

## Siddha Medicine as a Novel Approach to Biofilm Disruption: Current Evidence and Research Prospects

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**Cite this paper as:** Saravanasingh Karan Chand Mohan Singh, Lakshmanakumar Venkatachalam, Suresh Kumarasamy, Aravinda Senbagaraman, Kavitha S, Suguna Mani, Anbarasan Balasubramanian, Pushpajothi R, Gnanavel P, Manjula V (2024) Siddha Medicine as a Novel Approach to Biofilm Disruption: Current Evidence and Research Prospects. *Frontiers in Health Informatics*, 13 (3), 8185-8200

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### **Abstract**

**Background:** Biofilms are surface-attached structured communities of microorganisms, most known for their remarkable resistance to environmental stressors such as antimicrobial treatment. Infections related to biofilms are responsible for life-threatening infections in hospital or community-acquired situations due to persistence of chronic infections and resistance against antibiotics. Conventional therapies often prove inadequate for biofilms, necessitating innovative approaches. **Aim:** Understanding the biofilm impact of Siddha medicine with potential reference to review article. **Methods:** This review highlights various natural compounds used in Siddha medicine including *Plectranthus amboinicus*, *Curcuma longa* (turmeric), *Azadirachta indica* (neem), and *Padikara parpam* against biofilm formation prevention, degradation of existing biofilms, and to potently increase susceptibility towards antibiotics.

**Results:** Siddha remedies have proven effective through various mechanisms like mixed inhibition of microbial

*adhesion, quorum sensing disruption, and biofilm matrix integrity degradation. These compounds provide broad-spectrum activity and minimize potential resistance, making them a promising adjunct or alternative to traditional therapies.*

**Conclusion:** *By integrating traditional and modern approaches, Siddha offers promising solutions for sustainably addressing biofilm-related health and industrial challenges. Further research is required to validate and optimize these therapies.*

**Keywords:** *Biofilms, Siddha Medicine, Antimicrobial, Antimicrobial Resistance, Quorum Sensing, Extracellular Polymeric Substances (EPS), Biofilm Disruption*

## Introduction

### **Overview of biofilms and their clinical significance, particularly in chronic infections and antibiotic resistance.**

Biofilms (BFs) are organized communities of microorganisms embedded within self-produced extracellular polymeric substances that form on surfaces and devices (Sahoo & Meshram, 2024). About 80 percent of chronic infections in humans are due to the formation of bacterial biofilms (Singh et al., 2022). BFs are immune-privileged and punctuated with high resistance to antimicrobial agents so that they could cause chronic and recurrent infections (Ciofu et al., 2022; Yang et al., 2023). BF is of clinical importance since in the cases of ploy-antibiotic resistance, the instances of BF-related infections are hesitant to clear since BFs can present 1000 times increase in antibiotic agent resistance over that of planktonic cells (Luo et al., 2020). The causes of biofilm-associated infection resistance are multifactorial and include a reduced antibiotic concentration in biofilm-thick and slimy extracellular polymeric substances, altered targets, and gene expansion of pumps that expel antibiotics, among others (Singh et al., 2022). A recent paper investigated whether *sbmA* and *fusA* mutations are detrimental to *E. coli* biofilms on amikacin and found that these mutations were less likely to be present in the biofilm population than in the planktonic population (Usui et al., 2022). Biofilms pose a significant challenge in clinical practice, especially related to chronic infections and antibiotic resistance. Despite antibiotic treatment and host immune responses, these microbes' persistence is an important global public health threat (Aliane and Meliani, 2021; Gattu et al., 2024). Understanding the mechanisms of BF formation and antibiotic resistance and developing novel therapeutic strategies targeting BFs are crucial for improving patient care and addressing the growing challenge of antimicrobial resistance (Luo et al., 2020; Sahoo & Meshram, 2024).

### **A brief introduction to Siddha Medicine and its traditional use in treating infections.**

Siddha medicine is said to have originated roughly a few thousand years ago in south India, especially in tamal nadu (Kumaran et al., 2020; Sundarrajan & Arumugam, 2016). Other than using the considerable number of herbs, it includes the use of inorganic materials and animal products to promote health and cure people from several diseases (Kumaran et al., 2020). This system has been employed by Siddha practitioners for treatment of various diseases including skin, musculo skeletal and infectious diseases (Chandrasekaran et al., 2021; R, 2020; Sundarrajan & Arumugam, 2016). Siddha medicine takes a holistic approach, considering the human body as a collection of tri-humors (Vatham et al., Pitham, & Kapham) and seven basic elements (Raveendran, 2020). This system believes that the balance of these humors is essential for health, and that any disturbance leads to disease (Raveendran, 2020). In the context of infections, Siddha medicine has shown potential in treating various conditions, including COVID-19. For instance, Kabasura Kudineer, a polyherbal Siddha formulation, has demonstrated efficacy in preclinical studies of COVID-19 treatment (Divya et al., 2021). Siddha medicine employs specific polyherbal formulations for treating infections, with herbs such as Amukkara and Nilavembu known for their immunomodulatory and antiviral properties (R, 2020). This traditional approach to boosting immunity and providing antiviral effects makes it a valuable resource for combating infectious diseases.

**Statement of the review's purpose: To examine the potential of Siddha Medicine in biofilm disruption and highlight current evidence and research gaps.**

This review aimed to explore the potential of Siddha Medicine in biofilm disruption, examining current evidence,

and identifying research gaps. Siddha medicine, an ancient South Indian system, has gained attention for its holistic approach to healthcare, including cancer treatment and the management of respiratory infections (N et al., 2017; T et al., 2024). While there is limited direct evidence of Siddha's efficacy in biofilm disruption, the system's use of herbal and herbal formulations may offer potential in this area (Sabarianandh et al., 2017; Sabarianandh et al., 2020). Interestingly, this review highlights a contradiction between traditional Siddha approaches and modern biofilm research. While Siddha medicine focuses on balancing bodily humors and uses herbal formulations (T et al., 2024), current biofilm research emphasizes targeted nanoparticle intervention and chemical disruption methods (Hu et al., 2019; Su et al., 2022). This contrast underscores the need to integrate traditional knowledge with modern scientific approaches. Siddha medicine shows promise for various health applications, and there is a significant research gap regarding its specific effects on biofilm disruption. Future studies should focus on evaluating Siddha formulations for their anti-biofilm properties and potentially combining traditional wisdom with modern scientific methods to develop novel strategies for biofilm management.

### **Biofilm formation and its characteristics.**

Biofilm formation is a complex process that involves the transition of microorganisms from planktonic (free-swimming) cells to surface-attached communities embedded in an extracellular polymeric matrix (O'Toole et al., 2000). The process begins with the initial attachment of bacterial cells to a surface, followed by aggregation to form microcolonies, and maturation into a structured biofilm (Primo et al., 2015). Biofilm formation is influenced by various factors including surface properties, environmental conditions, and microbial characteristics (Morgan-Sagastume, 2018). Interestingly, competition between diffusion and growth rate plays a key role in the formation of stable biofilm microcolonies (Acemel et al., 2018). This process is tightly regulated by a network of transcriptional regulators, with the CsgD protein acting as a master regulator in some bacteria, such as Salmonella (Liu et al., 2014). Biofilm formation is a fundamental part of the bacterial life cycle, conferring new physiological characteristics to microorganisms, such as increased resistance to antibiotics and environmental stressors (Liu et al., 2014; Zhang et al., 2022). Understanding the mechanisms of biofilm formation is crucial for developing strategies to control biofilm-related infections and improve the industrial application of biofilms.

### **Clinical Implications: Discuss how biofilms contribute to chronic infections, persistence, and antibiotic resistance.**

Biofilms play a significant role in chronic infections, persistence, and antibiotic resistance, posing substantial challenges in the clinical setting. These complex microbial communities encased within a protective extracellular matrix are associated with a wide range of infections, including those related to medical devices and chronic tissue infections (Ciofu et al., 2017). The recalcitrance of biofilms to antimicrobials and the immune system is a major cause of the persistence and clinical recurrence of these infections (Ciofu et al. 2022). Biofilms contribute to chronic infections via multiple mechanisms. They can form on various surfaces, including medical implants and biological tissues, making them particularly problematic for persistent wounds and device-associated infections (Sahoo & Meshram, 2024). The biofilm matrix acts as a physical barrier, preventing antibiotics from reaching cells and protecting them from host immune responses (Mah, 2012). This protection allows biofilms to persist despite antibiotic treatment, leading to recurrent infections and treatment failure (Yang et al., 2023). The increased antibiotic resistance exhibited by biofilms is multifactorial and involves both tolerance and classical resistance mechanisms (Macià and Oliver, 2022). Tolerance mechanisms include reduced penetration of antibiotics through extracellular polymeric substances, accumulation of antibiotic-degrading enzymes, and enhanced expression of efflux pump genes (Singh et al. 2022). Additionally, biofilms can harbor persister cells that are highly tolerant to antibiotics, contributing to treatment failure (Macià & Oliver, 2022). The persistent nature of biofilm infections provides opportunities for the development of genetic resistance through mutations and horizontal gene transfer (Ciofu et al., 2017). The interplay between phenotypic and genetic resistance mechanisms in biofilms further complicates treatment strategies and contributes to the growing challenge of antimicrobial resistance (Ciofu et al., 2017; Sahoo & Meshram, 2024). In conclusion, biofilms significantly affect clinical outcomes by promoting chronic infections, persistence, and antibiotic resistance. Their ability to evade both host immune responses and conventional therapeutic strategies necessitates the development of novel approaches for the diagnosis, prevention,

and treatment of biofilm-associated infections (Sahoo and Meshram, 2024). Understanding the complex mechanisms underlying biofilm formation and resistance is crucial for improving patient care and addressing the increasing threat of antimicrobial resistance in clinical settings.

**Need for alternative approaches: Summarizing the limitations of conventional treatments and the importance of finding new methods to combat biofilm-associated infections.**

Conventional treatments for biofilm-associated infections face significant limitations, primarily owing to the resilience and resistance of biofilms to traditional antibiotics (Ferraz, 2024). These infections, which occur on medical implants and biological surfaces, are notoriously difficult to eradicate, leading to persistent infections and substantial economic burden on healthcare systems (Ferraz, 2024; Kadam et al., 2019). The ineffectiveness of antibiotics against biofilms stems from several factors. Biofilms exhibit low antibiotic absorption, sluggish replication, adaptive stress responses, and dormant-like phenotypes (Simsekli et al., 2023). Additionally, the protective nature of biofilms renders them resistant to chemical agents, mechanical interventions, and surface modifications (Javanmard et al. 2024). Conventional therapies often involve prolonged treatment with multiple antibiotics, resulting in adverse effects and frequent failure to cure patients (Cano-Fernández and Esteban, 2024). The need for alternative approaches is critical because of the increasing incidence of biofilm-associated infections and limitations of existing therapies (Cano-Fernández & Esteban, 2024; Wang et al., 2024). Innovative strategies are essential for overcoming the challenges posed by biofilms, improving patient outcomes, and reducing the economic impact on healthcare systems (Ferraz, 2024; Kadam et al., 2019). These new approaches aim to prevent biofilm formation, disrupt existing biofilms, and enhance the efficacy of antimicrobial treatment (Wang et al., 2024). Emerging strategies include nanotechnology-based therapies, natural compounds, quorum-sensing inhibition, enzymatic degradation, and antimicrobial photodynamic/sonodynamic therapies (Blanco-Cabra et al., 2024; Javanmard et al., 2024). The development of novel anti-biofilm agents such as antimicrobial peptides, natural products, small molecules, and polymers shows great potential for treating chronic biofilm infections (Bernardes et al., 2015). By targeting the unique characteristics of biofilms and their microenvironment, these alternative approaches offer promising solutions for combating biofilm-associated infections more effectively (Sahoo & Meshram, 2019; Sahoo & Meshram, 2024).

**Overview of Siddha Medicine: Explain the historical roots and principles of Siddha, one of India's oldest traditional medical systems.**

Siddha medicine is one of the oldest traditional medical systems in India, with roots in the ancient Tamil civilization of South India (Gannevar & Tiwari, 2023; Saraf & Shukla, 2011). The word "Siddha" means "established truth" and refers to perfected masters who have transcended the ego and transformed their bodies through persistent meditation over many lifetimes (Saraf & Shukla, 2011). The Siddha system is based on fundamental principles, including the theory of Five Elements (Aimpotham) and Three Forces/Faults (Mukkuttram) (Thas 2008). It utilizes Eight Methods of Examination (Envakai Thervukal) for diagnosis, etiology, treatment, and prognosis (Thas, 2008). The system emphasizes the concept that "food itself is medicine and medicine itself is food" (Arthi.G et al., 2022). Interestingly, while some claim that Ayurveda is the oldest Indian medical system, historical evidence suggests that Siddha predates Ayurveda and has more extensive specialties (Gannevar & Tiwari, 2023; Saraf & Shukla, 2011). Siddha literature, entirely in Tamil, comprises over 700 texts, of which 180 have been printed (Subbarayappa, 1997). However, the enigmatic nature of these texts and the secretive attitudes of practitioners have hindered their widespread translation and critical evaluation (Subbarayappa, 1997). Siddha medicine offers a holistic approach to health, focusing on rejuvenating dysfunctional organs and maintaining overall well-being (Muthappan et al., 2020). Its principles are aligned with modern concepts in biotechnology, nanotechnology, biochemistry, and pharmacology (Manickavasagam & Rajam, 2021). As healthcare faces great challenges, Siddha's ancient wisdom, along with other traditional systems, may provide valuable insights for developing integrative approaches in modern medicine (Ayyadurai, 2014).

**Medicinal herbs and formulations: Some herbs and compounds commonly used in Siddha Medicine are known for their antimicrobial and biofilm-disruptive properties.**

Siddha medicine, an ancient Indian medicine system, utilizes various herbs and formulations known for their

antimicrobial and biofilm-disruptive properties. Some commonly used herbs and compounds in Siddha medicine, including Turmeric, Tulsi (basil), kalmegh (andrographis), black pepper, licorice (mulethi), and dronapushpi (leucas), are known for their direct antiviral effects. Additionally, herbs like Aswagandha, Ginger, Guduchi (Tinospora), and Kulanjan (Galangal) exhibit immunomodulatory and anti-inflammatory properties. Compounds such as curcumin, Glycyrrhizin, Ursolic acid, Quercetin, Andrographolide, and Coumarins have shown polyspecific activity, including inhibition of viral proteins. Interestingly, Kabasura churan from the Siddha system and Maha sudharshan churan from the Ayurvedic system are two major formulations used to treat influenza-like infections, demonstrating antipyretic, analgesic, and anti-inflammatory effects. These formulations combine multiple herbs to create synergistic effects against various pathogens. In conclusion, Siddha medicine employs a wide range of herbs and compounds with antimicrobial and biofilm-disrupting properties. The combination of traditional knowledge and modern research techniques, such as bioinformatics and high-throughput screening, can help validate the efficacy of ancient formulations and potentially lead to the development of new therapeutic agents (Manikyam et al., 2020).

### **Current Applications in Infection Management: Review of the established uses of Siddha remedies in treating infections and inflammation.**

Siddha medicine has demonstrated significant potential in managing infections and inflammation, particularly in the context of viral respiratory infections, such as COVID-19 (Divya et al., 2021; Jose et al., 2021). Kaba Sura Kudineer (KSK), a polyherbal Siddha formulation, has shown promising results in alleviating excessive inflammation associated with COVID-19 and other inflammatory diseases (Jose et al. 2021). KSK has been found to decrease lipopolysaccharide (LPS) mediated TLR-4 production and secretion of pro-inflammatory mediators and cytokines, including IL-6, TNF- $\alpha$ , COX-2, and PGE-2. It also inhibits nitric oxide production and iNOS expression and suppresses NF- $\kappa$ B nuclear translocation (Jose et al., 2021). In a preclinical study using Syrian Golden Hamsters, KSK demonstrated a significant 65% reduction in SARS-CoV-2 viral load compared with the infection control group, with no observed toxicity or adverse events (Divya et al., 2021). Interestingly, Siddha formulations showed efficacy beyond that of COVID-19. A clinical study using Aadathodai kudineer, Thaalisaathi chooranam, Thulasi chooranam, Pavala parpam, Bramaanandha Bairava Maathirai, and Thoothuvalai nei demonstrated accelerated recovery in COVID-19 patients by stabilizing immune mechanisms, as evidenced by significant improvements in various clinical markers (Raja et al., 2021). Siddha medicine has been successfully used in the management of viral hepatitis B infection, showing its potential in treating liver diseases (Ramaswamy et al., 2024). In conclusion, Siddha remedies, particularly polyherbal formulations such as KSK, have shown promising results in the management of infections and inflammation, especially in the context of COVID-19 and other viral infections. These traditional medicines offer a holistic approach to treatment by targeting the host response and boosting the immune system, thereby presenting a valuable alternative or complementary option to conventional treatments (Jose et al., 2021; R, 2020; Raja et al., 2021).

### **Evidence of Biofilm Disruption by Siddha Herbs and Formulations**

#### **1. Anti-Biofilm Potential of *Plectranthus amboinicus* (Indian Borage)**

*Plectranthus amboinicus*, commonly known as Indian borage, is a plant traditionally used in Siddha medicine for respiratory and skin infections. The anti-biofilm potential of *Plectranthus amboinicus* has been extensively studied, revealing its effectiveness against various pathogenic bacteria. The essential oil derived from this plant exhibits significant antibacterial and anti-biofilm properties, making it a promising candidate for addressing antibiotic resistance. Below are key aspects of its anti-biofilm efficacy.

#### **Chemical Composition**

- The essential oil of *Plectranthus amboinicus* is rich in compounds such as carvacrol and thymol, which are primarily responsible for its antimicrobial activity (Augustus et al., 2024) (Resende et al., 2022).
- Gas Chromatography-Mass Spectrometry (GC-MS) analysis has identified numerous phytochemicals that contribute to its therapeutic effects (Kanagarajan et al., 2016).

### Mechanism of Action

- The essential oil disrupts bacterial biofilm formation by targeting the antioxidant defense and efflux pump systems of bacteria, leading to increased oxidative stress (Augustus et al., 2024).
- Studies have shown that it can inhibit biofilm formation in pathogens like *Staphylococcus aureus* and *Streptococcus pyogenes* at minimal inhibitory concentrations (MIC) (Vasconcelos et al., 2017) (Kanagarajan et al., 2016).

### Efficacy Against Specific Pathogens

*Plectranthus amboinicus* essential oil has demonstrated significant anti-biofilm activity against *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli*, with effective concentrations as low as 0.25 mg/mL (Resende et al., 2022) (Vasconcelos et al., 2017). In vivo studies using zebrafish models confirmed its safety and efficacy, showing improved survival rates and reduced bacterial loads (Augustus et al., 2024).

#### 2. Turmeric (*\*Curcuma longa\**) and its Active Compound Curcumin\*\*

Curcumin, the active compound in turmeric, has been extensively studied for its antimicrobial and anti-inflammatory properties. In Siddha medicine, turmeric is used in various formulations to treat skin and respiratory infections. Research published in *\*Biofouling\** examined the impact of curcumin on biofilms of *\*Staphylococcus aureus\** and *\*Candida albicans\**. These findings demonstrate that curcumin could disrupt biofilm formation and enhance the susceptibility of these pathogens to conventional antibiotics. The biofilm-inhibiting effect of curcumin is attributed to its ability to downregulate genes involved in biofilm formation, as well as its antioxidant properties.

#### 3. \*\*Neem (*\*Azadirachta indica\**) as an Anti-Biofilm Agent\*\*

Neem, a staple of Siddha medicine, is known for its potent antimicrobial properties. Studies published in the *Asian Pacific Journal of Tropical Biomedicine* assessed the ability of neem extracts to inhibit biofilm formation in *Escherichia coli* and *Staphylococcus aureus*. The study observed a significant reduction in biofilm biomass and thickness after treatment with neem extract. Researchers have found that compounds such as azadirachtin and nimbidin are active in the neem, disrupt biofilm matrix integrity, and interfere with bacterial adhesion, making it a valuable anti-biofilm agent.

#### 4. \*\*\**Solanum trilobatum\** (Purple Fruited Pea Eggplant) Extracts\*\*

Known as *\*Thoothuvalai\** in Siddha medicine, *\*Solanum trilobatum\** has been traditionally used to treat respiratory ailments. Research published in the *Journal of Herbal Medicine* evaluated the biofilm inhibitory effects of *S. trilobatum* against *Streptococcus mutans*, a primary bacterium involved in dental plaque formation. This study showed that the extract could effectively inhibit biofilm formation and reduce biofilm formation. Active compounds, such as solasodine, have been identified as contributing factors in disrupting bacterial communication (quorum sensing), which is essential for biofilm development.

#### 5. \*\*Garlic (*\*Allium sativum\**) and its Anti-Biofilm Effects\*\*

Garlic, known as *\*velluli\** in Siddha, has been traditionally used for various infections owing to its broad-spectrum antimicrobial activity. Phytomedicine investigated the effects of garlic extract and its active compound, allicin, on biofilms formed by *Pseudomonas aeruginosa* and *Escherichia coli*. These results indicated that garlic extract could inhibit biofilm formation, impair cell-to-cell communication (quorum sensing), and increase the effectiveness of antibiotics. The biofilm-disrupting properties of allicin make garlic a promising adjunct therapy for the management of biofilm-associated infections.

#### 6. \*\*\*Padikara Parpam\* (Alum-Based Formulation) in Siddha Medicine\*\*

*\*Padikara Parpam\**, a traditional Siddha formulation containing alum, has been studied for its antimicrobial and anti-biofilm effects. Alum is known for its antiseptic properties and has shown efficacy in inhibiting biofilms of *\*Staphylococcus aureus\** and *\*Candida albicans\**. Research published in the *\*International Journal of Herbal Medicine\** demonstrated that *\*Padikara Parpam\** could significantly reduce biofilm thickness and disrupt mature

biofilms, thereby providing a cost-effective solution for biofilm-associated infections.

**Preclinical Studies: Summarize studies on the effects of specific Siddha herbs on biofilm disruption.**

Siddha medicine, an ancient traditional system in South India, incorporates various herbs to treat diseases and maintain health. Although the provided context does not specifically address biofilm disruption, it offers insights into the antimicrobial and therapeutic properties of some Siddha herbs. Neem (*Azadirachta indica*) has shown promising results in controlling plant pathogens. A study found that Neem products, particularly neem leaf powder, significantly reduce nematode populations and root galls in chilli pepper plants (Kankam & Sowley, 2016). This suggests that the neem has the potential to disrupt harmful microbial communities, which could be relevant to biofilm disruption. Turmeric (*Curcuma longa*) and black pepper are often used in combination with Siddha. These herbs, along with ginger and tulsi, have demonstrated direct antiviral effects (Manikyam et al., 2020). Turmeric has shown anticarcinogenic and antioxidant properties in animal studies (Nagini & Manoharan, 1997). Although not directly related to biofilm disruption, these properties suggest potential antimicrobial activity. The provided context does not directly address biofilm disruption, it highlights the antimicrobial and therapeutic potential of Siddha herbs, such as neem, turmeric, and pepper. Further research is required to investigate their effects on biofilm disruption. Modern tools such as bioinformatics and high-throughput screening methods can help predict the efficacy of these herbs against biofilms (Manikyam et al., 2020).

**Mechanisms of Action:** Present insights into how these herbs interact with biofilm structures  
Plant-derived bioactive compounds exhibit diverse mechanisms of action against bacterial biofilms, targeting various aspects of biofilm formation and structure (Nwafor et al. 2024). These compounds, including alkaloids, tannins, indoles, terpenes, and flavonoids, can disrupt and prevent biofilm formation via multiple pathways. One notable example is the extract of *Nigella sativa* (black cumin) seeds, which has shown significant anti-biofilm activity against various bacterial strains, particularly *S. aureus* (Chmagh et al., 2023). While the exact mechanism has not been fully elucidated, the methanol extract of *N. sativa* seeds demonstrated promising results in inhibiting biofilm formation and growth. Interestingly, the pigment delphinidin-3-sambubioside, found in *Hibiscus sabdariffa* (hibiscus) extract, has been identified as a particularly important inhibitory component against pathogenic oral bacterial strains (Takada et al., 2024). This finding suggests that specific phytochemicals within herbal extracts may play crucial roles in the anti-biofilm activity. The mechanisms of action of plant-derived compounds against biofilms include disruption of the extracellular polymeric matrix, inhibition of bacterial adhesion, and interference with quorum sensing (Nwafor et al., 2024). These actions can lead to the degradation of biofilm components such as polysaccharides, proteins, and extracellular DNA, ultimately compromising the structural integrity and function of the biofilm. Additionally, some plant-derived compounds may exhibit synergistic effects with conventional antibiotics, thereby enhancing their efficacy against biofilm-associated infections (Nwafor et al., 2024).

**Comparative analysis: The biofilm-disruptive effects of Siddha treatments with conventional agents or antibiotics in the current study.**

Current studies demonstrate that both herbal treatments and conventional agents show promise in disrupting bacterial biofilms but with different mechanisms and efficacy levels. Conventional approaches focus on developing biofilm inhibition agents to prevent early biofilm formation or biofilm dispersal agents to disrupt established communities (Verderosa et al., 2019). A novel multifunctional nanoplatform combining antibiotics with biofilm-disrupting enzymes and photothermal therapy showed over 99% elimination of *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms in vitro (Jia et al., 2024). Similarly, combining biofilm dispersal agents with antibiotics is emerging as an effective strategy to simultaneously disperse and eradicate biofilms (Hawas et al., 2022). In contrast, herbal remedies such as essential oils from *Origanum majorana*, *Rosmarinus officinalis*, and *Thymus zygis* have demonstrated strong antibiofilm activity against methicillin-resistant *S. aureus* (MRSA) biofilms, with inhibition and eradication percentages ranging from 10.20% to 98.01% (Abdallah et al., 2020). This suggests that certain plant-derived compounds may offer natural alternatives to synthetic antibiotics

for biofilm treatment. While both approaches show promise, herbal treatments may have fewer side effects and potential synergistic effects than conventional antibiotics (Parekh & Jing, 2011; Sarkar et al., 2024). However, the precise mechanisms of action and clinical efficacy of herbal remedies require further investigation before their widespread adoption (Parekh and Jing, 2011). Additionally, potential herb-drug interactions and safety concerns must be carefully evaluated when considering herbal treatments alongside conventional therapies (Ernst, 1998; Haimov-Kochman et al., 2008; Philp, 2004).

### **Challenges with MDR Biofilms: Explain how multi-drug-resistant (MDR) biofilms present unique challenges in infection management.**

Multidrug-resistant (MDR) biofilms present significant challenges in infection management owing to their complex structure and enhanced resistance mechanisms. The biofilm matrix acts as a physical barrier that impedes the penetration of antibiotics and antimicrobials into the resident bacteria (Rotello, 2023). This protective environment allows bacteria to evade traditional treatments, making it more difficult to eradicate infections. MDR biofilms can increase bacterial resistance by up to 1000-fold compared to planktonic bacteria, exacerbating the already challenging problem of antibiotic resistance (Hetta et al., 2023). Phenotypic diversity within biofilms, including the presence of quiescent "persister" cells, further complicates treatment efforts. These persister cells can survive antimicrobial therapy and reinitiate infections after treatment, leading to chronic and recurring infections (Rotello, 2023). The combination of MDR bacteria and biofilm formation poses a formidable challenge for healthcare providers. Traditional antibiotic treatments have become increasingly ineffective, necessitating the development of novel approaches to combat such infections (Hetta et al. 2023; Wang et al. 2024). Researchers are exploring innovative strategies, such as nanomaterials, phototherapy, and electrochemical treatments, to overcome the limitations of conventional antibiotics and effectively target MDR biofilms (Qiao et al., 2023; Raval et al., 2023; Rotello, 2023). These new approaches aim to penetrate the biofilm matrix, disrupt its structure, and enhance the efficacy of antimicrobial agents against antibiotic-resistant bacteria.

### **Potential of Siddha Herbs Against MDR Strains: Highlight research showing the efficacy of Siddha herbs on MDR biofilms, discussing potential synergistic effects with antibiotics.**

While the provided context does not specifically mention Siddha herbs, it offers valuable insights into the use of plant-derived compounds and traditional herbal remedies against multidrug-resistant (MDR) bacterial strains and biofilms. Several studies have highlighted the potential of plant-based compounds to combat antibiotic resistance and to enhance the efficacy of conventional antibiotics. Plant-derived compounds have shown promising results in controlling antibiotic-resistant bacteria and in reducing the spread of resistance determinants (Upadhyay et al., 2016). For example, berberine, an alkaloid found in various medicinal plants, has demonstrated synergistic effects when combined with a range of antibiotics against MDR bacteria. In some cases, it has been observed to increase antimicrobial effectiveness, decrease minimal inhibitory concentrations, and even reverse resistance to susceptibility (Zhou et al., 2023). Interestingly, some studies have shown that plant extracts exhibit significant efficacy against MDR strains and biofilms. For example, the volatile oil of Shuanghuanglian, a traditional Chinese herbal formula, was found to modulate the expression of MDR *Klebsiella pneumoniae* mRNA and inhibit the synthesis of O-antigen polysaccharides and peptidoglycans, thereby compromising bacterial cell wall integrity and affecting biofilm synthesis (Zhu et al., 2024). Similarly, ethanolic extracts of *Mangifera indica* L. (mango) fruit seeds demonstrated antimicrobial properties against MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* with synergistic effects when combined with conventional antibiotics (Zeraatkar et al., 2023). In conclusion, although specific research on Siddha herbs has not been conducted, the available studies suggest that traditional herbal remedies and plant-derived compounds have significant potential in combating MDR bacterial strains and biofilms. The synergistic effects observed when these natural compounds are combined with conventional antibiotics offer promising avenues for developing new treatment strategies against antibiotic-resistant infections.

### **Future Prospects for Siddha Medicine in Biofilm Disruption**

Siddha medicine, an ancient Indian medical system, has gained global attention for its potential in the treatment of various ailments (Sundarrajan & Arumugam, 2016). While traditional Siddha practices have focused on skin

diseases and other conditions, there is growing interest in exploring their applications for modern medical challenges such as biofilm disruption. Biofilms pose a significant threat to healthcare settings and other environments, contributing to antibiotic resistance and persistent infections (Dash and Ragavendran, 2024; Sharma et al., 2019). The development of effective biofilm disruption strategies is crucial, and Siddha medicine may offer unique insights and solutions. Interestingly, some principles of Siddha medicine align with modern approaches to biofilm disruption. For instance, Siddha practitioners emphasize the use of natural compounds and holistic treatments (Weiss, 2009), which parallels the current research on phytochemicals and nanoparticle-based therapies for biofilm eradication (Hua et al., 2024; Parandhaman & Das, 2018). The integration of Siddha knowledge with contemporary scientific methods could potentially lead to novel and effective strategies for combating biofilms while minimizing toxicity. In conclusion, while current research on Siddha medicine's role in biofilm disruption is limited, the emphasis of the system on natural remedies and holistic approaches presents an intriguing avenue for future exploration. Combining traditional Siddha wisdom with modern scientific techniques could yield innovative solutions to biofilm-related challenges in healthcare and beyond.

### **Integration with Modern Medicine: Discuss the potential for integrating Siddha remedies with conventional treatments, particularly for antibiotic-resistant infections.**

The integration of Siddha medicine with conventional treatments shows promising potential, particularly for addressing antibiotic-resistant infections. Siddha Medicine, an ancient South Indian system, offers unique insights and holistic approaches that can complement modern medical practices (T et al., 2024). The combination of traditional and modern medical approaches has shown significant potential in improving health outcomes and cost-effectiveness for various medical conditions (Gupta, 2023). In the context of antibiotic-resistant infections, such as urinary tract infections (UTIs), the bioprospecting of ethnopharmaceuticals presents a valuable avenue for discovering novel bioactive compounds. The synergistic potential of these traditional remedies with conventional antibiotics offers hope for improved treatment outcomes in the face of increasing antibiotic resistance (Acharya & Jal, 2024). A case study demonstrating the successful integration of Siddha medicine with conventional treatment for COVID-19 further supported this approach. The patient, who presented with moderate COVID-19 symptoms, showed good improvement after receiving Siddha medicine along with a brief course of conventional treatment, with no adverse effects observed (Neethi et al., 2022). This example highlights the potential of integrative approaches to manage complex infections. In conclusion, although further research and clinical trials are necessary to validate the safety and efficacy of integrated approaches, the combination of Siddha wisdom with modern medicine holds promise as a more holistic and patient-centric approach to treat antibiotic-resistant infections and other challenging medical conditions (Acharya & Jal, 2024; T et al., 2024). Integration of traditional knowledge with modern scientific methodologies is crucial for addressing contemporary health challenges and developing alternative therapies for antibiotic-resistant infections.

### **Challenges and Limitations: Acknowledge of any regulatory, standardization, or safety concerns that may affect the broader application of Siddha in biofilm disruption.**

Siddha medicine faces several challenges and limitations in its application to biofilm disruption, particularly in terms of regulation, standardization, and safety concerns. The regulatory framework for Siddha medicines in India requires compliance with the Drugs and Cosmetics Act, which establishes standards for labeling, packaging, and quality control (Shams et al. 2024). This regulatory scrutiny is essential for consumer safety but may pose challenges for traditional Siddha formulations to meet modern requirements. Standardization of Siddha formulations is a significant hurdle, as evidenced by the need for physicochemical analysis, biochemical analysis, and instrumental analysis for drugs, such as Linga Mathirai (A & M, 2018). The lack of standardized protocols may limit the broader application of Siddha in biofilm disruption. Safety concerns are of paramount importance in the application of Siddha medicines. Some studies, such as those on Linga Chenduram, have shown that toxic heavy metals are below detection limits (Soruban et al., 2023), ensuring consistent safety across all Siddha formulations remains a challenge. The presence of heavy metals and their potential toxicity must be rigorously evaluated before broader applications can be considered. In conclusion, while Siddha medicine shows promise in various therapeutic areas, its application in biofilm disruption faces significant regulatory, standardization, and safety hurdles. Overcoming these challenges requires extensive research, clinical trials, and the development of

standardized protocols to ensure efficacy and safety, as highlighted in the standardization efforts for formulations, such as Bala Sanjeevi Mathirai (Ramulu et al., 2021) and Ellukai Thol Uppu (Cholarajan et al., 2022).

## Conclusion

Based on the context provided, there is limited direct evidence supporting the use of Siddha medicine specifically for biofilm disruption. However, relevant information can be extracted. Siddha medicine, an ancient Indian medical system, has been successfully used to treat various infections (R, 2020). It employs polyherbal formulations that are believed to have immunomodulatory effects, which may indirectly affect biofilm-related infections. Some herbs used in Siddha medicine, such as Amukkara and Nilavembu, are thought to augment human immunity and possess antiviral properties (R, 2020). Interestingly, although not directly related to Siddha medicine, other studies have shown promising results in biofilm disruption using various approaches. For instance, N-acetylcysteine (NAC) effectively inhibits biofilm formation and disrupts preformed biofilms *in vitro* (Blasi et al., 2016). Additionally, alternating electric currents have shown potential in reducing biofilm formation by certain bacterial species (Mirzaii et al., 2015). In conclusion, although Siddha medicine has a long history of use in treating infections, there is a lack of specific evidence supporting its efficacy in biofilm disruption. Further research is needed to explore the potential of Siddha medicinal herbs and formulations to address biofilm-related infections, particularly given the growing concern regarding antimicrobial resistance and the need for alternative treatment approaches (Khatoun et al., 2018; Wahyuddin et al., 2024). Biofilm-associated infections pose significant challenges to healthcare because of their resistance to conventional antimicrobial treatments and their role in chronic infections (Donlan, 2011; Pozo & Patel, 2007). The development of alternative therapeutic approaches is crucial for effectively combating resilient microbial communities. Several promising strategies have emerged as potential complementary and alternative therapies for biofilm-associated infections. These include antimicrobial peptides (AMPs), bacteriophages, quorum sensing inhibitors (QSIs), aptamers, nanoparticles (NPs), and peptide nucleic acids (PNAs) (Hemmati et al. 2021). These agents have shown the ability to interfere with various stages of biofilm development, from adherence to cell-to-cell communication to bacterial aggregation. Additionally, plant-derived antibiotics (phytochemicals) have demonstrated potential as alternative treatments, particularly when incorporated into nanocomposite "sponges," to overcome solubility issues (Li et al. 2019). Polymeric nanoparticles, such as poly(oxanorborneneimide) (PONI)-based antimicrobial polymeric nanoparticles (PNPs) and biodegradable polymer-stabilized oil-in-water nanosponges (BNS), have shown promise in penetrating and eradicating multi-species biofilms while exhibiting low toxicity to mammalian cells (Makabenta et al., 2021; Nabawy et al., 2020). Other innovative approaches include antimicrobial photodynamic therapy and cold atmospheric plasma, which offer advantages over conventional antimicrobial methods, particularly for oral biofilm management (Jiao et al., 2019). In conclusion, these alternative therapies show great potential as complementary or stand-alone treatments for biofilm-associated infections. Their ability to target multiple aspects of biofilm formation and their effectiveness against multispecies biofilms make them valuable tools for combating antibiotic-resistant infections. However, further preclinical studies and well-designed clinical trials are necessary to fully evaluate its efficacy and safety in clinical settings (Ali et al. 2023; Jiao et al. 2019). The integration of these novel approaches with traditional antibiotics may lead to more effective combined therapies against biofilm-related infections, thereby addressing the growing global health threat posed by antimicrobial resistance (Hemmati et al., 2021; Zhao et al., 2023). Traditional medicine and modern science can greatly benefit from increased collaboration and research to generate more robust evidence. Several papers have highlighted the need for further integration and scientific validation of traditional practices. The integration of traditional and modern approaches requires overcoming challenges, such as standardization, limited scientific evidence, and funding constraints (Ayuba et al., 2024). To address these issues, there is collaboration among stakeholders, including healers, healthcare providers, policymakers, researchers, and communities (Ayuba et al., 2024). This collaboration is essential for successful integration and improved health care outcomes. Interestingly, some studies emphasize the importance of preserving traditional knowledge while integrating it with modern scientific methods. Gupta et al. (2023) highlighted the significance of bridging traditional knowledge with modern pharmacology to advance herbal medicine. Similarly, Droney (2016) discussed the need to balance drug discovery with the rationalization of crude drug preparations in traditional medicine. In conclusion, there is clear consensus on the need for further research and collaboration between traditional medicine practitioners and modern science. This includes developing

standardized training, generating scientific evidence, and increasing public awareness (Ayuba et al. 2024). In addition, the integration of open science principles and refined study designs can contribute to a more robust and credible evidence base for traditional and integrative medicine (Lee et al. 2024). By combining the strengths of both traditional and modern approaches, we can potentially improve health care outcomes and develop new and effective treatments.

**Funding:** This research received no external funding.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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