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Integrative Pre-Treatment with Jalaukavacharana (Hirudotherapy) and Yashtimadhu Kwatha Prakshalan (Glycyrrhiza glabra) for Optimizing Split-Thickness Skin Graft Outcomes in Dushta Vrana (Chronic Non-Healing Ulcers): A Critical Narrative Review Bridging Ayurvedic Wound Science and Modern Reconstructive Surgery

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Background: Chronic non-healing ulcers, classified as Dushta Vrana in Ayurvedic nosology, constitute a major worldwide health burden, affecting approximately 1–2% of the adult population and imposing healthcare costs exceeding USD 25 billion annually in the United States alone. Ayurvedic classical texts, particularly the Sushruta Samhita, prescribe a systematic wound management paradigm (Shashti Upakrama) that emphasises preoperative optimisation of the wound bed through bloodletting (Raktamokshana), wound cleansing (Kshalana), and tissue regeneration (Ropana).

Objective: This narrative review critically examines the conceptual and scientific basis for integrating Jalaukavacharana (medicinal leech therapy) and Yashtimadhu Kwatha Prakshalana (Glycyrrhiza glabra decoction wound irrigation) as pre-treatment modalities to improve STSG acceptance in Dushta Vrana, aligning classical Ayurvedic frameworks with contemporary wound biology and systems medicine.

Methods: A PRISMA-guided literature search was conducted across PubMed, Scopus, AYUSH Research Portal, DHARA, and Google Scholar (2000–2025) using predefined keywords and inclusion–exclusion criteria. Classical Ayurvedic treatises were consulted for conceptual validation. Two independent reviewers screened articles at title, abstract, and full-text stages. Inter-reviewer agreement was quantified using Cohen's kappa coefficient (κ = 0.82, indicating substantial agreement).

Results: Leech saliva contains over 100 bioactive compounds—including hirudin, hyaluronidase, calin, and eglin—with demonstrated anticoagulant, anti-inflammatory, vasodilatory, and antimicrobial actions relevant to wound bed preparation. Glycyrrhizin and its derivatives exhibit wound healing, anti-ulcer, anti-inflammatory, and pro-angiogenic properties through modulation of NF-κB, COX-2, TNF-α, and collagen synthesis pathways.

Conclusion: The integrative pre-treatment model offers a biologically plausible approach to optimizing recipient wound beds for STSG. However, the current evidence is largely preclinical and conceptual, highlighting the requirement for rigorous multi-centre randomized controlled trials to establish clinical efficacy and uniform protocols. Research priorities include designing and executing robust RCTs comparing integrative and conventional pre-treatment strategies, developing uniform protocols for Jalaukavacharana and Yashtimadhu interventions, and validating outcome assessment tools that bridge Ayurvedic and modern wound scoring systems. These steps are essential for translating this conceptual model into evidence-based clinical practice.

Keywords: Dushta Vrana; Jalaukavacharana; Hirudotherapy; Yashtimadhu; Glycyrrhiza glabra; Split-Thickness Skin Graft; Chronic Non-Healing Ulcer; Integrative Wound Management

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Introduction

1. Global Burden of Chronic Non-Healing Ulcers

Chronic wounds constitute a growing global health challenge, driven by the rising prevalence of non-communicable diseases, including diabetes mellitus, peripheral vascular disease, and venous insufficiency. A systematic meta-analysis reported a pooled prevalence of chronic wounds of approximately 2.21 per 1,000 individuals globally, with chronic leg ulcers accounting for the majority at 1.51 per 1,000. In India, the prevalence of chronic wounds is estimated at 4.5 per 1,000 population, with approximately 1% in adults and 3.6% in individuals aged 65 years and older. The economic burden is substantial, with chronic wounds costing the United States healthcare system an estimated USD 25 billion annually, encompassing hospitalization, repeated dressing changes, and amputations.**[4][6][17]**

Venous ulcers represent approximately 80–90% of all lower extremity wounds. Diabetic foot ulcers (DFU) affect an estimated 40–60 million individuals globally, with 15% of diabetic patients developing a DFU during their lifetime and 14–24% of these requiring amputation.Biofilm formation, tissue ischaemia, persistent inflammation, and impaired neovascularization characterize chronic wound pathobiology and continue to challenge conventional wound management strategies.**[12][4][18][19][20][21]**

2. Split-Thickness Skin Grafting: Current Limitations

STSG remains the first-line reconstructive option for chronic wounds, involving harvesting of the epidermis and a portion of the dermis from a donor site and transplanting it onto the wound bed. The success of STSG depends critically on wound bed vascularity, absence of infection, and adequate nutritional supply during the phases of plasmatic imbibition, inosculation, and neovascularization. Reported graft take rates range from 70% to 90%. The causes of graft failure may be broadly categorised as modifiable, such as infection, wound contamination, and local vascularity, and intrinsic or less modifiable, such as patient comorbidities or anatomical shear forces. Infection, particularly by *Pseudomonas aeruginosa* (isolated in 58.1% of infected grafts), constitutes the most significant modifiable risk factor.**[3][5][22]**

In this context, each modifiable barrier to graft success can be explicitly mapped to *Ayurvedic* pre-treatment strategies: for example, *Jalaukavacharana* aims to address venous congestion and enhance local vascularity through bioactive salivary components, while *Yashtimadhu Kwatha Prakshalana* provides antimicrobial and anti-inflammatory effects to reduce infection risk and support tissue regeneration. These targeted interventions are proposed as practical adjuncts for optimizing the wound bed, offering surgeons an integrative approach that corresponds classical Ayurvedic principles with the clinical demands of modern reconstructive practice.**[22-28]**

3. Ayurvedic Surgical Heritage and Rationale for Integration

The surgical tradition of Ayurveda, *Shalyatantra*, offers a sophisticated wound management framework developed by Acharya Sushruta (c. 1000–800 BCE), acknowledged as the "Father of Plastic Surgery". The *Sushruta Samhita* describes rhinoplasty (*Nasikasandhanvidhi*), lobuloplasty (*Karnapalisandhanvidhi*), cheiloplasty (*Osthasandhanvidhi*), and comprehensive wound repair (*Sandhana Karma*)—procedures that established foundational principles of reconstructive surgery still recognized in contemporary practice. The pedicle forehead flap described by Sushruta is referred to as the "Indian Flap" in modern surgical parlance.**[2][29][1]**

The Ayurvedic paradigm of mandatory wound bed preparation (*Vrana Shodhana*) prior to grafting (*Sandhana Karma*), specifically through *Jalaukavacharana* (leech therapy) and *Yashtimadhu Kwatha Prakshalana* (liquorice decoction wash), constitutes a scientifically rational strategy to improve STSG outcomes. While classical texts such as the Sushruta Samhita and related treatises provide detailed descriptions of these modalities individually as part of holistic wound management, they do not explicitly advocate or systematically test the combined use of leech therapy together with licorice decoction in a coordinated pre-grafting protocol. Rather, the integrative application discussed in this review represents a contemporary synthesis that draws on classical principles, delivering a novel translational approach. This distinction highlights respect for the historical tradition while stressing the innovative nature of combining these modalities in the context of modern wound care.

The integration of these approaches is consistent with the emerging paradigm of translational Ayurveda and integrative wound care.[30][31][32]

Materials and Methods

Literature Search Methodology (PRISMA-Style)

1. Search Strategy

A comprehensive literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines adapted for narrative reviews. The following electronic databases were searched from January 2000 to December 2025: PubMed / MEDLINE, Scopus, Cochrane Library, AYUSH Research Portal, DHARA (Digital Helpline for Ayurveda Research Articles), Google Scholar, and Web of Science. Search term clusters were developed to systematically capture studies representing five key conceptual domains: (A) condition, (B) intervention 1 (leech therapy), (C) intervention 2 (liquorice-based therapies), (D) outcome (skin grafting endpoints), & (E) framework (*Ayurvedic* and integrative medicine context).

2. Search Terms

The search strategy employed Boolean operators combining the following keyword clusters:

- **Cluster A (Condition):** "*Dushta Vrana*" OR "chronic non-healing ulcer" OR "chronic wound" OR "venous ulcer" OR "diabetic foot ulcer"
- **Cluster B (Intervention 1):** "*Jalaukavacharana*" OR "leech therapy" OR "hirudotherapy" OR "*Hirudo medicinalis*" OR "hirudin"
- **Cluster C (Intervention 2):** "*Yashtimadhu*" OR "*Glycyrrhiza glabra*" OR "licorice" OR "glycyrrhizin" OR "glycyrrhizic acid"
- **Cluster D (Outcome):** "split-thickness skin graft" OR "STSG" OR "skin grafting" OR "wound bed preparation" OR "graft acceptance"
- **Cluster E (Framework):** "*Ayurveda*" OR "*Sushruta Samhita*" OR "*Vrana Chikitsa*" OR "*Shashti Upakrama*" OR "integrative medicine"

3. Inclusion and Exclusion Criteria

Inclusion criteria - encompassed original research articles, clinical trials, case series, systematic reviews, narrative reviews, Studies published in English or *Sanskrit* (with available translations), classical *Ayurvedic* texts (*Sushruta Samhita*, *Charaka Samhita*, *Ashtanga Hridaya*, *Bhavaprakasha Nighantu*, *Raj Nighantu*), preclinical studies demonstrating relevant wound healing mechanisms, and studies addressing wound bed preparation for skin grafting.

Exclusion criteria - comprised conference abstracts without full text, studies unrelated to wound healing or skin grafting, duplicate publications, and studies lacking methodological transparency.

4. Data Extraction and Synthesis

Data extraction included study design, population, interventions, bioactive mechanisms, wound-healing outcomes, and classical textual references. To facilitate cross-disciplinary interpretation, classical diagnostic criteria for *Dushta Vrana* were mapped to contemporary wound scoring systems. This mapping was guided by a structured comparison of symptom domains and objective features described in both systems. Key classical signs, such as 'foul odour,' 'discolouration,' 'excessive discharge,' and 'necrotic tissue,' were systematically matched to equivalent domains within established modern systems like the Wound Bed Score, PUSH Tool, and Bates-Jensen Wound Assessment Tool according to shared observable characteristics. For transparency and to facilitate replication, each pairing was based on a direct correspondence between how each classical sign manifests and the focus of modern scores. For example, 'foul odour' in classical descriptions was matched with the 'odour' component of the Wound Bed Score, as both directly assess the presence and degree of undesirable smell from the wound. 'Necrotic tissue' was paired with 'necrotic tissue type/amount' in the Wound Bed Score, reflecting the extent of dead tissue in both frameworks. 'Excessive discharge' was mapped to the exudate-related items in modern tools, while 'discolouration' corresponded to color or tissue appearance scores. Mappings were determined through consensus by two independent reviewers, who compared the clinical descriptors and reached agreement through discussion in cases of divergence. For instance, classical signs such as 'foul odour' and 'necrotic tissue' were correlated with the 'odour' and 'necrotic tissue type/amount' domains of Wound Bed Score, enabling standardization and comparison between Ayurvedic and modern wound assessment practices.

A narrative synthesis approach was employed due to the heterogeneity of evidence spanning classical texts, preclinical studies, and limited clinical data.

Classical Conceptual Framework

1. *Dushta Vrana*: *Ayurvedic* Nosology of Chronic Wounds

Vrana in Ayurveda denotes a structural deformity of skin and deeper tissues associated with pain, discharge, and functional impairment, arising from vitiated *Doshas* or external trauma. *Dushta Vrana* specifically refers to chronic, contaminated, difficult-to-heal ulcers characterised by foul odour (*Durgandha*), discolouration (*Vivarna*), excessive discharge (*Atistravi*), necrotic tissue (*Putimamsa*), and local temperature abnormalities.**[30][32]**

Acharya Sushruta (*Sushruta Samhita*, Sutra Sthana 22 and Chikitsa Sthana 1) provides detailed diagnostic criteria: excessive covering or exposure, hardness or softness, abnormal temperature, altered colours (black, red, or white), foul smell, pain, and discharge of pus and vitiated blood. The *Samprapti* (pathogenesis) of *Dushta Vrana* involves combined vitiation of *Tridosha* (Vata, Pitta, Kapha) along with *Rakta* (blood tissue) and *Mamsa Dhatu* (muscle tissue), leading to tissue necrosis, slough formation, and microbial overgrowth. This Ayurvedic pathogenetic model captures both local and systemic determinants of chronicity and parallels contemporary understanding of biofilm formation, ischaemia, oedema, and altered local immunity in chronic wound biology.**[30][32][33]**

2. *Shashti Upakrama*: The Sixty-Fold Wound Management Protocol

Acharya Sushruta described *Shashti Upakrama*—sixty specialized therapeutic procedures for comprehensive wound management—in *Chikitsa Sthana*, Chapter 1 of the *Sushruta Samhita*. This is an expansion of the *Sapta Upakrama* (seven treatment categories): *Vimlapana* (gentle kneading), *Avasechana* (bloodletting), *Upanaha* (poultice), *Patana Kriya* (incision/drainage), *Shodhana* (wound cleansing), *Ropana* (wound healing), and *Vaikrutapaha* (cosmetic repair).**[1][2][29]**

The clinical significance is found in the systematic, stage-wise approach: managing inflammation (*Vrana Shopha*), treating the wound or ulcer (*Vrana*), and repairing the scar (*Vrana Vastu*).

This methodology parallels contemporary wound management protocols, which include debridement, infection control, wound bed preparation, and reconstructive coverage, while also emphasizing cosmetic rehabilitation and recurrence prevention.

Shashti Upakrama remains one of the most ancient and comprehensive descriptions of staged wound management, with its principles validated in modern surgical practice.**[1][2][29][34][35]**

3. *Raktamokshana* as a Pre-Requisite for *Sandhana Karma*

A critical classical principle directly relevant to STSG is the mandate for *Raktamokshana* (bloodletting) before *Sandhana Karma* (tissue union/grafting).

Sushruta explicitly states (*Sushruta Samhita*, Sutra Sthana 16/17):

"Na Chaashuddhraktam Atipravruttaraktam Va Ksheenaraktam Va Sandadhyaat..."

Translation: "One should not attempt healing/union of a wound as long as the local blood remains impure, there is active haemorrhage, or the local blood is depleted."

The text further specifies that grafting with Vata-vitiated blood leads to re-opening; with *Pitta*-vitiated blood, burning and suppuration; with Kapha-vitiated blood, itching and numbness; and with active haemorrhage, swelling with discolouration.

This classical directive establishes the textual basis for pre-treatment blood purification via *Jalaukavacharana* before skin grafting, thereby mandating wound bed optimization in alignment with modern surgical principles.**[36]**

4. Sandhana Karma: Sushruta's Principles of Tissue Grafting

The *Sushruta Samhita* (Sutra Sthana 16) describes the pioneering technique of reconstructive surgery, detailing the measurement of a nasal defect using a leaf template, dissection of a living skin flap from the cheek, attachment to a rawened nasal stump, and precise suturing. This pedicle-flap technique laid the foundation for modern rhinoplasty. The principle of *Sandhana* (tissue union) is recommended specifically for ulcers that are free from suppuration, situated in fleshy body regions, and have wide openings (*Sushruta Samhita*, *Chikitsa Sthana* 1).**[37]**

Contemporary Scientific Evidence

1. Bioactive Constituents of Leech Saliva and Wound Healing Mechanisms

The saliva of *Hirudo medicinalis* and related species contains over 100 identified bioactive substances, representing a complex pharmacological armamentarium directly relevant to wound bed preparation.**[15][38][7]**

Table 1: Key Bioactive Components of Leech Saliva and Their Wound Healing Functions

Bioactive Compound	Mechanism of Action	Relevance to STSG Bed Preparation
Hirudin	Potent thrombin inhibitor; prevents fibrinogen-to-fibrin conversion[15]	Prevents hematoma formation beneath graft; sustains local bleeding for decongestion
Hyaluronidase	Degrades hyaluronic acid; increases tissue permeability ("spreading factor")[11]	Facilitates infiltration of bioactive substances; reduces oedema; improves tissue oxygenation
Calin	Inhibits von Willebrand factor-mediated platelet aggregation[11]	Prevents clot formation; sustains post-bite bleeding for venous decongestion
Bdellins	Inhibit trypsin and plasmin[15]	Anti-inflammatory effect; reduce proteolytic tissue damage
Eglins	Inhibit α-chymotrypsin, elastase, cathepsin G[15]	Anti-inflammatory; protect against granulocyte-mediated tissue destruction
Hirustasin	Selectively inhibits tissue kallikreins	Regulates blood pressure; contributes to intrinsic coagulation modulation
Destabilase	Fibrinolytic activity (dissolves existing clots)[37]	Clears existing microthrombi from wound vasculature
Histamine-like substances	Vasodilation[15]	Increases local blood flow; reduces swelling
Antimicrobial peptides	Broad-spectrum antimicrobial activity[11]	Reduces wound bioburden; addresses infection-related graft failure

A 2025 experimental study demonstrated that leech saliva extract (LSE) significantly enhanced incisional wound healing in rats by improving neovascularization, VEGF expression (75.60 ± 0.67% VEGF-positive cells vs. controls), granulation tissue formation, and fibroblast proliferation, while reducing inflammation. The persistent bleeding following leech application potentiates tissue decongestion by reducing venous congestion, decompressing nerve trunks, increasing lymph flow, Improving local haemodynamics and haemorheology, and enhancing oxygen supply, collectively eliminating tissue ischaemia.**[15][53]**

Contemporary clinical applications confirm that leech therapy has expanded beyond traditional Ayurvedic use, finding utility in reconstructive plastic surgery for salvaging congested flaps, with retrospective analyses indicating success rates exceeding 80%.

The FDA has approved *Hirudo medicinalis* as a medical device for the management of venous congestion. However, the risk of *Aeromonas hydrophila* infection must be considered, and prophylactic anti-*Aeromonas* antibiotics are recommended during leech therapy.**[36][39-61]**

2. The Classical Rationale: Selective Vitiated Blood Removal

Ashtanga Hridaya (*Sutra Sthana* 26/42) provides a metaphorical classical claim: the leech selectively draws only vitiated blood from the body, similar to the swan that drinks only milk from a mixture of milk and water. Although this metaphorical description is not literal in molecular terms, the selective actions of bioactive compounds—such as hirudin, which prevents coagulation of healthy blood, and hyaluronidase and antimicrobial peptides targeting pathological tissue components—offer a partial scientific explanation for this classical observation.**[11][15]**

3. *Yashtimadhu* (*Glycyrrhiza glabra*): Pharmacological Evidence for Wound Healing

3.1 Classical Textual Evidence

Multiple classical texts establish *Yashtimadhu* as a prime wound-healing drug:

- ***Bhavaprakasha Nighantu*** (*Madhyam Khanda*, verse 39): Describes *Yashtimadhu* as *Hima* (cooling), *Guru* (heavy), *Svaadvi* (sweet), *Chakshushya* (beneficial for eyes), *Balavarnaakrit* (strength and complexion enhancing), *Pitta-Anila-Astra-jit* (pacifies Pitta, Vata, and blood disorders), and *Vrana-Shotha-Visha-Chardi-Trushna-Glaani-Kshayapaha* (alleviates wounds, inflammation, toxicity, vomiting, thirst, debility, and emaciation).
- ***Raj Nighantu*** (*Pipalyadi Varga*): Describes *Yashtimadhu* as *Madhura* (sweet), slightly *Tikta* (bitter), *Sheetala* (cold), *Chakshushya*, *Pitta-hrit*, and *Shosha-Trushna-Vrana-apaha*.

- ***Charaka Samhita***: Advocates use in *Vataja* and *Raktaja* diseases in various contexts.
- ***Sushruta Samhita*:** Describes its use in pain management across surgical and medical conditions.

The classical pharmacodynamic profile—*Madhura Rasa* (sweet taste), *Sheeta Virya* (cold potency), *Madhura Vipaka* (sweet post-digestive effect), *Vata-Pitta Shamaka* (pacifies *Vata* and *Pitta*)—is consistent with the requirement for a cooling, anti-inflammatory, tissue-regenerating agent for chronic wound management.

3.2 Contemporary Pharmacological Evidence

Table 2: Pharmacological Properties of *Glycyrrhiza glabra* Relevant to Wound Bed Optimization

Active Constituent	Pharmacological Action	Evidence	Relevance to STSG
Glycyrrhizin / Glycyrrhizic acid	Anti-inflammatory (inhibits COX-2, NF-κB); immunomodulatory	Reduces TNF-α, IL-6, IL-1β in murine models[12]	Mitigates chronic inflammation in wound bed; creates favourable graft environment
Dipotassium Glycyrrhizinate (DPG)	Promotes collagen I/III synthesis; accelerates re-epithelialization	Enhanced neovascularization and fibroblast proliferation in rat wound models[12]	Optimizes granulation tissue quality for graft adherence
Glycyrrhizin hydrogels	Accelerates cutaneous wound closure; influences keratinocyte migration	Accelerated healing in both normoglycemic and diabetic murine models	Addresses diabetic wound pathology pre-graft
Sodium Glycyrrhizinate	Anti-ulcer activity; stimulates skin regeneration	Anti-ulcer and regenerative activity documented	Direct wound healing and anti-ulcer action
Licorice flavonoids	Antimicrobial against wound pathogens	Inhibited S. aureus and P. aeruginosa growth in vitro[14]	Reduces bioburden—addresses the dominant cause of graft infection
Licorice root extract (>8%)	Accelerates wound contraction and healing	Enhanced epithelialization, angiogenesis, collagen formation in burn models[14]	Comprehensive wound bed improvement
Polysaccharide (PSG)	Antioxidant; accelerates wound healing	Higher wound appearance scores and collagen content in rat wound models[9]	Natural bioactive polymer for wound bed preparation

A pivotal study on DPG reported significant improvements throughout all phases of wound healing: reduction of pro-inflammatory cytokines (TNF-α, COX-2, IL-8, NF-κB, IL-1) during the inflammatory phase, enhanced fibroblast proliferation and granulation tissue in the proliferative phase, and increased type I and III collagen deposition with elevated IL-10 anti-inflammatory cytokine levels during the remodelling phase.

A 2022 study specifically demonstrated that glycyrrhizin-based hydrogels accelerated cutaneous wound closure in both normoglycaemic and diabetic mice by influencing keratinocyte migration and proliferation—directly relevant to the diabetic chronic wound population that frequently requires STSG.**[12]**

A water-soluble polysaccharide isolated from *G. glabra* exhibited potential antioxidant activities and significantly accelerated wound healing, evidenced by higher wound appearance scores and higher collagen content confirmed by histological examination. The antimicrobial properties are particularly significant: licorice root extract demonstrated effective inhibition of both *S. aureus* and *P. aeruginosa* in vitro. However, direct evidence in humans remains extremely limited, with only one published clinical trial evaluating topical *Glycyrrhiza glabra* extracts in human chronic ulcer populations as of 2024, and no randomized controlled trials have been reported.**[14][13][62-75]**

Key translational barriers also persist, including the lack of standardization in licorice extract formulations, regulatory uncertainties around approval for clinical use, and challenges in identifying optimal patient selection criteria. These barriers must be addressed in future research to enable successful clinical translation and broader adoption in wound care practice.

Critical Analysis and Theoretical Integration

1. Conceptual Diagram: Integrative Pre-Treatment Mechanism (Textual Description)

Figure 1 (Conceptual): Proposed Mechanism of *Jalaukavacharana* and *Yashtimadhu Kwatha Prakhalan* as Pre-Treatment for STSG Optimization in *Dushta Vrana*

The diagram illustrates a three-phase integrative model:

Phase I - Wound Bed Pathology (*Dushta Vrana* / Chronic Non-Healing Ulcer):

Central node depicting the chronic wound bed with radiating pathological features: biofilm formation, venous congestion, tissue ischaemia, Tridoshic vitiation (*Vata-Pitta-Kapha* imbalance with *Rakta* and *Mamsa Dhatu* involvement), oedema, microbial overgrowth, necrotic slough, and impaired angiogenesis.

Phase II - Dual Pre-Treatment Intervention (Two Parallel Pathways):

- **Left pathway *(Jalaukavacharana):*** Leech application → Salivary bioactive release → Hirudin (anticoagulation, hematoma prevention) + Hyaluronidase (tissue permeability, oedema reduction) + Bdellins/Eglins (anti-inflammation) + Antimicrobial peptides (bioburden reduction) + Vasodilation (improved perfusion) → **Net effect:** Venous decongestion, local haemodynamic improvement, tissue oxygenation, microbial reduction (*Rakta Shodhana* achieved).**[11][15]**
- **Right pathway *(Yashtimadhu Kwatha Prakshalana):*** Topical wound wash → Glycyrrhizin/DPG release → COX-2/NF-κB inhibition (anti-inflammation) + Fibroblast/keratinocyte stimulation (granulation, re-epithelialization) + Collagen I/III promotion (tissue matrix) + Antimicrobial action + IL-10 upregulation → **Net effect:** Wound cleansing, inflammation resolution, healthy granulation tissue formation (*Vrana Shodhana* and *Vrana Ropana* achieved).**[14][12]**

Phase III - Optimized Recipient Bed for STSG:

Both pathways converge to produce: well-vascularized wound bed, absence of infection/biofilm, viable granulation tissue, resolved oedema, and optimal local haemodynamics → facilitating successful plasmatic imbibition → inosculation → neovascularization → enhanced graft take and long-term viability.**[3]**

2. Systems Biology Perspective

The proposed integrative model is consistent with the emerging framework of integrative biology in medicine, which incorporates holistic epigenetic regulation, the concept of self-organized criticality from complexity biology, and Ayurveda's systems-level understanding of organism function.

The *Tridosha* paradigm of wound pathology can be conceptualized as a systems-level description of the interplay among neurogenic inflammation (*Vata*), oxidative-inflammatory cascades (*Pitta*), and proliferative-fibrotic responses (*Kapha*).**[31]**

Network pharmacology—a systems-level strategy for elucidating compound–target–pathway interactions—provides a powerful framework for validating the multi-target mechanisms of traditional Ayurvedic wound interventions. *Jalaukavacharana* addresses the haemodynamic and haemostatic axes of wound pathobiology (primarily *Rakta Shodhana*), while *Yashtimadhu* modulates the inflammatory-proliferative axis (primarily *Pitta-Vata Shamana* and *Vrana Ropana*). Together, they target complementary nodes in the wound healing network, constituting a multi-target therapeutic strategy analogous to combination therapy in modern medicine.**[53][54][76-78]**

3. Comparative Analysis: Classical Ayurvedic vs. Modern Wound Bed Preparation

Table 3: Translational Correspondence Between Shashti *Upakrama* and Modern Wound Management

Ayurvedic Procedure (Shashti Upakrama)	Modern Equivalent	Relevance to Pre-STSG Preparation
Shodhana (wound cleansing)	Surgical debridement; wound irrigation[1]	Removes necrotic tissue; reduces bioburden
Raktamokshana / Jalaukavacharana (bloodletting via leeches)	Leech therapy for venous congestion; NPWT[36][59]	Decongests wound bed; improves perfusion
Kshalana (medicated wound wash)	Wound irrigation with antiseptic solutions[32]	Yashtimadhu Kwatha provides antimicrobial and anti-inflammatory cleansing
Lepa (topical medicated paste)	Topical wound care agents; growth factor application[32]	Creates pharmacologically active wound environment
Ropana (healing promotion)	Growth factor therapy; biological dressings[1]	Stimulates granulation and re-epithelialization
Bandhana (bandaging)	Modern wound dressings (foam, hydrocolloid, alginate)[3]	Protects wound bed; maintains moisture
Sandhana Karma (tissue union/grafting)	Split-thickness / full-thickness skin grafting[3]	Final reconstructive step upon optimized wound bed

This comparative analysis indicates that Sushruta's wound management paradigm was systematic and comprehensive,

Addressing therapeutic objectives such as debridement, decontamination, vascular optimization, tissue regeneration, and reconstructive coverage, all of which are recognized in contemporary wound care guidelines.[1][2][29][79][80][81]

4. Critical Appraisal of Current Evidence

Despite the biological plausibility and substantial classical textual support, several major limitations must be acknowledged: **Level of evidence:** The majority of evidence for leech therapy in wound healing derives from case reports, case series, animal studies, and narrative reviews. High-quality RCTs specifically evaluating *Jalaukavacharana* as a pre-treatment for STSG are absent from the indexed literature.[11][55][56]

- **Glycyrrhiza glabra wound healing data:** While preclinical evidence for glycyrrhizin's wound healing properties is compelling, clinical trials in human chronic wound populations remain scarce. The optimal concentration, formulation (decoction vs. hydrogel vs. extract), and application protocol for wound bed preparation are yet to be standardized.[12][13][14]
- **Conceptual nature of integration:** The proposed synergistic model combining leech therapy and licorice decoction for STSG bed preparation remains theoretical. No published clinical trial has evaluated this specific combination in a controlled setting.
- **Standardisation challenges:** Both leech therapy and herbal formulations present standardisation issues, including leech species selection, session duration, number of leeches, Yashtimadhu decoction concentration, application frequency, and outcome measurement tools, all of which require protocol development.[32][60] To address these barriers and facilitate multicentre collaboration, interim standardization steps are recommended. Consensus-based expert panels should be convened to define core intervention parameters, drawing on classical Ayurvedic texts and adapting them for clinical research. Standardized leech species (such as Hirudo medicinalis or Hirudinaria granulosa), minimum and maximum session durations, and initial leech number ranges should be specified.[82] Similarly, *Yashtimadhu* decoction should be prepared according to *Ayurvedic* Pharmacopoeia guidelines, with provisional recommendations for concentration, temperature, and application frequency reported transparently in study protocols. The development of detailed case report forms (CRFs) to document procedural steps, adverse events, and wound assessment parameters will enable uniform data collection and reporting. Establishing a minimum data set for multicentre studies and adopting a provisional checklist for intervention fidelity can support immediate clinical research while comprehensive, evidence-informed protocols are under development. To accelerate progress, convening a formal Delphi panel of Ayurveda scholars, wound care specialists, and plastic surgery experts is recommended. This interdisciplinary consensus-building process can enable the quick drafting of provisional standard operating procedures (SOPs), which can be pilot-tested and refined as additional evidence emerges. Engagement from the professional community is essential to produce pragmatic interim protocols that will support harmonized multicentre studies & promote global adoption.
- **Safety considerations:** Leech therapy carries risks of infection (*Aeromonas hydrophila*), allergic reactions, excessive bleeding, and scarring at bite sites. Glycyrrhizin may cause pseudoaldosteronism with prolonged systemic use, though topical application minimises this risk.[15][60]

Research Gaps

The following major gaps have been identified through this review. To provide clear guidance for funding agencies and research planners, these gaps are ranked by their likely clinical impact and feasibility of study. A high, medium, or low-priority key is included in brackets after each gap.

Absence of RCTs (High priority)**:** No published RCT evaluates the specific combination of *Jalaukavacharana* + *Yashtimadhu Kwatha Prakshalana* as pre-treatment for STSG in chronic ulcers.

1. Lack of dose-response studies (High priority): Optimal leech session parameters (number, duration, frequency, total sessions) and *Yashtimadhu* formulation specifications (concentration, volume, temperature, frequency) for wound bed preparation are undetermined.

2. No validated bridging outcome measures (High priority): Standardised outcome assessment tools that link Ayurvedic wound classification (*Dushta Vrana Lakshanas*) with modern wound scoring systems (PUSH, BWAT, Wound Bed Score) do not exist.

3. Insufficient pharmacokinetic data (Medium priority): The tissue-level bioavailability and sustained action of leech salivary compounds and glycyrrhizin metabolites in the wound microenvironment remain poorly characterized.

4. Wound microbiome interactions unexplored (Medium priority): The effects of leech therapy and liquorice decoction on the wound microbiome—particularly biofilm disruption and commensal restoration—have not been studied.

5. Absent health economics data (Medium priority): Cost-effectiveness analyses comparing integrative pre-treatment (leech + *Yashtimadhu* + STSG) versus conventional wound bed preparation + STSG are absent.

6. No long-term outcome data (Low priority): Data on graft durability, recurrence rates, cosmetic outcomes, and quality of life following integrative pre-treatment are unavailable.

7. Molecular mechanism elucidation needed (Low priority): The specific molecular crosstalk among hirudin-mediated anticoagulation, hyaluronidase-mediated tissue remodelling, and glycyrrhizin-mediated NF-kappaB modulation inside the wound-healing cascade requires integrated omics-level investigation.

Future Research Directions

1. Clinical Trial Design

A multi-arm, multi-centre RCT is recommended with the following design framework:

- **Arm 1:** Conventional wound bed preparation + STSG (control)
- **Arm 2:** *Jalaukavacharana* pre-treatment + STSG
- **Arm 3:** *Yashtimadhu Kwatha Prakshalana* pre-treatment + STSG
- **Arm 4:** Combined *Jalaukavacharana* + *Yashtimadhu Kwatha* pre-treatment + STSG

Primary outcome: Percentage graft take at Day 7 and Day 14.

Secondary outcomes: Time to complete healing, wound bed score (pre- and post-intervention), infection rates, pain scores (patient-reported), patient-reported mobility measures, graft durability at 3 and 6 months, and patient quality of life (SF-36/EQ-5D). Importantly, to enable direct comparison and robust analysis across systems, the study should incorporate bridging outcome assessment tools that integrate Ayurvedic parameters (such as *Dushta Vrana Lakshanas*) with modern wound scoring frameworks. Development or selection of such validated hybrid tools will facilitate rigorous integrative research and standardized reporting. The trial should comply with CONSORT 2025 guidelines as mandated by JAHM submission requirements.

2. Translational Research Priorities

- **Network pharmacology analysis:** Map the molecular targets of hirudin, hyaluronidase, glycyrrhizin, and DPG onto wound healing signalling networks (VEGF, TGF-β, NF-κB, MMP pathways) using computational systems biology tools.**[53][54][78]**
- **Wound microbiome profiling:** 16S rRNA sequencing of wound microbiota before and after leech therapy and *Yashtimadhu* application to characterize antimicrobial effects and biofilm disruption.
- **Proteomics/metabolomics:** Characterize the wound exudate proteome and metabolome following integrative pre-treatment to identify biomarkers of graft readiness.
- **Histopathological validation:** Punch biopsies of wound beds pre- and post-intervention to quantify angiogenesis, collagen density, inflammatory cell infiltration, and fibroblast activity.

3. Standardization and Protocol Development

- Develop GCP-compliant Standard Operating Procedures (SOPs) for *Jalaukavacharana* in the pre-STSG context, including species specification (*Hirudo medicinalis Hirudinaria granulosa*), leech number, placement sites, session frequency, and safety monitoring.**[60]**
- Standardize *Yashtimadhu Kwatha* preparation per Ayurvedic Pharmacopoeia of India (API) guidelines, with quality control parameters including glycyrrhizin content, pH, microbial limits, and shelf-life stability.

- Develop and validate a composite wound bed assessment tool integrating Ayurvedic parameters (*Dushta Vrana Lakshanas*) with the modern Wound Bed Score.

4. Interdisciplinary Convergence

- **Tissue engineering:** Explore glycyrrhizin-loaded biomaterial scaffolds as adjuncts to STSG.
- **Digital health integration:** Develop AI-based wound assessment tools including both Ayurvedic and modern wound classification systems for standardized outcome documentation.
- **Global health relevance:** Position the integrative model as a low-cost, accessible wound management strategy for low-resource settings in South Asia and Africa, where chronic wound burden is highest and conventional surgical infrastructure may be limited.**[4][21][32]**

Conclusion

This critical narrative review demonstrates that the Ayurvedic paradigm of mandatory wound bed optimisation through *Jalaukavacharana* (leech therapy) and *Yashtimadhu Kwatha Prakshalana* (*Glycyrrhiza glabra* decoction wash) before *Sandhana Karma* (tissue grafting) is grounded in a sophisticated classical framework (*Shashti Upakrama*) and supported by substantial preclinical evidence. Leech salivary cocktail—featuring hirudin, hyaluronidase, bdellins, eglins, and antimicrobial peptides—targets the critical barriers to STSG success: hematoma, venous congestion, infection, and poor vascularity. Glycyrrhizin and its derivatives complement this by modulating the inflammatory-proliferative wound healing cascade through NF-κB/COX-2 inhibition, collagen synthesis promotion, fibroblast stimulation, and antimicrobial action.

Nevertheless, current evidence is primarily preclinical and conceptual. Translation from laboratory research to clinical application requires rigorously designed, multicentre, randomised controlled trials with standardised protocols, validated outcome measures, and long-term follow-up. Two near-term priorities are identified: (1) development and validation of standardized bridging outcome assessment tools between Ayurvedic wound classification & modern wound scoring systems, And (2) dose-response studies to establish optimal leech session parameters and *Yashtimadhu* formulation specifications. Until clinical validation is obtained, the integrative pre-treatment model should be regarded as a biologically plausible hypothesis warranting systematic investigation rather than an evidence-based clinical recommendation. To summarize, this approach is promising but unproven, and only rigorous trials will determine its definitive role in wound care.

To facilitate progress from preclinical findings toward real-world clinical application, a stepwise translational roadmap is proposed:

Step 1: Continued preclinical validation, including in vitro mechanism studies and animal models assessing optimal dosing, application techniques, and safety for both interventions.
Step 2: Feasibility and pilot studies in a controlled clinical setting to assess safety, preliminary efficacy, and protocol standardization for *Jalaukavacharana* and *Yashtimadhu* application in chronic wound patients receiving STSG.
Step 3: Small-scale, single-centre randomized pilot trials focused on optimal intervention parameters, wound readiness markers, and integrated outcome assessment bridging Ayurvedic and modern criteria.
Step 4: Multicentre, larger-scale randomized controlled trials with strong methodology, adequate power, and harmonized outcome measures for generalizability and external validity.
Step 5: Health economics and implementation studies evaluating cost-effectiveness, patient acceptability, and scalability within diverse health care settings.

This translational pathway aims to provide clear guidance for researchers and funding agencies, thereby systematically building the evidence needed to adopt integrative wound care interventions into routine clinical practice.

This review contributes to discussion of translational Ayurveda & situates Sushruta-inspired integrative wound management paradigm within the global framework of evidence-based integrative medicine.

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