

## TRANSLATIONAL PHARMACOLOGICAL ANALYSIS OF LOCAL ORAL THERAPEUTICS (GAṆḌŪṢA, KAVALA, AND PRATISĀRAṆA) IN ŚĀRṆGADHARA SAMHITĀ

<sup>1</sup>\*Dr. Disha Gupta, <sup>2</sup>Dr. Samhita Hegde, <sup>3</sup>Dr. Gagana, <sup>4</sup>Dr. Eyazhalene Pa T.,  
<sup>5</sup>Rushikesh Joshi

<sup>1</sup>BAMS, MD (Ayu), Assistant Professor, Faculty of Health and Wellness, Sri Sri University, Kataka Odisha.

<sup>2</sup>BAMS, MS(Ayu), Assistant Professor, Dept. of Shalakya Tantra, FIMS, SGT University, Gurgaon, Harayana.

<sup>3</sup>BNYS, MSc, Faculty of Health and Wellness, Sri Sri University, Kataka Odisha.

<sup>4</sup>BNYS, Msc, MPH Scholar, Balaji Vidyapeeth University, Pondicherry.

<sup>5</sup>MBA, Assistant Professor, Sri Sri University, Kataka Odisha.

Article Received on 28 August 2026,  
Article Revised on 18 September 2026,  
Article Published on 01 Oct. 2026,

<https://doi.org/10.5281/zenodo.23032654>

### \*Corresponding Author

Dr. Disha Gupta

BAMS, MD (Ayu), Assistant Professor, Faculty of Health and Wellness, Sri Sri University, Kataka Odisha.



**How to cite this Article:** <sup>1</sup>\*Dr. Disha Gupta, <sup>2</sup>Dr. Samhita Hegde, <sup>3</sup>Dr. Gagana, <sup>4</sup>Dr. Eyazhalene Pa T., <sup>5</sup>Rushikesh Joshi. (2026). Translational Pharmacological Analysis of Local Oral Therapeutics (Gaṇḍūṣa, Kavalā, and Pratisāraṇa) In Śārṇgadharā Samhitā. World Journal of Pharmaceutical Research, 15(18), 165–184.

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### ABSTRACT

**Background:** The Śārṇgadharasamhitā, a seminal 13th-century Ayurvedic compendium, systematically codifies local oral therapeutic procedures—Gaṇḍūṣa (mouth holding), Kavalā (gargling), and Pratisāraṇa (topical powder application)—in its Madhyama and Uttara Khaṇḍas. Despite their clinical prevalence in traditional practice, these modalities lack comprehensive translational pharmacological frameworks connecting classical descriptions to modern mucosal drug delivery science. **Objective:** To establish a translational pharmacological framework analyzing Gaṇḍūṣa, Kavalā, and Pratisāraṇa through integrated textual exegesis of Śārṇgadharasamhitā and contemporary oral mucosal drug delivery research. **Methods:** Systematic review of Śārṇgadharasamhitā chapters on Gaṇḍūṣa-Kavalā-Pratisāraṇa Vidhi, correlated with modern pharmacological literature on buccal/sublingual absorption, mucoadhesion, permeability

enhancement, and clinical studies on Ayurvedic oral formulations. **Results:** Classical procedures demonstrate sophisticated understanding of oral mucosal pharmacokinetics: Gaṇḍūṣa achieves static distension maximizing mucosal contact time; Kavala enables dynamic distribution with mechanical cleansing; Pratisāraṇa provides localized high-concentration powder application. Modern evidence confirms sublingual/buccal routes bypass hepatic first-pass metabolism, with thin mucosal layers (500–800 μm buccal; thinner sublingual) permitting rapid lipid-soluble compound absorption. Clinical trials show Khadira, Triphala, and Yashtimadhu-based Pratisāraṇa formulations effectively manage stomatitis, periodontitis, and oral ulcers. **Conclusion:** Gaṇḍūṣa, Kavala, and Pratisāraṇa represent pharmacologically sophisticated local delivery systems anticipating modern principles of mucoadhesion, permeability enhancement, and targeted mucosal therapy. A five-dimensional translational framework (HP1–HP5) is proposed for future standardization and clinical validation.

**KEYWORDS:** Gaṇḍūṣa, Kavala, Pratisāraṇa, Śārṅgadharasaṃhitā, oral mucosal drug delivery, translational pharmacology, Ayurveda.

## 1. INTRODUCTION

### 1.1 Historical and Textual Context

The Śārṅgadharasaṃhitā, attributed to Śārṅgadharācārya (circa 13th century CE), occupies a unique position in Ayurvedic literature as a systematic pharmaceutical compendium emphasizing practical formulation science (Bhaiṣajya Kalpanā). Unlike the Bṛhat-trayī (Caraka, Suśruta, Aṣṭāṅgahṛdaya), which prioritize theoretical foundations, Śārṅgadharasaṃhitā focuses on standardized dosage forms, posology, and administration protocols—making it particularly relevant for translational pharmacological analysis.

#### The text is structured into three Khaṇḍas (sections)

- **Prathama Khaṇḍa:** Definitions, pharmaceutical principles, diagnostics
- **Madhyama Khaṇḍa:** Twelve chapters detailing dosage forms (Svarasa, Kvātha, Phāṇṭa, Hima, Kalka, Cūrṇa, Guṭikā, Avaleha, Sneha, Sandhāna, Dhātu Śodhana-Maraṇa, Rasa Kalpanā)
- **Uttara Khaṇḍa:** Therapeutic procedures including Gaṇḍūṣa-Kavala-Pratisāraṇa Vidhi (Chapter 10).<sup>[1-4]</sup>

Chapter 10 of Uttara Khaṇḍa, titled "Gandusa-Kavala Pratisarana Vidhi," systematically describes three local oral therapeutic procedures alongside Nasya, Dhūmapāna, Lepa, and other bāhya (external) therapies. This chapter's placement within a section dedicated to administration routes (Aushadha Sevana Marga) reflects sophisticated understanding of site-specific drug delivery.

## 1.2 Rationale for Translational Analysis

Translational pharmacology bridges traditional medical knowledge with modern biomedical frameworks, requiring bidirectional validation: (1) textual fidelity to classical descriptions, and (2) pharmacological plausibility through contemporary mechanisms. Recent frameworks propose five pharmacological dimensions for Ayurvedic translation:

- **HP1:** Pharmacokinetic characterization of classical herbs
- **HP2:** Herb-drug interaction profiling
- **HP3:** Bioavailability enhancement strategies
- **HP4:** Dose-response and standardization
- **HP5:** Pharmacodynamic target identification<sup>[5,6]</sup>

### Local oral therapeutics present a unique opportunity for translation because

1. **Anatomical accessibility:** Oral mucosa is directly observable and measurable.
2. **Established modern parallels:** Buccal/sublingual drug delivery is a validated modern pharmaceutical route.
3. **Clinical evidence base:** Multiple randomized trials exist for Ayurvedic oral formulations.
4. **Mechanistic plausibility:** Mucosal absorption, permeability enhancement, and local anti-inflammatory effects are measurable endpoints.

## 1.3 Objectives

### This paper aims to

1. Provide critical exegesis of Gaṇḍūṣa, Kavala, and Pratisāraṇa as described in Śārṅgadharasaṃhitā
2. Correlate classical procedures with modern oral mucosal drug delivery mechanisms
3. Analyze pharmacological actions (local vs. systemic) through contemporary pharmacokinetic frameworks
4. Review clinical evidence for Ayurvedic oral formulations
5. Propose a translational research agenda for standardization and validation

## 2. Textual Analysis: Gaṇḍūṣa, Kavala, and Pratisāraṇa in Śārṅgadharasamhitā

### 2.1 Definitional Distinctions

Classical texts distinguish Gaṇḍūṣa and Kavala primarily by volume, movement, and retention time:

#### Gaṇḍūṣa (Mouth Holding)<sup>[7]</sup>

- **Etymology:** From root *gaṇḍ* (cheek) + *ūṣa* (holding), literally "cheek-filling"
- **Definition:** "Mouth is completely filled with liquid so that it cannot be moved"
- **Procedure:** Patient sits in warm, breeze-free environment with sunlight; face slightly elevated; liquid held until lacrimation, nasal discharge, or kapha (mucous) accumulation occurs
- **Volume:** "Full mouth" (complete distension, no movement possible)
- **Duration:** Until physiological responses (lacrimation, nasal secretion) indicate sufficient absorption/pressure

#### Kavala (Gargling)

- **Etymology:** From root *kval* (to agitate, move)
- **Definition:** "Lesser amount of fluid taken such that mouth can be moved easily; liquid swished/gargled"
- **Procedure:** Mouth filled ~3/4 capacity; liquid actively moved around oral cavity, including posterior throat; spat out after specific time
- **Volume:** "Three-fourths mouthful" allowing movement
- **Duration:** Fixed time period (typically 3–5 minutes in classical descriptions)

#### Pratisāraṇa (Topical Powder Application)

- **Etymology:** From *prati* (towards) + *srj* (to apply, rub)
- **Definition:** "Applying powdered or granular medicines inside the mouth with the tip of the finger"
- **Forms:**
  - Cūrṇa (powder)
  - Kalka (paste)
  - Rasakriyā (solidified decoction)<sup>[8,9]</sup>
- **Indications:** Primarily Kapha-origin diseases; same herbs as Gaṇḍūṣa

## 2.2 Procedural Specifications

### Pre-procedure Preparation (Pūrvakarma)

According to Śārṅgadharasaṃhitā and commentaries:

1. **Environment:** Warm, sunlight-exposed, breeze-free location
2. **Patient posture:** Sitting erect, attentive, face slightly elevated
3. **Preparatory therapies:** Mild fomentation (svedana) and massage over throat, cheeks, forehead
4. **Mental state:** Concentration, avoidance of swallowing medication

### Administration Protocol

| Step        | Gaṇḍūṣa                           | Kavala                       | Pratisāraṇa                                  |
|-------------|-----------------------------------|------------------------------|----------------------------------------------|
| Volume      | Full mouth (complete distension)  | 3/4 mouthful (movable)       | 2g powder + vehicle (honey/ghee)             |
| Movement    | Static (no movement)              | Dynamic (swishing, gargling) | Manual application with finger               |
| Duration    | Until lacrimation/nasal discharge | Fixed time (3–5 min)         | 2–3 minutes application, repeated 2–3×/day   |
| Termination | Spit out (not swallowed)          | Spit out                     | May be left in situ or spat after absorption |
| Temperature | Sukhoṣṇa (warm)                   | Sukhoṣṇa (warm)              | Room temperature or warm paste               |

### Post-procedure Care (Paścātkarma)

- Avoid immediate food/water intake
- Maintain warmth, avoid cold exposure
- Observe for therapeutic responses (reduced pain, improved salivation, ulcer healing)

## 2.3 Formulation Categories

Śārṅgadharasaṃhitā classifies Gaṇḍūṣa/Kavala formulations by base material (dravya):

### 1. Sneha Gaṇḍūṣa (Oleaginous)

- Base: Medicated oils (taila) or ghee (ghṛta)
- Processing: Fats processed with sweet, sour, salty tastes
- Indications: Vāta disorders, dryness, stomatitis

### 2. Kvātha Gaṇḍūṣa (Decoction-based)

- Base: Herbal decoctions (e.g., Triphala, Nimba, Khadira)
- Preparation: Boiled concentrates, often warm
- Indications: Kapha-Pitta disorders, infections, inflammation<sup>[8,9]</sup>

### 3. Phāṇṭa/Hima Gaṇḍūṣa (Infusion-based)

- Base: Hot/cold infusions of powdered herbs
- Indications: Pitta disorders, burning sensations

### 4. Cūrṇa Pratisāraṇa (Powder Application)

Common formulations from classical and contemporary sources:

| Condition (Mukharoga)                  | Classical Formulation                         | Modern Equivalent                                     |
|----------------------------------------|-----------------------------------------------|-------------------------------------------------------|
| <b>Mukhapaka (Stomatitis)</b>          | Triphala Cūrṇa + Madhu                        | Triphala + honey Pratisāraṇa                          |
| <b>Dantapuppūṭa (Gingival abscess)</b> | Pañcalavaṇa/Yavakṣāra + Madhu                 | Alkaline salt + honey                                 |
| <b>Upakuṣa (Gingivitis)</b>            | Trikaṭu + Madhu + Saindhava                   | Piper spp. + honey + rock salt                        |
| <b>Sheetada (Scurvy)</b>               | Mustādi Cūrṇa                                 | Cyperus-based powder                                  |
| <b>Jihvā-kaṇṭaka (Tongue lesions)</b>  | Guggulu/Lodhra/Pippalyādi Cūrṇa               | Commiphora/Symplocos/Piper                            |
| <b>Diabetic Periodontitis</b>          | Yashtimadhu + Sarjakṣāra + Śuṇṭhi + Saindhava | Glycyrrhiza + alum + ginger + salt <sup>[10,11]</sup> |

### 3. Modern Pharmacological Correlates

#### 3.1 Oral Mucosal Anatomy and Drug Absorption

Modern oral mucosal drug delivery research validates classical distinctions between static (Gaṇḍūṣa) and dynamic (Kavala) procedures through anatomical and physiological understanding:

#### Mucosal Subregions

The oral cavity comprises distinct mucosal types with varying permeability:

| Region                     | Type        | Thickness  | Keratinization         | Permeability                          |
|----------------------------|-------------|------------|------------------------|---------------------------------------|
| <b>Buccal mucosa</b>       | Lining      | 500–800 μm | Non-keratinized        | High                                  |
| <b>Sublingual mucosa</b>   | Lining      | 100–200 μm | Non-keratinized        | Very high (thinnest, highly vascular) |
| <b>Gingiva/Hard palate</b> | Masticatory | Variable   | Keratinized            | Low (barrier function)                |
| <b>Dorsal tongue</b>       | Specialized | Variable   | Keratinized (papillae) | Moderate                              |

#### Absorption Mechanisms

##### 1. Passive Diffusion

- Primary route for lipid-soluble compounds
- Paracellular (between cells) and transcellular (through cells) pathways
- Non-keratinized regions (buccal, sublingual) favor paracellular transport<sup>[12]</sup>

## 2. Carrier-Mediated Transport

- Amino acid, peptide, nucleoside transporters
- Relevant for herbal glycosides, alkaloids

## 3. Receptor-Mediated Endocytosis

- CD44 receptor binding (hyaluronic acid interactions)
- Exploited in modern GAG-based formulations<sup>[13]</sup>

## Vascular Drainage

Drugs absorbed via sublingual/buccal routes enter systemic circulation through:

- Deep lingual vein → Internal jugular vein → Systemic circulation
- **Key advantage:** Bypasses hepatic first-pass metabolism. This correlates directly with classical observations that Gaṇḍūṣa/Kavala produce both local and systemic effects, including rapid onset for certain conditions.

## 3.2 Pharmacokinetic Advantages of Oral Mucosal Delivery

### Bioavailability Enhancement

Modern studies confirm several mechanisms by which Gaṇḍūṣa/Kavala formulations achieve enhanced bioavailability:

#### 1. First-Pass Metabolism Avoidance

- Hepatic metabolism bypassed → higher systemic concentrations
- Particularly relevant for compounds like glycyrrhizin (Yashtimadhu), curcumin (Haridra), tannins (Khadira)

#### 2. Temperature-Enhanced Permeability

- Classical texts specify "sukhoṣṇa" (warm) preparations
- Modern evidence: Elevated temperature increases vascular permeability, enhancing absorption
- Mechanism: Heat-induced vasodilation, increased molecular kinetic energy

#### 3. Mechanical Pressure Effects

- Gaṇḍūṣa's "complete distension" creates hydrostatic pressure on mucosa
- Modern correlate: Pressure enhances transmucosal flux, increases capillary permeability

#### 4. Mucoadhesion and Residence Time

- Oils (Sneha Gaṇḍūṣa) and viscous decoctions prolong mucosal contact

- Modern GAG-based systems (hyaluronic acid, chitosan) exploit mucoadhesion for sustained release.<sup>[14]</sup>

### Permeability Enhancement Mechanisms

Classical formulations contain compounds that modern research identifies as permeation enhancers:

| Classical Ingredient      | Active Compound        | Permeation Mechanism                              |
|---------------------------|------------------------|---------------------------------------------------|
| Saindhava (Rock salt)     | NaCl, minerals         | Osmotic gradient, tight junction modulation       |
| Trikatu (Piper spp.)      | Piperine               | P-glycoprotein inhibition, tight junction opening |
| Madhu (Honey)             | Fructose, enzymes      | Mucoadhesion, hydration enhancement               |
| Yashtimadhu (Glycyrrhiza) | Glycyrrhizin           | Anti-inflammatory, mucosal protection             |
| Nimba (Neem)              | Nimbidin, azadirachtin | Antimicrobial, biofilm disruption                 |

### 3.3 Local vs. Systemic Actions

#### Local Actions

##### 1. Mechanical Cleansing

- Kavala's swishing action removes debris, bacteria, food particles
- Modern correlate: Mechanical debridement reduces bacterial load, improves oral hygiene

##### 2. Direct Mucosal Contact

- High local concentration of active compounds
- Pratisāraṇa powders adhere to ulcerated/affected areas
- Modern parallel: Mucoadhesive patches, gels for localized delivery<sup>[15]</sup>

##### 3. Anti-inflammatory Effects

- Triphala, Yashtimadhu, Khadira reduce local inflammation
- Mechanisms: COX/LOX inhibition, cytokine modulation

##### 4. Antimicrobial Activity

- Neem, Triphala, Trikatu show broad-spectrum antimicrobial effects
- Biofilm disruption, pH modulation

##### 5. Salivary pH Normalization

- Clinical studies show Kavala/Gaṇḍuṣa normalize acidic salivary pH
- Mechanism: Buffering capacity of herbal decoctions, stimulation of bicarbonate secretion

## Systemic Actions

### 1. Rapid Systemic Absorption

- Sublingual/buccal absorption → systemic circulation within minutes
- Lipid-soluble compounds (essential oils, alkaloids) particularly well-absorbed

### 2. Vascular Permeability Enhancement

- Warm preparations + chemical irritants (Trikatu, Saindhava) increase capillary permeability
- Classical description: "Until lacrimation and nasal discharge" indicates systemic absorption threshold.<sup>[16]</sup>

### 3. Neurological Effects

- Classical texts indicate Gaṇḍūṣa/Kavala treat headaches, neck disorders, ear diseases
- Modern correlate: Trigeminal nerve stimulation, reflex pathways, systemic anti-inflammatory effects

### 4. Metabolic Effects

- Some absorbed compounds may influence systemic metabolism
- Example: Glycyrrhizin (Yashtimadhu) has mineralocorticoid effects when absorbed systemically

## 4. Clinical Evidence and Translational Studies

### 4.1 Randomized Controlled Trials

#### Study 1: Khadira Cūrṇa Pratisāraṇa in Pediatric Stomatitis

- **Design:** Controlled clinical study
- **Population:** Children with Mukhapaka (stomatitis)
- **Intervention:** Khadira (Acacia catechu) Cūrṇa + Madhu (honey), 2g applied 3×/day
- **Control:** Tannic acid + choline salicylate (standard care)
- **Outcomes:** Significant reduction in pain, ulcer size, healing time vs. control
- **Mechanism:** Tannins (astringent), anti-inflammatory, antimicrobial effects<sup>[17]</sup>

#### Study 2: Triphala Cūrṇa + Honey in Mukhapaka

- **Design:** Case study with standardized formulation
- **Intervention:** Triphala Cūrṇa (Amalaki, Bibhītaki, Harītakī) + Madhu Pratisāraṇa
- **Outcomes:** Rapid symptom relief, ulcer healing, reduced inflammation

- **Mechanism:** Antioxidant (vitamin C from Amalaki), anti-inflammatory, immunomodulatory

### Study 3: Yashtimadhu-Based Pratisāraṇa + Ganduṣa in Diabetic Periodontitis

- **Design:** Randomized controlled trial (CTRI/2026/04/107753)
- **Intervention**
  - Yashtimadhu + Sarjakṣāra + Śuṇṭhi + Saindhava Cūrṇa (650 mg, 2×/day, 2 min application)
  - Pañcākṣiri Vṛkṣa Kaṣāya Gaṇḍuṣa (70 ml, 5 min hold, 2×/day)
- **Duration:** 1 month
- **Outcomes:** Reduced gingival index, plaque index, improved salivary microbiome
- **Mechanism:** Anti-inflammatory (glycyrrhizin), antimicrobial, pH modulation

### Study 4: Peruka vs. Khadira Cūrṇa Pratisāraṇa

- **Design:** Randomized controlled study
- **Intervention:** Peruka Cūrṇa 2g 3×/day with honey
- **Control:** Khadira Cūrṇa 2g 3×/day with honey
- **Duration:** 7 days
- **Outcomes:** Both effective; Peruka showed faster pain relief, Khadira better long-term healing
- **Mechanism:** "False inflammatory response" from Pratisāraṇa increases capillary permeability, enhances local immune response

## 4.2 Observational and Case Studies<sup>[18-21]</sup>

### Oral Aphthous Ulcers

- Saptapaṇa (Alstonia scholaris) Cūrṇa Pratisāraṇa showed efficacy in recurrent aphthous stomatitis
- Mechanism: Anti-inflammatory, wound healing, immunomodulatory

### Sheetada (Scurvy/Gingival Bleeding)

- Mustādi Cūrṇa Pratisāraṇa (Cyperus-based formulations)
- Classical indication supported by astringent, hemostatic properties

### Dantapuppuṭa (Gingival Abscess)

- Pañcalavaṇa (five salts) + Madhu Pratisāraṇa

- Osmotic drainage, antimicrobial effects

#### 4.3 Systematic Reviews

##### Kavala & Gaṇḍūṣa for Oral Health

- Comprehensive review of classical and modern literature
- Conclusions: Effective for oral hygiene, plaque reduction, gingivitis management[
- Mechanisms: Mechanical cleansing, antimicrobial, anti-inflammatory, pH normalization[

##### Pratisāraṇa Therapy

- Review of powder application techniques across Ayurvedic texts
- Indications: Mukharoga (oral diseases), Vraṇa (ulcers), Danta-roga (dental disorders)
- Standardization challenges: Particle size, vehicle selection, application frequency

### 5. Translational Pharmacological Framework

#### 5.1 Five-Dimensional Framework (HP1–HP5) for Oral Therapeutics<sup>[18-22]</sup>

Adapting the translational herbal pharmacology framework to local oral therapeutics:

##### HP1: Pharmacokinetic Characterization

- **Objective:** Quantify absorption, distribution, metabolism, excretion (ADME) of Gaṇḍūṣa/Kavala/Pratisāraṇa formulations
- **Methods**
  - In vitro: Caco-2/buccal cell permeability assays
  - In vivo: Salivary/plasma concentration-time profiles
  - Ex vivo: Porcine buccal mucosa permeation studies
- **Key Parameters**
  - Permeability coefficient (Papp)
  - Bioavailability (%F)
  - T<sub>max</sub>, C<sub>max</sub>, AUC
  - Mucosal retention time

##### HP2: Herb-Drug Interaction Profiling

- **Objective:** Assess interactions between Ayurvedic oral formulations and conventional medications

- **Relevant Interactions**

- CYP450 enzyme modulation (e.g., piperine from Trikatu inhibits CYP3A4)[
- P-glycoprotein inhibition/induction
- Protein binding displacement
- **Clinical Relevance:** Patients on anticoagulants, antidiabetics, antihypertensives using Ayurvedic oral therapies

### HP3: Bioavailability Enhancement

- **Objective:** Optimize formulations for maximal mucosal absorption
- **Strategies**
  - **Permeation Enhancers:** Saindhava (NaCl), Trikatu (piperine), Madhu (fructose)<sup>[22]</sup>
  - **Mucoadhesive Systems:** GAG-based carriers (hyaluronic acid, chitosan)<sup>[23]</sup>
  - **Nanoparticulate Delivery:** Liposomes, solid lipid nanoparticles for herbal actives<sup>[15]</sup>
  - **Temperature Optimization:** Sukhoṣṇa (warm) preparations enhance vascular permeability<sup>[16]</sup>

### HP4: Dose-Response and Standardization

- **Objective:** Establish evidence-based dosing protocols
- **Parameters**
  - **Volume:** Gaṇḍūṣa (full mouth ~50–70 ml), Kavala (3/4 mouthful ~30–50 ml)<sup>[14]</sup>
  - **Concentration:** Cūrṇa:Madhu ratios (typically 1:1 to 1:3)<sup>[23]</sup>
  - **Frequency:** 2–3×/day for Pratisāraṇa; 1–2×/day for Gaṇḍūṣa/Kavala<sup>[24]</sup>
  - **Duration:** Until symptom resolution or fixed course (7–30 days)<sup>[24]</sup>
- **Standardization Challenges**
  - Herbal extract variability
  - Particle size distribution (Cūrṇa)
  - Vehicle consistency (Madhu, Ghṛta, Taila)

### HP5: Pharmacodynamic Target Identification

- **Objective:** Map classical indications to molecular targets
- **Examples**

| Classical Indication   | Modern Correlate                        | Molecular Targets                                           |
|------------------------|-----------------------------------------|-------------------------------------------------------------|
| Mukhapaka (Stomatitis) | Oral ulceration, inflammation           | COX-2, TNF- $\alpha$ , IL-6, NF- $\kappa$ B <sup>[15]</sup> |
| Dantapuppuṭa (Abscess) | Periodontal infection                   | Bacterial biofilms, MMPs <sup>[16]</sup>                    |
| Sheetada (Scurvy)      | Gingival bleeding, vitamin C deficiency | Collagen synthesis, capillary fragility <sup>[14]</sup>     |

|                               |                          |                                                         |
|-------------------------------|--------------------------|---------------------------------------------------------|
| <b>Upakūṣa (Gingivitis)</b>   | Gingival inflammation    | Plaque bacteria, inflammatory cytokines <sup>[13]</sup> |
| <b>Diabetic Periodontitis</b> | Inflammation + dysbiosis | AGE-RAGE pathway, oxidative stress <sup>[15]</sup>      |

## 5.2 Proposed Translational Research Agenda

### Short-Term Priorities (1–2 years)

#### 1. Standardization of Classical Formulations

- Develop monographs for common Gaṇḍūṣa/Kavala/Pratisāraṇa formulations
- Establish quality control parameters (marker compounds, microbial limits, heavy metals)

#### 2. In Vitro Permeability Studies

- Caco-2 and TR146 (buccal cell line) models for key formulations
- Permeability coefficients for Triphala, Yashtimadhu, Khadira extracts

#### 3. Clinical Pilot Studies

- Small RCTs (n=30–50) for common indications (stomatitis, gingivitis)
- Standardized outcome measures (pain scores, ulcer size, gingival index)

### Medium-Term Priorities (3–5 years)

#### 1. Pharmacokinetic Studies

- Salivary and plasma concentration-time profiles
- Bioavailability comparisons (oral mucosal vs. oral ingestion)

#### 2. Mechanistic Studies

- Anti-inflammatory pathways (cytokine profiling)
- Antimicrobial mechanisms (biofilm disruption, microbiome modulation)

#### 3. Formulation Optimization

- GAG-based mucoadhesive systems for Ayurvedic extracts
- Nanoparticulate delivery for poorly soluble compounds<sup>[18–22]</sup>

### Long-Term Priorities (5–10 years)

#### 1. Large-Scale Multicenter Trials

- Phase III RCTs for priority indications
- Comparative effectiveness vs. standard care

## 2. Regulatory Pathways

- Drug-device combination classification for Pratisāraṇa formulations
- Integration into national oral health programs

## 3. Integration with Modern Dentistry

- Adjunctive therapy protocols for periodontitis, oral mucositis
- Preventive applications (oral hygiene, caries prevention)

## 6. Comparative Analysis: Classical vs. Modern Oral Mucosal Delivery

### 6.1 Conceptual Parallels

| Classical Concept                       | Modern Correlate                              | Evidence Level                                |
|-----------------------------------------|-----------------------------------------------|-----------------------------------------------|
| <b>Gaṇḍūṣa (static holding)</b>         | Mucoadhesive patches, sustained-release films | High (anatomical/physiological plausibility)  |
| <b>Kavala (dynamic gargling)</b>        | Oral rinses, mouthwashes, dispersive sprays   | High (mechanical cleansing + chemical action) |
| <b>Pratisāraṇa (powder application)</b> | Mucoadhesive powders, wafers, lozenges        | Moderate-High (clinical trials exist)         |
| <b>Sukhoṣṇa (warm preparations)</b>     | Temperature-enhanced permeability             | Moderate (physiological plausibility)         |
| <b>Sneha Gaṇḍūṣa (oil-based)</b>        | Lipophilic formulations, lipid nanoparticles  | Moderate (enhanced lipid-soluble absorption)  |
| <b>Kvātha Gaṇḍūṣa (decoctions)</b>      | Aqueous extracts, hydrophilic matrices        | High (standard modern formulation)            |

### 6.2 Advantages of Classical Approaches

#### 1. Holistic Formulation Design

- Multi-herb combinations target multiple pathways simultaneously
- Synergistic effects (e.g., Triphala's antioxidant + anti-inflammatory + antimicrobial actions)

#### 2. Patient-Centric Administration

- Non-invasive, self-administered
- Minimal equipment required
- Culturally acceptable in traditional contexts

#### 3. Cost-Effectiveness

- Locally sourced herbs
- Simple preparation methods
- Lower cost than synthetic alternatives

#### 4. Safety Profile

- Long historical use suggests favorable safety
- Local administration minimizes systemic exposure
- Classical texts describe contraindications and precautions

### 6.3 Limitations and Challenges

#### 1. Standardization

- Herbal variability (geographical, seasonal, processing)
- Lack of marker compound quantification
- Inconsistent particle sizes (Cūrṇa)

#### 2. Dosing Precision

- Classical descriptions use relative measures ("full mouth," "until lacrimation")
- Modern pharmacology requires absolute doses, concentrations

#### 3. Quality Control

- Microbial contamination risk (especially in water-based Kvātha)
- Heavy metal contamination (if minerals included)
- Stability/shelf-life issues

#### 4. Evidence Base

- Limited large-scale RCTs
- Heterogeneous study designs, outcome measures
- Publication bias (positive results more likely published)

#### 5. Regulatory Ambiguity

- Drug vs. device vs. combination product classification
- Varying regulatory frameworks across countries
- Intellectual property concerns (traditional knowledge protection)

### 7. Future Directions and Research Gaps

#### 7.1 Priority Research Questions

1. What is the bioavailability of key Ayurvedic compounds (glycyrrhizin, curcumin, tannins) via Gaṇḍūṣa/Kavala vs. oral ingestion?
  - Requires: LC-MS/MS quantification, crossover studies

**2. Do classical temperature specifications (sukhoṣṇa) measurably enhance mucosal permeability?**

- Requires: Controlled temperature studies, TEER measurements

**3. What is the optimal Cūrṇa:Madhu ratio for Pratisāraṇa in different conditions?**

- Requires: Formulation optimization studies, clinical dose-ranging trials

**4. Can GAG-based mucoadhesive systems improve residence time and efficacy of Ayurvedic extracts?**

- Requires: Formulation development, ex vivo/in vivo permeation studies

**5. What are the long-term safety profiles of daily Gaṇḍūṣa/Kavala/Pratisāraṇa use?**

- Requires: Longitudinal observational studies, adverse event monitoring

## **7.2 Methodological Recommendations**

### **In Vitro Studies**

- Use TR146 (buccal carcinoma) or EpiOral (reconstructed human buccal epithelium) models
- Measure TEER (transepithelial electrical resistance) for barrier integrity
- Include permeability enhancers (positive controls) and vehicle controls[15,17,19]

### **Ex Vivo Studies**

- Porcine buccal mucosa (anatomically similar to human)
- Franz diffusion cells for permeation kinetics
- Texture analyzer for mucoadhesion testing (pull-off force  $\geq 0.5$  N/cm<sup>2</sup>, shear  $\geq 2.0$  N/cm<sup>2</sup>)

### **In Vivo Studies**

- Salivary sampling for local concentration-time profiles
- Plasma sampling for systemic absorption
- Non-invasive imaging (fluorescence, radiolabeling) for mucosal retention

### **Clinical Trials**

- CONSORT-compliant RCT designs
- Standardized outcome measures (pain VAS, ulcer size mm<sup>2</sup>, gingival index, plaque index)
- Microbiome analysis (16S rRNA sequencing) for dysbiosis-related conditions
- Biomarker panels (cytokines, oxidative stress markers)

### 7.3 Integration with Modern Oral Healthcare

#### Potential Applications

##### 1. Adjunctive Periodontal Therapy

- Gaṇḍūṣa/Kavala as adjuncts to scaling/root planing
- Pratisāraṇa for localized pocket therapy

##### 2. Oral Mucositis Management

- Cancer therapy-induced mucositis
- Triphala, Yashtimadhu-based formulations

##### 3. Recurrent Aphthous Stomatitis

- Khadira, Triphala Pratisāraṇa
- HA-based gels (modern parallel)

##### 4. Preventive Oral Hygiene

- Daily Kavala/Gaṇḍūṣa for plaque control
- Integration into public health programs

##### 5. Xerostomia Management

- Sneha Gaṇḍūṣa for dry mouth
- Mucoadhesive formulations for prolonged lubrication<sup>[14,18,24]</sup>

### 8. CONCLUSION

The Gaṇḍūṣa, Kavala, and Pratisāraṇa procedures codified in Śārṅgadharasamhitā represent pharmacologically sophisticated local oral therapeutic systems that anticipate modern principles of mucosal drug delivery by centuries. Classical distinctions between static (Gaṇḍūṣa) and dynamic (Kavala) administration correlate with contemporary understanding of mucoadhesion, residence time, and permeability enhancement. Pratisāraṇa's topical powder application parallels modern mucoadhesive powders, wafers, and patches.

Modern pharmacological research validates several mechanisms underlying these procedures:

- **Buccal/sublingual absorption** bypasses hepatic first-pass metabolism[
- **Warm preparations** enhance vascular permeability
- **Mechanical pressure** (Gaṇḍūṣa) and **dynamic distribution** (Kavala) optimize mucosal contact

- **Herbal compounds** (Triphala, Yashtimadhu, Khadira) demonstrate anti-inflammatory, antimicrobial, and wound-healing activities

Clinical evidence, though limited in scale, supports efficacy for stomatitis, periodontitis, and oral ulcers. Randomized trials show Ayurvedic formulations are non-inferior or superior to standard care in some contexts.

A five-dimensional translational framework (HP1–HP5) is proposed to guide future research:

1. **HP1:** Pharmacokinetic characterization
2. **HP2:** Herb-drug interaction profiling
3. **HP3:** Bioavailability enhancement
4. **HP4:** Dose-response and standardization
5. **HP5:** Pharmacodynamic target identification[

Priority research gaps include:

- Standardized formulations with marker compound quantification
- In vitro/in vivo permeability studies
- Large-scale multicenter RCTs
- Long-term safety data
- Regulatory pathway clarification[

Integration of Gaṇḍūṣa, Kavala, and Pratisāraṇa into modern oral healthcare offers opportunities for:

- Cost-effective adjunctive therapies
- Culturally acceptable preventive interventions
- Novel mucoadhesive formulation development
- Personalized oral medicine approaches[

The translational pharmacological analysis presented here bridges classical Ayurvedic wisdom with contemporary pharmaceutical science, providing a framework for evidence-based integration of these time-tested local oral therapeutics into modern healthcare systems.

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