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Review Article

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Biofilm-Driven Antibiotic Resistance: Mechanistic Insights and Emerging Complementary Interventions from Ayurveda

Gupta C[1*], Thakur I[2], Dhiman G[3]

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[1*] Chandni Gupta, Associate Professor, Department of Dravya Guna, Rajiv Gandhi Government Post Graduate Ayurvedic College, Paprola, Himachal Pradesh, India.
[2] Ilsa Thakur, Post Graduate Scholar, Department of Dravya Guna, Rajiv Gandhi Government Post Graduate Ayurvedic College, Paprola, Himachal Pradesh, India.
[3] Gunjan Dhiman, Post Graduate Scholar, Department of Dravya Guna, Rajiv Gandhi Government Post Graduate Ayurvedic College, Paprola, Himachal Pradesh, India.

Background: Biofilm formation is a major contributor to chronic infections and antibiotic resistance. Bacteria residing within biofilms exhibit profound tolerance to antimicrobial agents due to restricted drug penetration, metabolic dormancy, quorum sensing–mediated gene regulation, efflux pump overexpression, and horizontal transfer of resistance determinants. Nearly 80% of chronic and recurrent infections are now linked to biofilm-associated pathogens, particularly in wounds, urinary tract infections, respiratory infections, dental plaque, and device-related infections. Ayurveda describes chronic infective and non-healing conditions under concepts such as Krimi (pathogenic organisms), Dushta vraṇa (chronic infected wound), Kapha (the structural and cohesive biological principle), Avaraṇa (obstruction), Ama (metabolic toxins), and Ojakṣaya (depletion of immune vitality) offering a host-centered perspective that parallels modern understanding of biofilm persistence, relapse, and immune evasion.

Objectives: This review aims to synthesize contemporary microbiological evidence on biofilm-mediated antibiotic resistance and correlate it with Ayurvedic pathophysiology and therapeutic principles.

Methods: A narrative review methodology was adopted. Literature from PubMed, Scopus, Web of Science, and classical Ayurvedic texts was critically assessed to identify herbs, formulations, and procedures with documented antibiofilm, quorum-sensing inhibitory, resistance-modifying, immunomodulatory, and wound-healing potential.

Results: Key Ayurvedic interventions such as Curcuma longa L., Azadirachta indica A. Juss., Terminalia chebula Retz., Tinospora cordifolia (Willd.) Hook.f. & Thomson, Triphala, and Panchavalkala demonstrate promising antibiofilm and antibiotic-synergistic effects through multi-target mechanisms including disruption of biofilm matrix, modulation of quorum sensing, enhancement of host immunity, and support of tissue repair.

Conclusion: Integrative strategies combining conventional antibiotics with validated Ayurvedic interventions, along with Rasayana (immunomodulator therapy) and local wound-management approaches, may help reduce chronicity, recurrence, and antibiotic burden in biofilm-associated infections. However, robust standardization, mechanistic studies, synergy testing, and well-designed clinical trials are urgently needed to translate these insights into evidence-based integrative protocols.

Keywords: Biofilm; Antibiotic resistance; Ayurveda; Krimi; Lekhana; Antibiofilm; Integrative medicine

Corresponding Author

Chandni Gupta, Associate Professor, Department of Dravya Guna, Rajiv Gandhi Government Post Graduate Ayurvedic College, Paprola, Himachal Pradesh, India.
Email: kaurachandni17@gmail.com

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Introduction

Antimicrobial resistance (AMR) represents one of the most critical public health threats of the present century.[1] Despite the continuous development of newer antibiotics, treatment failure, recurrent infections, and chronicity of microbial diseases are increasing worldwide. Among various mechanisms responsible for antimicrobial resistance, biofilm formation has emerged as a dominant and clinically challenging factor.[2-4] It is now estimated that nearly 80% of chronic and recurrent infections are associated with microbial biofilms, including infections of wounds, urinary tract, lungs, dental tissues, and implanted medical devices.[2,5-7]

A biofilm is structured microbial community encased within self-produced extracellular polymeric substance (EPS), which enables microorganisms to adhere to biological or inert surfaces.[2,8] Organisms within biofilms exhibit drastically altered genetic expression, metabolic activity, and antimicrobial susceptibility when compared to free-floating planktonic bacteria.[5,6,9] This altered physiology renders conventional antibiotics largely ineffective, resulting in persistent infections, prolonged hospital stays, and increased mortality.[3,4,6]

From a traditional medical perspective, Ayurveda offers a unique, host-centered understanding of disease pathogenesis that is fundamentally different from microbe-centric model of modern medicine. Chronic infective conditions are described under concepts such as *Krimi*, *Dushta Vrana*, *Kapha Pradhan Vyadhi* (diseases dominated by *Kapha*), *Avaraṇa*, *Ama* & *Ojakshaya*.[10-12] These classical descriptions show remarkable conceptual overlap with the modern understanding of biofilm-mediated persistence, relapse, and immune evasion.[4,13,14]

In recent years, increasing scientific evidence has demonstrated that several Ayurvedic herbs and formulations possess antibiofilm, quorum-sensing inhibitory, resistance-modifying, and immunomodulatory properties.[15,17-21] However, a comprehensive integrative review linking modern biofilm biology with Ayurvedic concepts and therapeutic strategies remains largely unexplored, particularly in the context of antibiotic resistance. Therefore, the present review critically analyses the molecular mechanisms of biofilm-mediated antibiotic resistance and integrates Ayurvedic theoretical foundations, phytochemical evidence, And therapeutic principles relevant to biofilm disruption and infection control.

Methodology

Methods of Literature Search and Selection

This review was conducted using a narrative review methodology, suitable for integrative analysis of biomedical evidence alongside classical Ayurvedic literature.[16] Classical Ayurvedic texts including *Charaka Samhita*, *Sushruta Samhita*, and *Ashtanga Hridaya* were systematically examined to extract conceptual frameworks related to *Krimi*, *Dushta Vrana*, *Kapha*, *Avaraṇa*, *Lekhana*, *Kṣhara* (alkaline cauterization), *Rasayana*, and *Shodhana* (purification).[10-12]

Boolean operators (AND, OR, NOT) and predefined filters (language, publication year, peer-review status) were applied to refine the search strategy. Contemporary scientific literature addressing biofilm biology, antimicrobial resistance, quorum sensing, and antibiofilm pharmacology was retrieved from electronic databases including PubMed, Scopus, Google Scholar, and Web of Science.[2-9] Only peer-reviewed articles published in English were included. Experimental, mechanistic, and review-based studies evaluating herbal antibiofilm activity and resistance-modifying effects were considered.[15,17-21] This review was conducted using a narrative review methodology, which is appropriate for integrative synthesis of heterogeneous biomedical evidence and traditional knowledge systems, as described in established typologies of review designs.[16]

Purely anecdotal reports, non-indexed sources, and non-scientific literature were excluded. The selected studies were critically analysed to synthesize mechanistic insights and develop integrative correlations between modern biofilm resistance mechanisms and Ayurvedic therapeutic principles.[3,15,21]

Table 1: Search strategy used for identifying relevant literature

Component	Details
Databases	PubMed, Scopus, Web of Science, Google Scholar
Keywords	Biofilm, Antibiotic Resistance, Ayurveda
Boolean operators	AND, OR, NOT
Filters	English language; peer-reviewed; 2000–2024
Inclusion criteria	Antibiofilm studies, Ayurvedic herbs, review articles
Exclusion criteria	Anecdotal reports, non-indexed sources

Results

Modern Mechanisms of Biofilm-Mediated Antibiotic Resistance

Biofilm formation represents a highly sophisticated survival strategy adopted by microorganisms to withstand hostile environmental conditions, including exposure to antimicrobial agents and host immune defences.**[1,3,4,6]** Unlike planktonic bacteria, biofilm-embedded microorganisms exist within a complex, multicellular architectural framework that promotes persistence, chronicity, and resistance.**[1,3,5]** Biofilm-mediated resistance is now regarded not merely as drug resistance but as a multifactorial phenotypic tolerance involving physical, metabolic, genetic, and biochemical mechanisms.**[3-6]** The structural organization of biofilms and the major mechanisms contributing to antimicrobial resistance are illustrated in Figure 1.

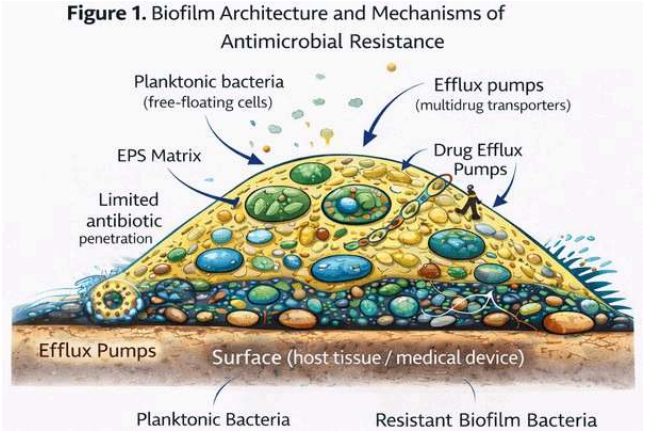


Figure 1. Biofilm Architecture and Mechanisms of Antimicrobial Resistance

1. Structure and Composition of Biofilm Matrix

The defining feature of a mature biofilm is its extracellular polymeric substance (EPS) matrix, which constitutes approximately 80–90% of the total biofilm biomass.**[2,6]** The EPS matrix is a highly organized, self-produced scaffold composed primarily of polysaccharides, structural proteins, lipids, and extracellular DNA (eDNA).**[2,6]**

This matrix functions as both a physical and chemical barrier, significantly restricting the penetration of antimicrobial agents.**[2,5,6]** Hydrophobic antibiotics become entrapped within the polysaccharide network, whereas charged antimicrobial molecules interact electrostatically with matrix components, resulting in sub-therapeutic drug concentrations in deeper biofilm layers.**[5,10]**

In addition, degradative enzymes present within the matrix can chemically inactivate certain antibiotics before they reach their intracellular targets.**[6,10]**

2. Altered Metabolic State and Persister Cell Formation

Biofilm-embedded bacterial populations exhibit marked metabolic heterogeneity, wherein surface-associated cells remain metabolically active, while deeper layers consist of slow-growing or dormant persister cells.**[7,9]** These persister cells are not genetically resistant; rather, they display phenotypic tolerance to antibiotics due to: reduced metabolic activity, suppressed DNA replication and decreased protein synthesis.**[7]**

Because most antibiotics target active cellular processes such as cell wall synthesis, protein translation, or nucleic acid replication, dormant persister cells survive antimicrobial exposure and subsequently repopulate the infection site, leading to relapse and chronic infection [7,10].

3. Quorum Sensing and Coordinated Gene Regulation

Quorum sensing is a cell-to-cell chemical communication system that enables bacteria to sense population density and regulate gene expression in a coordinated manner.**[8]** Within biofilms, autoinducer molecules accumulate and activate signaling cascades that regulate:

EPS synthesis
Virulence factor secretion
Stress response pathways
Multidrug efflux pump expression**[8,9]**

Through these mechanisms, quorum sensing governs the transition from the planktonic to the biofilm phenotype and plays a central role in antibiotic tolerance by synchronizing protective genetic programs across the biofilm community. **[8,9]**

4. Efflux Pump Overexpression

Biofilm-associated bacteria demonstrate upregulated expression of multidrug efflux pumps, which actively expel antibiotics from the bacterial cell.**[5,9]** These efflux systems:

Reduce intracellular antibiotic concentrations
Prevent achievement of bactericidal drug levels
Facilitate multidrug resistance.**[5,9]**

Efflux pump activation is frequently regulated by quorum-sensing networks and biofilm-specific transcription factors, making it a critical resistance-modulating mechanism in biofilm-associated infections.[8,9]

5. Horizontal Gene Transfer within Biofilms

Biofilms provide an optimal microenvironment for horizontal gene transfer (HGT) through mechanisms such as conjugation, transformation, and transduction.[6] The high microbial density and abundance of extracellular DNA within the EPS matrix markedly increase the probability of genetic exchange, including the transfer of resistance determinants such as β-lactamases, carbapenemases, and multidrug-resistance operons.[4,6]

Consequently, biofilms function as evolutionary reservoirs and amplification hubs for the dissemination of antimicrobial resistance.[4,6]

6. Biofilm-Associated Immune Evasion

Biofilms confer substantial protection against host immune defenses by:

Preventing penetration of phagocytic cells
Inhibiting complement activation
Restricting antibody access
Inducing chronic, ineffective inflammatory responses[4,6]

This persistent immune stimulation without effective microbial clearance results in progressive tissue damage, contributing to non-healing wounds, fibrosis, and organ dysfunction.[24,25]

7. Device-Associated Biofilm Infections

Medical devices provide ideal abiotic surfaces for biofilm establishment and persistence.[6] Major device-associated biofilm infections include:

Catheter-associated urinary tract infections
Endotracheal tube–associated pneumonia
Prosthetic joint infections
Cardiac implantable electronic device infections
Central venous catheter–associated bloodstream infections [6,9]

Once biofilms are established on implant surfaces, systemic antibiotic therapy alone is often ineffective, and device removal frequently becomes the only curative option.[4,6]

8. Clinical Consequences of Biofilm-Mediated Resistance

The clinical consequences of biofilm-mediated resistance include:

- Recurrent infections despite appropriate antibiotic therapy[1,4]
- Prolonged hospitalization[4,6]
- Increased healthcare expenditure[4]
- Elevated morbidity and mortality[5,6]
- Accelerated spread of multidrug-resistant organisms[3,4]

Biofilm-driven resistance therefore represents a distinct clinical entity that necessitates therapeutic strategies extending beyond conventional antimicrobial monotherapy.[4,5,15]

Ayurvedic Conceptual Correlation of Biofilm-Mediated Infections

Ayurveda does not describe microbial biofilms in explicit microbiological terms; however, the classical understanding of chronic, recurrent, slimy, and non-healing infective conditions is remarkably aligned with the modern concept of biofilm-mediated infections.[4,6,24,25]

The doctrines of *Krimi*, *Kapha*, *Picchila Guna*, *Avaraṇa*, *Ama*, *Dushta Vrana*, and *Ojakshaya* collectively provide a sophisticated theoretical framework that mirrors the pathophysiological behavior of biofilms.[10-12]

Unlike the microbe-centric approach of modern medicine, Ayurveda emphasizes the host–microbe–environment triad, which is particularly relevant in biofilm persistence and relapse.[4,6] The conceptual parallels between biofilm-mediated infection mechanisms and classical Ayurvedic pathophysiology are summarized in **Figure 2**.

Figure 2. Correlation between Biofilm Pathology and Ayurvedic Concepts

Modern Biofilm Pathologies	Ayurvedic Concepts
• Biofilm Matrix (EPS)	Kapha, Picchila Guna
• Obstruction to Flow	Avarana
• Chronic Persistence	Ama
• Immune Evasion	Ojakshaya
• Non-Healing Wounds	Dushta Vrana

1. *Krimi Siddhanta* and Microbial Colonization

In Ayurveda, *Krimi* refers to both macroscopic and microscopic living organisms capable of producing disease.[10] *Charaka Samhita* classifies *Krimi* into *Bahya* (external) and *Abhyantara* (internal), with further subdivisions based on their origin from *Kapha*, *Pitta*, *Vata*, *Rakta*, and *Mala.*[10] The description of *Shleshmaja Krimi* - organisms thriving in moist, slimy, and nutrient-rich environments - closely corresponds with modern biofilm-forming bacteria that preferentially colonize wet surfaces and mucosal linings.[1,6,9]

Ayurveda emphasizes that the mere presence of *Krimi* does not cause disease; rather, disease manifests when host factors become permissive due to impaired *Agni*, accumulated *Ama*, and dominance of *Kapha.*[10-12] These parallels modern observations that biofilm formation is favoured by devitalized tissue, foreign bodies, hyperglycaemia, and immune compromise.[4,6,24,25]

2. *Kapha, Picchila Guna* and Extracellular Polymer Matrix

The extracellular polymeric substance (EPS) matrix of biofilms is fundamentally responsible for microbial adhesion, protection, and chronic persistence.[2,6] This matrix exhibits viscosity, stickiness, cohesion, and moisture retention.[2]

In Ayurveda, these attributes are described under *Kapha Dosha* and the *Picchila*, *Snigdha*, and *Guru Gunas.*[10-12] *Kapha*-dominant pathological states are characterized by excessive secretion, stagnation, and adherence - features that closely resemble biofilm behavior.[2,6] Thus, biofilm formation may be interpreted as a *Kapha*-predominant pathological microenvironment supporting microbial persistence.[10-12]

3. Avaraṇa and Biofilm-Associated Obstruction

Avaraṇa denotes functional obstruction of physiological flow within *Srotas* (channels) by pathological elements.[10-12] Biofilms similarly create mechanical and biochemical obstruction by:

Restricting antibiotic penetration
Preventing immune cell access
Limiting nutrient and oxygen diffusion[2,4,6]

This leads to selective survival of dormant bacteria within deeper biofilm layers, analogous to *Avaraṇa - janya Dushti.*[7,10-12]

Hence, biofilms may be conceptualized as a *micro-Avaraṇa phenomenon* at the tissue and cellular level.[4,6,10-12]

4. *Ama, Agnimandya* and Biofilm Persistence

Ama represents incompletely metabolized waste formed due to impaired *Agni.*[10-12] It is described as heavy, sticky, foul-smelling, and obstructive—properties closely resembling the biofilm matrix.[2,6]

Persistent *Agnimandya* results in continuous *Ama* production, providing a fertile substrate for chronic microbial colonization.[10-12] From an Ayurvedic perspective, biofilm chronicity reflects a sustained *Ama*-dominant internal milieu.[4,24,25,10-12]

5. Dushta Vrana and Chronic Non-Healing Biofilm Wounds

Sushruta Samhita describes *Dushta Vrana* as chronic wounds characterized by persistent discharge, foul odor, induration, discoloration, and delayed healing.[11] These features are identical to modern biofilm-associated chronic wounds such as diabetic foot ulcers, pressure sores, and venous ulcers.[24,25] The classical pathogenesis involves *Kapha–Pitta* dominance, *Rakta Dushti*, *Krimi* involvement, and *Srotas* obstruction,[11,12] indicating that Ayurveda recognized biofilm-like wound pathology long before its modern microbiological elucidation.[4,24,25]

6. *Ojas* (vital essence), *Vyadhi-Kshamatva* and Immune Evasion

Ojas is the essence of all *Dhatus* and the basis of *Vyadhi-Kshamatva* (immunity).[10-12] Biofilm-associated infections frequently occur in individuals with diabetes, malnutrition, malignancy, chronic illness, and immune suppression,[4,6,24,25] conditions corresponding to *Ojakshaya* in Ayurveda.[10-12] Biofilms evade immune clearance through physical shielding and immune exhaustion, paralleling the Ayurvedic observation that depletion of *Ojas* results in recurrent and non-healing infections.[4,6,24,25,10-12]

7. Ayurvedic Interpretation of Biofilm Relapse and Recurrence

Recurrent infections following apparently successful therapy are a defining feature of biofilm pathology.[1,4,5,7]

Ayurveda attributes recurrence to persistence of *Beeja Dosha*, incomplete removal of *Ama*, failure to eliminate *Mula Karana*, and unresolved *Agni Dushti.* **[10-12]**

Thus, unless systemic correction of *Agni*, *Ama*, and *Dosha* imbalance is achieved, eradication of surface pathogens alone does not ensure cure.**[10-12]**

This principle provides a strong explanatory framework for the failure of antibiotic monotherapy in biofilm-mediated infections.**[4,5,7]**

Ayurvedic Herbs and Phytochemicals with Antibiofilm Potential

The rapid failure of conventional antibiotics against biofilm-associated infections has shifted global research interest toward alternative and complementary antibiofilm agents.**[1,4,5,7]**

Medicinal plants used in Ayurveda constitute a vast repository of bioactive phytochemicals with demonstrated antibiofilm, quorum-sensing inhibitory, efflux pump–modulating, and resistance-modifying properties.**[15,17–21,24–25]**

Unlike conventional antibiotics that usually target a single molecular pathway, phytochemicals often act through multi-target mechanisms, making them particularly relevant for complex biofilm systems. **[15,21,24,25]** The multi-target antibiofilm mechanisms of Ayurvedic herbs and phytochemicals are depicted in **Figure 3**.

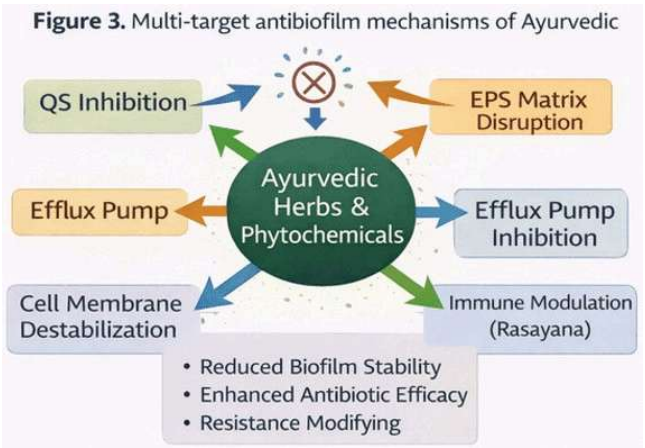


Figure 3. Multi-target antibiofilm mechanisms of Ayurvedic

1. Phytochemical Classes Involved in Antibiofilm Activity

Several major classes of plant-derived secondary metabolites have been identified as key antibiofilm agents:

Table 2: Phytochemical Classes Involved in Antibiofilm Activity

Phytochemical Class	Major Antibiofilm Mechanisms	Functional Impact on Biofilm
Polyphenols and Tannins [2,6,17-19]	Disrupt extracellular polymeric substance (EPS) proteins Precipitate surface adhesins Inhibit initial bacterial attachment Destabilize mature biofilm architecture	Weakening of biofilm structural integrity and impairment of early biofilm development
Flavonoids [15,21,25]	Suppress quorum sensing gene expression Inhibit biofilm thickness and maturation Reduce virulence factor production Exhibit efflux pump inhibitory activity	Attenuation of coordinated biofilm growth, virulence, and multidrug resistance
Alkaloids [15,21,25]	Alter bacterial cell membrane integrity Interfere with DNA replication Inhibit efflux transporter systems	Direct bactericidal effect and enhancement of intracellular antibiotic concentration
Terpenoids and Essential Oils[24]	Increase cell membrane permeability Disrupt lipid-rich EPS components Inhibit surface colonization and biofilm maturation	Enhanced antibiotic penetration and prevention of stable biofilm establishment

These mechanisms collectively weaken biofilm stability and enhance antibiotic penetration.

Among the various phytochemical classes summarized in Table 2, several Ayurvedic herbs rich in polyphenols, flavonoids, and tannins have been extensively investigated for their antimicrobial and antibiofilm activities, and selected representative examples are discussed below.

2. Curcuma longa L. (*Haridra*) and Curcumin

Curcuma longa is one of the most extensively studied Ayurvedic herbs for antimicrobial and antibiofilm activity.**[15,19]** Curcumin, its principal bioactive polyphenol, exhibits strong antibiofilm effects through quorum-sensing inhibition,**[13]** suppression of virulence gene expression,**[8,13]** EPS matrix destabilization,**[6,15]** and efflux pump modulation.**[15,21]**

Curcumin disrupts biofilm formation in *Pseudomonas aeruginosa* and *Staphylococcus aureus* by downregulating quorum-sensing regulators,**[13,15]**

And enhances antibiotic susceptibility by increasing membrane permeability and reducing efflux activity. **[15,21]**

From an Ayurvedic perspective, *Haridra* is *Tikta–Katu Rasa Pradhana*, *Kapha–Pitta Shamaka*, and indicated in *Dushta Vrana*, *Krimi*, and chronic inflammatory conditions, aligning with its modern antibiofilm role.**[10-12]**

3. Azadirachta indica A.Juss. (Nimba) and Limonoids

Nimba exhibits potent antibiofilm activity attributed to limonoids such as azadirachtin, nimbin, and salannin.**[18,20]** Neem extracts inhibit initial bacterial adhesion, cell surface hydrophobicity, biofilm biomass accumulation, and virulence factor production.**[8,18]**

Neem demonstrates activity against biofilm-forming *Escherichia coli*, *Staphylococcus aureus*, and *Candida* species.**[17-18]** In Ayurveda, *Nimba* is described as *Tikta Rasa*, *Laghu–Ruksha Guna*, and is indicated for *Krimi*, *Vrana Shodhana*, and *Kaphaja Vyadhi*, supporting its biofilm-disruptive pharmacology.**[10-12]**

4. *Terminalia chebula* Retz. *(Haritaki)* and Hydrolysable Tannins

Haritaki, a constituent of *Triphala*, contains hydrolysable tannins such as chebulinic acid and gallic acid. These tannins precipitate surface adhesion proteins, disrupt EPS polymer stability, inhibit quorum-sensing signaling, and suppress multispecies biofilm maturation.**[11,12,19]**

Haritaki exhibits broad-spectrum antibiofilm activity against Gram-positive and Gram-negative organisms.**[19]** Its Ayurvedic properties—*Tridosha Shamaka*, *Ruksha*, and *Lekhana* - are particularly suited for reversing *Kapha*-dominant biofilm environments.**[10-12]**

5. *Tinospora cordifolia* (Wild.) Hook.f. & Thomsan *(Guduchi):* Dual Host–Biofilm Modulator

Guduchi functions as both an antimicrobial and a *Rasayana (rejuvenative therapy)* drug.**[20,21]** While its direct antibiofilm action is moderate, its principal contribution lies in immunomodulation, macrophage activation, cytokine balance restoration, and reduction of biofilm-associated inflammation. **[21,24,25]**

By enhancing host immune clearance and *Ojas*, *Guduchi* supports immune-assisted biofilm eradication, making it valuable in chronic biofilm infections.**[21]**

6. *Ocimum sanctum* L. *(Tulsi)* and Eugenol

Tulsi essential oil, rich in eugenol, disrupts bacterial membranes and inhibits surface colonization.**[24,25]** It demonstrates quorum-sensing inhibition,**[8,24]** reduced EPS synthesis,**[6,24]** and anti-inflammatory and antioxidant activity.**[4,24]**

Tulsi is particularly useful in respiratory biofilms associated with sinusitis and chronic bronchitis. **[6,9,24,25]**

7. Mechanistic Summary of Ayurvedic Antibiofilm Actions

Ayurvedic herbs inhibit microbial adhesion,**[18,19]** disrupt EPS matrix,**[2,6,19]** suppress quorum sensing,**[8,19]** inhibit efflux pumps,**[15]** destabilize cell membranes and potentiate host immunity. **[21,24–25]**

This multi-target pharmacology is ideally suited for the complex architecture of biofilm-associated infections.**[4,5]**

Ayurvedic Formulations and Integrative Therapeutic Model for Biofilm-Associated Infections

While single-herb interventions demonstrate promising antibiofilm effects, Ayurveda traditionally emphasizes polyherbal synergy, systemic correction, and local purification in the management of chronic infective conditions.**[11,12]** Biofilm-mediated infections, characterized by persistence, recurrence, and resistance, require a multi-dimensional therapeutic strategy rather than antimicrobial monotherapy.**[4,5,7,10]** The Ayurvedic approach to such conditions integrates *Shodhana* (detoxification), *Shamana* (pacification), *Rasayana* (rejuvenation), and local wound-cleansing measures, which together align well with modern integrative biofilm management.**[21,24,25]**

1. Classical Polyherbal Formulations with Antibiofilm Relevance

Triphala

Triphala remains the most extensively studied Ayurvedic formulation with documented antibiofilm & antibiotic-synergistic activity. Its actions include:

- Disruption of mature biofilm architecture
- Inhibition of quorum-sensing-controlled virulence
- Efflux pump modulation
- Enhancement of antibiotic sensitivity**[15]**

Recent evidence further supports the antimicrobial relevance of *Triphala*, demonstrating that nanoformulation of its constituents significantly enhances antibacterial efficacy and bioavailability, highlighting its translational potential in resistant infections.**[17]**

Classically, *Triphala* is described as *Deepana, Pachana, Lekhana, Rasayana,* and *Tridosha Shamaka*, making it systemically suitable for *Kapha*-dominant biofilm environments.**[10,12]**

Panchavalkala Kashaya

This formulation is especially indicated for *Dushta vrana* and *Sravi Vrana* (discharging chronic wounds).**[11]** Its tannin-rich constituents provide:

- Local biofilm matrix protein precipitation
- Reduction of microbial surface adherence**[6]**
- Promotion of healthy granulation
- Decrease in wound bioburden**[24–25]**

It is particularly relevant in diabetic foot ulcers, pressure sores, and post-surgical wound infections.

Khadirarishta

Khadirarishta is widely prescribed in chronic skin infections, fistulae, and non-healing ulcers, where biofilms frequently dominate.**[24,25]** It exerts:

- Systemic antimicrobial support**[15,21]**
- *Rakta Shodhana***[24,25]**
- *Kapha–Pitta* pacification**[10-12]**
- Anti-inflammatory and antioxidant effects**[24,25]**

Nimba–Haridra Yoga

The combination of *Neem* and *Haridra* is classically indicated for *Krimi, Kandu, Vrana*, and *Rakta Dushti.* **[10-12]** This formulation is particularly useful where:

- Recurrent skin infections dominate**[4,24,25]**
- Fungal–bacterial biofilms coexist**[17-18]**
- Persistent inflammatory discharge is present**[23,24,25]**

2. Local Therapeutic Procedures Targeting Biofilms

***Vrana Prakshalana* (Wound Irrigation)**

Use of decoctions such as Panchavalkala or Triphala for wound irrigation provides:

- Mechanical biofilm disruption
- Chemical destabilization of EPS**[6,11]**
- Reduction of microbial burden
- Enhancement of wound bed receptivity**[24,25]**

***Dhoopana* (Medicated Fumigation)**

Medicated fumigation using antimicrobial resins and herbs:

- Reduces surface microbial load
- Limits environmental biofilm contamination
- Plays a role in hospital infection control
- Is especially relevant in operating theaters and wound-care rooms**[24]**

Kṣhara* (alkaline cauterization) *Karma

Kṣhara (alkaline cauterization) possesses penetrating, scraping & debriding properties**[11,12]**:

- Breaks thick biofilm-laden necrotic tissue
- Facilitates healthy tissue regeneration
- Useful in fistulae, sinus tracts, and chronic infected granulation**[24]**

3. Systemic Therapy: *Rasayana* and Immune Restoration

Biofilm infections are sustained not only by microbial factors but also by host immune failure. **[4,6,24,25]** Therefore, *Rasayana* therapy forms a crucial pillar in their management.**[10-12]**

Key *Rasayana* Drugs

- ***Tinospora cordifolia (Guduchi)*** – Immunomodulation and macrophage activation**[21]**
- ***Emblica officinalis (Amalaki)*** – Antioxidant, tissue rejuvenation**[25]**
- ***Withania somnifera (Ashwagandha)*** – Stress modulation, immune strengthening**[22]**

These drugs enhance:

- Phagocytic capacity
- Cytokine regulation

- Tissue repair
- Ojas restoration**[10-12]**

All of which aid in biofilm clearance and relapse prevention.**[25]**

4. Clinical Framework for Integrative Biofilm Management

An evidence-informed integrative model for biofilm infections may be structured as follows.

Table 3: Evidence-informed integrative therapeutic model for biofilm-associated infections

Therapeutic Domain	Modern Approach	Ayurvedic Complement
Microbial killing	Antibiotics	Tikta–Katu Dravya[15]
Biofilm disruption	Enzymes, dispersal agents	Lekhana, Kṣhara (alkaline cauterization)[6,11,12]
Wound cleansing	Antiseptics	Panchavalkala, Triphala[25]
Host immunity	Nutritional support	Rasayana[10]
Recurrence prevention	Surveillance	Agni & Ojas correction[10-12]

This **layered therapeutic strategy** aligns well with the chronic, relapsing nature of biofilm-associated infections.**[1,4,5,7,10]**

5. Clinical Conditions Most Amenable to Integrative Biofilm Management

The integrative Ayurvedic–biomedical model is particularly relevant in:

- Diabetic foot ulcers
- Chronic osteomyelitis
- Recurrent urinary tract infections
- Dental plaques and periodontal disease
- Chronic otitis and sinusitis
- Catheter & implant-associated infections**[4,6,9]**

An integrative Ayurvedic–biomedical framework for the management of biofilm-associated infections is presented in **Figure 4**.

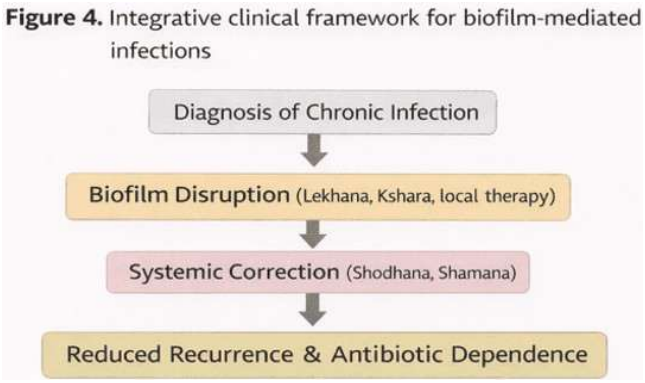


Figure 4. Integrative clinical framework for biofilm-mediated infections

Discussion

Clinical Implications and Translational Relevance

Biofilm-mediated infections represent a major clinical challenge due to their persistent nature, high relapse rates, and poor response to standard antibiotic therapy.**[1,4,5,7]**

The translational relevance of integrating Ayurvedic strategies into biofilm management lies in their multi-target, host-centered, and resistance-modifying actions.**[15,21,25]**

From a clinical standpoint, the incorporation of Ayurvedic antibiofilm approaches has several tangible implications:

1. Reduction in Chronicity and Recurrence

By disrupting the biofilm matrix (*Lekhana, Kṣhara* (alkaline cauterization)) and enhancing host immunity *(Rasayana),* Ayurveda may reduce bacterial persistence and recurrence after apparent clinical resolution.**[25]**

2. Adjunctive Enhancement of Antibiotic Efficacy

Herbal agents such as *Triphala, Haridra* and *Nimba* improve antibiotic penetration and suppress resistance mechanisms, potentially lowering the required antibiotic dose and duration.**[18]**

3. Improved Wound Healing Outcomes

Local therapies such as *Panchavalkala prakshalana, Vrana ropana dravya* and *Dhoopana* improve wound bed preparation, reduce microbial burden, and support granulation in biofilm-dominated chronic ulcers.**[24]**

4. Better Management of Device-Associated Infections

In catheter and implant-associated infections, Ayurveda-based local antisepsis and systemic *Rasayana* therapy may act as supportive measures to prevent recolonization.[4]

5. Public Health and Antibiotic Stewardship

Integrative approaches that reduce antibiotic dependency in recurrent, mild, or early-stage infections can significantly contribute to antimicrobial stewardship programs.**[14]**

Thus, the translation of Ayurvedic antibiofilm strategies into evidence-based integrative protocols has the potential to reshape chronic infection management and reduce resistance pressure at the population level.[15]

Research Gaps and Future Directions

Despite encouraging experimental findings, several critical gaps must be addressed before Ayurvedic antibiofilm strategies can be translated into routine clinical practice.

1. Standardization of Herbal Preparations

Most available antibiofilm studies rely on crude herbal extracts with considerable variability in phytochemical composition, which limits reproducibility and clinical applicability. Therefore, there is an urgent need for:

- **Phytochemical standardization** to ensure consistent bioactive profiles
- **Batch-to-batch quality control** to improve reliability and comparability of outcomes
- **Dose–response validation** to establish therapeutic efficacy and safety margins[14]

Addressing these challenges is essential for advancing Ayurvedic antibiofilm agents from experimental settings to evidence-based integrative clinical use.

2. Mechanistic Molecular Studies

Future research should prioritize in-depth mechanistic investigations to elucidate the molecular basis of Ayurvedic antibiofilm activity. Key areas include gene-expression profiling of quorum-sensing regulatory pathways, characterization of efflux pump modulation, enzymatic degradation of the extracellular polymeric substance (EPS) matrix by phytochemicals, & application of multi-omics approaches such as genomics, proteomics, & metabolomics to understand system-level effects.[21]

3. Synergy Studies with Priority Pathogens

Systematic synergy studies employing checkerboard assays and time–kill kinetics are required to evaluate the interaction of Ayurvedic agents with antibiotics against priority drug-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)–producing *Escherichia coli*, carbapenem-resistant *Klebsiella* species, and multidrug-resistant *Pseudomonas aeruginosa.*[21]

4. Clinical Trials with Antibiotic-Sparing Endpoints

Well-designed randomized controlled clinical trials are necessary to validate the translational efficacy of Ayurvedic antibiofilm interventions. Such trials should assess antibiotic-sparing endpoints, including reduction in antibiotic dose and duration, decreased recurrence rates, improved wound-healing outcomes, and enhanced quality-of-life measures.[25]

5. Safety and Herb–Drug Interaction Studies

Comprehensive pharmacovigilance and safety studies are essential to evaluate the long-term use of Ayurvedic antibiofilm agents. Critical aspects include assessment of hepatic and renal safety, investigation of cytochrome P450–mediated herb–drug interactions, and evaluation of potential additive or antagonistic effects when combined with conventional antibiotics.[21–23]

6. Systems Biology and Artificial Intelligence Integration

The integration of digital *Dravyaguna* databases with systems biology, artificial intelligence, and network pharmacology platforms has the potential to accelerate the identification and validation of novel antibiofilm phytocompounds and multi-target therapeutic networks.[15,21]

Limitations of Current Evidence

While the integrative antibiofilm potential of Ayurveda is promising, several limitations exist:

- Most existing data are in vitro or animal-based, with limited high-quality human trials.
- Variability in herbal extraction methods leads to poor reproducibility.
- Lack of standardized antibiofilm testing protocols for Ayurvedic drugs.
- Many studies focus on antibacterial activity without specifically addressing biofilm architecture or resistance reversal.
- Limited funding and interdisciplinary collaboration hinder large-scale translational research.

Recognizing these limitations is essential to ensure scientific rigor and responsible integration of Ayurveda into antimicrobial strategies.

Conclusion

Biofilm-associated antibiotic resistance has emerged as a major therapeutic challenge in contemporary infectious disease management. The ability of microorganisms to evade antibiotics, persist in hostile environments, and cause recurrent infections demands therapeutic strategies that extend beyond conventional antimicrobial monotherapy.

Ayurveda provides a rational, system-oriented complementary framework for addressing biofilm-associated infections through:

- *Lekhana* and *Kṣhara* for biofilm disruption
- *Tikta–Katu rasa* herbs for microbial suppression
- *Rasayana* for immune restoration
- Local therapies for wound and device-related biofilms
- Resistance-modifying synergy with antibiotics

Rather than functioning in opposition to modern biomedicine, Ayurveda aligns seamlessly with the current paradigm of integrative, multi-target, and host-directed therapy. When supported by rigorous experimental validation and clinical trials, Ayurvedic antibiofilm strategies have the potential to become a valuable component of global antimicrobial resistance containment programs.

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