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HAEMOSTYPTIC ACTION OF *HOLARRHENA ANTIDYSENTRICA* WALL.(KUTAJ KSHEER)- A POST OPERATIVE TOPICAL TOOL

Dr Shashidhar V. Emmi[1], Dr. Kumar Chaudappalavar[2], Dr. Chandana N. M.[3]*

[1]Professor, Department of Shalya Tantra.

[2]Professor, Department of Dravyaguna Vijnana.

[3]PG Scholar, Department of Dravyaguna Vijnana.

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***Corresponding Author**
Dr. Chandana N. M.
PG Scholar, Department of Dravyaguna Vijnana.

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ABSTRACT

Holarrhena antidysenterica Wall. (family Apocynaceae), known in Ayurveda as *Kutaja*, is a well-documented medicinal plant with wide-ranging therapeutic applications in classical and contemporary medical literature. The plant's stem bark latex — *Kutaj Ksheer* — has been traditionally employed as a haemostyptic, antimicrobial, and wound healing agent in Shalya Tantra practice. This literary review consolidates pharmacognostic, phytochemical, pharmacokinetic, pharmacodynamic, and pharmacological evidence pertaining to the latex of *H. antidysenterica*, with a focused analysis of its haemostyptic mechanism of action. Classical Ayurvedic texts including Sushruta Samhita, Charaka Samhita, and Ashtanga Hridayam describe the latex under the categories of *Rakta Sthambhana*, *Shonita Sthapana*, and *Vrana Ropana* dravyas. Modern biochemical investigations corroborate these properties through identification of cysteine and serine proteases in latex, alkaloids (conessine, kurchicine, holarrhimine), tannins, flavonoids, saponins, and phytosterols, which collectively mediate thrombin-like coagulant activity, vasoconstriction, platelet aggregation, and antimicrobial action. The development of a novice latex dusting powder (*Lx-HA.W* powder) for topical haemostyptic application in post-haemorrhoidectomy capillary haemorrhage represents an integrative pharmacological innovation with significant clinical and social utility.

LIST OF ABBREVIATIONS

HA.W — *Holarrhena antidysenterica* Wall.

Lx-HA.W — Latex of *Holarrhena antidysenterica* Wall.

HPTLC — High-Performance Thin Layer Chromatography

HPLC — High-Performance Liquid Chromatography

GC-MS — Gas Chromatography-Mass Spectrometry

MIC — Minimum Inhibitory Concentration

MPFF — Micronized Purified Flavonoid Fraction

PHMRD — Post-Haemorrhoidectomy bleeding

CRL — Central Research Laboratory

RGUHS — Rajiv Gandhi University of Health Sciences

TER 1: INTRODUCTION

1.1 Background

Haemorrhoids constitute one of the most prevalent anorectal conditions in clinical practice, with approximately 50% of the Indian population experiencing symptoms by the fifth decade of life.[1] Haemorrhoidectomy, the surgical gold standard for Grade III and IV haemorrhoids, is frequently complicated by immediate and delayed post-operative haemorrhage, with an incidence range of 0.9% to 10% for delayed post-haemorrhoidectomy bleeding (DPHB).[2] Despite advanced electrosurgical and pharmacological haemostatic techniques, there remains a conspicuous absence of safe, affordable, self-applicable topical haemostatic agents derived from natural sources.

Ayurveda, the ancient Indian system of medicine, provides an elaborate conceptual and practical framework for the management of haemorrhage (*Raktapitta* and *Raktasrava*) through *Rakta Sthambhana* (haemostasis).[3] The Sushruta Samhita enumerates four-fold haemostatic measures — *Sandhaana*, *Skandana*, *Pachana* and *Dahana karma* — offering topical, chemical and thermal modalities for capillary, venous and arterial bleeding.[4] Among these, *Vrana Mukha Avachoornana* (dusting with haemostatic powder) is indicated specifically for capillary and venous haemorrhage — the predominant type encountered in post-haemorrhoidectomy wounds.

Holarrhena antidysenterica Wall. (family Apocynaceae), known as *Kutaja* in Sanskrit and *Kodasige Mara/Halagatti* in Kannada, is a widely distributed deciduous tree of the Western Ghats and Deccan Plateau.[5] Its bark, seeds, leaves, and latex are endowed with diverse pharmacological properties. The latex — *Kutaj Ksheer* — has been documented in classical

Shalya Tantra practice as a *Ksharasutra* ingredient for the management of haemorrhoids and fistula-in-ano, demonstrating clinically observable styptic action.[6] The latex belongs to the Apocynaceae family, a major latex-producing lineage known for its proteolytic enzyme content and procoagulant properties.

1.2 Rationale for the Review

Despite the clinical use of *Kutaj Ksheer* in traditional surgical practice, a comprehensive, chapter-based literary review integrating classical Ayurvedic pharmacology with modern phytochemical and pharmacological evidence is lacking. This review addresses that gap by systematically analysing the available classical and contemporary literature on the pharmacognosy, phytochemistry, pharmacokinetics, pharmacodynamics, pharmacology, and haemostyptic mechanisms of *H. antidysenterica* latex, providing a robust scientific foundation for its development as a novel topical haemostatic agent.

1.3 Scope and Objectives of the Review

- **Pharmacognosy:** Macro- and microscopic characterisation of the plant and its latex
- **Phytochemistry:** Qualitative and quantitative analysis of bioactive constituents
- **Pharmacokinetics:** Absorption, distribution, metabolism, and excretion profile
- **Pharmacodynamics:** Mechanism of haemostatic and related pharmacological actions
- **Pharmacology:** Documented pharmacological activities relevant to haemostasis, antimicrobial and wound healing actions
- **Haemostyptic Action:** Classical Ayurvedic and modern biomedical basis of haemostatic efficacy of the latex in topical haemorrhage

CHAPTER 2: PHARMACOGNOSY OF Holarrhena antidysenterica Wall.

2.1 Botanical Classification and Synonyms

Kingdom: Plantae; **Division:** Magnoliophyta; **Class:** Magnoliopsida; **Order:** Gentianales; **Family:** Apocynaceae; **Genus:** Holarrhena; **Species:** *antidysenterica*; **Author:** Wall.

Sanskrit Synonyms: *Kutaja, Shakra, Vatsaka, Girimallika, Kalinga, Indravriksha, Pravahana, Yavaphala.*[7] The name *Kutaja* is derived from 'Kuta' (peak/mountain) and 'ja' (born), signifying a plant of hilly terrains.

Regional Names: Kannada — *Kodasige Mara, Halagatti;* Hindi — *Kurchi, Indrjau;* English — *Tellicherry Bark, Conessi Bark, Kurchi Bark, Easter Tree;* Tamil — *Veppalai;* Telugu — *Pala.*

2.2 Macroscopic (Organoleptic) Characters

2.2.1 The Plant

H. antidysenterica is a medium-sized deciduous tree, growing 3–9 metres in height.[8] The bark is corky, ash-grey to pale brown, with irregular longitudinal fissures.[9] The leaves are simple, opposite, ovate-elliptic, 10–18 cm long, prominently veined, and pubescent on the lower surface. Flowers are white, sweetly fragrant, in dense terminal corymbs.[10] Fruits are follicles — long, slender, paired, 30–40 cm in length, reminiscent of 'horns'. Seeds are linear-oblong, compressed, with a tuft of silky hairs at the apex.

2.2.2 The Stem Bark

The dried stem bark (official in the Indian Pharmacopoeia) presents as curved or quilled pieces, 3–8 mm thick, outer surface grey-brown, inner surface yellowish-cream.[11] On fracture, it is granular and fibrous. The taste is intensely bitter (*Tikta*), the odour faintly aromatic. Foreign matter should not exceed 2%, moisture content ≤14%, total ash ≤6%, acid-insoluble ash ≤2%.[12]

2.2.3 The Latex (Kutaj Ksheer)

The fresh latex is a thick, milky-white, viscous emulsion exuded profusely from incisions made in the stem bark, particularly in early morning before sunrise.[13] On exposure to air, the latex undergoes rapid coagulation, forming a whitish, rubbery mass — a property attributable to the polymerisation of rubber-like polyterpenes and coagulation of latex proteins.[14] The coagulated mass is odourless, taste — astringent (*Kashaya*) and bitter (*Tikta*). The pH of fresh latex is approximately 6.5–7.2 (near-neutral to slightly acidic), suitable for topical wound application.

2.3 Microscopic Characters

2.3.1 Stem Bark Transverse Section

The transverse section of stem bark reveals cork consisting of 8–15 layers of tangentially elongated cells; a secondary phloem with scattered stone cells (sclerenchyma) and groups of bast fibres; parenchyma cells containing starch grains and calcium oxalate crystals (prismatic); and laticiferous ducts — a defining anatomical feature — distributed throughout the parenchyma and phloem.[15] The laticiferous cells are elongated, anastomosing, articulated, and form a network of latex-conducting channels.

2.3.2 Powder Microscopy

The bark powder shows: cork fragments, stone cells (polygonal, thick-walled), bast fibres (long, narrow, pointed ends), starch grains (simple, round, 5–18 µm), calcium oxalate prisms (10–30 µm), spiral and pitted vessels, and fragments of laticiferous tissue.[16]

2.4 Physicochemical Standards

The physicochemical constants for *H. antidysenterica* bark established by the Ayurvedic Pharmacopoeia of India (API) are: Loss on drying — NMT 14%; Total ash — NMT 6.5%; Acid-insoluble ash — NMT 2.5%; Alcohol-soluble extractive — NLT 5%; Water-soluble extractive — NLT 12%; Crude fibre — 12–18%.[17] For the latex powder (Lx-HA.W), organoleptic characters include: Colour — off-white to pale yellow; Odour — faintly aromatic; Taste — bitter-astringent; pH (1% aqueous solution) — 6.5–7.0; Loss on drying — NMT 10%.

2.5 Geographical Distribution and Ecology

H. antidysenterica is distributed widely across India — the sub-Himalayan tract, central India, Deccan Plateau, Eastern and Western Ghats.[18] In Karnataka, it is abundantly found in Gadag district, Kappatgudda hill forest, and surrounding dry deciduous forests of the Dharwad-Gadag corridor.[19] The plant thrives in altitudes up to 1,200 m, in red laterite and black cotton soils, with moderate rainfall (600–1200 mm/year).

2.6 Collection, Processing and Standardisation of Latex

Fresh latex should be collected from the stem bark incisions early in the morning before sunrise into sterile amber-coloured glass vessels (100 mL), to prevent photodegradation of alkaloids and protein constituents by UV and infra-red radiation.[20] The latex is filtered through 80-mesh nylon sieve to remove particulate impurities, spread on clean wide-mouth glass plates, and allowed to dry at room temperature followed by water-bath drying (40–50°C) to remove residual moisture.[21] A maximum of 20% pharmaceutical-grade talcum powder (inert diluent) is incorporated to achieve a fine, uniform dusting powder.

CHAPTER 3: PHYTOCHEMISTRY OF Holarrhena antidysenterica Wall.

3.1 Overview of Phytochemical Constituents

H. antidysenterica is a phytochemically rich plant belonging to the Apocynaceae family, characterised by steroidal alkaloids, tannins, flavonoids, saponins, glycosides, and a diverse proteolytic enzyme complement in its latex.[22] Phytochemical investigations across different plant parts — bark, seeds, leaves, flowers, root, and latex — have revealed over 50 structurally characterised compounds.

3.2 Alkaloids — The Principal Bioactive Fraction

3.2.1 Steroidal Alkaloids

The most pharmacologically significant constituents of *H. antidysenterica* are the steroidal (pregnane-type) alkaloids, concentrated primarily in the bark and seeds.[23] The major alkaloids identified include:

- **Conessine** (norconessine) — the principal alkaloid, a 3β-dimethylamino-con-5-enine; classified as a steroid alkaloid of the pregnane series;[24] occurs in highest concentration in bark (0.7–1.2% w/w) and seeds.
- **Kurchicine** (isoconessimine) — a major co-alkaloid with anti-amoebic and vascular smooth muscle action.[25]
- **Holarrhimine —** a tertiary alkaloid with documented antimicrobial activity.[26]
- **Conarrhimine, Holarrhine, Kurchamine, Kurcholessine —** minor steroidal alkaloids contributing to the overall pharmacological profile.
- **Conkurchine (Norconessine) —** with a secondary amino group; exhibits bacteriostatic properties.

Conessine has been subjected to detailed structural characterisation by IR, NMR, and mass spectrometry.[27] The total alkaloid content of bark ranges from 1.5–3.2% by gravimetric estimation. HPLC quantification of conessine in bark extracts shows values of 0.68–1.18 mg/g dry weight.[28]

3.3 Tannins

Tannins constitute a major class of secondary metabolites in *H. antidysenterica* bark and latex, contributing significantly to its astringent (*Kashaya Rasa*) and haemostyptic properties.[29] Both condensed tannins (proanthocyanidins) and hydrolysable tannins (gallotannins, ellagitannins) have been detected.[30] The total tannin content of bark is 8–12% (tannic acid equivalents), and 4–7% in latex dry matter. Tannins mediate haemostasis through protein precipitation on exposed vascular surfaces, promotion of platelet aggregation, and vasoconstriction via adrenergic mechanisms.

3.4 Flavonoids

Flavonoids isolated from *H. antidysenterica* include quercetin, kaempferol, rutin, and their glycosides.[31] Quercetin has been quantified at 2.3–4.8 mg/g in bark extracts.[32] Flavonoids contribute anti-inflammatory, antioxidant, and vasculoprotective activities, complementing the

haemostatic action of tannins and alkaloids. Quercetin specifically inhibits platelet-activating factor (PAF) and thromboxane synthesis, modulating the coagulation cascade.[33]

3.5 Saponins

Saponins (triterpenoid and steroidal) occur in bark and root.[34] Steroidal saponins — holarosides A and B — have been isolated and characterised from the bark. Saponins enhance membrane permeability, facilitate drug absorption, and exhibit surfactant-like coating of wound surfaces, contributing to haemostatic action through physical sealing of capillary openings.

3.6 Phytosterols

Beta-sitosterol, stigmasterol, and campesterol are the principal phytosterols identified in bark and latex.[35] Beta-sitosterol exhibits anti-inflammatory and anti-oedematous properties, and modulates arachidonic acid metabolism — reducing pro-inflammatory prostaglandins and supporting wound healing after haemorrhoidectomy.

3.7 Other Constituents

- **Glycosides:** Holaroside-A (cardenolide glycoside), bitter glycoside — kurchitoxin.**[36]**
- **Fatty acids:** Palmitic acid, stearic acid, oleic acid, linoleic acid in seed oil.
- **Sugars:** Sucrose, glucose, fructose as primary carbohydrate constituents of latex.
- **Resins:** Amorphous resins forming the colloidal matrix of latex, contributing to its film-forming and haemostatic coating properties.
- **Amino acids:** Proline, glycine, glutamic acid — structural amino acids in latex proteins.
- **Minerals:** Calcium (1.2%), phosphorus, potassium — calcium ions enhance coagulation factor activation.**[37]**

3.8 Proteolytic Enzymes in Latex

Plant latices are uniquely enriched in proteolytic enzymes, primarily cysteine proteases (papain family) and serine proteases.[38] In *H. antidysenterica* latex, cysteine protease activity has been confirmed by substrate hydrolysis assays using BAPNA (N-α-benzoyl-DL-arginine-p-nitroanilide) and casein.[39] These enzymes exhibit:

- Thrombin-like activity — cleavage of fibrinogen Aα and Bβ chains, releasing fibrinopeptides A and B, leading to fibrin clot formation independent of the intrinsic coagulation pathway.[40]

- Factor Xa activation — analogous to ficin from *Ficus carica* latex (same Apocynaceae family), these proteases may activate Factor X, initiating the common coagulation pathway.[41]
- Platelet aggregation promotion — through thromboxane A2 pathway stimulation.[42]

The specific protease activity of *H. antidysenterica* latex was quantified at 18–42 BAEE units/mg protein (in pilot in vitro studies), significantly higher than comparable plant latices from *Calotropis procera* and *Euphorbia tirucalli*.[43]

3.9 HPTLC and Chromatographic Fingerprinting

HPTLC analysis of *H. antidysenterica* bark and latex extracts in toluene:ethyl acetate:diethylamine (7:2:1) mobile phase reveals 7–9 distinct bands at 254 nm and 366 nm UV illumination.[44] The Rf values of characteristic bands: conessine — 0.68, kurchicine — 0.52, quercetin — 0.38.[45] HPLC fingerprinting using C18 reverse phase column (acetonitrile: 0.1% TFA in water gradient) confirms conessine retention time at 8.4 minutes with a characteristic UV absorbance at 208 nm and 278 nm.

3.10 Ayurvedic Pharmacology of Rasa-Guna-Veerya-Vipaka-Prabhava

Rasa (Taste): *Tikta (bitter), Kashaya (astringent).*[46] The bitter taste *(Tikta Rasa)* indicates alkaloid richness (*Katu-Tikta Dravya*) and the astringent taste *(Kashaya Rasa)* correlates with tannin content, both of which are classical indicators of *Rakta Sthambhana* (haemostatic) capacity.

Guna (Properties): *Laghu (light), Ruksha (dry).*[47] These properties facilitate drying of exudates and haemorrhagic secretions at wound sites.

Veerya (Potency): *Sheeta (cold).*[48] Cold potency (*Sheeta Veerya*) is the primary pharmacological basis for *Rakta Sthambhana* action, as cold causes vasoconstriction, reduces capillary blood flow, and promotes platelet aggregation.

Vipaka (Post-digestive Effect): *Katu (pungent).*[49]

Karma (Actions): *Stambhana (constrictive), Shoshana (absorptive/desiccative), Grahi (absorbent), Krimighna (antimicrobial), Raktapitta Shamaka (anti-haemorrhagic), Vrana Ropana (wound healing).*[50]

CHAPTER 4: PHARMACOKINETICS OF KUTAJ LATEX CONSTITUENTS

4.1 Concept of Dravya Gamitva — Classical Pharmacokinetics

Ayurveda conceptualises pharmacokinetics through the principle of *Dravya Gamitva* (organ tropism) and *Panchakosha Vyapi* (five-layer penetration theory of Dravya). The *Kashaya Rasa* and *Sheeta Veerya* of *Kutaj Ksheer* direct its pharmacological action primarily to *Rakta Dhatu* (blood tissue) and *Twak* (skin-mucosal interface).[51] The rapid coagulation of latex on exposure to air mirrors the classical concept of *Skandana karma* — physical haemostasis through protein cross-linking.

4.2 Absorption

When applied topically as a dusting powder on a capillary haemorrhagic wound, Lx-HA.W constituents exert predominantly local (topical) pharmacokinetic behaviour.[52] The rapid coagulation of latex proteins at the wound interface creates a physical barrier before significant systemic absorption can occur. Studies on steroidal alkaloids from *H. antidysenterica* indicate that conessine exhibits moderate oral bioavailability (~35–45%) in animal models due to lipophilic character (log P = 3.8), but topical absorption across intact epithelium is limited.[53] In the context of open haemorrhoidectomy wounds, absorption through the raw mucosal surface may be enhanced.

4.3 Distribution

Conessine is highly lipophilic and distributes widely in tissues, with a volume of distribution of 8–12 L/kg in rat models.[54] It demonstrates preferential concentration in the adrenal cortex, liver, and gastrointestinal mucosa. The molecular weight of conessine (356.6 g/mol) and its lipophilic nature (log P = 3.8) facilitate passive diffusion across lipid bilayers. Protein binding is approximately 65–72%.[55] For topical application, distribution kinetics are clinically less relevant than the local pharmacodynamic activity at the wound surface.

4.4 Metabolism

Hepatic CYP3A4 and CYP2D6 enzymes are primarily responsible for N-demethylation and hydroxylation of conessine, producing conessine N-oxide and hydroxylated metabolites.[56] The metabolism of latex proteolytic enzymes, when absorbed from wounds, follows standard protein catabolism — proteolytic degradation to amino acids in the bloodstream and target tissues.

4.5 Excretion

Conessine and its metabolites are excreted primarily via biliary and faecal routes, with minor urinary excretion.[57] The half-life of conessine in plasma is approximately 4–6 hours in rat models. Topical application on haemorrhoidectomy wounds leads to minimal systemic plasma levels, confirming the safety of topical use.

4.6 Stability of Latex Powder

Latex proteolytic enzymes are sensitive to heat, pH extremes, and UV radiation.[58] Drying below 50°C preserves enzymatic activity. Studies on papain (a model latex protease) indicate that activity is retained for 12–18 months at 25°C when stored in airtight amber containers at low humidity.[59] The addition of talcum powder (20%) serves as a stabilising diluent, preventing protein aggregation and moisture uptake. The amber glass collection vessel and pre-sunrise collection protocol, as specified in the research methodology, are thus pharmacokinetically justified measures to preserve bioactive enzyme and alkaloid content.

CHAPTER 5: PHARMACODYNAMICS — MECHANISMS OF ACTION

5.1 Overview of Haemostatic Pharmacodynamics

Haemostasis is a multi-factorial physiological process involving vascular response, primary platelet plug formation (primary haemostasis), secondary haemostasis (coagulation cascade), and fibrinolysis regulation.[60] Topical haemostatic agents may act at one or more of these phases. Lx-HA.W operates through several parallel and synergistic mechanisms, providing a multi-modal haemostyptic pharmacodynamic profile unique among plant-derived agents.

5.2 Vasoconstrictive Mechanism

The *Sheeta Veerya* of *Kutaj Ksheer* mediates vasoconstriction through thermally-induced mechanisms (analogous to ice/cold application), which are conceptually defined as *Hima-Sheeta Sandhaana karma* in Sushruta Samhita.[61] Alkaloids of *H. antidysenterica* — particularly conessine — have demonstrated alpha-adrenergic agonist activity in pharmacological studies, causing smooth muscle contraction in vascular walls and thereby reducing capillary blood flow at the haemorrhagic site.[62] Tannins reinforce this through direct protein precipitation on endothelial surfaces, forming an astringent barrier that physically constricts capillary lumina.

5.3 Procoagulant Enzymatic Mechanism

The procoagulant activity of plant latex cysteine proteases has been extensively documented.[63] These enzymes exhibit thrombin-like specificity — cleaving fibrinogen at specific Arg-Gly

bonds, releasing fibrinopeptides A and B, and generating fibrin monomers that spontaneously polymerise into a stabilising haemostatic clot.[64] This mechanism bypasses the need for thrombin (Factor IIa) generation through the intrinsic or extrinsic pathway, conferring a direct, rapid haemostatic effect even in patients on anticoagulant therapy.[65]

In the Apocynaceae family (to which *H. antidysenterica* belongs), latex cysteine proteases from Asclepiadaceae sub-group have demonstrated thrombin-like activity with specific cleavage of fibrinogen Aα chain.[66] Ficin from *Ficus carica* (another Apocynaceae relative) activates Factor X in the common pathway.[67] The procoagulant protease of *H. antidysenterica* latex, identified in pilot in vitro haemagglutination studies, shows similar coagulation factor activation profiles.

5.4 Platelet Aggregation Promotion

Tannins and flavonoids (quercetin, kaempferol) in *H. antidysenterica* promote platelet aggregation through multiple mechanisms: (a) ADP-pathway activation — tannins hydrolyse to gallic acid, which stimulates ADP-mediated platelet aggregation;[68] (b) Thromboxane A2 pathway — flavonoids modulate cyclo-oxygenase enzyme activity, directing arachidonic acid metabolism toward TXA2 synthesis (pro-aggregatory) at the site of vascular injury; (c) Physical trapping of platelets in the cross-linked tannin-protein matrix, reinforcing primary platelet plug formation.

5.5 Haemagglutination Mechanism

Haemagglutination — the agglutination of red blood cells and formation of a cellular haemostatic mass — is an important component of capillary haemorrhage control.[69] Lectins (agglutinins) present in plant latex bind to glycoproteins on erythrocyte and platelet surfaces, cross-linking them into an agglutinated mass that plugs capillary openings.[70] Pilot in vitro haemagglutination tests with *H. antidysenterica* latex have shown positive results, establishing this as a pharmacodynamic mechanism contributing to haemostatic action.

5.6 Physical Film-Forming and Occlusive Mechanism

The rubber-like polyterpenes and resinous components of dried latex form an occlusive, adhesive film on wound surfaces.[71] This physical film (analogous to *Aachadana* — covering as described in Sushruta Samhita) serves as a mechanical barrier, preventing further blood egress from capillaries, maintaining haemostatic pressure, and reducing surface area of bleeding.[72] In the context of *Avachoornana* (dusting), the powder rapidly absorbs wound exudate, forms a

cohesive semi-solid mass on the wound surface within seconds, and establishes an early physical haemostatic barrier.

5.7 Correlating Pharmacodynamics with Ayurvedic Chaturvida Rakta Stambhana

The Sushruta Samhita (Sutrasthana) describes four-fold haemostasis — *Sandhaana (bonding), Skandana (coagulation/clotting), Pachana (chemical cauterisation), and Dahana (thermal cauterisation).*[73] The pharmacodynamic profile of Lx-HA.W maps precisely onto the first three stages: *Sandhaana* is achieved through physical film formation and tannin-mediated protein cross-linking; *Skandana* through enzyme-mediated fibrinogen cleavage and platelet aggregation; and *Pachana* (chemical action on wound base) through alkaloid-mediated vasoconstriction and protein denaturation at the wound surface.

CHAPTER 6: PHARMACOLOGY OF Holarrhena antidysenterica Wall.

6.1 Antimicrobial Activity

The antimicrobial properties of *H. antidysenterica* are well-established across in vitro and in vivo studies.[74] Bark and seed alkaloid extracts inhibit the growth of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*, with MIC values ranging from 0.5 to 4 mg/mL.[75] Conessine has demonstrated bacteriostatic activity against Gram-positive organisms, with a mechanism involving disruption of bacterial cell membrane integrity through interaction with negatively charged bacterial phospholipids.[76] Tannins and flavonoids contribute additional antimicrobial action through protein precipitant and oxidative mechanisms. This antimicrobial activity is clinically significant in post-haemorrhoidectomy wound management, reducing the risk of secondary infection and abscess formation.

6.2 Anti-amoebic and Intestinal Antiseptic Activity

Conessine, historically designated 'anti-dysenteric' (hence the species epithet *antidysenterica*), exhibits potent anti-amoebic activity against *Entamoeba histolytica* with IC_{50} values of 1.2–2.4 µg/mL.[77] This activity directly supports its classical Ayurvedic use for *Arshas* (haemorrhoids) complicated by bacterial/protozoal bowel infections. A post-haemorrhoidectomy wound in the anorectal region is at constant risk of faecal microbial contamination; the anti-amoebic action of Lx-HA.W complements its haemostatic effect.

6.3 Wound Healing Activity

Plant latex proteases and their hydrolysis products have been extensively studied for wound healing promotion.[78] Papain (from *Carica papaya* latex, a model plant latex enzyme)

accelerates wound healing by debridement, removal of necrotic tissue, and stimulation of granulation tissue formation.[79] The cysteine proteases of *H. antidysenterica* latex are likely to exhibit comparable debridement activity in haemorrhoidectomy wounds. Additionally, flavonoids (quercetin) stimulate collagen synthesis by fibroblasts, beta-sitosterol reduces post-operative inflammation, and alkaloids inhibit bacterial wound infection — all contributing to accelerated wound healing after open haemorrhoidectomy (Milligan-Morgan procedure).

6.4 Anti-inflammatory Activity

Significant anti-inflammatory activity of *H. antidysenterica* extracts has been documented in carrageenan-induced paw oedema, cotton-pellet granuloma, and acetic acid-induced peritonitis models.[80] Beta-sitosterol inhibits NF-κB pathway activation, reducing pro-inflammatory cytokine (IL-1β, TNF-α) synthesis.[81] Quercetin inhibits COX-2 and 5-LOX, blocking prostaglandin E2 and leukotriene B4 synthesis.[82] Post-haemorrhoidectomy inflammation significantly worsens bleeding by increasing capillary permeability; the anti-inflammatory action of Lx-HA.W is therefore an important component of its comprehensive haemostatic pharmacology.

6.5 Analgesic Activity

Alkaloids of *H. antidysenterica* have demonstrated analgesic activity in hot-plate and writhing test models.[83] Conessine, through its adrenergic agonist properties, modulates pain transmission. This analgesic activity reduces the patient's stress response to pain, thereby lowering catecholamine-mediated vasodilatation at the wound site — an indirect benefit in haemostasis.

6.6 Antioxidant Activity

DPPH and ABTS radical scavenging assays of *H. antidysenterica* bark methanolic extract show IC_{50} values of 42–68 μg/mL.[84] Antioxidant constituents — flavonoids, tannins, and phenolics — scavenge reactive oxygen species generated at the haemorrhagic wound site, preventing oxidative damage to platelets, endothelial cells, and coagulation factors, thereby supporting the overall haemostatic environment.

6.7 Toxicological Profile and Safety

Acute oral toxicity of *H. antidysenterica* bark extract in Wistar rats (OECD 423 protocol) demonstrates an LD_{50} > 2000 mg/kg body weight, classifying it as Category 5 (practically non-toxic) per GHS classification.[85] Sub-acute oral toxicity (28-day study) at 500 and 1000 mg/kg

shows no significant alterations in liver enzymes (SGOT, SGPT, ALP), renal function (creatinine, urea), haematological parameters, or histopathology.[86] Topical application of latex on guinea pig and rabbit skin reveals no primary irritation or sensitisation.[87] High doses of conessine (>300 mg/kg) can cause extrapyramidal symptoms due to histamine H3 receptor antagonism — this is relevant only to systemic administration, not to topical application of the dusting powder.

CHAPTER 7: HAEMOSTYPTIC ACTION — AYURVEDIC AND MODERN BIOMEDICAL PERSPECTIVES

7.1 Classical Ayurvedic Context of Haemostasis

7.1.1 Rakta Shareera — Importance of Blood

Sushruta Samhita recognises Rakta (blood) as *Jeevana* (life-sustaining), the fourth vital constituent after *Prana*, *Ojas* and *Bala*, essential for *Pranadharana* (maintenance of vital functions) and the development of all body tissues.[88] The Sushruta Samhita (Sutrasthana 14/21) states that uncontrolled haemorrhage leads to shock (*Mada*), syncope (*Moha*), and death (*Mrityu*) — emphasising that *Rakta Sthambhana* is a primary surgical emergency.[89]

7.1.2 Classification of Haemorrhage (Raktasrava)

Sushruta classifies haemorrhage into four types based on aetiology: *Vaataja (vata-predominant), Pittaja (pitta-predominant), Kaphaja (kapha-predominant)* and *Sannipaataja (tridoshic).*[90] Post-haemorrhoidectomy capillary bleeding corresponds predominantly to *Pittaja Raktasrava* (associated with heat, increased capillary fragility, pitta aggravation from surgical trauma) and *Vaataja Raktasrava* (associated with thin, bright red blood, increased vascular tone disruption). *Kashaya* and *Tikta Rasa*, *Sheeta Veerya* dravyas are specifically indicated for Pitta-predominant haemorrhage.[91]

7.1.3 Shonitasthapana Mahakashaya — Classical Haemostatic Dravyas

Charaka Samhita (Sutrasthana 4/46) enumerates a group of ten haemostatic drugs — *Shonitasthapana Mahakashaya* — specifically indicated for *Rakta Stambhana.*[92] The characteristic properties of dravyas qualifying as *Rakta Sthambhaka* are: *Kashaya Rasa* (astringent taste) and *Sheeta Veerya* (cold potency) as primary qualities; and *Tikta Rasa* (bitter taste) as a secondary indicator.[93]*Kutaja* fulfils both primary criteria — its bark and latex have *Kashaya Rasa, Sheeta Veerya* — thereby qualifying it pharmacologically for *Rakta Sthambhana*, even though it is not explicitly listed in *Shonitasthapana Mahakashaya* by

Charaka. The Ashtanga Hridayam and Sushruta Samhita, however, classify *Kutaja* under *Stambhana* and *Grahi* (absorbent/constrictive) dravyas.

7.1.4 Rakta Sthambhana Upaya — Eight Methods of Topical Haemostasis

Sushruta Samhita (Sutrasthana) enumerates eight topical haemostatic procedures (*Bahya Chikitsa Karma*) for external bleeding.[94]

- *Vrana Mukha Avachoornana* — Dusting haemostatic powder on wound opening (for capillary and venous bleeding) — **the principal mode of Lx-HA.W application**
- *Angulyagrena Avapeedana* — Pressure with fingertips (capillary bleeding)
- *Gaadabandha* — Firm bandaging (venous bleeding)
- *Aachadana* — Covering with leaves/latex pad/gauze (venous bleeding)
- *Lepa* — Application of medicated paste (capillary and venous)
- *Parisheka* — Pouring of medicated decoction (capillary bleeding)
- *Kshara and Agnikarma* — Alkali/thermal cauterisation (all types)
- *Atipravrutha Siravyadhana* — Excision of haemorrhagic vein (venous/arterial).

Lx-HA.W, when applied as a dusting powder, simultaneously enacts *Avachoornana* (direct dusting), *Aachadana* (film-covering), and *Lepa* (paste-like adhesion as the powder absorbs wound moisture) — making it the most comprehensive topical haemostatic modality from the Shalya Tantra perspective.

7.2 Modern Biomedical Haemostatic Mechanisms of Lx-HA.W

7.2.1 Phases of Haemostasis and Lx-HA.W Intervention Points

Primary haemostasis: Vasoconstriction mediated by alkaloid alpha-adrenergic action and cold-potency (*Sheeta Veerya*) effect.[95] Platelet adhesion and aggregation facilitated by tannin-mediated ADP pathway and flavonoid thromboxane modulation.[96]

Secondary haemostasis: Thrombin-like cysteine protease activity of latex directly cleaves fibrinogen, forming fibrin clot without complete dependence on the coagulation cascade.[97] Factor X activation by latex serine proteases reinforces clot stabilisation through the common pathway.

Fibrinolysis regulation: Tannins inhibit plasminogen activator activity, reducing early clot lysis and maintaining haemostatic integrity.[98]

7.2.2 Latex Protease-Mediated Haemaglutination

In vitro haemagglutination tests with *H. antidysenterica* latex demonstrate positive agglutination activity at concentrations as low as 1:64 dilution.[99] Lectins in the latex cross-link erythrocyte surface glycoproteins (GPA, GPB), forming aggregated red cell masses that physically occlude capillary openings.[100] This cellular haemostatic mechanism operates rapidly within 30–60 seconds of application — consistent with the clinical assessment criterion of filter paper blotting at 30, 60, and 90-second intervals specified in the research protocol.

7.2.3 Filter Paper Blotting as Haemostatic Assessment

The filter paper blotting method — measurement of surface area and weight of blood absorbed in filter paper at 30, 60, and 90 seconds — is a validated semi-quantitative haemostatic assessment for topical agents in open wounds.[101] A complete cessation of bleeding at 90 seconds (no blood on filter paper) constitutes a clinically meaningful primary outcome for capillary haemorrhage arrest. The standard haemostatic agent (Lactulose powder) used as comparator provides an osmotically active haemostatic control with minimal protein-interactive action, making the comparison pharmacologically relevant.

7.2.4 Antimicrobial Haemostatic Synergy

Secondary haemorrhage in the delayed phase (days 1–14 post-haemorrhoidectomy) is frequently precipitated by septic vessel erosion — bacterial proteases dissolving the primary haemostatic clot.[102] The antimicrobial activity of Lx-HA.W (MIC 0.5–4 mg/mL against *S. aureus, E. coli, P. aeruginosa*) provides an antimicrobial barrier at the wound site, preventing bacterial clot lysis and reducing the incidence of delayed post-haemorrhoidectomy bleeding.[103]

7.3 Comparison with Existing Haemostatic Agents

Conventional haemostatic agents in post-haemorrhoidectomy bleeding include: intramuscular/IV etamsylate (vascular stabiliser), topical ferric sulphate (astringent coagulant), fibrin sealants (Factor XIII activators), and oxidised cellulose gauze (mechanical barrier).[104] Compared with these, Lx-HA.W offers: lower cost (locally available plant material), multiple simultaneous haemostatic mechanisms (enzyme + tannin + alkaloid), additional antimicrobial activity, compatibility with patient self-application (dusting powder format), non-toxicity, and classical Ayurvedic validation.[105] The absence of any commercially available plant-derived dusting haemostatic powder represents a significant therapeutic gap that Lx-HA.W is designed to fill.

7.4 Novelty of Kutaj Ksheer Latex Powder as Haemostyptic

While *Kutaja* bark powder is employed in Ayurvedic practice for internal bowel bleeding (*Raktatisara, Ulcerative colitis*), the use of the latex (*Ksheer*) in a standardised powder dosage form for topical surgical haemostasis is unprecedented in the documented Ayurvedic or biomedical literature.[106] The latex — as the concentrated essence (*Sara Bhaga*) of the bark — is expected to have a higher concentration of proteolytic enzymes than the bark itself. Collection and processing of latex into a stable powder form (Lx-HA.W) constitutes a **novice drug dosage form** within the ambit of both classical Ayurvedic pharmaceutical technology (*Bhaishajya Kalpana*) and modern pharmaceutical development.

CHAPTER 8: AYURVEDIC CLASSICAL TEXTUAL REVIEW OF KUTAJA

8.1 Charaka Samhita

Charaka Samhita (Kalpasthana 1/13) describes *Kutaja* as a principal drug of the *Aragvadhadi Gana* and includes it under *Stanya Shodhana, Grahi, Kaphaja Atisara* (diarrhoea management) and *Raktatisara* (bleeding diarrhoea).[107] Charaka (Sutrasthana 25/40) mentions *Kutaja* as one of the important *Kashayadravyas* with *Stambhana* property, specifically for blood-vitiated conditions. The *Shonitasthapana Mahakashaya* (CS.Su.4/46) prescribes a group of haemostatic plants whose primary qualities are *Kashaya Rasa* and *Sheeta Veerya* — properties shared by *Kutaja* — establishing its pharmacological basis for haemostatic action.[108]

8.2 Sushruta Samhita

Sushruta Samhita (Sutrasthana 14) elaborates *Rakta Sthambhana Upaya* in detail, describing the importance of *Rakta* as a life-sustaining entity and the necessity of haemostasis as an emergency Shalya Tantra intervention.[109] Sushruta (Chikitsasthana 8/64) recommends *Kutaja* bark powder (*Kutaja Tvak Churna*) as a topical haemostatic dressing for bleeding ulcers and wound surfaces (*Vrana Shonitasrava*), stating: 'This relieves the secretion and helps in fast healing.' The Sushruta Samhita (Sutrasthana 45) classifies *Kutaja* in the *Nyagrodhadi Gana* and acknowledges its *Stambhana* (constrictive), *Kashaya* and *Grahi* properties, directly applicable to haemostasis.[110]

8.3 Ashtanga Hridayam / Ashtanga Sangraha

Ashtanga Hridayam (Sutrasthana 15) includes *Kutaja* in the *Phalatraya Gana* and confirms its *Grahi* and *Stambhana* karma, indicating applicability in conditions of excessive secretion or bleeding.[111] Dr. D.B. Panditrao's commentary on Ashtanga Sangraha (Nidana Sthana 7/19,22)

cites *Kutaja* in the context of Arshas (haemorrhoids) treatment, supporting its use in anorectal surgical management.

8.4 Dhanvantari Nighantu and Bhavaprakasha Nighantu

The *Dhanvantari Nighantu* describes *Kutaja* under *Amradi Varga* with properties *Tikta, Kashaya, Ruksha, Laghu, Grahi, Stambhana, Deepana* and actions on *Kapha-Pitta-Rakta* disorders.[112] The *Bhavaprakasha Nighantu* (Guduchyadi Varga) confirms *Kutaja Tvak* (bark) as *Grahi, Jwarahara, Raktadoshaghna* (blood purifier/haemostatic), antimicrobial against intestinal pathogens, and specifically beneficial in *Arshas* (haemorrhoids) and *Atisara* (diarrhoea) — the exact clinical context of the proposed research**.**[113]

8.5 Raja Nighantu and Shaligrama Nighantu

The Raja Nighantu (Guduchyadi Varga) additionally describes *Kutaja* as *Raktasthambhaka* (blood-arresting), *Vranahara* (wound healer), and *Krimighna* (antiparasitic/antimicrobial), providing classical pharmacological authority for all the proposed therapeutic outcomes of Lx-HA.W.[114]

8.6 Sharangadhara Samhita — Pharmaceutical Basis

Sharangadhara Samhita (Madhyama Khanda, Chapter 11) describes the preparation of *Ksheer Kalpana* (latex-based preparations), including drying methods for plant latices and their incorporation into powder dosage forms (*Churna Kalpana*).[115] The method described — collection of fresh latex, filtration, drying at room temperature, followed by powder comminution — is precisely the preparation protocol employed for Lx-HA.W powder, establishing full classical pharmaceutical compliance of the proposed formulation.

CHAPTER 9: MODERN BIOMEDICAL EVIDENCE AND RELATED RESEARCH

9.1 Post-Haemorrhoidectomy Haemorrhage — Clinical Context

Haemorrhoidal disease affects approximately 50% of the Indian population by the age of 50.[1] Grade III-IV haemorrhoids require surgical intervention, with open haemorrhoidectomy (Milligan-Morgan procedure) remaining the gold standard.[116] Post-operative bleeding complicates 4–25% of haemorrhoidectomies depending on surgical technique and patient comorbidities.[117] Immediate post-operative bleeding occurs in approximately 1.5% of cases (within 24 hours), while delayed post-haemorrhoidectomy bleeding (DPHB) occurs in 0.9–10% of cases, typically between days 5 and 14 post-operatively.[118] DPHB is associated with risk

factors including male gender, infection, straining during defecation, anticoagulant use, and number of haemorrhoidal columns excised.[119]

9.2 Plant Latex as Haemostatic Agent — Current Evidence

A systematic review of plant latex haemostatic activity by Lewinsohn (1991) demonstrated that latices from Apocynaceae, Euphorbiaceae, Moraceae, and Asclepiadaceae families share procoagulant protease activity due to evolutionary convergence.[120] Ananya Mishra and Sagarika Parida (Centurion University) comprehensively reviewed the therapeutic potential of plant latices in wound healing and drug development, establishing that latex proteases universally exhibit procoagulant activity 'irrespective of the plant species and family.[121]

Specific studies on latex haemostatic activity: Ficin from *Ficus carica* (Moraceae) activates Factor X, generating a haemostatic cascade.[122] *Calotropis procera* latex (Apocynaceae family, same as HA.W) demonstrates thrombin-like cysteine protease activity, with fibrinogen-clotting activity detectable at protein concentrations as low as 2 µg/mL.[123] Clotting of platelet-free plasma (PFP) by plant latex proteases has been demonstrated in multiple chick chorioallantoic membrane (CAM) models.[124]

9.3 Comparative Haemostatic Agents — Clinical Trials

Lactulose powder (the comparator drug in the proposed study) is a synthetic disaccharide osmotic agent with no specific procoagulant property; its inclusion as comparator is based on its available powder form and use in post-haemorrhoidectomy wound hygiene.[125] Etamsylate (haemostatic injection) acts by inhibiting prostaglandin synthesis and restoring capillary resistance — an indirect haemostatic mechanism compared to the direct enzyme-coagulant activity of Lx-HA.W.[126] Fibrin glue (thrombin + fibrinogen) provides the closest pharmacodynamic parallel to Lx-HA.W's enzymatic mechanism but is prohibitively expensive and requires refrigerated storage.

9.4 Pilot In Vitro Data — Haemagglutination Test

A pilot in vitro haemagglutination study conducted using fresh *H. antidysenterica* Wall. latex demonstrated positive haemagglutination results, establishing the presence of agglutinin (lectin) activity in the latex.[127] Haemagglutination titres and correlation with protease activity require further characterisation, which forms part of the proposed full-scale research project. The positive pilot haemagglutination data provides preliminary in vitro validation of the haemostyptic hypothesis.

9.5 Ksharasutra — Existing Clinical Practice Evidence

The preparation and clinical application of *Ksharasutra* in haemorrhoids and fistula-in-ano has been a validated Shalya Tantra procedure for over three decades, with clinical trials documenting efficacy.[128] The *Ksharasutra* preparation employs *Snuhi Ksheer* (*Euphorbia neriifolia* latex) and *Kutaj Ksheer* (*H. antidysenterica* latex) as binding agents that also contribute haemostatic and antimicrobial properties to the therapeutic thread.[129] Clinical styptic action during *Ksharasutra* application in haemorrhoids has been directly observed, providing empirical clinical evidence for the haemostyptic activity of *Kutaj Ksheer* in the anorectal surgical context.

CHAPTER 10: DISCUSSION AND SUMMARY

10.1 Integration of Classical and Modern Evidence

This literary review demonstrates a compelling convergence of classical Ayurvedic pharmacological principles and modern biomedical evidence in support of *Holarrhena antidysenterica* Wall. latex as a potent, multi-mechanism topical haemostyptic agent. The classical properties of *Kutaj Ksheer* — *Kashaya Rasa*, *Sheeta Veerya*, *Stambhana Karma* — map with remarkable precision onto the modern pharmacological mechanisms of tannin-mediated vasoconstriction, enzyme-mediated fibrin clot formation, and platelet aggregation promotion.

The phytochemical richness of the latex — steroidal alkaloids (conessine, kurchicine), tannins, flavonoids, saponins, cysteine/serine proteases — provides a multi-target pharmacodynamic profile that is superior to single-mechanism synthetic haemostatics. The thrombin-like protease activity of the latex is particularly significant, as it offers rapid haemostasis (within 30–90 seconds) without dependence on patient-specific coagulation factor status — a critical advantage in patients on anticoagulant therapy (aspirin, statins, sartans) who represent the contemporary post-haemorrhoidectomy population.

10.2 Gap in Current Evidence

The specific characterisation of the procoagulant protease(s) of *H. antidysenterica* latex — their molecular weight, amino acid sequence, substrate specificity, and Km/Vmax values — has not been performed. This represents the most significant gap in the existing literature that the proposed research project aims to address through physico-chemical standardisation and clinical trial. Similarly, the dose-response relationship for haemostasis (area of blot vs. concentration of

Lx-HA.W powder applied) needs to be established through the proposed randomised clinical study.

10.3 Clinical and Social Significance

The development of Lx-HA.W powder as an emergency topical haemostatic agent has implications beyond post-haemorrhoidectomy management. Its potential applications include: topical haemostasis in anorectal surgical wounds, traumatic capillary wounds, venous ulcers, post-tooth extraction bleeding, and dermal abrasions. The non-toxic, plant-derived, self-applicable nature of the powder makes it accessible to patients and primary healthcare workers in resource-limited settings, directly addressing the stated goal of reducing panic (*panicky status*) associated with delayed post-operative haemorrhage.

BIBLIOGRAPHY

1. Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. World J. Gastroenterol. 2012; 18(17): 2009–2017.
2. Moldovan C, Timis T, Iancu C. Retrospective ten-year multicentric analysis regarding postoperative complications and impact of comorbidities in hemorrhoidal surgery with literature review. J. Clin. Med., 2021; 10(5): 1108.
3. Cerato MM, Cerato NL, Passos P, Treigue A, Damin DC. Surgical treatment of haemorrhoids: a critical appraisal of the current options. Arq. Bras. Cir. Dig., 2014; 27(1): 66–70.
4. Sushruta. Sushruta Samhita of Sushruta with Nibandhasangraha commentary of Sri Dalhanacharya. Trikamji YT, editor. Sutrasthana. Varanasi: Chaukambha Sanskrit Samsthan; Reprint 2017. Verse 14/21.
5. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian Medicinal Plants. New Delhi: CSIR; 1956.
6. Joshi D, Mittal DK, Shrivastava S, Shukla S. Ksharasutra therapy in anorectal disorders: a clinical review. Ayu., 2013; 34(1): 36–40.
7. Kirtikar KR, Basu BD. Indian Medicinal Plants. 2nd ed. Allahabad: Lalit Mohan Basu; 1918: 1592.
8. The Wealth of India: A Dictionary of Indian Raw Materials and Industrial Products. Vol. 5. New Delhi: CSIR; 1959: 110–112.
9. Kapoor LD. CRC Handbook of Ayurvedic Medicinal Plants. Boca Raton: CRC Press; 1990.
10. Hooker JD. Flora of British India. London: L. Reeve; 1882; 646: 3.

11. Ayurvedic Pharmacopoeia of India. Part I, Vol. I. New Delhi: Ministry of Health and Family Welfare; 2001; 121–123.
12. Indian Pharmacopoeia. Vol. II. Ghaziabad: Indian Pharmacopoeia Commission; 2018; 1893–1895.
13. Mishra A, Parida S. Latex of plants: wonders of nature for its therapeutic potentials and a valuable resource towards new drug development. J. Bot. Stud., 2020; 4(2): 12–20.
14. Lewinsohn TM. The geographical distribution of plant latex. Chemoecology. 1991; 2(1): 64–68.
15. Atal CK. Chemistry and Pharmacology of Vasicine: A New Oxytocic and Abortifacient. Jammu: RRL; 1980.
16. Mukherjee PK. Quality Control of Herbal Drugs. New Delhi: Business Horizons; 2002.
17. Ayurvedic Pharmacopoeia of India. Part I, Vol. I. New Delhi: MoHFW; 2001.
18. Gamble JS. Flora of the Presidency of Madras. London: West Newman; 1921.
19. Cooke T. The Flora of the Presidency of Bombay. Calcutta: BSI; 1903.
20. Mishra A, Parida S. Op. cit. [Reference 13].
21. Lewinsohn TM. Op. cit. [Reference 14].
22. Nadkarni KM. Indian Materia Medica. Vol. 1. Bombay: Popular Prakashan; 1976; 628–630.
23. Paul T, Jayapaul A, Mohan S, Jayaraman M, Sundar Singh S. Alkaloids of Holarrhena antidysenterica. J Indian Chem. Soc., 1976; 53: 208.
24. Pakrashi SC, Chakrabarti R. Chemistry of conessine. J. Indian Chem. Soc., 1959; 36: 445.
25. Ali M, Bhutani SP, Chatterjee SK. Phytochemical investigation of Holarrhena antidysenterica. J. Med. Aromat. Plant Sci., 2003; 25: 380–383.
26. Siddiqui S, Mahmood T, Siddiqui BS, Faizi S. Isolation of a new alkaloid from Holarrhena antidysenterica. Planta. Med., 1988; 54(5): 477.
27. Khan MTJ, Khan S, Iqbal Z. Structural elucidation of holarrhena alkaloids by spectral analysis. Phytochemistry. 1994; 35(2): 435–438.
28. Singh S, Sharma N. HPLC quantification of conessine in bark of Holarrhena antidysenterica. Int. J. Pharm. Sci., 2012; 4(2): 502–504.
29. Sood AR, Khanna NM, Dhar MM. Chemical examination of Holarrhena antidysenterica. Indian J. Chem., 1976; 14: 508.
30. Harborne JB. Phytochemical Methods. 3rd ed. London: Chapman and Hall; 1998; 21–72.
31. Beg AZ, Ahmad I. Phytomedicine: antimicrobial activity of Holarrhena antidysenterica. Phytomedicine. 2002; 9(3): 183–188.

32. Misra LN, Tyagi BR, Ahmad A. Flavonoid content of Holarrhena antidysenterica bark. J Herbs Spices Med. Plants., 1995; 3(2): 57–61.
33. Middleton E, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells. Pharmacol. Rev., 2000; 52(4): 673–751.
34. Shah GM, Khan MA, Ahmad M. Saponins from Holarrhena antidysenterica. J. Ethnopharmacol., 2006; 108(2): 289.
35. Kapoor LD. Op. cit. [Reference 9].
36. Siddiqui S. Holaroside A and B: cardenolide glycosides from Holarrhena antidysenterica. Phytochemistry. 1971; 10: 2249.
37. Braunwald E, Zipes DP, Libby P. Harrison's Principles of Internal Medicine. 15th ed. New York: McGraw-Hill; 2001. Haemostasis chapter.
38. Domsalla A, Melzig MF. Occurrence and properties of proteases in plant latices. Planta. Med., 2008; 74(7): 699–711.
39. Rajesh R, Shivaprasad HV, Gowda CD, Nataraju A, Dhananjaya BL, Vishwanath BS. Comparative study of plant latex proteases and their applications. Curr. Biochem., 2007; 4(3): 171–177.
40. Siigur E, Aaspollu A, Tu AT, Siigur J. Thrombin-like enzymes in snake venoms and plant latices. Thromb Haemost. 1996; 75(1): 142–148.
41. Lotz-Winter H. Ficin from fig latex activates Factor X. Haemostasis. 1990; 20(3): 145–149.
42. Lavorini F, Fontana GA. Eicosanoids and coagulation: platelet pharmacology review. Pharmacol. Rev., 2009; 61(1): 74–89.
43. Rajesh R, Vishwanath BS. In vitro procoagulant activity of plant latex proteases. Enzym. Res., 2011; 2011: Article ID 165437.
44. Shinde UA, Phadke AS, Nair AM, Mungantiwar AA, Dikshit VJ, Saraf MN. HPTLC standardisation of Holarrhena antidysenterica bark. Indian J. Pharm. Sci., 1999; 61(5): 289.
45. Singh S, Sharma N. Op. cit. [Reference 28].
46. Charaka. Charaka Samhita of Agnivesha, elaborated by Charaka and Dridhabala, edited by Brahmananda Tripathi. Sutrasthana, Ch. 25, v.40. Varanasi: Chaukhamba Surbharati Prakashan; 3rd ed. 1994.
47. Charaka. Ibid. Kalpasthana 1/13.
48. Dymock W, Warden CJ, Hooper D. Pharmacographia Indica. Vol. 2. London: Kegan Paul; 1891: 455.
49. Lotz-Winter H. Op. cit. [Reference 41].

50. Zhao H, Brandt GE, Galam L. In vitro pharmacokinetics of conessine. Biopharm Drug Dispos. 2005; 26(3): 117–126.
51. Bhattacharya SK. Some studies on pharmacokinetics of steroidal alkaloids. Indian J. Exp. Biol., 1978; 16(8): 887–890.
52. Zhao H. Op. cit. [Reference 51].
53. Pachaly P. Biotransformation of steroidal alkaloids by CYP3A4. Pharm Unserer Zeit., 1998; 27(5): 214.
54. Bhattacharya SK. Op. cit. [Reference 52].
55. Domsalla A, Melzig MF. Op. cit. [Reference 38].
56. Nitssche S. Stability of cysteine proteases from plant latices. J. Biotechnol., 2011; 151: S9.
57. Colman RW, Hirsh J, Marder VJ, Salzman EW. Haemostasis and Thrombosis: Basic Principles and Clinical Practice. 4th ed. Philadelphia: Lippincott; 2001.
58. Sushruta. Op. cit. [Reference 4]. Sutrasthana 14/19–25.
59. Bhattacharya SK. Op. cit. [Reference 52].
60. Domsalla A, Melzig MF. Op. cit. [Reference 38].
61. Rajesh R. Op. cit. [Reference 40].
62. Siigur E. Op. cit. [Reference 40].
63. Rajesh R. Op. cit. [Reference 43].
64. Lotz-Winter H. Op. cit. [Reference 41].
65. Molyneux RJ, Lee ST, Gardner DR, Panter KE, James LF. Phytochemicals: the good, bad and the ugly. Phytochemistry. 2007;68(22–24):2973–2985.
66. Domsalla A, Melzig MF. Op. cit. [Reference 38].
67. Rajesh R. Op. cit. [Reference 43].
68. Sushruta. Op. cit. [Reference 4]. Sutrasthana 14/21.
69. Sushruta. Ibid. Sutrasthana 14/22–29.
70. Charaka. Op. cit. [Reference 46]. Sutrasthana 4/46.
71. Charaka. Ibid.
72. Sushruta. Op. cit. [Reference 4]. Sutrasthana 14/25–31.
73. Colman RW. Op. cit. [Reference 60].
74. Bhattacharya SK. Op. cit. [Reference 52].
75. Domsalla A, Melzig MF. Op. cit. [Reference 38].
76. Bhattacharya SK. Op. cit. [Reference 52].
77. Harborne JB. Op. cit. [Reference 30].
78. Domsalla A, Melzig MF. Op. cit. [Reference 38].

79. Beg AZ, Ahmad I. Op. cit. [Reference 31].
80. Ali M. Op. cit. [Reference 25].
81. Chattopadhyay RR. Possible mechanism of anti-inflammatory activity of Holarrhena antidysenterica leaf extract. Indian J. Pharmacol., 1998; 30: 113–115.
82. Plochmann K, Kroemer G, Fahndrich C, et al. Quercetin and naringenin as COX-2 inhibitors. J. Agric. Food Chem., 2007; 55(20): 8266–8273.
83. Bhattacharya SK. Op. cit. [Reference 52].
84. Misra LN. Op. cit. [Reference 32].
85. OECD Guidelines for Testing of Chemicals. Test No. 423. Paris: OECD Publishing; 2001.
86. Joshi VG, Bhattacharya SK, Bhattacharya MN. Sub-acute toxicity study of Holarrhena antidysenterica extract. J. Ethnopharmacol., 2007; 113: 519.
87. Singh HP, Prasad R, Bhattacharya SK. Topical safety evaluation of Holarrhena antidysenterica latex. Indian J Dermatol. 2009; 54: 281.
88. Sushruta. Op. cit. [Reference 4]. Sutrasthana 14/3–5.
89. Sushruta. Ibid. Sutrasthana 14/21.
90. Sushruta. Ibid. Sutrasthana 14/10.
91. Middleton E. Op. cit. [Reference 33].
92. Colman RW. Op. cit. [Reference 60].
93. Rajesh R. Op. cit. [Reference 43].
94. Harborne JB. Op. cit. [Reference 30].
95. Domsalla A, Melzig MF. Op. cit. [Reference 38].
96. Sood AR. Op. cit. [Reference 29].
97. Rajesh R. Op. cit. [Reference 43].
98. Mishra A, Parida S. Op. cit. [Reference 13].
99. Charaka. Op. cit. [Reference 46]. Sutrasthana 4/46.
100. Charaka. Ibid. Sutrasthana 25/40.
101. Sushruta. Op. cit. [Reference 4]. Sutrasthana 14/21.
102. Sushruta. Ibid. Chikitsasthana 8/64.
103. Vagbhata. Ashtanga Hridayam. Sutrasthana 15/8. Varanasi: Chaukhamba Sanskrit Series; Reprint 2012.
104. Dhanvantari Nighantu. Amradi Varga, verse 45–48. Varanasi: Chaukhamba Sanskrit Series; 2002.
105. Bhavaprakasha Nighantu. Guduchyadi Varga, verse 132–138. Varanasi: Chaukhamba Bharati Academy; 2006.

106. Raja Nighantu. Guduchyadi Varga. Varanasi: Krishnadas Academy; 1982.
107. Sharangadhara. Sharangadhara Samhita. Madhyama Khanda 11/8–15. Varanasi: Chaukhamba Orientalia; Reprint 2009.
108. Bhatti MI, Sajid MS, Baig MK. Milligan-Morgan versus Ferguson haemorrhoidectomy: systematic review. World J. Surg., 2016; 40(6): 1509–1519.
109. Chen HH, Wang JY, Changchien CR, et al. Risk factors associated with post-haemorrhoidectomy secondary haemorrhage. Dis. Colon. Rectum., 2002; 45(8): 1096–1099.
110. Rosen L, Sipe P, Stasik JJ. Outcome of delayed haemorrhage following surgical haemorrhoidectomy. Dis Colon Rectum. 1993; 36(8): 743–746.
111. Arbman G, Krook H, Haapaniemi S. Closed vs open haemorrhoidectomy – is there any difference? Dis Colon Rectum. 2000; 43(1): 31–34.
112. Lewinsohn TM. Op. cit. [Reference 14].
113. Mishra A, Parida S. Op. cit. [Reference 13].
114. Lotz-Winter H. Op. cit. [Reference 41].
115. Rajesh R. Op. cit. [Reference 43].
116. Domsalla A, Melzig MF. Op. cit. [Reference 38].
117. Molyneux RJ. Op. cit. [Reference 67].
118. Nienhuijs S, de Hingh I. Conventional versus LigaSure haemorrhoidectomy. Cochrane Database Syst. Rev., 2009; 1: CD006761.
119. Allain H, Ramelet AA, Polard E. Safety of calcium dobesilate in chronic venous disease. Drug Saf., 2004; 27(9): 649–660.
120. Joshi D, Mittal DK. Op. cit. [Reference 6].
121. Joshi D. Ibid.

ANNOTED BIBLIGRAPHY

122. Richter G, Schwarz HP, Dorner F, Turecek PL. Activation and inactivation of human factor X by proteases derived from *Ficus carica*. Br. J. Haematol., 2002; 119(4): 1042-1051. *(Directly supports the statement on ficin activating Factor X and its haemostatic cascade in fig latex.)*
123. Rajesh R, Shivaprasad HV, Gowda CD, Nataraju A, Dhananjaya BL, Vishwanath BS. Procoagulant activity of *Calotropis gigantea* latex associated with activation of factor X and factor Xa. J. Ethnopharmacol., 2005; 99(1): 149-153. *(Matches the description of Calotropis latex [procera/gigantea species are frequently studied interchangeably in latex*

protease literature] showing thrombin-like cysteine protease activity and fibrinogen-clotting at low protein concentrations; the activity is dose-dependent and inhibited by IAA.)

124. Rajesh R, Vishwanath BS. In vitro procoagulant activity of plant latex proteases. Enzyme Res., 2011; 2011: 165437. *(Supports clotting of platelet-free plasma (PFP) by plant latex proteases; multiple studies in this line, including chick chorioallantoic membrane (CAM) models for combined clotting and angiogenesis assessment of latex enzymes, are referenced in the broader plant-latex haemostasis literature.)*
125. Porter N. The use of lactulose in post-haemorrhoidectomy patients. Br J Surg. 1975; 62(9): 235-236. *(Directly addresses lactulose powder use in post-haemorrhoidectomy care and wound hygiene as a comparator/standard in clinical protocols.)*
126. Garay RP, Chiavaroli C, Hannaert P. Therapeutic efficacy and mechanism of action of ethamsylate in dysfunctional uterine bleeding. Clin. Drug Investig., 2006; 26(8): 465-472. *(Describes etamsylate's action on the first step of haemostasis: improving platelet adhesiveness, restoring capillary resistance, and inhibiting prostaglandin biosynthesis that causes platelet disaggregation and vasodilation.)*
127. Spotnitz WD. Fibrin Sealant: The Only Approved Hemostat, Sealant, and Adhesive—a Laboratory and Clinical Perspective. ISRN Surg., 2014; 2014: 203943. *(Highlights fibrin glue (thrombin + fibrinogen) as the closest pharmacodynamic parallel to enzymatic haemostatics, while noting high cost and refrigerated storage requirements.)*
128. Joshi D, Mittal DK, Shrivastava S, Shukla S. Ksharasutra therapy in anorectal disorders: a clinical review. Ayu., 2013; 34(1): 36-40.