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WOUND HEALING EFFECT OF *MAMSAROHINI* (*Soymida febrifuga* A Juss.) IN THE MANAGEMENT OF *VRUNA* (WOUND): A SYSTEMATIC CLASSICAL, PHYTOCHEMICAL, PHARMACOLOGICAL AND CLINICAL EVIDENCE REVIEW

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ABSTRACT

Background: *Vruna* (wound) management is one of the most ancient and systematically developed domains of *Ayurvedic Shalya Tantra* (surgery), with Sushruta Samhita dedicating an entire *Dvivraniya Adhyaya* (chapter on two types of wounds) to its pathogenesis, classification, and treatment *Mamsarohini (Soymida febrifuga* A. Juss, Family: Meliaceae) classified as a principal *Vrunaropana* (wound-healing) *dravya* across Charaka, Sushruta, and multiple *Nighantus* has received significant contemporary scientific attention for its multi-mechanistic wound-healing pharmacology. Despite this established classical and experimental evidence base, a comprehensive systematic review integrating classical textual, phytochemical, pharmacological, and clinical dimensions is lacking in international literature. **Objective:** To systematically review the classical Ayurvedic textual evidence, botanical profile, phytochemical constituents, molecular mechanisms of wound healing, classical formulations, clinical evidence, quality standardisation parameters, and safety profile of *Mamsarohini* in *Vruna* management with special reference to wound healing. **Materials and Methods:** Classical Ayurvedic texts (Charaka Samhita, Sushruta Samhita, Ashtanga Hridayam, Bhavaprakasha Nighantu, Dhanvantarı Nighantu, Raja Nighantu, Chakradatta, Sharangadhara Samhita), botanical taxonomic databases, PubMed, Scopus, Web of Science,

AYUSH Research Portal, DHARA, Google Scholar, and pharmacognostic literature were systematically searched. **Results:** *Mamsarohini* bark contains a rich and pharmacologically active phytochemical matrix including limonoids (rohitukine, swietenolide), triterpenoids (ursolic acid, lupeol, B-sitosterol), tannins (ellagic acid, gallic acid, 450-650 mg GAE/g), flavonoids (quercetin, kaempferol, luteolin), coumarins (scopoletin), and minerals (zinc, calcium). These constituents collectively address all four phases of wound healing: haemostasis (tannin-protein film formation), inflammation: (NF-κB/COX-2/5-LOX inhibition), proliferation (fibroblast migration via TGF-VERK1/2, angiogenesis via VEGF, collagen synthesis via TGF-β/Smad2/3, re-epithelialisation via PI3K/Akt), and re modelling (lysyl oxidase support, MMP balance), Broad-spectrum antimicrobial activity against wound pathogens (MIC 62.5-500 µg/ml) prevents wound infection from impeding healing. Clinical studies demonstrate 40-78% faster wound healing, significant reduction in wound area and infection, and favourable safety profiles. **Conclusion:** *Mamsarohini* (*Soymida febrifuga* A.Juss) represents a pharmacologically validated, multi-mechanistic wound-healing agent with applications spanning all wound types- acute surgical, chronic non-healing, infected/*Dushta Vruna*, and diabetic ulcers. Its phytochemical profile provides simultaneous antimicrobial, anti-inflammatory, pro-proliferative, and remodelling support, making it a superior natural wound care alternative or complement to synthetic dressings. Standardised extract formulations, clinical RCTs with validated wound assessment tools, and pharmacokinetic profiling are recommended to consolidate its evidence base for international adoption.

KEYWORDS: *Soymida febrifuga, Vruna,* Wound Healing, *Vranaropana,* Rohitukine, *Shalya Tantra.*

INTRODUCTION

Wound healing remains one of the most complex and clinically significant biological processes in human medicine. Globally, chronic wounds affect an estimated 6.5 million patients in the United states alone, with an economic burden exceeding USD 25 billion annually The World Health Organization estimates that wound-related complications particularly in the context of Diabetes Mellitus (affecting 537 million adults globally, 2021 IDF Atlas), surgical site infections, and venous ulcers represent a major and escalating public health burden.[1]

In *Ayurveda*, the science and art of *Vruna* (wound) management constitute the very

foundation *Shalya Tantra* Ayurvedic surgery systematised by Acharya Sushruta over **2,500** years Sushruta's *Vruna* classification (*Nija and Agantuja*), his description of wound healing (*Shophavasta, Pakavastha, Ropanavastha*), and his sophisticated pharmacopoeia of *Vranaropana* dravyas (wound-healing drugs) represent a clinical knowledge system whose molecular basis is only now being fully elucidated.[2]

Mamsarohini - **"the one that regenerates *Mamsa* (muscle/flesh tissue)"** is one of the most evocative and precisely named drugs in the Ayurvedic pharmacopoeia. Its Sanskrit name encodes t therapeutic identity: ***Mamsa* (flesh/granulation tissue) + *Rohini* (one that causes growth/restoration)** This name has been applied in classical texts to *Soymida febrifuga* A. Juss (Family: Meliaceae), a large deciduous tree of the Indian dry deciduous forests whose bark has been used in *Shalya Tantra* since the Vedic period.[3]

Despite being described across **Nine** major classical texts (Charaka Samhita, Sushruta Samhita, Ashtanga Hridayam, Bhavaprakasha, Dhanvantari Nighantu, Raj Nighantu, Chakradama Sharangadhara Samhita, and Astanga Sangraha) as a principal *Vranaropana* agent, *Mamsarohini* has received disproportionately limited systematic pharmacological and clinical investigation compared to its therapeutic significance. Contemporary research, however, has begun to characterise it’s phytochemical composition including the discovery of rohitukine (a unique CDK inhibitor firs isolated from this species), swietenolide-class limonoids, ursolic and oleanolic acid, ellagic/gallic and tannins, and quercetin/kaempferol flavonoids revealing a rich multi-mechanistic wound-healing pharmacology.[4]

Current challenges in wound management include: antibiotic resistance in wound pathogens (MRSA, P. aeruginosa biofilms), cytotoxicity of standard wound antiseptics (povidone-iodine, hydrogen peroxide) to regenerating fibroblasts and keratinocytes, failure of moist wound dressings in infected and exuding wounds, and high cost/limited accessibility of bioengineered wound products in resource-limited settings. ***Mamsarohini* addresses each of these challenges through its multi-constituent phytochemistry: broad-spectrum antimicrobial activity without fibroblast cytotoxicity. simultaneous anti-inflammatory and pro-proliferative signalling, and mineral-rich composition supporting collagen synthesis and tissue mineralization.[5]**

This systematic literature review comprehensively integrates the classical, botanical phytochemical, pharmacological, clinical, and safety dimensions of Mamsarohini in Vruna

management.

CLASSICAL AYURVEDIC PERSPECTIVE

2.1 *Vruna* in Classical Ayurvedic Texts

2.1.1 Sushruta Samhita - Primary Classical Source

Sushruta Samhita Sutra Sthana (Chapter 22, *Vranaprashna Adhyaya*) defines *Vruna* as "*Twak Mamsa Shonitanam Bhedanam Vruna Uchyate"* any disruption in the continuity of *Twak* (skin), *Mamsa* (muscle), and *Shonita* (blood vessels). Sushruta classifies wounds into two fundamental types (*Dvivraniya*): *Nija Vruna* (internally caused by *Dosha* vitiation, as in diabetic/trophic ulcers) and *Agantuja Vruna* (externally caused traumatic, surgical, burn wounds)[2]

Sushruta describes six stages of wound healing in *Chikitsa Sthana* (Chapter 1, *Vruna Chikitsa*)
(1) Sama *Vrana* (fresh wound), (2) *Shopha* (inflammatory swelling), (3) *Paka* (suppuration). (4) *Ropana* (granulation and epithelialisation), (5) *Shodhana* (cleansing), and (6) *Sandhi* Karana (scar remodelling). Each stage requires specific *Shodhana* (cleansing), Ropana (healing), and *Vedanasthapana* (analgesic) interventions. *Mamsarohini* is specifically named in Chapters 1-2 of Sushruta Chikitsa Sthana for wound washing (*Prakshalana*) and wound dressing (*Vrana Lepa* and *Vrana Bandha*) across multiple healing stages.[6]

2.1.2 Charaka Samhita

Charaka Samhita Chikitsa Sthana (25th Chapter, *Vruna Chikitsa Adhyaya*) provides comprehensive wound treatment protocols. Charaka classifies *Vrunaropana dravyas* (wound-healing drugs) into specific categories: *Shodhana* (wound-cleansing), *Ropana* (wound-healing/granulation). *Vedanasthapana* (analgesic), *Shothaghna* (anti-oedema), and *Stambhana* (haemostatic). *Mamsarohini* (Rohini) is listed in the *Shodhana-Ropana* dual-action category uniquely capable of both cleansing infected wounds and promoting tissue regeneration.[7]

2.1.3 Ashtanga Hridayam

Vagbhata in Ashtanga Hridayam Sutra Sthana (15th Chapter) lists *Mamsarohini* in the *Shodhana-Ropaniya Dravya* group. *Ashtanga Hridayam Uttara Sthana* (*Bhagna Chikitsa*, fracture wound management) specifically recommends *Mamsarohini*-based preparations for *Gambhira Vruna* (deep wounds) involving *Mamsa* and *Snayu* layers a clinical indication

corresponding precisely to the observed promotion of deep tissue fibroblast proliferation and collagen synthesis in contemporary pharmacological studies.[8]

2.1.4 Nighantus and Post-Classical Texts

Bhavaprakasha Nighantu (Guduchyadi Varga) provides the most detailed classical pharmacological description of *Mamsarohini. Rasa Tikta-Kashaya; Guna-Laghu, Ruksha; Virya - Ushna; Vipaka Katu, Karma Vranaropana, Shothaghna, Raktashodhaka, Kapha-Pitta Shamaka, Deepana, Krumighna, Kushthaghna*. The *Kashaya* (astringent) and *Tikta* (bitter) *rasas* directly correspond to the tannin-mediated haemostatic-antiseptic properties and the flavonoid/ liminoid anti- inflammatory properties respectively. Dhanwantari Nighantu and Raja Nighantu confirm these properties and add *Krimighna* action.[9]

TABLE 1- COMPARITIVE CORRELATION: VRUNA (AYURVEDA) vs. WOUND/ WOUND HEALING (MODERN MEDICINE).

PARAMETER	VRUNA(Ayurveda)	WOUND/WOUND HEALING
Definition	*Vruna*: Any break in continuity of skin/ tissue with *Srava* (discharge), *Shotha* (Oedema), *Shoola* (Pain) and *Daha* (Burning); caused by *Agantuja* (External) or *Nija* (Internal) factors	Wound: disruption of the normal anatomical structure and function of skin/ tissue; classified as acute(surgical, traumatic) or chronic(diabetic, venous ulcer, pressure ulcer)
Stages of Healing	*Shophavasta* (Inflammatory), *Pakavastha* (Suppuration/ Proliferation), *Ropanavastha* (Granulation), *Sandhikarana* (Remodelling)	Haemostasis, inflammation (0-3 days), Proliferation(3-21 days), remodelling/ Maturation(21 days- 2 years)
Pathogenic factors	*Pancha Dosha Dushti*(esp. *Pitta-Rakta)*; *Saptadhatu kshaya*; *Krimi* (microbial), Ama	Bacterial biofilm, proteolytic enzymes(MMP-2/9), ROS, impaired angiogenesis, cytokine imbalance (TNF- α, IL-1β)
Key issues	Twak (Skin), Mamsa(Muscle), Sira snayu (Vessels/ tendons), Asthi (Bone)	Epidermis, dermis, hypodermis, fascia; fibroblass, keratinocytes, endothelium
Healing criteria (Samyak ropana)	*Sama Vrana Mukha* (Even surface), *Sama Vrana* (Normal colour), *Nirmala twak* (Clean skin), Absence of *Srava/ Shotha/ Shoola*	Complete re-epithelialisation; normalised TEWL; tensile strength restoration; absence of infection/ inflammation
Classical drug category	*Vranaropana (Wound healer), Shodhana (Cleansing), Ropana (Healing), Vedanasthapana (Analgesic), Shothaghna (Anti- oedema)*	Wound cleaning agents, antimicrobials, growth factor stimulants(EGF, PDGF), collagen matrices, moist wound dressings.
Mamsaroh ini role	*Vranaropana dravya- Restores Mamsa Dhatu; Shodhana+ Ropana+ Vedanasthapana actions; indicated for all Vruna types*	Multi- mechanistic: Anti microbial, Anti inflammatory, collagen synthesis stimulation, angiogenesis promotion antioxidant

2.2 *Vruna Samprapti* and Healing Principles

The *Samprapti* (pathogenesis) of *Vruna* and its healing impairment follows a defined sequence: *Nidana (*trauma/*Dosha* vitiation) → *Siras Bheda* (disruption of blood vessels and tissue channels) Rakta Srava (haemorrhage) → *Pitta-Rakta Prakopa Shopha* (inflammatory oedema) → *Paka* (suppuration when *Kapha* involvement leads to *Ama* production) → *Srava* (discharge) → *Mamsa Kshaya* (tissue deficiency requiring regeneration).

Impaired wound healing (*Duroodha Vruna* non-healing wound) in Ayurvedic understanding results from: (1) persistent *Tridosha Dushti* in the wound; (2) *Ama* in the wound bed (*Ama Vruna* analogous to biofilm-colonised wounds); (3*) Majja-Snayu Kshaya* (deep tissue depletion); (4) Systemic *Mandagni* (metabolic impairment as in diabetes mellitus). The *Shodhana-Ropana* treatment principle addresses all four: *Shodhana* clears *Ama*/infection, *Ropana* restores *Mamsa Dhatu, Vedanasthapana* resolves *Vata*-mediated pain, and *Rasayana* support addresses systemic *Dhatu* deficiency.

2.3 Classical Formulations containing *Mamsarohini*

Table 2: Classical Formulations Of *Mamsarohini* For *Vruna* Management.

Formulation	Ingrediants/ Composition	Route/ Application	Primary indication (*Vruna*)
Mamsarohini kwatha	Mamsarohini bark(Principal), *Triphala*, *Nimba* bark, *Haridra* - Decoction (1:16 reduces to 1/4)	Oral (Internal) + V*rana prakshalana* (Topical woundwash)	*Dushta vrana* (Infected wounds), *Pitta rakta* dominant wounds, wound debridement
Mamsarohini ghrita	*Mamsarohini kwatha* (Decoction base) + Go *ghrita* - Classical preparation	Oral + Topical dressing; *vrana ropana ghrita* application	*Shushka vrana* (Dry wounds), *Gambhira vrana* (Deep wounds), Post- surgical wound care, burns
Mamsarohini taila	*Mamsarohini* bark *kwatha*+ *Tila taila* - classical preparation with Manjishtha, Haridra, Daru haridra kalka	Topical application (wound dressing oil); *Abyanga* over wound margins	*Vrana ropana*, *Pitta* Dominant wounds, Infected wounds, chronic non healing wounds
Mamsarohini churna	Dried bark powder (fine sieve, 80 mesh), *Triphala churna, Shankha bhasma*	Dusting powder (*Vrana avacharana*) or oral with Honey or Ghee	*Dushta vrana shodhana*, wound deodorisation, *srava* reduction
Mamsarohini lepa	Fresh bark paste or dried bark fine powder + *Go ghrita/ Go dugdha*/ haridra as excipient	Topical *lepa* (Paste application) to wound and margins	Shallow wounds, Skin ulcers, burns, post-operative wounds; *Shotha* + *Shoola* + Srava reduction
Mamsarohini	Mamsarohini kwatha +	Rectal (For fistula-in-	Bhagandhara (Anal

kashaya basti	Triphala kashaya - Medicated enema	ano/ Bhagandhara, internal wounds)	fistula wound) internal pitta-rakta wounds; *Srotoshodhana*
Compound formulations	*Jatyadi taila (Mamsarohini* as one of the ingrediant), *Triphala Ghrita* with *Mamsarohini*, various *Dushta vrana lepa*	Topical Compound formulations	Chronic/ infected wounds, diabetic ulcers, *Nadi Vrana*) Sinus wounds)

3. BOTANICAL PROFILE AND PHARMACOLOGY

3.1 Taxonomic identity

Accepted Botanical name	Soymida febrifuga A. Juss (1830)
Synonyms	*Swietenia febrifuga* Roxb.; *Chloroxylon febrifuga* (Roxb.) Wight & Arn.; *Soymida febrifuga* var. Wightii
Family	Meliaceae (Mahogany family)
Common names	Rohini, Mamsarohini, Rohitaka, Indian Redwood, Bastard Cedar, Gum-Kino Tree
Sanskrit synonyms	*Mamsarohini, Rohini, Rohitaka, Lohitaka, Raktadruma, Bhumidruma, Tiktarohini*
Distribution	Dry deciduous forests of peninsular India (Karnataka, Tamil Nadu, Andhra Pradesh, Maharashtra, Orissa, Madhya Pradesh); up to 1000 m elevation
Parts used	Bark (stem bark principal medicinal part); root bark; heartwood; leaves
Morphology	Large deciduous tree (15-25 m); deeply furrowed reddish-brown bark; pinnate leaves; small white fragrant flowers; dry capsular fruits with winged seeds (diagnostic for Meliaceae)
Bark characterisitics	Thick (2-4 cm), deeply furrowed, reddish-brown outer bark; inner bark astringent-bitter; exudes reddish kino-like gum (Rohini Niryasa) on incision
Ecology	Xerophytic; drought-resistant; typical of laterite rocky soils; associated with dry teak forests
IUCN/ Conservation	Near Threatened; slow-growing; bark over-harvesting threatens wild populations; cultivation recommended
Authentication marker	Presence of tetranortriterpenes (limonoids) and swietenolide class compounds on TLC/HPTLC; specific Rf values in toluene:ethyl acetate (7:3) system

3.2 Pharmacognostic Characteristics

The bark of *Soymida febrifuga* exhibits the following diagnostic microscopic characteristics relevant to authentication: (1) Cork cells with reddish-brown content (kino/condensed tannin); (2) Calcium oxalate prismatic crystals in parenchyma cells, (3) Thick-walled fibre bundles with narrow lumen (diagnostic for Meliaceae); (4) Starch grains in medullary rays; (5) Sclereids with prominent pit canals; (6) Phloem parenchyma with tannin-containing idioblasts. The reddish-brown colour of the powdered bark (due to condensed tannins and kino) and its intensely bitter-astringent taste are organoleptic authentication markers.[11]

3.3 Ethnobotanical and Traditional Use

- ✓ Beyond classical Ayurveda, *Soymida febrifuga* has extensive ethno medicinal documentation:
- ✓ Tribal medicine (Karnataka, Tamil Nadu, Andhra Pradesh): bark decoction for wound washing. fever, diarrhoea, and skin diseases (Lambada, Konda Dora, Chenchu tribes).
- ✓ Siddha medicine: Rohini pattai (bark) in wound healing formulations; used in Varmam therapy for muscle injuries.
- ✓ Folk medicine: fresh bark paste applied to cuts, ulcers, and skin infections, bark ash used as wound-dressing powder.
- ✓ Veterinary applications: bark decoction for animal wounds, especially livestock skin ulcers.
- ✓ Conservation concern: bark stripping from wild trees for medicinal use threatens population viability, API-guided cultivation programmes needed.

4. PHYTOCHEMICAL CONSTITUENTS

4.1 Overview of Phytochemical Profile

The bark of *Soymida febrifuga* A.Juss is remarkably rich in diverse phytochemical classes. Unlike many medicinal plants with a single dominant active compound, *Mamsarohini* exhibits a synergistic poly-pharmacological profile where multiple compound classes simultaneously address different phases of wound healing a phytochemical architecture precisely aligned with its classical multi action *Vranaropana-Shodhana-Vedanasthapana* designation.

Rohitukine a unique chromone alkaloid CDK inhibitor first isolated from *Soymida febrifuga* deserves special attention as a marker compound and pharmacological curiosity: its cell-cycle. regulatory property has implications for controlled keratinocyte and fibroblast proliferation in wound healing, preventing dysregulated proliferation (hypertrophic scarring) while supporting normal regenerative cell cycling.[12]

TABLE 4: PHYTOCHEMICAL PROFILE OF *Soymida febrifuga* BARK COMPOUNDS AND WOUND HEALING PHARMACOLOGY.

Phytochemical class	Key compounds Identified	Wound healing/ Pharmacological relevance
Liminoids (Tetranortriterpenes)	Swietenolide, rohitikine, nimbolide analogues, febrifugine-related	Primary bioactive class; inflammatory (NF-kB, COX-2); antibacterial against wound pathogens (S. aureus, P. aeruginosa); antifungal; accelerate

	diterpenes, mexicanolide-type liminoids	fibroblast migration; anti-biofilm activity
Triterpenoids	B- sitosterol, stigmasterol, lupeol, betulinic acid, oleonolic acid, ursolic acid	Ursolic + oleanolic acid: TGF-β/Smad pathway activation ← collagen I synthesis; lupeol: potent NF-KB inhibitor; ß-sitosterol: keratinocyte proliferation; betulinic acid: anti-infective + pro-apoptotic on wound bacteria
Tannins (Hydrolysable + Condensed)	Ellagic acid, gallic acid, ellagitannins, catechin, epicatechin, procyanidins	Quercetin:VEGF-A mRNA upregulation; rutin: capillary protection + new vessel integrity; kaempferol: endothelial cell migration (scratch assay); limonoids: HIF-1α pathway support; ß-sitosterol: endothelial tube formation assay confirmed
Flavanoids	Quercitin, Kaempferol, Rutin, Luteolin, apigenin, vitexin, naringenin, isorhamnetin	Quercetin: VEGF upregulation (angiogenesis), COX-2/NF-KB inhibition, antioxidant protection of granulation tissue; kaempferol: fibroblast proliferation (ERK1/2); luteolin: MMP-2/9 inhibition (prevents matrix degradation); rutin: Capillary protection, anti-oedema (reducing vascular permeability).
Alkaloids	Rohitukine (CDK inhibitor), swietine, febrifugine analogues, rohitukinal	Rohitukine: inhibition cell cycle regulation in CDK2/cyclin DI keratinocyte antimicrobial, proliferation, anti-inflammatory, unique compound identified first in *Soymida febrifuga*
Coumarins	Scopoletin, umbelliferone, esculetin, fraxetin	Scopoletin: anti-inflammatory (COX-2/5-LOX inhibition), antimicrobial, promotes fibroblast migration; - umbelliferone: antioxidant, anti-bacterial; esculetin: inhibits 5-LOX mediators in wound inflammatory phase
Saponins	Steroidal saponins, oleanane- type triterpene saponins	Membrane-permeabilising antimicrobial activity; promote cell hydration and tissue turgor, anti-oedema; haemostatic; surfactant-mediated wound cleansing
Fixed oils and fatty acids	Linoleic acid, oleic acid, palmitic acid, stearic acid(seed/ bark wax)	Linoleic acid: essential for skin barrier repair (ceramide synthesis); oleic acid: anti-inflammatory; fatty acid composition similar to skin lipids → accelerates epidermal barrier restoration
Sterols and Phytosterols	B sitosterol (dominant), campesterol, stigmasterol, ergosterol	Promote keratinocyte proliferation; anti-inflammatory (NF-kB); sitosterol clinically shown to improve wound healing speed and tensile strength in controlled studies
Minerals (Bark ash)	Calcium (high), Magnesium, Iron, Zinc, Potassium, Silica	Zinc: essential cofactor for MMP enzymes and collagen synthesis; Ca/Mg: cell signalling in wound contraction; Iron: haemoglobin-mediated Oz delivery to wound tissue; Silica: stimulates fibroblast collagen synthesis
Polyphenols (Total)	High total polyphenol content (450- 650mg GAE/g dry bark extract)	Synergistic antioxidant protecting wound bed from ROS-mediated modulate secondary tissue damage; anti-biofilm; antimicrobial synergy; macrophage polarisation (M1-M2 transition)

4.2 Extraction methods and Yield

- Aqueous extract (Kwatha equivalent classical method): optimum for tannins, saponins, polyphenols, minerals, yield 15-22% (w/w); corresponds to classical Kashaya preparation. Ethanolic extract (70% ethanol): optimum for flavonoids, limonoids, triterpenoids, rohitukine, yield 12-18% (w/w), highest total wound-healing activity in in vivo models.
- Methanolic extract: highest rohitukine and limonoid extraction; used for alkaloid-specific studies.
- Petroleum ether extract: sterols, fixed oils, waxes, relevant for membrane-active antimicrobial and wound barrier effects.
- Sequential extraction (petroleum ether chloroform ethanol water): recommended for comprehensive phytochemical characterisation for standardisation purposes
- Ghrita preparation (classical): lipid extraction of fat-soluble constituents (ß-sitosterol, limonoids, fatty acids) into Ghrita base uniquely different from aqueous/alcoholic extracts; represents the *Mamsarohini Ghrita Ropana* preparation**.**

5. MODERN PATHOPHYSIOLOGY OF WOUND HEALING CORRELATES AYURVEDIC

4.3 The Four-Phase Wound Healing Cascade

Phase 1: Haemostasis (Seconds to Hours - *Stambhana* in Ayurveda)

Tissue injury triggers immediate vasoconstriction, platelet activation, and the coagulation cascade. Platelet-derived growth factors (PDGF, TGF-B, EGF) are released from platelet alpha granules, initiating the wound healing cytokine cascade. Fibrin clot formation provides the provisional extracellular matrix scaffold. In *Ayurveda*, this phase corresponds to *Stambhana* (haemostasis) *Kashaya* (astringent) *rasa* of *Mamsarohini* tannins directly supports this phase through protein precipitation and fibrin network stabilisation.[13]

Phase 2: Inflammation (0-72 hours *Shophavasta* in Ayurveda)

Neutrophil migration (0-6h), followed by monocyte-to-macrophage differentiation (24-48h), establishes the wound inflammatory milieu. MI macrophages produce pro-inflammatory cytokines delayed or persistent M (TNF-4, IL-1B, IL-6) for pathogen clearance and debridement. The transition to M2 macrophage polarisation by 48-72h is critical for initiating the proliferative phase polarisation is a hallmark of chronic non-healing wounds NF-kB is the master transcriptional regulator of pro-inflammatory cytokine production. MMP-2 and MMP-9 (matrix metalloproteinases) at this phase are beneficial for matrix remodelling but become

pathological if overexpressed in chronic wounds.[14]

Phase 3: Proliferation (Days 3-21 *Ropanavastha* in *Ayurveda*)

Proliferation involves four concurrent processes (a) Granulation tissue formation fibroblast migration (TGF-B/Smad2/3 pathway, PDGF) and myofibroblast differentiation (a-SMA, wound endothelial cell sprouting driven by VEGF/VEGFR-2 signalling contraction), (b) Angiogenesis procollagen I/III secretion by fibroblasts requiring HIF-la stabilisation, (c) Collagen synthesis. Vitamin C-dependent prolyl/lysyl hydroxylation; cross-linking by lysyl oxidase (Cu-dependent); (d) Re-epithelialisation keratinocyte migration from wound margins (EGF/EGF-R, PI3K/Akt, Racl signalling), followed by stratification and basement membrane reconstitution.[15]

Phase 4: Remodelling (Weeks 3 to 2 years- *Sandhikarana in Ayurveda*)

Collagen type III (rapidly deposited in proliferation) is progressively replaced by the stronger collagen ope I through MMP-mediated remodelling balanced by TIMP (tissue inhibitors of metalloproteinases) Maximum tensile strength (approximately 80% of pre-wound skin) is achieved by 3-6 months. Dysregulation at this phase results in either insufficient healing (atrophic scar) or excessive collagen deposition (hypertrophic scar/keloid). The MMP/TIMP balance is the molecular arbiter of scar quality.[16]

4.4 Pathology of Chronic and Non-Healing Wounds

Chronic wounds (diabetic foot ulcers, venous leg ulcers pressure ulcers) are characterised by pathological persistence of the inflammatory phase elevated MMP-2/9 (exceeding TIMP capacity), high TNF-a/IL-18, reduced TGF-B and growth factor bioavailability, bacterial biofilm colonisation (particularly MRSA, P. aeruginosa), and impaired angiogenesis (reduced VEGF in diabetic wounds). This corresponds to Ayurvedic *Duroodha Vruna* (non-healing wound) caused by persistent Ama-Pita-Rakta Dushti in the wound bed.[17]

4.5 Ayurvedic-Modern Wound Healing Correlation

TABLE 1 (above) provides the Vruna-Wound Healing correlation. The following additional correlations are noted

Dushta Vruna (infected/non-healing wound) Biofilm-colonised chronic wound with persistent M1 macrophage polarisation and elevated MMP-2/9 *Mamsarohini's Shodhana* (cleansing) action corresponds to biofilm disruption (tannins, gallic acid) M1 M2 polarisation shift (quercetin, lupeol). *Shuddha Vruna* (clean wound ready for healing) Wound bed preparation

state, low bacterial burden, balanced proteolytic activity, high growth factor bioavailability. *Mamsarohini's Ropana* action corresponds to TGF-B/VEGF upregulation and collagen synthesis promotion in this state.

5. MECHANISM OF ACTION - MOLECULAR PHARMACOLOGY

5.1 Multi-Phase Wound Healing Mechanism- Overview

Mamsarohını (*Soymida febrifuga* A. Juss) demonstrates one of the most comprehensive multi-phase wound healing pharmacological profiles among natural wound care agents. Unlike single-mechanism synthetic wound dressings, its phytochemical matrix simultaneously supports all four phases of healing while providing continuous antimicrobial wound bed protection. This multi-target activity directly explains the classical designation of simultaneous *Shodhana* (cleansing) and *Ropana* (healing) actions a pharmacological duality that is impossible to achieve with single-compound wound care agents.

TABLE 5: PHASE-SPECIFIC MOLECULAR MECHANISMS OF *MAMSAROHINI* IN WOUND HEALING.

Wound Healing Phase	Molecular targets/ Pathways	Mamsarohini phytochemicals involved
Phase1: Haemostasis (0hrs)	Platelet aggregation enhancement; fibrin clot formation; vasoconstriction	Tannins: protein precipitation wound surface film (haemostatic plug); ellagic acid: platelet aggregation promotion; astringent *Kashaya Rasa Srotosankochana* (vessel constriction); β-sitosterol: platelet activation
Phase 2: Inflammation (0-72 hours)	NF-κB pathway suppression; COX-2/5-LOX inhibition; TMF-α/IL-1β/IL-6 reduction; Macrophage polarisition M1→M2	Lupeol + quercetin: NF-KB IKKB inhibition; scopoletin: COX-2 + 5-LOX dual inhibition; gallic acid: TNF-a mRNA suppression; luteolin: IL-1B processing (NLRP3 inflammasome) inhibition; rohitukine: CDK-mediated inflammatory kinase regulation
Phase 3: Proliferation - Fibroblast migration + Proliferation (Days 3-14)	TGF-β/ Smad2/3 signalling; ERK1/2 MAPK pathway; PDGF receptor signalling; fibroblast-to-myofibroblast differentiation (α-SMA)	Ursolic acid + oleanolic acid: TGF- upregulation → Smad2/3 activation collagen I/III synthesis; kaempferol: ERK1/2 → fibroblast proliferation; rohitukine CDK modulation: controlled cell cycle progression in fibroblasts; β sitosterol: fibroblast migration assay confirmed
Phase 3: Proliferation-Angiogenesis (Days 3- 21)	VEGF/ VEGFR- 2 signalling; HIF-1α stabilisation; endothelial cell migration; capillary tube formation	Quercetin: VEGF-A mRNA upregulation; rutin: capillary protection + new vessel integrity; kaempferol: endothelial cell migration (scratch assay); limonoids: HIF-

		1α pathway support; ß-sitosterol: endothelial tube formation assay confirmed
Phase 3: Proliferation-Collagen synthesis (Days 5- 21)	Procollagen→ collagen I/III maturation; propyl/ lysyl hydroxylase (Vit C- dependent); MMP-12/9 regulation (matrix metalloproteinase balance)	Ellagic + gallic acid (Vit C-like action): prolyl hydroxylase cofactor support ← hydroxyproline-rich collagen; ursolic acid: collagen I gene (COL1A1) upregulation; luteolin: MMP-2/9 inhibition (prevents premature matrix degradation); zinc (bark mineral): MMP cofactor regulation
Phase 3: Re-epithelialisation (Days 3-14)	Keratinocyte migration + proliferation(EGF/EGF-R, P13K/Akt); basement membrane formation (laminin, fibronectin deposition)	Quercetin + kaempferol: PI3K/Akt keratinocyte proliferation; sitosterol: keratinocyte migration (scratch wound assay); ellagic acid: EGF-R pathway modulation; lupeol: keratinocyte differentiation support; flavonoids: fibronectin synthesis stimulation
Phase 4: Remodelling (Weeks 3 to 2 years)	Collagen I/III cross linking (lysyl oxidase); tensile strength restoration; MMP/TIMP balance	Silica (bark ash): stimulates fibroblast collagen I synthesis and cross-linking; ellagic acid: LOX (lysyl oxidase) support; tannins: protein cross-linking analogous to collagen maturation; ursolic acid: sustained Smad2/3 collagen remodelling signal; anti-fibrotic balance: quercetin TGF-β fine-tuning prevents hypertrophic scarring
Anti microbial protection (All phases)	Bacterial membrane disruption; biofilm inhibition; quorum sensing interference; DNA gyrase inhibition	Gallic acid: membrane disruption (MIC 1-4 µg/mL); tannins: protein binding disabling bacterial adhesins; saponins: permeabilisation; rohitukine: DNA gyrase inhibition; limonoids: anti-biofilm (Pseudomonas quorum sensing); combined effect: broad-spectrum wound bed protection
Antioxidant protection (Ongoing)	ROS scavenging; Nrf2/HO-1 pathway activation; Fe^{3+} chelation; SOD/ CAT/ GPX support	High polyphenol content (450-650 mg GAE/g): direct DPPH/ABTS radical scavenging; ellagitannins: Fe^{3+}chelation preventing Fenton reaction in wound exudate; quercetin: Nrf2 nuclear translocation → HO-1/NQ01 antioxidant enzymes; gallic acid: glutathione (GSH) restoration

5.2 Key Mechanistic Pathways in Detail

5.2.1 NF-κB Pathway Suppression Anti-inflammatory Foundation

NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) is the master transcriptional regulator of the wound inflammatory response. Persistent NF-κB activation in chronic wounds drives continuous TNF-a, IL-1B, IL-6 production, maintaining the pathological MI macrophage state and preventing transition to the proliferative phase.

Multiple Mamsarohini constituents independently suppress NF-κB.[18]

- Lupeol (triterpenoid): IKKß phosphorylation inhibition prevents IκBα degradation - NF-κB remains cytoplasmic (inactive) IC308.4 µM in LPS-stimulated macrophages.
- Quercetin (flavonoid): dual NFκB + AP-1 pathway suppression, reduces TNF-α, IL-1β, IL-6 mRNA expression in wound macrophages, promotes M1→M2 polarisation shift.
- Gallic acid (tannin monomer) IKKβ inhibition ROS scavenging (removes NP-sating signals); combined NF-κB suppression at submicromolar concentrations.
- Limonoids swietenolide class): AP-1 (activator protein-1) pathway suppression synergistic κB inhibition with flavonoids at physiological wound exudate concentrations.

5.2.2 TGF-p/Smad2/3 Asis Collagen Synthesis and Fibroblast Activation

Transforming growth β (TGF β)is the master regulator of fibroblast activation, collagen I/ III synthesis, and myofibroblast differentiation in wound healing. Smad2/3 phosphorylation is the canonical TGF β signal trasduction pathway. Ursolic acid and oleanolic acid (triterpenoids in mamsarohini bark) are potent TGF β pathway activators, upregulating COL1A1(collagen I alpha-1 chain) gene expression in dermal fibroblast at concentrations of 1-10 µM. Simultaneously, rohitukune's CDK2/ cyclin D1 modulation provides cell cycle control, ensuring that fibroblast proliferation is orderly and complete rather than dysregulated (preventing hyperthrophic scar formation).

5.2.3 VEGF-Mediated Angiogenesis

Quercetin upregulates VEGF-A mRNA expression through HIF-la (hypoxia-inducible factor-la) stabilisation in wound hypoxic conditions. Kaempferol promotes endothelial cell migration (confirmed in scratch wound assay of HUVEC cells 72% closure at 24h vs 41% control at 25 µM). β-Sitosterol promotes endothelial tube formation in Matrigel assay, providing VEGFR-2-independent angiogenic support. This multi-compound angiogenic promotion is particularly relevant in diabetic wounds where VEGF signalling is impaired by AGE (advanced glycation end-product) modification.[20]

5.2.4 MMP Balance→ Prevention of Matrix Degradation

In chronic wounds, MMP-2 and MMP-9 are upregulated 2-10 fold, degrading the fibronectin-collagen provisional matrix and destroying growth factor receptors, preventing wound closure. Luteolin inhibits both MMP-2 and MMP-9 at the promoter level (AP-1 site inhibition) and at the protein level (zinc chelation luteolin binds the catalytic zinc of MMPs). This MMP inhibitory activity makes *Mamsarohini* a natural TIMP-mimetic, directly

addressing the proteolytic imbalance of chronic wounds without the adverse effects of synthetic MMP inhibitors (which broadly inhibit all MMPs including beneficial ones).[21]

5.2.5 Haemostatic Tannin Film

The high tannin content (20-30% of bark dry weight) of *Soymida febrifuga* creates a distinctive haemostatic mechanism. protein-binding tannins precipitate serum proteins on the wound surface, forming a self-adhesive protein-tannin film that physically seals the wound bed, reduces exudate, and provides a scaffold for initial fibrin deposition. This mechanism corresponds precisely to the *Stambhana* (haemostatic) property of *Kashaya Rasa* in Ayurveda and to the classical use of *Mamsarohini* bark in acute bleeding wounds. Additionally, ellagic acid specifically promotes platelet aggregation through TXA, pathway activation.

5.2.6 Antimicrobial and Anti-biofilm Activity

Wound infection particularly biofilm colonisation is the leading cause of wound chronicity *Mamsarohini*'s antimicrobial activity is mediated by multiple non-overlapping mechanisms.[23]

- ✧ Gallic acid bacterial membrane disruption (MIC 1-4 µg/mL for S. aureus); iron chelation depriving bacteria of essential Fe^{2+}/Fe^{3+} co-factors.
- ✧ Rohitukine: DNA gyrase inhibition (topoisomerase II- like mechanism); active against both Gram positive and Gram negative organisms.
- ✧ Tannins: Protein binding of bacterial adhesins→prevents biofilm initiation; anti-virulence rather than bactericidal (reduces selection pressure for resistance)
- ✧ Limonoids: anti-biofilm activity against *P. aeruginosa* quorum sensing (las/rhl system disruption). active at sub-MIC concentrations.
- ✧ Saponins membrane permeabilisation of Gram-positive organisms, potentiates other antimicrobial constituents.
- ✧ Synergistic action: gallic acid + tannins rohitukine combination shows 2-4 fold redaction in MIC vs individual compounds (checkerboard assay: FICI ≤0.5-synergy).

TABLE 6: ANTIMICROBIAL ACTIVITY OF *Soymida febrifuga* AGAINST WOUND PATHOGENS.

Organism (Wound Pathogen)	MIC(Bark extract)	Zone of Inhibition (mm)	Clinical significane
Staphylococcus aureus (MRSA)	120- 125µg/ ml	18- 24mm (Disc	Primary wound biofilm pathogen; gallic acid + rohitukine synergy; anti-

		diffusion)	biofilm at sub-MIC concentration
Staphylococcus aureus (MSSA)	62.5-125µg/ ml	22- 28mm	Most common acute wound pathogen; highly sensitive to tannin + flavanoid fraction
Pseudomonas aeruginosa	250- 500µg/ ml	14- 18mm	Chronic wound/ burns pathogen; reduced quorum sensing; anti-biofilm effect via tannins
Escherichia coli	125- 250µg/ ml	15- 22mm	Common wound contaminant; membrane disruption by saponins + gallic acid
Klebsiella pneumoniae	251- 500µg/ ml	12- 16mm	Hospital acquired wound infection; moderate sensitivity
Streptococcus pyogenes	62.5-125µg/ ml	19- 26mm	Cellulitis/ erysipelas pathogen; highly sensitive to tannin fraction
Candida albicans (Fungal)	250- 500µg/ ml	13- 18mm	Fungal wound colonisation; ergosterol disruption by triterpenoids
Bacillus subtilis	62.5-125µg/ ml	24- 30mm	Reference organism; confirms broad-spectrum antibacterial activity

6. CLASSICAL TEXTUAL REFERENCES- SYSTEMATIC REVIEW

TABLE 7: MAMSAROHINI IN CLASSICAL AYURVEDIC TEXTS- VRANA-SPECIFIC REFERENCES.

Classical Texts	Reference/ context	Indication for Vruna/ Wound
Charaka Samhita	*Sutra sthana* 4th chapter (*Shadvrechana shatashriteeya adhyaya*)- *Rohini* listed among *Shodhana* dravyas; *Chikitsa sthana* 25th Chapter (*Vruna chikitsa*)	*Vranaropana, Shodhana, Dushta Vruna*; recommended in *Pitta-Rakta* dominant wounds; used in *Vruna Prakshalana* (wound washing)
Sushruta Samhita	*Sutra sthana* 38th chapter *(Dravyaguna sangraha)- Mamsarohini* described in detail; Chikitsa sthana 1st chapter (*Vruna chikitsa- Dwivraneeya adhaya*) and 2nd chapter	*Vrunaropana Karma, Dushta Vruna Shodhana*; specifically named in wound management protocols; *Mamsarohini Kwatha f*or wound washing; *Mamsarohini Ghrita* for wound dressing
Astanga Hridayam	*Sutra sthana* 15th chapter (*Shodhana ropaneeya dravya); Uttara sthana (Vrana chikitsa)*	*Shodhana; Vrunaropana, Mamsarohini* included in *Shodhana-Ropana* category; fracture wound healing
Bhavaprakasha	*Guduchyadi varga- Mamsarohini* entry; *Chikitsa sthana (Vruna adhyaya)*	*Mamsarohini Ghrita, Mamsarohini Churna, Mamsarohini Taila* indicated for *Vruna* management; *Dushta Vruna, Duroodha Vruna*
Dhanwantari Nighantu	*Shatapushpadi varga-Mmasarohini* classified; *Rohini* synonyms confirmed	*Vranaropaka, Kapha-Pitta Shamaka, Raktashodhaka, Shothaghna;* specific for *Dushta Vruna*
Raja Nighantu	*Pippalyadi varga- Rohini/ Mamsarohini* entry	*Vrunaropana, Raktapitta Shamaka, Kushthaghna;* wound healing and

		skin disease management
Chakradatta	*Vruna chikitsa Adhyaya- Mamsarohini* based formulations	*Vrunaropaka, Deepana, Pitta-Kapha Shamaka, Kusthaghna, Krumighna* (antimicrobial)
Sharangadhara samhita	*Madhyama khanda 7th chapter (Lepa Kalpana); Uttarakhanda (Vruna chikitsa)*	*Mamsarohini Lepa* (topical paste) for *Vrana Shodhana* and *Ropana;* incorporated in wound pastes and medicated oils
Ashtanga sangraha	*Sutra sthana- Shodhana dravya varga*	*Vrunaropana*, wound cleaning, *Pitta-Rakta Shamaka*; recommended in post-surgical wound care in *Shalya Tantra*

6.1 Sushruta's *Dvivraniya Adhyaya* Detailed Analysis

Sushruta's Chikitsa Sthana Chapter 1 (*Dvivraniva Adhyaya*) provides the most comprehensive classical wound management protocol. Sushruta describes sixty *Upakramas* (therapeutic measures) for *Vruna* management the *"Shashti Upakrama"* of which *Mamsarohini* is specifically indicated in the *Shodhana* (cleansing), *Ropana* (healing), and *Vruna Prakshalana* (wound washing) categories. This multi-categorical classical indication precisely aligns with the multi-phase wound healing mechanisms characterised in contemporary pharmacology.[6]

Sushruta's description of *Mamsarohini Kwatha* in wound *prakshalana* (Chapter 2) specifies its use for *Dushta Vruna* (infected/chronic wounds) wounds with putrid smell (*Puyavasa*), excessive *Srava* (discharge), raised irregular margins (*Vrana Mukha Asamata*), and persistent pain. This clinical description corresponds precisely to biofilm-colonised chronic wounds with persistent inflammatory discharge, wound bed proteolytic degradation, and hyperalgesia conditions directly addressed by Mamsarohini's anti-biofilm (gallic acid + tannins), anti-inflammatory (NF-kB suppression), and MMP-inhibitory (luteolin) pharmacology.[23]

6.2 The *Mamsarohini-Rohini* Nomenclature Debate

Classical scholars and pharmacognosists have debated the authentic identity of "*Mamsarohini*, "*Katuki Rohini* primarily hepatic), with three candidate species identified. *Soymida febrifuga* A.Juss (Meliaceae bark-dominant toxic). The API (Ayurvedic Pharmacopoeia of India) application), *Picrorrhiza kurroa* Royle (Scrophulariaceae and *Gloriosa superba* Linn. (Colchicaceae resolution, supported by the wound-healing clinical tradition of *Shalya Tantra*, designates *Soymida febrifuga* as the authentic *Mamsarohini* for *Vruna* applications, based on:

(1) morphological consistency with classical descriptions, (2) geographic distribution matching classical harvest regions, (3) pharmacological profile concordance with *Vrunaropana* properties, (4) traditional practice of Shalya Tantra practitioners.[3]

7. PHARMACOLOGICAL EVIDENCE-IN VITRO AND IN VIVO STUDIES

7.1 In Vitro Evidence

7.1.1 Antimicrobial Studies

Multiple in vitro studies have characterised the antimicrobial spectrum of *Soymida febrifuga* bark extracts. Verma et al. (2019, J Nat Prod) systematically tested ethanolic, methanolic, and aqueous bark extracts against 12 wound-relevant organisms, demonstrating MIC values of 62.5-500 µg/ml. across all tested organisms. Critically, anti-biofilm activity was demonstrated at sub-MIC concentrations (0.25 MIC) against P. aeruginosa and S. aureus biofilms, a property absent in conventional antiseptics. The tannin fraction showed the strongest bacteriostatic activity, while the alkaloid fraction (containing rohitukine) showed bactericidal activity through DNA gyrase inhibition.[24]

7.1.2 Fibroblast and Keratinocyte Studies

Gupta et al (2018, Phytomedicine) demonstrated 78% closure in an 1929 fibroblast scratch assay at 48 hours using standardised bark extract (12.5 µg/mL) compared in the vehicle control. Type I collagen immuno fluorescence was increased ($P < 0.01$), and u SMA (myofibroblast marker) expression was appropriately upregulated, confirming both fibroblast migration and functional differentiation. MTT cell viability assay confirmed the extract was non cytotoxic at wound-relevant concentrations (IC_{20}> 200 µg/mL) contrasting with povidone-iodine's significant fibroblast cytotoxicity at 0.5% concentration.[25]

7.1.3 Antioxidant Studies

DPPH radical scavenging activity ICs of 18.4-24.6 µg/mL (ethanolic bark extract) comparable to ascorbic acid (IC2†15.2 µg/mL) ABTS IC2† 14.8 µg/mL., FRAP (ferric reducing antioxidant power):$FeSO_4$ equivalent/g extract. Nrf2/HO-1 pathway activation confirmed in wound fibroblast cell culture, demonstrating upregulation of endogenous antioxidant enzymes (SOD, CAT, GPx) at 24h post-treatment providing- sustained antioxidant protection beyond direct radical scavenging.[26]

7.2 In Vivo Evidence

7.2.1 Excision Wound Model

Hegde et al. (2013, Indian J. Exp. Biol.,) and Krishnamurthy et al. (2014, J Ethnopharmacol) conducted comprehensive in vivo wound healing studies using Wistar rat excision wound models with standardised bark extract topical application. Key findings

- Wound contraction: 92.3% by day 14 (vs 78.6% control), epithelialisation period reduced to 12.4 days (vs 18.2 days control) -a 31.9% reduction.
- Hydroxyproline content (collagen marker): 4.82 mg/g tissue (vs 2.94 mg/g control) 63.9% increase, confirming enhanced collagen synthesis.
- Histopathology: Dense, well-organised collagen fibres, mature granulation tissue with rich vascular network, complete re-epithelialisation, reduced inflammatory infiltrate by day 10.
- Tensile strength (incision wound model): 358.4 g (vs 210.6 g control) confirming improved wound maturation and collagen cross-linking. 70.2% increase.

7.2.2 Anti-inflammatory Studies

Carrageenan-induced paw oedema model (rat): bark extract (200mg / k * g oral) produced 68.3% inhibition of oedema at 4h (vs diclofenac: 72.1%) confirming potent anti-inflammatory activity, cotton pellet granuloma model: 54.6% inhibition of chronic granuloma formation, confirming proliferative inflammatory activity relevant to wound chronicity prevention, acetic acid writhing tesmalgesic): 71.4% inhibition of writhing (vs aspirin 64.3%), confirming Vedanasthapana (analgesic) classical action.[27]

7.3 Specific Phytochemical Mechanism Studies

Rohitukine - A Unique CDK Inhibitor in Wound Healing Context

Rohitukine (6-1[3-(dimethylaminopropionyl)-5-hydroxy-2-methyl-4H-1-benzopyran-4-one)) was first solated from *Soymida febrifuga*, making this species the botanical origin of an important scaffold for CDK (cyclin-dependent kinase) inhibitor drug development. In the wound healing context, rohitukine's CDK2/cyclin D1 inhibitory activity provides cell-cycle regulatory control over fibroblast and keratinocyte proliferation: it prevents dysregulated proliferation (which leads to hypertrophic scarring/keloids) while supporting the controlled, sequential proliferation required for normal granulation tissue formation. This dual cell-cycle regulatory property is unique among wound healing phytochemicals.[12]

Ursolic Acid -TGF-β/Smad Pathway Activation

Ursolic acid concentration in *Mamsarohini* bark (0.8-1.2% w/w) is among the highest reported in any medicinal plant bark. Multiple studies have confirmed ursolic acid's TGF-B/Smad2/3 pathway activation, leading to upregulation of COLIAI, COL3A1 (collagen III), ACTA2 (a-SMA), and the complete molecular signature of functional fibroblast-to-FIBRONECTIN-1 genes myofibroblast differentiation and wound contraction. At 5-10 µM (achievable in wound tissue from topical application), ursolic acid also inhibits TGF-B/Smad3-mediated excess fibrosis through explaining its ability to promote healing without hypertrophic PI3K/Akt pathway cross-talk scarring.[19]

8. CLINICAL EVIDENCE[28,29,30,31,33]

8.1 Summary of clinical studies

TABLE 8: CLINICAL AND PRE CLINICAL STUDIES ON MAMSAROHINI (*Soymida febrifuga*) IN WOUND HEALING.

Author/ Year	Study design	Sample	Key Findings	Reference/ Journal
Patil.et al. (2009)	Randomised controlled trial-Mamsarohini Taila vs Povidone Iodine in surgical wounds	n = 60 (30 + 30)	*Mamsarohini taila*: Significantly faster wound healing (P<0.01); reduced infection rate; better granulation tissue quality; fewer dressing changes required	AYU Journal 2009; 30(3)
Sharma K et. Al (2011)	Clinical study-Mamsarohini kwatha wash in Dushta Vruna (infected chronic wounds)	n = 40	Complete wound	J. Res., Ayurveda Pharm 2011
Hegde R et al. (2013)	In vivo- excision wound model (Wistar rats) with Mamsarohini bark extract (ethanolic)	n = 30 rats(5 groups)	Significant wound contraction (92.3% by day 14 vs 78.6% control) epithelialisation period reduced (2.4 vs 18.2 days); increased hydroxyproline content; histology; dense collagen + mature granulation tissue	Indian J. Exp. Biol., 2013
Krishnamurthy et al. (2014)	Excision + incision wound models - aqueous extract topical application	Rat model (n = 36)	Wound contraction improved by 40.6% over control; tensile strength of incision wound: 358.4g vs 210.6g (control); collagen synthesis	J Ethnophar macol 2014; 154

			markers elevated; anti-inflammatory activity confirmed.	
Nair S et al, (2015)	Randomised clinical trial - Mmasarohini Lepa in post-operative wounds (Shalya tantra)	n = 50 (25 + 25) vs standard dressing	Lepa group: 40% reduction in healing time; 78% reduction in wound discharge by day 7; pain (VAS) significantly lower; no adverse reactions	Anc. Sci. Life 2015; 35(2)
Rao V et al. (2016)	Clinical trial - Mamsarohini ghrita in nadi vruna (Sinus wound/ fistula)	n = 30	Sinus tract closure achieved in 73.3% cases within 6 weeks; pain and discharge reduction significant (P<0.001); no recurrence at 3 month follow up	IJAM 2016; 7(3)
Gupta A et al.	In vitro - fibroblast migration (starch assay)+ MTT assay, bark extract	L929 fibroblast cell line	78% wound closure in scratch assay at 48h (vs 45% control); IC_{200} for fibroblast proliferation = 12.5 µg/mL; significant increase in type I collagen immunofluorescence	Phytomedicine 2018; 48
Verma P et al.(2019)	Antimicrobial susceptibility - bark extracts vs wound pathogens	In vitro (n = 12 organisms)	MIC 62.5- 500µg/mL against all tested organisms; MRSA inhibition (MIC 250 µg/mL); superior biofilm inhibition vs ciprofloxacin at sub- MIC concentrations	J Nat Prod 2019; 82(6)
Srinivas M et al. (2021)	Randomised trial Mamsarohini Churna dusting in diabetic foot ulcer wounds	n = 40 (20+ 20) vs standard care	Significant improvement in wound area reduction (56.8% vs 34.2%, P<0.05); PUSH tool score improvement; reduced exudate and slough; no adverse events.	J Wound care 2021; 30(8)
Patel D et al.	Systematic review + meta analysis- Ayurvedic wound preparations including Mamsarohini	12 RCTs pooled (n = 654)	Mamsarohini - containing preparations showed pooled ES of 1.42 (95% CI 1.12-1.78) for wound contraction rate vs control; significant ati- infective and anti-inflammatory benefit; no serious AEs reported	JAIMS 2022; 7(4)

Evidence synthesis - Wound contraction and Healing time

Pooled analysis of available clinical studies demonstrates consistent superiority of *Mamsarohini*-based preparations over standard care comparators (povidone-iodine dressing, saline wash, standard Ayurvedic wound preparations without *Mamsarohini*) in the following

parameters

- Wound contraction rate: 40-78% faster than control in clinical studies; 92.3% contraction by day 14 in animal models vs 78.6% control.
- Epithelialisation period: reduced by 31-45% compared to standard dressings.
- Wound infection rate: 60-78% reduction in wound swab culture positivity with *Mamsarohini Kwatha prakshalana.*
- Wound discharge (*Srava*): 78% reduction by day 7 (Nair et al., 2015) *Shodhana* action. confirming rapid *Shodhana* action.
- Tensile strength: 70.2% improvement over control in incision wound models relevant for surgical wound integrity.
- Diabetic ulcer outcomes: Srinivas et al. (2021) demonstrated 56.8% vs 34.2% wound area reduction ($P<0.05$) in diabetic foot ulcers addressing the clinically most challenging wound type.

9.3 Clinical Assessment Parameters for Future Trials

For rigorous RCTs assessing Mamsarohini preparations in Vruna management, the following validated assessment tools are recommended

- Primary wound outcome: Wound area measurement (acetate tracing/digital planimetry Visitrak), PUSH Tool (Pressure Ulcer Scale for Healing) for chronic wounds, BATES-Jensen Wound Assessment Tool (BWAT).
- Secondary outcomes: Wound exudate assessment (DRAIN system); Wound bed preparation (TIME framework: Tissue, Infection/Inflammation, Moisture, Edge); Wound pain (VAS 0-10); Odour assessment.
- Microbiological Quantitative wound swab culture (semi-quantitative), biofilm detection (FISH fluorescence in situ hybridisation), wound pH.
- Tissue biomarkers (biopsy-based). MMP-2/9 ELISA, TGF-B, VEGF, hydroxyproline (collagen), IL-6/TNF-a, histopathology (H&E, Masson's trichrome for collagen).
- Ayurvedic outcome parameters: *Vrana Mukha* (wound surface quality), *Srava* (discharge), *Shotha* (peri-wound oedema), *Shoola* (pain), *Varna* (colour), *Gandha* (odour) - all graded 0-4.

TABLE 9: QUALITY STANDARDISATION AND PHARMACEUTICAL CONSIDERATIONS.

Quality Parameter	Specification/ Standard	Analytical method
Botanical identity	*Soymida febrifuga* A.Juss; macroscopic (Reddish brown deeply furrowed back) + microscopic (Calcium oxalate prisms, cork cells, fibre bundles)	Visual + light microscopy; TLC fingerprint; ITS2 DNA barcoding for authentication
Moisture content	≤12% (w/w) for dried bark powder	Loss on drying at 105℃, 3 hours
Total ash	≤10% (w/w)	Muffle furnace at 600℃
Acid Insoluble ash	≤2% (w/w)	HCl extraction of total ash
Water soluble extractive	≥18% (w/w)	Cold maceration in distilled water, 6 hours
Alcohol soluble extractive	≥15% (w/w)	Cold maceration in70% ethanol, 6 hours
Total Tannin content	Total Tannin content≥20% (w/w equivalent) as pyrogallol	Folin- Ciocalteu; Gallic acid standard curve
Total polyphenol content	≥450 mg GAE/g dry extract	Folin- Ciocalteu method; Uv-Vis spectrophotometry at 700nm
Rohitukine (Marker compound)	≥0.12% (w/w) in bark; ≥ 0.8% in standardised extract	HPLC-PDA (mobile phase: acetonitrile: 0.1% TFA 25:75; ƛ 254 nm; Rf= 0.54 in butanol: acetic acid:water 4:1:5
β-Sitosterol (Triterpenoid marker)	≥0.5% (w/w) extract In ethanolic	GC- MS; TLC (hexane: ethyl acetate 7:3)
Heavy metal limits	Pb≤ppm;As ≤ 1ppm; Cd ≤o.3 ppm;Hg ≤ 0.1ppm	ICP- MS or AAS
Microbial limits	Total viable count≤ 10^5 CFU/g;Absence of *E.coli*, *Salmonella*, *S.aureus;* Yeast + mould ≤ 10^3 CFU/g	USP/ WHO microbial limit test methods

10.2 Pharmaceutical Formulation Considerations

Modern pharmaceutical development of *Mamsarohini*-based wound care products should considerations

- ✓ Standardised Hydrogel Wound Dressing: aqueous bark extract (standardised to 20% tannins + 0.12% rohitukine) incorporated into carbopol/hydroxypropyl methylcellulose gel matrix, pH adjusted to 5.5-6.5 (wound-compatible); moist wound healing environment maintained.
- ✓ Standardised Ointment/Cream: ethanolic extract (standardised to ß-sitosterol + ursolic acid) in cetomacrogol base, suitable for Ropana phase (proliferation support); compatible

with classical *Mamsarohini Taila* concept.

- ✓ Lyophilised Powder (*Churna* equivalent) spray-dried aqueous extract standardised to total polyphenols 2450 mg GAE/g), for direct wound dusting (haemostatic-antimicrobial); stable at room temperature 24 months.
- ✓ Nanotechnology applications, chitosan nanoparticles loaded with *Mamsarohini* extract (proposed): targeted sustained release at wound interface, improved bioavailability at wound tissue; prolonged antimicrobial and anti-inflammatory effect.
- ✓ Combination approach: *Mamsarohini* extract + honey (*Madhu* classical *Lepa* component): synergistic antimicrobial (MGO + gallic acid + rohitukine); osmotic wound dehydration + anti-inflammatory, supports classical *Madhu-Mamsarohini Lepa* preparation.

11. SAFETY PROFILE

The safety evaluation of *Soymida febrifuga* A.Juss bark preparations encompasses acute toxicity, sub-chronic toxicity, genotoxicity, drug interactions, and contraindication profiling across both topical and oral routes of administration:

Safety Parameter	**Topical Use (Lepa/ Taila/Kwatha wash)**	**Oral/ Systemic use (Kwatha/ Churna/ Ghrita)**
Acute toxicity	No acute skin irritation, Sensitization or phototoxicity reported in clinical studies;	Oral LD20 (bark extract, rat model)>2000 mg/kg b.w. (WHO Category V - practically non-toxic);
	patch test recommended before large area application; tannin content may cause mild astringency	No acute toxicity at standard Ayurvedic doses (3-6g bark *kwatha)*
Sub acute/ Chronic Toxicity	Prolonged application; no evidence of contact dermatitis, skin atrophy or photosensitisation in 28day repeat application studies; safe for 3-6 months wound management courses	28day oral toxicity (250-500mg/kg rats): no significant changes in biochemical parameters (LFT, RFT, CBC); no histopathological abnormalities in liver/ kidney; NOAEL established at 500mg/kg
Hepatotoxicity	Not applicable (topical)	No hepatotoxic compounds identified; tannins at high doses may theoretically impair liver function-monitor in prolonged oral use; standard dose (3-6g bark decoction) is safe; liver protective activity reported at therapeutic doses
Genotoxicity	Not applicable	No mutagenicity in Ames test (bark extract, TA98/ TA100 strains); no chromosomal aberrations in micronucleus test; genotoxically safe at therapeutic concentrations

Drug interactions	May enhance topical antibiotic activity (synergy with mupirocin, fusidic acid confirmed in vitro); tannins may chelate topically co applied metal ions	Tannins may bind oral iron/ zinc supplements- administer 2h apart; may enhance anticoagulant effect of Warfarin (Ellagic acid platelet modulation)- monitor in anticoagulated patients; flavonoids may mildly inhibit CYP3A4 at high doses
Contraindications (Topical)	Active oozing wounds with excessive moisture(astrigent tannins may promote premature surface closure over infected base); documented hypersensitivity to Meliaceae family	Pregnancy(Insufficient data); severe renal impairment (tannin load); known hypersensitivity; concurrent oral iron therapy (chelation)
Adverse Events (Clinical)		<3% incidence; predominantly: mild GI discomfort (tannin astringency); rare mild nausea with concentrated *Kwatha* on empty stomach; no serious AEs in clinical trials
Comparision with Standard Dressings	Superior antimicrobial profile vs. Normal saline; comparable to Povidine- I is cytotoxic to fibroblasts at >0.5%); no interference with granulation tissue formation (unlike hydrogen peroxide)	Safer GI and systemic profile than oral NSAIDs used for wound pain; no renal/ GI risk; complements modern wound care without known clinically significant interactions.

Mamsarohini's safety profile compares exceptionally favourably to current standard wound care antiseptics:

- vs Povidone-Iodine (PVP-I): PVP-I at concentrations >0.5% is significantly cytotoxic to fibroblasts and keratinocytes (50-90% viability reduction) - paradoxically impairing healing while disinfecting. Mamsarohini extract is non-cytotoxic to fibroblasts at wound-relevant concentrations (IC2† >200 µg/mL) while providing equivalent or superior antimicrobial activity.

- vs Hydrogen Peroxide: H2O2 at any concentration >0.3% causes direct oxidative tissue damage, impairs granulation tissue, and releases damaging hydroxyl radicals. Mamsarohini's antioxidant activity (Nrf2/HO-1 activation) actively protects wound tissue from oxidative damage.

- vs Oral NSAIDs: NSAIDs used for wound pain management carry significant GI, renal, and cardiovascular risks with prolonged use. Mamsarohini's oral analgesic-anti-inflammatory activity (confirmed at 71.4% inhibition, acetic acid writhing test) is achieved without COX non-selective inhibition, avoiding the GI/renal adverse effect profile.

12. DISCUSSION

This systematic review presents *Mamsarohini* (*Soymida febrifuga* A Juss) as a pharmacologically exceptional multi-phase wound healing agent whose classical *Vranaropana-Shodhana* designation is now extensively validated at the molecular level. The key insight emerging from this integrated classical-pharmacological review is the remarkable correspondence between the classical *Shodha Ropana* dual action and the contemporary molecular understanding of wound bed preparation (ant biofilm/anti-inflammatory) followed by tissue regeneration (pro-proliferative/angiogenic/collagen synthetic)- a pharmacological sequence that single-mechanism synthetic wound dressings cannot replicate.

The phytochemical architecture of *Mamsarohini* bark reveals an evolutionary design of complementary wound-healing compounds: tannins for immediate haemostasis, gallic/ellagic acid for wound bed antimicrobial protection and NF-κB anti-inflammatory action; quercetin/kaempferol for VEGF-mediated angiogenesis and PI3K/Akt re-epithelialisation, ursolic acid for TGF- mediated collagen synthesis; luteolin for MMP balance (preventing matrix degradation), rohitukine for controlled cell-cycle regulation preventing scarring; and silica/zinc minerals for collagen cross-linking completion. This multi-phase, multi-target pharmacological cascade is precisely what is needed in the wound healing continuum but cannot be provided by any single-molecule drug.

CDK inhibitor The discovery of rohitukine *Soymida febrifuga* positions this plant at the intersection of wound healing and oncology as a unique compound first isolated from pharmacology. Rohitukine's CDK2/cyclin D1 inhibition provides an elegant wound healing function that has been largely overlooked controlled cell cycle progression in regenerating wound cells prevents the transition to dysregulated proliferation (hypertrophic scarring/keloid) that plagues 70 million wound patients annually This anti-scarring mechanism, combined with TGF- promotion of functional collagen, gives Mamsarohini a theoretical advantage over growth factor-only therapies (EGF, PDGF) that promote cellular proliferation without corresponding cycle regulation.

The classical formulation diversity (*Kwatha, Ghrita, Taila, Lepa, Churna, Basti*) reflects a sophisticated understanding of wound healing pharmacokinetics. The *Ghrita* and *Taila* preparations deliver lipophilic constituents (ursolic acid, ß-sitosterol, limonoids) optimally to deep tissue layers. The *Kwatha* and *Lepa* provide hydrophilic tannin-polyphenol wound surface activity. The Churna dusting achieves haemostatic tannin film formation on acute

bleeding wounds. This multi-formulation strategy mirrors modern wound care's recognition that different wound types and healing phases require different drug delivery formats.

Significant research gaps remain (1) No large-scale multi-centre RCTs with DXA-validated wound assessment exist for *Mamsarohini*; (2) Pharmacokinetic data on skin/wound tissue penetration of key phytochemicals (ursolic acid, rohitukine) from topical formulations are lacking, (3) Rohitukine's anti-scarring mechanism in wound healing has not been prospectively tested; (4) Combination studies with modern wound dressings (silver-impregnated dressings, hydrocolloids) are absent, (5) Conservation and cultivation protocols for sustainable supply are urgently needed given near-threatened status. These gaps define the future research agenda.

13. CONCLUSION

This comprehensive systematic review definitively establishes *Mamsarohini* (*Soymida febrifuga* A.Juss) as a pharmacologically validated, multi-mechanistic, and clinically supported wound-healing agent one of the most pharmacologically complete natural wound care agents documented in the scientific literature.

The classical designation of *Mamsarohini* as a principal *Vranaropana dravya* in nine major Ayurvedic texts providing simultaneous *Shodhana* (wound cleansing), *Ropana* (tissue regeneration). *Vedanasthapana* (analgesia), and *Stambhana* (haemostasis) - finds precise molecular validation in its phytochemical constituents ability to: (1) disrupt wound biofilm and prevent infection through gallic acid, tannins, rohitukine, and limonoids (2) resolve wound inflammation through NF-κB/COX-2/5-LOX inhibition by lupeol, quercetin, scopoletin; (3) promote granulation tissue through TGF-Sma 3 activation by ursolic acid: (4) stimulate angiogenesis through VEGF upregulation by quercetin kaempferol; (5) accelerate re-epithelialisation through PI3K/Akt pathway by quercetin βsitosterol (6) complete remodelling through MMP balance by luteolin and controlled collagen cross linking by silica/ zinc, and (7) prevent hypertrophic scarring through rohitukine CDK2 regulation.

Both topical and oral *Mamsarohini* preparations exhibit favourable safety profiles, with no toxicity to regenerating wound cells a critical advantage over povidone-iodine and hydrogen comide. Clinical studies demonstrate 40-78% faster wound healing across multiple wound types including the clinically challenging diabetic foot ulcer

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