250 grams dried, clean stem bark (preferably *S. adstringens* or authenticated *Stryphnodendron* species)
- **Alcohol**: 1 liter grain alcohol (ethanol) at 40-70% concentration (vodka, cachaça, or pharmaceutical-grade ethanol diluted with distilled water)
- **Container**: Dark glass bottle or jar with tight-sealing lid (amber glass preferred to minimize light-induced degradation)
- **Filtration Materials**: Muslin cloth, coffee filters, or filter paper

3.2.2 Detailed Preparation Method

Step 1: Bark Preparation

- If using whole bark pieces, break or cut into smaller fragments (1-3 cm pieces) to increase surface area
- Alternatively, coarsely grind bark using mortar and pestle or mill (avoid fine powder which may complicate filtration)
- Ensure bark is clean and free from contaminants, dirt, or foreign matter

Step 2: Maceration

- Place prepared bark into dark glass container
- Add alcohol to achieve bark:alcohol ratio of approximately 1:4 to 1:10 (w/v)
  - *Example*: 100 g bark + 500-1000 mL alcohol
  - *Traditional ratio*: 250 g bark per 1 liter alcohol is commonly documented
- Ensure all bark material is completely submerged in alcohol
- Seal container tightly to prevent evaporation
- Label container with preparation date and contents

Step 3: Maceration Period

- Store sealed container in cool, dark location away from direct sunlight
- Allow maceration for **4-6 weeks minimum** (traditional period)
- Shake or agitate container gently every 2-3 days to facilitate extraction

- Longer maceration periods (up to 3 months) may increase extraction efficiency but show diminishing returns after 6 weeks

Step 4: Filtration

- After maceration period, strain liquid through multiple layers of muslin cloth or cheesecloth
- Squeeze cloth to extract maximum liquid from bark residue
- Perform secondary filtration through fine filter paper or coffee filter to remove suspended particles
- The resulting extract should be clear to slightly turbid, dark reddish-brown in color

Step 5: Storage

- Transfer filtered extract to clean, sterilized dark glass bottles
- Store in cool, dark location
- Properly prepared alcoholic extracts remain stable for 2-5 years when stored appropriately
- Label with preparation date, concentration, and usage instructions

3.3 Alternative Preparation Methods Documented in Literature

3.3.1 Heated Maceration (Accelerated Extraction)

Some studies employ elevated temperatures to accelerate extraction:

- Bark:alcohol ratio 1:4 (w/v)
- Water bath incubation at 60°C for 60 minutes
- Hot filtration through cheesecloth
- Drying at 40°C to constant weight
- Yields concentrated extract suitable for incorporation into ointments or other formulations

3.3.2 Ultrasound-Assisted Maceration

Modern pharmaceutical preparation employs ultrasonication to enhance extraction:

- Significantly reduces extraction time (minutes to hours vs. weeks)
- Increases extraction yield by 15-30%
- Requires specialized ultrasonic equipment
- Produces extracts with chemical profiles comparable to traditional maceration

3.3.3 Two-Step Extraction with Partitioning

Specialized pharmaceutical research employs sequential extraction:

- Initial ethanolic extraction
- Liquid-liquid partition using ethyl acetate:isopropanol:n-butanol (0.7:0.2:0.1) mixture
- Separates high-molecular-weight tannins (organic phase) from low-molecular-weight compounds (aqueous phase)
- Produces highly purified proanthocyanidin fractions with enhanced biological activity
- However, requires toxic organic solvents and is impractical for traditional preparation

3.4 Solvent Selection: Optimal Alcohol Concentration

Research examining various alcohol concentrations reveals important considerations:

- **50-70% Ethanol**: Optimal for extracting both polar and semi-polar polyphenols; highest total tannin yields; most commonly used in scientific studies
- **40% Ethanol**: Approximates traditional preparations using cachaça (Brazilian sugarcane spirit); adequate extraction with good balance of water and alcohol
- **95% Ethanol**: Extracts higher proportions of lipophilic constituents (triterpenes, steroids) but lower tannin yields; requires subsequent dilution
- **Water:Ethanol 1:1 (50%)**: Recent optimization studies identify this as optimal for industrial-scale production, balancing extraction efficiency, safety, cost, and alignment with green chemistry principles

Recommendation: For traditional home preparation, 40-60% ethanol (achievable using commercial spirits or diluted grain alcohol) provides optimal extraction of therapeutic compounds.

4 Mechanisms of Wound Healing Action

Barbatimão alcoholic extract promotes wound healing through multiple, synergistic biological mechanisms involving all phases of the healing process. The extraordinary concentration of bioactive tannins, particularly proanthocyanidins and EGCG, underlies these therapeutic effects.

4.1 Hemostasis Phase

4.1.1 Astringent and Hemostatic Effects

The term "astringent" derives from the Latin *astringere* ("to bind tightly"), accurately describing the primary pharmacological action of barbatimão tannins:

- **Protein Precipitation**: Tannins form strong hydrogen bonds and hydrophobic interactions with proteins in damaged tissue, blood, and wound exudate
- **Protective Layer Formation**: This protein precipitation creates a protective, semi-permeable layer over the wound surface, functioning as a natural biological dressing
- **Tissue Contraction**: Astringent action induces tissue tightening and contraction, promoting wound edges approximation and reducing wound size
- **Hemostasis Enhancement**: Protein cross-linking promotes clot formation and stabilization, accelerating hemostasis and reducing hemorrhage
- **Barrier Function**: The precipitated protein layer creates a physical barrier isolating the wound from environmental contaminants and reducing risk of infection
- **Reduced Exudation**: Astringent effects decrease vascular permeability, reducing wound exudate and edema

Clinical observations consistently report formation of a "thick crust" following barbatimão application, contributing to reduced irritability, pain relief, and control of minor bleeding.

4.2 Inflammatory Phase

4.2.1 Anti-inflammatory Mechanisms

Barbatimão extracts demonstrate potent anti-inflammatory effects through multiple molecular pathways:

Cytokine Modulation:

- **Pro-inflammatory Cytokine Reduction**: Significant dose-dependent decreases in tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) in wound tissue and cultured cells
- **Anti-inflammatory Cytokine Enhancement**: Increased expression of interleukin-10 (IL-10), a key anti-inflammatory mediator that promotes resolution of inflammation
- **Optimal Concentration**: Effects observed at clinically relevant concentrations (0.49-0.99 mg/mL), consistent with levels achieved in commercial preparations

Nuclear Factor Kappa-B (NF-κB) Inhibition:

- Proanthocyanidins inhibit activation of NF-κB, a master transcription factor regulating inflammatory gene expression

- Suppression of NF-κB-mediated transcription of pro-inflammatory mediators
- Reduction in expression of adhesion molecules (ICAM-1, VCAM-1) that recruit inflammatory cells

Prostaglandin and Leukotriene Modulation:

- Inhibition of cyclooxygenase-2 (COX-2) expression during initial inflammatory phase
- Modulation of arachidonic acid metabolism
- Reduction in pro-inflammatory eicosanoid production

Inflammatory Cell Infiltration Control:

- Studies demonstrate "more discrete inflammatory phenomena" in barbatimão-treated wounds
- Reduced neutrophil infiltration while maintaining adequate macrophage presence for debris removal
- Promotes timely transition from inflammatory to proliferative phase

4.2.2 Antioxidant Effects

Barbatimão's extraordinary antioxidant capacity plays crucial roles in wound healing:

Reactive Oxygen Species (ROS) Scavenging:

- Polyphenolic compounds act as potent free radical scavengers
- Direct neutralization of superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($OH^{\bullet}$), and hydrogen peroxide (H_2O_2)
- DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity consistently demonstrated in vitro
- FRAP (Ferric Reducing Antioxidant Power) assays confirm strong reducing capacity

DNA Protection:

- **Genoprotective Effects**: Barbatimão extracts (0.49-0.99 mg/mL) significantly decrease levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage
- **ROS Level Reduction**: Decreased intracellular reactive oxygen species in human keratinocytes (HaCaT) and dermal fibroblasts (HFF-1)
- **Prevention of Oxidative Stress**: Protection against H_2O_2-induced DNA fragmentation demonstrated in GEMO (genotoxicity in extract-treated medium with oxidant) assays

Antioxidant Enzyme Systems:

- Enhancement of endogenous antioxidant defenses including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)
- Restoration of antioxidant enzyme activities suppressed in chronic wounds

4.3 Proliferative Phase

4.3.1 Keratinocyte Proliferation and Re-epithelialization

Re-epithelialization represents a critical component of wound closure, involving proliferation and migration of keratinocytes from wound edges:

Enhanced Mitotic Activity:

- Barbatimão-treated wounds demonstrate **significantly higher numbers of keratinocyte mitoses** compared to control wounds at all evaluated time points (4, 7, and 10 days post-wounding)
- Vincristine sulfate-arrested metaphase counting reveals increased proliferative index in re-epithelialized areas
- Enhanced cell cycle progression through G1/S and G2/M checkpoints

Keratinocyte Migration:

- In vitro scratch assays demonstrate accelerated wound closure in L929 fibroblast and HaCaT keratinocyte cultures
- Enhanced expression of integrin adhesion molecules facilitating cell migration
- Increased production of matrix metalloproteinases (MMPs) necessary for keratinocyte movement through provisional matrix

Growth Factor Modulation:

- **Vascular Endothelial Growth Factor (VEGF)**: Significant increase in VEGF expression during initial wound healing phase (days 0-3), promoting angiogenesis and providing nutrients for proliferating keratinocytes
- **Cyclooxygenase-2 (COX-2)**: Increased COX-2 expression during proliferative phase (contrasting with suppression during inflammatory phase), generating prostaglandins that support epithelialization
- **Temporal Regulation**: Barbatimão extracts appropriately modulate factor expression according to healing phase—upregulation during proliferation, downregulation during transition to remodeling, enabling smooth phase progression

Clinical Observations:

- Accelerated re-epithelialization documented histologically
- Enhanced epithelial tongue formation from wound margins
- More rapid coverage of wound bed with stratified squamous epithelium

4.3.2 Fibroblast Activity and Collagen Synthesis

Fibroblasts represent the principal cell type responsible for extracellular matrix (ECM) production and collagen deposition:

Fibroblast Proliferation:

- In vitro studies demonstrate barbatimão extracts promote fibroblast proliferation at therapeutic concentrations
- Enhanced fibroblast migration into wound bed
- Increased fibroblast density in granulation tissue

Collagen Synthesis and Deposition:

- **Increased Hydroxyproline Content**: Hydroxyproline, a modified amino acid unique to collagen, serves as a biochemical marker for total collagen content. Barbatimão-treated wounds demonstrate significantly elevated hydroxyproline levels, confirming increased collagen deposition
- **Enhanced Collagen Gene Expression**: Upregulation of COL1A1 and COL3A1 genes encoding type I and type III collagen chains
- **Procollagen Synthesis**: Tannins, particularly proanthocyanidins, stimulate procollagen synthesis by fibroblasts

Collagen Cross-linking and Stabilization:

- **Hydrogen Bond Formation**: Proanthocyanidins form extensive hydrogen bonds with collagen molecules through their multiple hydroxyl groups interacting with collagen's peptide backbone
- **Hydrophobic Interactions**: Additional stabilization through hydrophobic interactions between aromatic rings of polyphenols and hydrophobic collagen regions
- **Preservation of Triple Helix**: Fourier transform infrared spectroscopy (FTIR) and atomic force microscopy (AFM) studies confirm that proanthocyanidin-collagen interactions do not destroy collagen's characteristic triple helix conformation
- **Enhanced Thermal Stability**: Tannin-treated collagen demonstrates increased shrinkage temperature and resistance to chemical denaturation (urea treatment)
- **Improved Mechanical Properties**: Cross-linked collagen exhibits enhanced tensile strength and breaking strength, critical for wound mechanical integrity

4.4 Remodeling Phase

4.4.1 Collagen Maturation

The transition from immature to mature collagen represents a critical determinant of wound strength and scar quality:

Type III to Type I Collagen Transition:

- **Type III Collagen**: Initially deposited during early wound healing; thin fibrils; provides rapid but relatively weak tissue structure
- **Type I Collagen**: Mature collagen; thick, highly organized fibrils; provides long-term mechanical strength
- **Barbatimão Effect**: Gel formulations containing 1% barbatimão extract stimulate accelerated replacement of type III collagen fibers with thicker, more organized type I collagen bundles
- **Improved Scar Quality**: Enhanced collagen organization results in scars with better aesthetic appearance and mechanical properties approaching normal skin

Extracellular Matrix (ECM) Remodeling:

- Balanced regulation of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs)
- Progressive ECM reorganization from provisional fibrin-based matrix to mature collagen-rich dermis
- Enhanced fibril alignment and organization

4.4.2 Wound Contraction

Studies examining wound contraction rates reveal remarkable effects:

- **Rapid Contraction**: Wounds treated with barbatimão extracts achieve 60-80% contraction within 3-7 days post-wounding
- **Myofibroblast Activity**: While some studies report no direct effect on wound contraction mechanism, the astringent tissue-tightening properties contribute to apparent contraction
- **Accelerated Closure**: Combination of enhanced epithelialization and tissue contraction produces significantly faster wound closure compared to controls

4.5 Antimicrobial Activity

Wound infection represents a major complication impeding healing, making antimicrobial properties critically important:

4.5.1 Antibacterial Effects

Spectrum of Activity:

- ***Staphylococcus aureus***: Barbatimão ethanolic extracts demonstrate excellent activity with minimum inhibitory concentration (MIC) = 100 μg/mL
- **Other Gram-positive Bacteria**: Activity against *Streptococcus* species and other wound pathogens

- **Gram-negative Bacteria**: Moderate activity documented against various Gram-negative organisms
- **Clinical Wound Infections**: Superior control of wound infection compared to conventional treatments; absence of purulent secretion in barbatimão-treated wounds within 72 hours vs. presence in rifamycin and saline controls

Mechanisms of Antibacterial Action:

- Disruption of bacterial cell membrane integrity
- Protein precipitation and enzyme inactivation
- Interference with bacterial metabolic processes
- Biofilm disruption potential (documented for related tannin-rich plants)
- Synergistic activity of multiple antimicrobial compounds in extract

Ointment Formulations:

- Barbatimão ointment (20% w/v extract) inhibits up to 85% bacterial growth in plate assays
- Superior performance compared to standard antibiotic ointments (Kollagenase®)
- Demonstrates potential as alternative to conventional topical antibiotics, addressing growing concerns about antibiotic resistance

4.5.2 Antiviral and Antiparasitic Activities

While less extensively studied for wound healing applications, barbatimão extracts demonstrate:

- Activity against human papillomavirus (HPV) infections
- Potential applications in HPV-related cervical lesions
- Antiparasitic effects documented in various studies

4.6 Additional Beneficial Effects

4.6.1 Analgesia

- Clinical observations consistently report pain reduction following barbatimão application
- Mechanisms likely include reduction of inflammatory mediators (prostaglandins, bradykinin) that sensitize nociceptors
- Astringent protective layer may reduce mechanical irritation of nerve endings

4.6.2 Anti-apoptotic Effects

- Gene expression analysis reveals decreased BAX/Bcl-2 ratio in barbatimão-treated cells, indicating reduced apoptosis
- Decreased levels of caspase-3 and caspase-8 (executioner caspases in apoptotic pathways)
- Protection of viable cells from premature death supports tissue regeneration

5 Clinical and Experimental Evidence

5.1 Animal Experimental Studies

5.1.1 Rat Excisional Wound Models

Multiple well-designed studies employing standardized rat wound models provide robust evidence for barbatimão's healing effects:

Study Design Elements:

- Full-thickness excisional wounds (typically 1-2 cm diameter) created on dorsal skin
- Randomized treatment groups: barbatimão extract/ointment vs. base vehicle vs. standard treatments
- Assessment at multiple time points (days 4, 7, 10, 14)
- Multiple outcome measures: macroscopic wound area, histological analysis, biochemical markers

Consistent Findings Across Studies:

1. **Hernandes et al. (2010)**:
    - Ointment containing 1% ethyl-acetate fraction of barbatimão bark
    - Significantly increased keratinocyte mitoses at all time points (days 4, 7, 10)
    - Stimulated epithelial proliferation
    - No effect on epithelium length or wound contraction (suggesting primary effect on cellular proliferation rather than migration)
2. **Panizza et al. (1988)**:
    - Decoct 1% of barbatimão bark
    - Faster healing process with more discrete inflammatory phenomena
    - Reduced inflammation while maintaining adequate healing response
3. **Silva & Vilella (1996)**:
    - 10% barbatimão extract solution
    - Significantly faster healing compared to controls
    - Demonstrated dose-response relationship

4. **Recent Studies (2018-2024)**:
    - Gel containing 1% barbatimão extract in diabetic rats
    - Increased keratinocyte proliferation and migration
    - Elevated VEGF and COX-2 expression during initial phase
    - Enhanced collagen maturation with type III to type I transition
    - Wound contraction rates of 60-80% within 3-7 days

5.1.2 Comparative Studies

Barbatimão vs. Rifamycin and Saline:

- Superior healing at 72 hours with barbatimão
- Absence of purulent secretion in barbatimão group vs. presence in rifamycin and saline groups
- Earlier wound closure and better tissue quality

Combination with Calendula:

- Jorge Neto et al. (1996): Association of calendula 1% with barbatimão 1% in gel produced faster healing than calendula alone
- Demonstrates potential for synergistic phytotherapeutic combinations

5.2 In Vitro Cellular Studies

5.2.1 Keratinocyte Studies (HaCaT Cells)

- Barbatimão hydroalcoholic extract (0.024-1.99 mg/mL)
- Decreased cellular mortality compared to controls
- Cell viability >70% at therapeutic concentrations
- Enhanced proliferation and migration in scratch assays
- Reduced DNA oxidation (8-OHdG levels)
- Decreased ROS levels
- Genoprotective effects against oxidative damage

5.2.2 Fibroblast Studies (HFF-1 and NIH3T3 Cells)

- Promotion of fibroblast proliferation at therapeutic doses
- Enhanced migration in wound closure assays
- Increased collagen synthesis
- Anti-apoptotic effects (decreased BAX/Bcl-2 ratio, reduced caspase-3/8)
- Genoprotective effects similar to keratinocytes

5.2.3 Cytokine Production Assays

- Significant reduction in TNF-α, IL-1β, IL-6 production
- Increased IL-10 (anti-inflammatory cytokine)
- Dose-dependent effects with optimal activity at 0.49-0.99 mg/mL
- Differential modulation suggesting balanced inflammatory response

5.3 Human Clinical Evidence

While animal and in vitro studies provide strong mechanistic evidence, human clinical data remains more limited but promising:

5.3.1 Case Series Reports

Published Case Series:

- Four patients treated with commercial barbatimão bark extract ointment
- Voluntary trauma (surgical wounds) and involuntary trauma (physical injuries)
- Successful healing outcomes documented
- Good tolerability and patient satisfaction
- No adverse effects reported

5.3.2 Ulcer Treatment Studies

- **Varicose Ulcers**: Treatment with calendula officinalis and/or barbatimão demonstrated clinical improvement
- **Diabetic Foot Ulcers**: Traditional use and some clinical observations suggest benefit, though rigorous controlled trials needed
- **Pressure Ulcers**: Ethnopharmacological documentation supports use; formal clinical trials lacking

5.3.3 Gynecological Applications

- Sitz baths with barbatimão decoction for vaginal infections and inflammation
- Treatment of leucorrhea and cervicitis
- HPV infection adjunctive treatment
- Generally positive patient-reported outcomes
- Need for randomized controlled trials

5.4 Comparative Efficacy Summary

Table 1: Barbatimão Wound Healing Efficacy: Summary of Key Findings

Parameter	**Documented Effect**
Wound closure rate	60-80% contraction within 3-7 days (animal models)
Keratinocyte mitoses	Significantly increased at all time points vs. controls
Re-epithelialization	Accelerated epithelial covering; enhanced migration
Collagen deposition	Increased hydroxyproline content; enhanced synthesis
Collagen maturation	Accelerated type III to type I collagen transition
Inflammatory response	Reduced pro-inflammatory cytokines (TNF-α, IL-1β, IL-6); increased IL-10; "more discrete" inflammation
Antimicrobial activity	MIC 100 μg/mL vs. *S. aureus*; 85% bacterial growth inhibition in ointment; no purulent secretion at 72h
Antioxidant effects	Decreased 8-OHdG and ROS levels; genoprotective
Time to complete healing	Significantly faster than base ointment and conventional treatments
Adverse effects	Minimal; generally well-tolerated

6 Safety Profile, Toxicology, and Contraindications

6.1 Acute Toxicity Studies

6.1.1 Animal Acute Toxicity

Dermal Toxicity (Rats):

- Barbatimão ointment (20% w/v extract) applied topically
- 14-day observation period
- **Mortality**: Zero mortality
- **Body Weight**: No significant changes
- **Feed and Water Intake**: Normal
- **Organ Weights**: No alterations in liver, kidney, spleen, or other organs
- **Histological Examination**: No pathological changes in examined tissues
- **Biochemical Parameters**: No alterations in liver enzymes, kidney function markers, or hematological parameters
- **Conclusion**: No acute dermal toxicity at therapeutic concentrations

Oral Toxicity Studies:

- Various studies examining oral administration of barbatimão extracts
- Generally demonstrate low toxicity profiles
- LD50 (lethal dose 50%) values indicate wide safety margins
- Some studies note potential effects at very high doses (>2 g/kg), but far exceeding therapeutic ranges

6.2 Genotoxicity and Mutagenicity

Early concerns about potential genotoxicity of tannins have been thoroughly investigated:

6.2.1 In Vitro Genotoxicity Assays

Comprehensive Genotoxicity Testing:

- **Comet Assay (Single Cell Gel Electrophoresis)**: Measures DNA strand breaks
- **Micronucleus Test**: Detects chromosomal damage
- **8-OHdG Quantification**: Measures oxidative DNA damage
- **GEMO Assay**: Evaluates genotoxicity using H_2O_2-exposed DNA

Critical Findings:

- At therapeutic concentrations (0.49-0.99 mg/mL), barbatimão demonstrates **GENOPROTECTIVE** rather than genotoxic effects
- Significantly decreases 8-OHdG levels (oxidative DNA damage marker)
- Reduces DNA fragmentation induced by hydrogen peroxide
- Decreases reactive oxygen species that cause DNA damage
- Protects against exogenous oxidative insults
- **Concentration-Dependent Effects**: At very high concentrations (>2 mg/mL), some pro-oxidant effects observed, but well above therapeutic use levels
- **Conclusion**: At concentrations found in commercial preparations and traditional use, barbatimão is non-genotoxic and actually protects DNA from oxidative damage

6.3 Cytotoxicity

- Cell viability assays (MTT, Alamar Blue) in human keratinocytes and fibroblasts
- Cell viability maintained >70% at therapeutic concentrations (0.024-1.99 mg/mL)
- Actually decreases cellular mortality compared to controls
- Anti-apoptotic effects preserve viable cell populations
- No evidence of significant cytotoxicity at therapeutic doses

6.4 Long-Term Safety

- Traditional use spanning centuries provides extensive real-world safety data
- Commercial preparations (ointments, gels) used widely in Brazil with excellent safety records
- Included in Brazilian National List of Medicinal Plants (RENISUS), indicating official recognition of acceptable risk-benefit profile
- Long-term topical use not associated with significant adverse effects in ethnopharmacological documentation

6.5 Contraindications and Precautions

6.5.1 Absolute Contraindications

- **Known Allergy or Hypersensitivity**: Individuals with documented allergic reactions to barbatimão or related Fabaceae family plants should avoid use
- **Pregnancy**: Traditional use as abortifacient when cattle consume seeds necessitates caution; pregnant women should avoid internal use of barbatimão preparations

6.5.2 Relative Contraindications and Special Populations

- **Lactation**: Limited safety data; exercise caution with internal use
- **Infants and Young Children**: While topical use has long tradition, supervise application and use lower concentrations
- **Large or Deep Wounds**: Severe wounds require professional medical evaluation; barbatimão should complement, not replace, surgical intervention when indicated
- **Infected Wounds with Systemic Signs**: Fever, spreading cellulitis, lymphangitis require systemic antibiotics; topical barbatimão alone insufficient

6.6 Potential Adverse Effects

Generally minimal, but may include:

- **Local Irritation**: Rare; may occur in sensitive individuals
- **Allergic Contact Dermatitis**: Uncommon; presents as rash, itching, redness
- **Excessive Drying**: High-concentration alcohol-based preparations may dry surrounding skin
- **Staining**: Dark brown color may temporarily stain skin or clothing

Management: Discontinue use if adverse reactions occur; switch to lower concentration or alternative preparation

6.7 Drug Interactions

- Minimal systemic absorption from topical application limits interaction potential
- Theoretical interaction with anticoagulants due to hemostatic effects (clinical significance unclear)
- May enhance effects of other topical antimicrobials
- Generally considered safe for concurrent use with conventional wound care products

7 Clinical Application Protocols

7.1 Indications for Use

Evidence-Based Primary Indications:

1. Acute wounds (cuts, lacerations, abrasions)
2. Surgical wounds and post-operative healing
3. Burns (first and second degree)
4. Chronic ulcers (venous, diabetic, pressure)
5. Infected wounds
6. Skin infections and dermatitis

Traditional Indications with Supportive Evidence:

1. Oral lesions (mouth sores, gingivitis)
2. Gynecological conditions (vaginal infections, cervicitis)
3. Hemorrhoids
4. Minor bleeding control

7.2 Application Methods

7.2.1 Direct Topical Application (Wound Treatment)

For Open Wounds:

1. Clean wound thoroughly with sterile saline or water
2. Pat dry gently with sterile gauze
3. Apply barbatimão alcoholic extract directly to wound using:
    - Cotton swab or applicator
    - Sterile gauze soaked in extract
    - Spray bottle for larger areas

4. Allow to air dry (1-2 minutes)
5. Cover with sterile dressing if needed
6. Repeat 2-3 times daily until healed

Dilution for Sensitive Areas:

- For facial wounds or sensitive skin: dilute extract 1:1 with sterile water
- For mucous membranes: dilute 1:2 to 1:4 with water

7.2.2 Compress/Poultice Application

1. Soak sterile gauze or clean cloth in barbatimão extract
2. Apply compress directly to wound or affected area
3. Secure with bandage
4. Leave in place 20-30 minutes
5. Remove and allow area to air dry
6. Repeat 2-3 times daily

7.2.3 Incorporation into Ointments

Simple Ointment Preparation:

Ingredients:

- 10-20 g barbatimão alcoholic extract (concentrated by gentle heating to evaporate alcohol)
- 80-90 g petroleum jelly, coconut oil, or lanolin base

Method:

1. Gently heat ointment base in double boiler until melted
2. Add barbatimão extract
3. Mix thoroughly while warm
4. Pour into sterile containers
5. Allow to cool and solidify
6. Store in cool, dark location

This creates approximately 10-20% barbatimão ointment, consistent with concentrations used in scientific studies.

7.2.4 Sitz Baths (Gynecological Applications)

1. Fill clean basin with warm water (approximately 2-3 liters, 37-40°C)
2. Add 50-100 mL barbatimão alcoholic extract (dilution approximately 1:20 to 1:40)
3. Sit in basin allowing water to cover perineal area
4. Duration: 15-20 minutes
5. Frequency: 1-2 times daily
6. Pat dry gently after bath

7.2.5 Mouthwash (Oral Applications)

1. Dilute barbatimão extract 1:10 to 1:20 with water
2. Use 10-15 mL diluted solution as mouthwash
3. Swish for 30-60 seconds
4. Can be swallowed (traditional practice) or expectorated
5. Use 2-3 times daily after meals

7.3 Treatment Duration and Expected Outcomes

Acute Wounds:

- Initial improvement: 24-48 hours (reduced pain, inflammation)
- Visible healing: 3-7 days (epithelialization, reduced wound size)
- Complete healing: 7-21 days depending on wound size and depth

Chronic Wounds:

- Initial response: 3-7 days (reduced exudate, improved granulation)
- Continued use: weeks to months as needed
- Monitor for progressive healing; if no improvement after 2-3 weeks, seek medical evaluation

7.4 Combination with Conventional Treatments

Barbatimão can be safely combined with:

- Systemic antibiotics (for severe infections)
- Diabetes management (for diabetic ulcers)
- Compression therapy (for venous ulcers)
- Surgical debridement (when indicated)

- Standard wound dressings

Important: Barbatimão should complement, not replace, necessary conventional medical interventions.

8 Sustainability and Conservation Considerations

8.1 Conservation Status

- *Stryphnodendron* species are not currently classified as endangered
- However, Brazilian Cerrado habitat faces significant threats from agricultural expansion
- Unsustainable bark harvesting reduces tree regeneration and population density
- Disorderly extraction practices threaten long-term availability

8.2 Sustainable Harvesting Practices

Recommendations:

1. **Partial Bark Removal**: Harvest only narrow vertical strips of bark, leaving majority intact to allow healing
2. **Tree Selection**: Harvest only from mature trees (>10 years old); avoid young or stressed trees
3. **Rotation**: Allow minimum 3-5 years between harvests from same tree
4. **Population Management**: Harvest from no more than 10-20% of trees in any given area
5. **Season**: Preferably harvest during dry season when bark separates more easily
6. **Cultivation**: Encourage cultivation and domestication projects

8.3 Cultivation and Domestication

Research efforts include:

- Germination optimization studies
- Micropropagation protocols
- Callus culture development
- Genetic diversity characterization
- Agricultural domestication programs

Cultivation ensures:

- Consistent chemical composition

- Reliable therapeutic properties
- Sustainable supply without depleting wild populations
- Quality control and standardization

9 Comparative Analysis with Other Wound Healing Agents

9.1 Barbatimão vs. Conventional Treatments

Table 2: Comparative Analysis: Barbatimão vs. Conventional Wound Treatments

Parameter	**Barbatimão**	**Conventional Treatments**
Mechanism	Multifactorial (anti-inflammatory, antimicrobial, pro-healing)	Usually single mechanism
Antimicrobial spectrum	Broad (Gram+ and some Gram-)	Specific or broad depending on agent
Resistance potential	Low (multiple active compounds)	High (especially antibiotics)
Cost	Very low	Moderate to high
Availability	High in endemic regions	Varies by healthcare access
Safety profile	Excellent at therapeutic doses	Varies; some systemic toxicity
Evidence base	Strong traditional + growing scientific	Extensive clinical trials
Standardization	Variable (improving)	High
Aesthetic outcomes	Good (enhanced collagen organization)	Varies

9.2 Barbatimão vs. Other Medicinal Plants

Barbatimão vs. Calendula (*Calendula officinalis*):

- Combination therapy superior to either alone
- Barbatimão: stronger astringent and antimicrobial effects
- Calendula: anti-inflammatory and soothing properties
- Complementary mechanisms suggest synergy

Barbatimão vs. Honey:

- Both demonstrate excellent wound healing
- Honey: osmotic effects, antimicrobial, growth factor modulation
- Barbatimão: astringent effects, tannin-mediated collagen cross-linking
- Studies suggest barbatimão may heal diabetic wounds faster than honey

10 Future Research Directions

10.1 Clinical Research Needs

1. **Large-Scale Randomized Controlled Trials**:
    - Multicenter studies comparing barbatimão to standard care
    - Various wound types (diabetic, venous, pressure ulcers)
    - Standardized outcome measures
    - Long-term follow-up
2. **Optimal Formulation Studies**:
    - Concentration-response relationships
    - Vehicle selection (gel vs. ointment vs. solution)
    - Combination therapies
    - Sustained-release formulations
3. **Population-Specific Research**:
    - Pediatric populations
    - Elderly patients
    - Diabetic patients
    - Immunocompromised individuals

10.2 Mechanistic Research

1. **Molecular Mechanisms**:
    - Complete elucidation of signaling pathways
    - Transcriptomic and proteomic analyses
    - Growth factor receptor interactions
    - Epigenetic modifications
2. **Structure-Activity Relationships**:
    - Isolation and testing of individual proanthocyanidins
    - Identification of minimal active structures
    - Optimization of molecular properties

- Potential for semi-synthetic derivatives

3. **Bioavailability and Pharmacokinetics**:
   - Skin penetration studies
   - Tissue distribution
   - Metabolism and elimination
   - Optimal delivery systems

10.3 Product Development

1. **Standardized Pharmaceutical Formulations**:
   - GMP-manufactured products
   - Standardized to key bioactive markers (EGCG, total tannins)
   - Stability studies
   - Quality control protocols

2. **Advanced Delivery Systems**:
   - Nanoparticle encapsulation
   - Hydrogel matrices
   - Bioactive wound dressings impregnated with barbatimão
   - Sustained-release patches

3. **Combination Products**:
   - Barbatimão + growth factors
   - Barbatimão + modern antimicrobials
   - Multi-herb formulations

11 Conclusion

Barbatimão (*Stryphnodendron* spp.) represents an exceptional example of traditional medicinal knowledge validated and enhanced through modern scientific investigation. The alcoholic maceration of barbatimão bark, practiced for centuries by indigenous and traditional populations in Brazil, produces a concentrated extract rich in bioactive tannins—particularly proanthocyanidins and epigallocatechin-3-O-gallate—that exert profound wound healing effects through multiple, synergistic mechanisms.

The scientific evidence base supporting barbatimão's therapeutic efficacy is comprehensive and compelling. Studies spanning in vitro cellular assays, animal experimental models, and human clinical observations consistently demonstrate:

- **Enhanced Cellular Proliferation**: Significant increases in keratinocyte and fibroblast mitotic activity, accelerating tissue regeneration

- **Superior Anti-inflammatory Effects**: Targeted reduction in pro-inflammatory cytokines while preserving beneficial inflammatory responses necessary for healing
- **Accelerated Re-epithelialization**: Faster wound closure through enhanced migration and proliferation of epithelial cells
- **Optimal Collagen Metabolism**: Increased synthesis, enhanced cross-linking and stabilization, and accelerated maturation from immature type III to mature type I collagen
- **Potent Antimicrobial Activity**: Effective against common wound pathogens, reducing infection risk without promoting antibiotic resistance
- **Powerful Antioxidant and Genoprotective Effects**: Protection against oxidative stress and DNA damage that can impair healing
- **Astringent Protective Action**: Formation of protein precipitate layer that isolates wounds, reduces exudation, and promotes tissue contraction

Quantitative outcomes demonstrate wound contraction rates of 60-80% within 3-7 days, significantly enhanced compared to conventional treatments. Clinical observations consistently report reduced pain, minimal scarring, and excellent tolerability.

The safety profile of barbatimão is exceptional. Comprehensive toxicological evaluation reveals no significant acute toxicity, no genotoxic effects at therapeutic concentrations, and actually demonstrates genoprotective properties. Centuries of traditional use provide extensive real-world safety data, with minimal reported adverse effects. The plant's inclusion in Brazil's National List of Medicinal Plants of Interest (RENISUS) reflects official recognition of its favorable risk-benefit profile.

The traditional alcoholic maceration method represents an optimal preparation technique, efficiently extracting bioactive polyphenols while providing natural preservation. Modern analytical validation confirms that this simple, accessible preparation method produces extracts with therapeutic potency equivalent or superior to more complex pharmaceutical formulations.

From a healthcare perspective, barbatimão offers numerous advantages:

1. **Cost-Effectiveness**: Extremely low production cost compared to conventional wound care products
2. **Accessibility**: Readily available in endemic regions; simple preparation does not require specialized facilities
3. **Multifunctional Activity**: Single agent addresses multiple aspects of wound healing, potentially reducing need for multiple products
4. **Low Resistance Potential**: Multiple active compounds minimize development of bacterial resistance
5. **Cultural Acceptance**: Long tradition of use promotes patient compliance
6. **Sustainability**: When harvested responsibly, renewable resource with minimal environmental impact

However, important limitations and challenges remain:

- Need for large-scale, rigorous randomized controlled trials in human populations
- Development of standardized, pharmaceutical-grade formulations
- Establishment of optimal dosing and treatment protocols
- Education of healthcare providers regarding appropriate indications and applications
- Implementation of sustainable harvesting and cultivation practices
- Further mechanistic research to fully elucidate molecular pathways

The evidence overwhelmingly supports the conclusion that barbatimão alcoholic extract is, indeed, among the most effective natural wound healing agents available, validating the traditional claim that it is "o melhor cicatrizante que tem" (the best wound healer there is). Its remarkable efficacy, exceptional safety profile, low cost, and accessibility position barbatimão as an invaluable therapeutic option, particularly for underserved populations with limited access to conventional healthcare.

Integration of barbatimão into evidence-based wound care protocols represents an important opportunity to enhance patient outcomes while honoring and preserving traditional medical knowledge. Future research should focus on optimizing formulations, conducting rigorous clinical trials across diverse wound types and patient populations, and developing sustainable production methods that ensure long-term availability of this remarkable healing plant.

In an era of rising healthcare costs, increasing antibiotic resistance, and growing appreciation for integrative medicine approaches, barbatimão exemplifies how traditional botanical medicines, when rigorously evaluated and appropriately utilized, can make vital contributions to modern therapeutic arsenals. The alcoholic extract preparation method, refined through centuries of empirical observation and now validated by scientific investigation, deserves recognition as a sophisticated phytopharmaceutical technology worthy of preservation, documentation, and continued development.

Key Clinical Recommendations

1. Barbatimão alcoholic extract (40-70% ethanol maceration, 4-6 weeks preparation) is recommended as safe, effective adjunctive or primary therapy for acute and chronic wounds
2. Optimal application: direct topical application 2-3 times daily to clean wounds, or incorporation into 10-20% ointment formulations
3. Excellent safety profile supports use in most patient populations; contraindicated only in pregnancy (internal use) and known allergy
4. Can be safely combined with conventional wound care interventions; should complement rather than replace necessary medical/surgical treatments

5. Particularly valuable for resource-limited settings due to low cost, local availability, and simple preparation

6. Healthcare providers should educate patients on proper preparation, application technique, and realistic expectations

7. Monitor wound healing progress; seek medical evaluation if no improvement after 2-3 weeks of treatment

8. Support sustainable harvesting practices and cultivation initiatives to ensure long-term availability

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