Plant-Derived Compounds as Inhibitors of Quorum Sensing and Biofilm Formation in Antibiotic-Resistant Bacteria: Mechanisms, Therapeutic Potential, and Future Perspectives

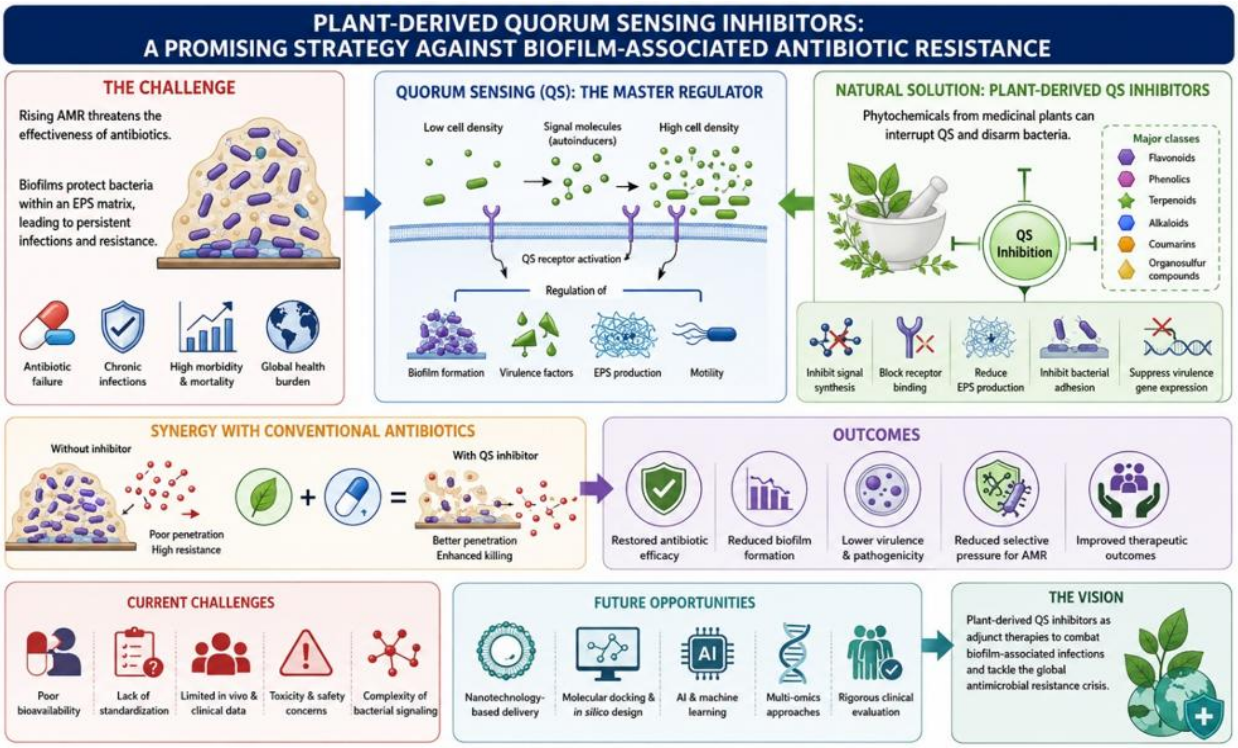
Shaurya Miteshkumar Patel[1], Pranati Das[2], Rupak Roy[3]
[1,2,3]*SHRM Biotechnologies Pvt Ltd, Kolkata*

***Abstract*—Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges, significantly compromising the effectiveness of conventional antibiotics. A major contributor to persistent bacterial infections is the formation of biofilms, highly structured microbial communities embedded within an extracellular polymeric substance (EPS) matrix that restricts antibiotic penetration and facilitates resistance. Quorum sensing (QS), a bacterial cell-to-cell communication system, plays a central role in regulating biofilm development, virulence factor production, and coordinated bacterial behavior. Consequently, targeting QS rather than bacterial viability has gained considerable attention as a promising anti-virulence strategy. This review comprehensively summarizes the potential of plant-derived compounds as natural inhibitors of quorum sensing and biofilm formation in antibiotic-resistant bacteria. Major classes of phytochemicals, including flavonoids, phenolics, terpenoids, alkaloids, coumarins, and organosulfur compounds, are critically discussed with respect to their chemical characteristics, structure–activity relationships, molecular targets, and mechanisms of action. Their ability to interfere with signal molecule synthesis, receptor binding, extracellular polymeric substance production, bacterial adhesion, and virulence gene expression is highlighted. Furthermore, recent evidence supporting synergistic interactions between phytochemicals and conventional antibiotics is examined, demonstrating their potential to restore antibiotic efficacy while reducing selective pressure for resistance development. The review also discusses current limitations, including poor bioavailability, lack of standardization, limited clinical validation, and toxicity concerns, while highlighting emerging opportunities involving nanotechnology, molecular docking, artificial intelligence, and multi-omics approaches. Overall, plant-derived quorum sensing inhibitors represent promising adjunctive therapeutics that may complement existing antimicrobial strategies and help address the growing burden of antimicrobial resistance.**

***Index Terms*—Antimicrobial resistance, Biofilm inhibition, Quorum sensing, Phytochemicals, Anti-virulence therapy**

I. INTRODUCTION

Antimicrobial resistance is growing rapidly and is one of the most significant problems for public health today; as a result, traditional antibiotic therapies can no longer address it. The development of microbial communities known as biofilms is a defense strategy of bacteria against adverse environments and host defenses. A biofilm is a community of microorganisms, typically composed of multiple species, that are embedded in a matrix, which is the extracellular polymeric substance (EPS) produced by bacteria. The matrix consists mostly of polysaccharides, proteins, lipids, and extracellular DNA (eDNA). In fact, the changing and moving matrix has been one of the main ways of maintaining biofilm integrity by forming strong structural units that, at the same time, act as strong barriers to diffusion, so that only a very tiny amount of an antimicrobial gets into the innermost regions. The biocoating process is a multi-phase process involving different levels of attachment and organization. Planktonic (free-moving) bacterial cells are first weakly attached to the surface by a reversible attachment mechanism through very weak physical and chemical forces.



The cells then undergo irreversible attachment and adhesion, which is the most important event governed by bacterial surface elements like different kinds of flagella, pili, and particular kinds of adhesins. Cells form microcolonies and then become a maturing community of biofilms, creating three-dimensional, complicated structures. These mature community systems provide physiological gradients of oxygen, nutrients, and pH to the microorganisms, resulting in metabolic heterogeneity, which in turn activates stress-resistance pathways, efflux pumps, and the creation of dormant, antibiotic-tolerant "persisters". Finally, individual cells leave the mature biofilm aggregate to spread and infect new clinical settings.

- Besides playing an important role in structuring, regulation of this development relies heavily on quorum sensing (QS), which is cell density-dependent communication in bacteria. QS enables bacteria to coordinate group behaviors such as virulence factors and EPS matrix production through the synthesis and perception of small signaling molecules (autoinducers) that serve as communication tools. In Gram-negative species, the signal is mainly LuxI-type enzyme-produced N-acyl homoserine lactones (AHLs), and the LuxR-type transcriptional regulator is the sensor. Whereas Gram-positive systems mostly use autoinducing peptides (AIPs) that are part of a signal transduction network (two-component). Since QS regulates the mechanisms that make biofilms structurally resistant and pathologically destructive, interfering with these communication networks, known as quorum quenching, has become an effective approach against virulence. Unlike conventional antibiotics, which exert severe selective pressure on a bacterial population by killing or inhibiting its proliferation, anti-QS & anti-biofilm agents target bacterial protection and regulation systems without immediately triggering resistance evolution mechanisms. Within such structures, botanical extracts, bioactive compounds, and phytochemistry have become an important field of research. Their variety in structure and composition allows plant metabolites to interfere with biofilm development at several stages - blocking initial attachment, the EPS matrix, and QS regulation pathways.
- The paper will analyze and describe in detail these molecular mechanisms that underlie plant-derived compounds' suppression abilities of quorum sensing and biofilm pathways, offering new ways to fight against drug-resistant microbes.

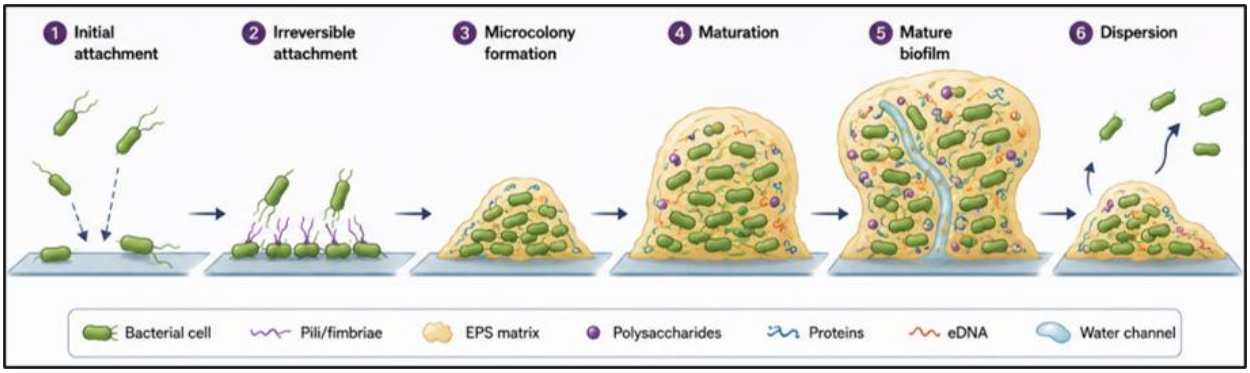


Fig 1 Biofilm development proceeds through sequential stages: initial reversible attachment, irreversible adhesion, microcolony formation, EPS-mediated maturation into a structured biofilm, and eventual dispersion of cells to new sites.

Central to biofilm development and bacterial virulence is quorum sensing (QS), a sophisticated cell-to-cell communication mechanism that enables bacteria to coordinate gene expression in response to population density. QS relies on the production, release, and detection of small signaling molecules known as autoinducers, such as N-acyl homoserine lactones (AHLs) in Gram-negative bacteria and autoinducing peptides (AIPs) in Gram-positive bacteria (Miller & Bassler, 2001). Once a threshold concentration of these molecules is reached, QS systems activate transcriptional networks that regulate a wide range of physiological processes, including biofilm formation, virulence factor production, motility, and antibiotic resistance (Papenfort & Bassler, 2016). In pathogens such as P. aeruginosa, interconnected QS systems (Las, Rhl, and Pseudomonas quinolone signal [PQS]) play a pivotal role in orchestrating pathogenicity and biofilm maturation.

Given the limitations of traditional antibiotics, there has been a paradigm shift toward anti-virulence strategies that target bacterial communication and biofilm formation rather than directly inhibiting growth. This approach is particularly attractive because it exerts reduced selective pressure for the development of resistance, as it does not directly threaten bacterial survival (Rasko & Sperandio, 2010). Among the various anti-virulence strategies, the disruption of QS commonly referred to as quorum quenching has emerged as a promising avenue for controlling bacterial infections.

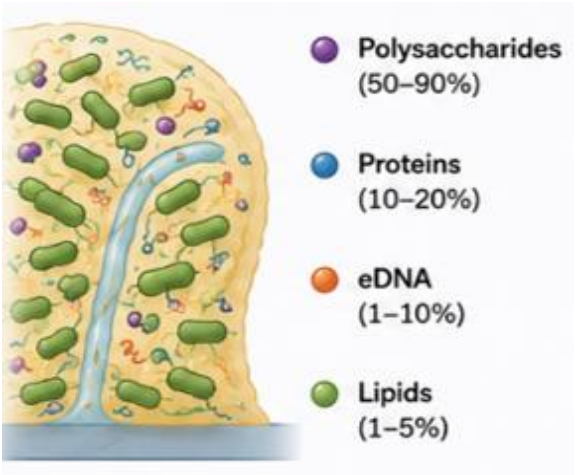


Fig 2 Biofilm matrix composition: The biofilm matrix consists primarily of polysaccharides, proteins, extracellular DNA (eDNA), and lipids, which collectively provide structural integrity and protection.

In recent years, plant-derived compounds have gained considerable attention as potential quorum sensing inhibitors (QSIs) and anti-biofilm agents. Plants produce a diverse array of secondary metabolites, including flavonoids, phenolic acids, terpenoids, alkaloids, and coumarins, many of which exhibit significant antimicrobial and anti-virulence activities (Daglia, 2012; Borges et al., 2016). These phytochemicals can interfere with QS systems through multiple mechanisms, such as inhibiting signal molecule synthesis, degrading signaling compounds, blocking receptor binding, and suppressing QS-regulated gene expression (Kalia, 2013). Unlike conventional antibiotics, these compounds often attenuate virulence without inhibiting bacterial

growth, thereby minimizing the likelihood of resistance development.

Notably, several well-studied phytochemicals, including quercetin, Eugenol, naringenin, coumarin, and allicin, have demonstrated significant efficacy in inhibiting QS-regulated pathways and disrupting biofilm formation in a variety of clinically relevant pathogens (Packiavathy et al., 2014; Vattem et al., 2007; Zhou et al., 2020). Furthermore, emerging evidence suggests that plant-derived QS inhibitors can act synergistically with conventional antibiotics, enhancing their efficacy against resistant strains and biofilm-associated infections (Brackman & Coenye, 2015).

Despite these promising findings, the translation of plant-derived anti-QS compounds into clinical applications remains limited. Challenges such as poor bioavailability, variability in phytochemical composition, lack of standardized extraction methods, and insufficient in vivo and clinical studies continue to hinder their development as therapeutic agents (Lu et al., 2019). Additionally, a comprehensive understanding of the molecular mechanisms underlying QS inhibition and the structure–activity relationships (SAR) of these compounds is still evolving.

In this context, the present review aims to provide a comprehensive and critical evaluation of plant-derived compounds as inhibitors of quorum sensing and biofilm formation in antibiotic-resistant bacteria. Specifically, this review will (i) discuss the role of biofilms and QS in bacterial pathogenicity, (ii) classify major phytochemicals with anti-QS and anti-biofilm activities, (iii) analyze their molecular mechanisms of action, (iv) provide a comparative assessment of key compounds based on experimental evidence, and (v) highlight current limitations and future perspectives for their therapeutic application. By integrating recent advances in this field, this review seeks to contribute to the development of innovative, sustainable strategies to combat antimicrobial resistance.

II. BIOFILM FORMATION AND ITS ROLE IN ANTIBIOTIC RESISTANCE

Biofilm formation is a highly organized and dynamic process that enables bacteria to survive in hostile environments and contributes significantly to the persistence of infections and antimicrobial resistance. Biofilms are structured microbial communities embedded in a self-produced extracellular polymeric substance (EPS) matrix composed primarily of polysaccharides, proteins, lipids, and extracellular DNA (eDNA) (Flemming et al., 2016). This matrix not only provides structural integrity but also acts as a protective barrier against environmental stressors, including antibiotics, disinfectants, and host immune responses.

Biofilm formation occurs through a series of well-defined stages. Initially, planktonic bacterial cells reversibly attach to a surface through weak physicochemical interactions such as van der Waals forces and hydrophobic interactions. This is followed by irreversible attachment mediated by bacterial surface structures, including pili, fimbriae, and adhesins (O'Toole et al., 2000). Subsequently, the attached cells proliferate and form microcolonies, which are further embedded within the EPS matrix. As the biofilm matures, it develops a complex three-dimensional architecture with water channels that facilitate nutrient transport and waste removal. In the final stage, cells disperse from the biofilm, enabling colonization of new niches and dissemination of infection (Hall-Stoodley et al., 2004).

Biofilm-associated bacteria exhibit markedly enhanced resistance to antimicrobial agents compared to their planktonic counterparts. This resistance is multifactorial and involves both physical and physiological mechanisms. The EPS matrix acts as a diffusion barrier, limiting the penetration of antibiotics into the deeper layers of the biofilm (Stewart & Costerton, 2001). Additionally, the presence of metabolically inactive or slow-growing "persister cells" within the biofilm contributes to antibiotic tolerance, as many antibiotics are more effective against actively dividing cells (Lewis, 2010). The biofilm environment also promotes horizontal gene transfer, facilitating the spread of antibiotic resistance genes among bacterial populations (Madsen et al., 2012).

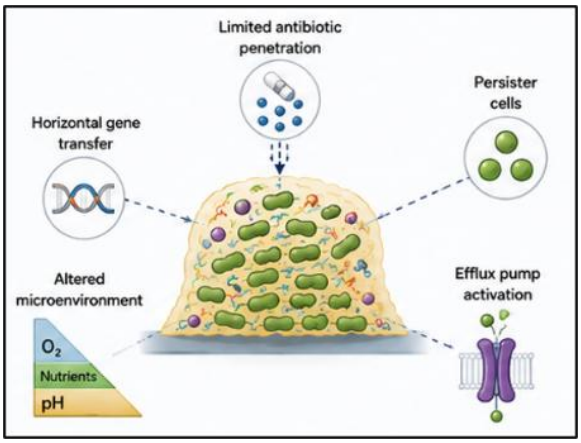


Fig 3 Mechanisms of antibiotic resistance in biofilms: Biofilm-associated resistance arises from limited antibiotic penetration, persister cells, horizontal gene transfer, altered microenvironment, and efflux pump activity

Another critical factor contributing to biofilm-associated resistance is the altered microenvironment within the biofilm. Gradients of oxygen, nutrients, and pH create heterogeneous conditions that influence bacterial metabolism and gene expression. These variations activate stress response pathways and efflux pump systems, further enhancing resistance to antimicrobial agents (Mah & O'Toole, 2001). Moreover, biofilms can evade host immune defenses by preventing phagocytosis and reducing the effectiveness of immune mediators, thereby promoting chronic and recurrent infections (Høiby et al., 2010).

Clinically, biofilm formation is associated with a wide range of persistent infections, including chronic wounds, urinary tract infections, cystic fibrosis-associated lung infections, and infections related to indwelling medical devices such as catheters, prosthetic joints, and implants (Jamal et al., 2018). Among the most problematic biofilm-forming pathogens are members of the ESKAPE group, including Pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter baumannii, and Klebsiella pneumoniae, which are responsible for a significant proportion of hospital-acquired infections and exhibit high levels of multidrug resistance (Rice, 2008).

Importantly, biofilm formation is tightly regulated by quorum sensing (QS) systems, which coordinate gene expression in response to cell density. QS signaling controls the production of EPS components, virulence factors, and enzymes involved in biofilm maturation and dispersal. In Pseudomonas aeruginosa, for example, the Las and Rhl QS systems regulate the expression of genes involved in exopolysaccharide production, elastase activity, and rhamnolipid synthesis, all of which are essential for biofilm development (Papenfort & Bassler, 2016). Similarly, in Gram-positive bacteria such as Staphylococcus aureus, the accessory gene regulator (agr) system modulates biofilm formation and virulence.

Given the critical role of biofilms in antimicrobial resistance and chronic infections, targeting biofilm formation has emerged as a promising strategy for combating resistant pathogens. Unlike traditional antibiotics that aim to kill or inhibit bacterial growth, anti-biofilm strategies focus on disrupting the structural integrity and regulatory mechanisms of biofilms. Approaches include inhibiting initial adhesion, degrading the EPS matrix, interfering with QS signaling, and enhancing the penetration and efficacy of antimicrobial agents (Brackman & Coenye, 2015).

In this context, plant-derived compounds have shown considerable potential as anti-biofilm agents due to their ability to interfere with multiple stages of biofilm development. These phytochemicals can disrupt bacterial adhesion, inhibit EPS production, modulate QS pathways, and enhance antibiotic susceptibility, making them promising candidates for alternative or adjunctive therapies against biofilm-associated infections. A deeper understanding of the mechanisms underlying biofilm formation and resistance is therefore essential for the rational design and application of such anti-virulence strategies.

III. QUORUM SENSING SYSTEMS IN BACTERIA

Quorum sensing (QS) is a cell density-dependent communication mechanism that enables bacteria to coordinate gene expression through the production and detection of small signaling molecules known as autoinducers. This process regulates a wide range of physiological activities, including biofilm formation, virulence factor production, motility, and antibiotic resistance (Miller & Bassler, 2001; Papenfort & Bassler, 2016).

In Gram-negative bacteria, QS is primarily mediated by N-acyl homoserine lactones (AHLs), synthesized by LuxI-type enzymes and detected by LuxR-type

transcriptional regulators. A well-characterized example is Pseudomonas aeruginosa, which possesses multiple interconnected QS systems, including the Las, Rhl, and Pseudomonas quinolone signal (PQS) systems. The Las system (LasI/LasR) regulates the production of virulence factors such as elastase, while the Rhl system (RhlI/RhlR) controls rhamnolipid synthesis and biofilm maturation. The PQS system further integrates with these pathways to fine-tune gene expression and enhance pathogenicity (Papenfort & Bassler, 2016).

In Gram-positive bacteria, QS typically involves autoinducing peptides (AIPs) that are secreted and detected via two-component signal transduction systems. A prominent example is the accessory gene regulator (agr) system in Staphylococcus aureus, which modulates virulence, toxin production, and biofilm dynamics (Novick & Geisinger, 2008).

Additionally, the autoinducer-2 (AI-2) system functions as a universal signaling mechanism facilitating interspecies communication. AI-2-mediated QS plays a role in coordinating mixed-species biofilm formation and regulating metabolic and virulence-associated pathways across diverse bacterial populations (Pereira et al., 2013).

QS systems are tightly linked to biofilm development, as they regulate genes involved in EPS production, adhesion, and structural organization. Disruption of QS pathways referred to as quorum quenching has therefore emerged as an effective strategy to attenuate bacterial virulence and inhibit biofilm formation without exerting strong selective pressure for resistance (Kalia, 2013).

Understanding the molecular architecture of QS systems provides a critical foundation for the development of plant-derived quorum sensing inhibitors (QSIs), which can interfere with signal synthesis, receptor binding, or downstream gene expression, thereby offering promising alternatives to conventional antimicrobial therapies.

IV. PLANT-DERIVED COMPOUNDS AS INHIBITORS OF QUORUM SENSING AND BIOFILM FORMATION

Plant secondary metabolites are a group of compounds that are chemically diverse and a rich source of agents capable of preventing bacterial virulence by interfering with bacterial communication and the construction of biofilms, and doing it in various places along the pathway. Compared to conventional antibiotics, most phytochemicals hardly, if at all, act as direct bactericides. Plant-derived compounds have emerged as a promising class of anti-virulence agents capable of disrupting quorum sensing (QS) systems and inhibiting biofilm formation in antibiotic-resistant bacteria. Unlike conventional antibiotics that exert bactericidal or bacteriostatic effects, phytochemicals often attenuate pathogenicity by interfering with bacterial communication pathways, thereby reducing selective pressure for resistance development (Kalia, 2013; Borges et al., 2016).

Phytochemicals encompass a diverse array of secondary metabolites, including flavonoids, phenolic compounds, terpenoids, alkaloids, and coumarins. These compounds are biosynthesized by plants as part of their defense mechanisms and exhibit a wide range of biological activities, including antimicrobial, antioxidant, and anti-inflammatory effects (Daglia, 2012). Increasing evidence suggests that many of these compounds specifically target QS-regulated pathways and biofilm-associated processes in clinically relevant pathogens. The phenolics, like phenylpropanoids and phenolic terpenoid derivatives, cause interference and breakdown of Quorum Sensing (QS) as well as biofilm by acting both on the membrane and the QS signal. One of the most effective QS inhibitors, Eugenol, which is a phenylpropanoid present in many clove-like aromatic plants, is very effective against both Gram+ and Gram- bacteria. Its phenolic ring, in combination with an allylic side chain, results in partitioning into the bacterial membrane, which causes perturbation of membrane fluidity and, secondarily, leads to a failure in localization of QS receptor proteins and efflux pumps (Marchese et al. 2017). The combination of membrane destabilization through dual action and QS suppression indirectly makes phenolics stand out among other QS inhibitors that work purely by receptor blocking, like flavonoids.

4.1 Classification of Plant-Derived Anti-QS and Anti-Biofilm Compounds

Phytochemicals can be broadly categorized based on their chemical structure and mode of action:

- Flavonoids (e.g., quercetin, naringenin, kaempferol) are among the most extensively studied QS inhibitors. They have been shown to interfere with AHL-mediated signaling,

particularly in Pseudomonas aeruginosa, by inhibiting receptor binding and downregulating QS gene expression (Vandeputte et al., 2011).

- Phenolic compounds (e.g., gallic acid, tannic acid) disrupt biofilm formation by inhibiting EPS production and altering cell surface properties, thereby reducing bacterial adhesion (Borges et al., 2016).
- Terpenoids (e.g., carvacrol, thymol, Eugenol) exhibit strong anti-biofilm activity through membrane disruption and modulation of QS pathways. Eugenol, in particular, has demonstrated the ability to downregulate virulence genes and inhibit biofilm formation across multiple bacterial species (Marchese et al., 2017).
- Alkaloids (e.g., berberine) inhibit biofilm formation by interfering with EPS synthesis and bacterial adhesion mechanisms, particularly in Gram-positive pathogens such as Staphylococcus aureus (Sun et al., 2019).
- Coumarins (e.g., coumarin, esculetin) have been shown to suppress QS signaling and reduce biofilm formation by modulating gene expression and signal molecule activity (Gutiérrez-Barranquero et al., 2015).
- Organosulfur compounds (e.g., allicin from garlic) inhibit QS-regulated pathways by interfering with AHL signaling and reducing virulence factor production (Vattem et al., 2007).

4.2 Molecular Mechanisms of Action

Plant-derived QS inhibitors (QSIs) act through multiple mechanisms, often targeting different stages of QS signaling and biofilm development:

1. Inhibition of signal molecule synthesis: Certain phytochemicals downregulate enzymes such as LuxI homologs, reducing the production of AHLs.
2. Signal degradation or inactivation: Some compounds chemically modify or degrade autoinducers, preventing signal accumulation.
3. Receptor antagonism: Many flavonoids and phenolics bind to QS receptors (e.g., LuxR-type proteins), blocking signal recognition and transcriptional activation.
4. Suppression of QS-regulated genes: Phytochemicals can downregulate genes involved in virulence, motility, and EPS production, thereby impairing biofilm formation.
5. Disruption of biofilm matrix: Compounds such as tannins and terpenoids interfere with EPS synthesis and stability, weakening the biofilm structure.

These multi-target mechanisms provide a significant advantage over conventional antibiotics, as they reduce the likelihood of resistance development and can act synergistically with existing antimicrobial agents (Brackman & Coenye, 2015).

4.3 Comparative Evaluation of Key Phytochemicals

Among the wide range of plant-derived compounds, certain molecules have demonstrated particularly strong anti-QS and anti-biofilm activities:

- Quercetin has been shown to inhibit LasR and RhlR signaling pathways in P. aeruginosa, leading to reduced production of virulence factors such as elastase and pyocyanin (Vandeputte et al., 2011).
- Naringenin interferes with QS signal transduction and significantly reduces biofilm formation and motility.
- Eugenol exhibits broad-spectrum activity by targeting multiple QS pathways and disrupting membrane integrity, making it highly effective against both Gram-positive and Gram-negative bacteria (Marchese et al., 2017).
- Coumarin derivatives inhibit QS signaling and have demonstrated efficacy in reducing biofilm formation across diverse bacterial species (Gutiérrez-Barranquero et al., 2015).
- Allicin acts as a QS inhibitor by modulating AHL-mediated communication and reducing virulence expression (Vattem et al., 2007).

Despite their promising activity, the efficacy of these compounds varies depending on bacterial species, concentration, and experimental conditions, highlighting the need for standardized evaluation protocols.

4.4 Synergistic Interactions with Antibiotics

A key advantage of plant-derived QS inhibitors is their ability to enhance the efficacy of conventional antibiotics. Several studies have demonstrated synergistic interactions between phytochemicals and antibiotics, resulting in improved bacterial clearance and reduced biofilm formation. For instance, quercetin and Eugenol have been reported to enhance the activity of antibiotics such as ciprofloxacin and gentamicin against resistant pathogens (Brackman &

Coenye, 2015). These synergistic effects are particularly important in overcoming biofilm-associated resistance and restoring antibiotic susceptibility.

Overall, plant-derived compounds represent a versatile and promising strategy for targeting QS systems and biofilm formation. Their multi-target mechanisms, reduced propensity for resistance development, and potential for synergistic use with antibiotics make them attractive candidates for the development of novel anti-virulence therapies.

Table 1. Key plant-derived quorum sensing inhibitors and structure–activity relationships (SAR)

Compound	Class	Target	QS/Biofilm Effect	Key SAR Feature	Reference
Quercetin	Flavonoid	P. aeruginosa	High QS inhibition	Multiple –OH groups enhance receptor binding	Vandeputte et al., 2011
Naringenin	Flavonoid	P. aeruginosa	Moderate–High	Reduced hydroxylation improves permeability	Vandeputte et al., 2011
Eugenol	Phenylpropanoid	Multi-species	High	Phenolic ring + allyl chain disrupt membranes	Marchese et al., 2017
Carvacrol	Terpenoid	P. aeruginosa	High	Hydrophobic ring enhances signal disruption	Kalia, 2013
Coumarin	Coumarin	Mixed bacteria	High	Lactone ring mimics AHL signals	Gutiérrez-Barranquero et al., 2015
Berberine	Alkaloid	S. aureus	Moderate	Planar structure inhibits adhesion/EPS	Sun et al., 2019
Allicin	Organosulfur	Gram-negative	Moderate	Reactive sulfur modifies QS enzymes	Vattem et al., 2007

4.5 Emerging Phytochemicals with Anti-Quorum Sensing and Anti-Biofilm Potential

Recent research has expanded the repertoire of plant-derived quorum sensing inhibitors (QSIs), identifying several emerging phytochemicals with promising anti-biofilm and anti-virulence activities. These compounds exhibit diverse mechanisms of action, including interference with quorum sensing (QS) signaling, inhibition of extracellular polymeric substance (EPS) synthesis, disruption of bacterial adhesion, and suppression of virulence gene expression.

Hordenine, a naturally occurring phenethylamine alkaloid isolated from barley (Hordeum vulgare), has demonstrated potent anti-QS activity against Pseudomonas aeruginosa. It downregulates the LasI/LasR and RhlI/RhlR signaling systems, resulting in reduced pyocyanin production, bacterial motility, and biofilm formation without significantly affecting bacterial growth (Zhou et al., 2020).

Baicalin, a flavone glycoside obtained from Scutellaria baicalensis, has emerged as a promising anti-virulence compound due to its ability to inhibit QS-regulated genes and enhance the susceptibility of bacterial biofilms to conventional antibiotics. Its immunomodulatory and anti-inflammatory properties further support its therapeutic potential in chronic biofilm-associated infections (Luo et al., 2017).

Resveratrol, a polyphenolic stilbene found in grapes and berries, inhibits bacterial adhesion and biofilm maturation by suppressing QS-dependent pathways. In addition to its antioxidant properties, resveratrol has demonstrated synergistic activity with conventional antibiotics against multidrug-resistant pathogens, making it a promising adjunctive therapeutic agent (Lee et al., 2014).

Among phenylpropanoids, cinnamaldehyde, the principal bioactive constituent of cinnamon (Cinnamomum spp.), has attracted considerable attention for its ability to interfere with AHL-mediated signaling, inhibit EPS production, and reduce the expression of virulence-associated genes in Gram-negative bacteria (Niu & Gilbert, 2004).

Similarly, epigallocatechin-3-gallate (EGCG), the major catechin in green tea (Camellia sinensis), has demonstrated broad-spectrum anti-biofilm activity by inhibiting bacterial adhesion, reducing EPS production, and modulating QS-regulated pathways. EGCG has also been reported to potentiate the activity of several antibiotics against resistant bacterial strains (Steinmann et al., 2013).

Collectively, these emerging phytochemicals broaden the spectrum of naturally occurring QS inhibitors and

provide valuable lead molecules for the development of next-generation anti-virulence therapeutics. Future investigations integrating molecular docking, structure–activity relationship (SAR) studies, and in vivo validation will be essential for translating these promising compounds into clinical applications.

Table 2. Emerging Plant-Derived Quorum Sensing Inhibitors

Compound	Plant source	Primary target	Major anti-QS/anti-biofilm activity	Reference
Hordenine	Hordeum vulgare	P. aeruginosa	Downregulates Las/Rhl systems; inhibits pyocyanin and biofilm	Zhou et al., 2020
Baicalin	Scutellaria baicalensis	P. aeruginosa, S. aureus	Suppresses QS genes; enhances antibiotic susceptibility	Luo et al., 2017
Resveratrol	Grapes (Vitis vinifera)	E. coli, P. aeruginosa	Inhibits adhesion and biofilm maturation	Lee et al., 2014
Cinnamaldehyde	Cinnamomum spp.	Gram-negative bacteria	Inhibits AHL signaling and EPS production	Niu & Gilbert, 2004
EGCG	Camellia sinensis	Mixed bacterial species	Reduces adhesion, EPS synthesis, and biofilm biomass	Steinmann et al., 2013

V. MOLECULAR MECHANISMS OF QUORUM SENSING AND BIOFILM INHIBITION BY PLANT-DERIVED COMPOUNDS

Plant-derived quorum sensing inhibitors (QSIs) disrupt bacterial communication and biofilm formation through multi-target molecular mechanisms. A primary mode of action involves inhibition of signal molecule synthesis, where phytochemicals downregulate enzymes such as LuxI homologs, reducing the production of autoinducers (Kalia, 2013).

Another key mechanism is receptor antagonism, in which compounds such as flavonoids bind to LuxR-type receptors, preventing autoinducer recognition and subsequent gene activation. This leads to suppression of QS-regulated virulence factors and biofilm-associated genes (Vandeputte et al., 2011).

Phytochemicals also induce signal interference or degradation, either by chemically modifying autoinducers or preventing their accumulation, thereby disrupting the QS signaling cascade (Vattem et al., 2007). In parallel, many compounds exert transcriptional repression of QS-controlled genes, including those involved in EPS production, motility, and toxin synthesis (Borges et al., 2016).

In addition to QS-specific effects, several plant-derived compounds directly target biofilm architecture by inhibiting EPS synthesis and destabilizing the biofilm matrix, leading to enhanced antibiotic penetration and reduced structural integrity (Brackman & Coenye, 2015). Some phytochemicals further impair bacterial motility (swarming and twitching), which is essential for early biofilm development.

Importantly, these mechanisms often act synergistically, enabling phytochemicals to attenuate bacterial virulence without significantly affecting growth. This multi-target mode of action reduces the likelihood of resistance development and highlights the therapeutic potential of plant-derived QSIs as anti-virulence agents.

VI. SYNERGISTIC INTERACTIONS OF PLANT-DERIVED COMPOUNDS WITH ANTIBIOTICS

The combination of plant-derived quorum sensing inhibitors (QSIs) with conventional antibiotics represents a promising strategy to combat biofilm-associated and multidrug-resistant infections. Unlike antibiotics alone, which often fail to penetrate biofilms or are rendered ineffective by resistance mechanisms, phytochemicals can enhance antibiotic efficacy by disrupting quorum sensing and weakening biofilm architecture (Brackman & Coenye, 2015).

Several studies have demonstrated that flavonoids such as quercetin and naringenin significantly enhance the activity of antibiotics like ciprofloxacin and tobramycin against Pseudomonas aeruginosa by inhibiting QS-regulated virulence pathways (Vandeputte et al., 2011). Similarly, Eugenol and carvacrol have been shown to increase membrane permeability, facilitating improved antibiotic uptake and leading to synergistic antibacterial effects (Marchese et al., 2017).

In Gram-positive bacteria, compounds such as berberine exhibit synergistic effects with β-lactam and tetracycline antibiotics by inhibiting efflux pumps and reducing biofilm formation in Staphylococcus aureus (Sun et al., 2019).

Table 3. Synergistic Effects of Plant-Derived Compounds with Conventional Antibiotics

Plant-derived compound	Antibiotic	Target pathogen	Synergistic effect	Proposed mechanism	Reference
Quercetin	Ciprofloxacin	Pseudomonas aeruginosa	Enhanced inhibition of biofilm and virulence	Las/Rhl quorum sensing inhibition; reduced pyocyanin and elastase production	Vandeputte et al., 2011
Naringenin	Tobramycin	P. aeruginosa	Increased antibiotic susceptibility	Suppression of QS-regulated genes and EPS production	Vandeputte et al., 2011
Eugenol	Ciprofloxacin	Escherichia coli, P. aeruginosa	Improved antibacterial efficacy	Increased membrane permeability and disruption of biofilm matrix	Marchese et al., 2017
Carvacrol	Gentamicin	P. aeruginosa	Reduced biofilm biomass	Membrane destabilization and inhibition of AHL-mediated signaling	Kalia, 2013
Berberine	Ampicillin/Tetracycline	Staphylococcus aureus	Restored antibiotic sensitivity	Efflux pump inhibition and reduced bacterial adhesion	Sun et al., 2019
Allicin	Vancomycin/Ciprofloxacin	Gram-positive and Gram-negative bacteria	Enhanced bacterial killing	Modification of thiol-containing proteins involved in QS and metabolism	Vattem et al., 2007
Curcumin	Ciprofloxacin	Uropathogenic E. coli	Significant reduction in biofilm formation	QS inhibition and suppression of bacterial motility	Packiavathy et al., 2014
Hordenine	Tobramycin	P. aeruginosa	Increased antibiotic effectiveness	Downregulation of Las and Rhl signaling pathways	Zhou et al., 2020

Additionally, organosulfur compounds like allicin enhance antibiotic susceptibility by interfering with thiol-dependent enzymes involved in bacterial metabolism and signaling (Vattem et al., 2007).

These synergistic interactions not only improve therapeutic outcomes but also allow for reduced antibiotic dosages, thereby minimizing toxicity and slowing the emergence of resistance. Importantly, the multi-target action of phytochemicals makes it more difficult for bacteria to develop resistance compared to single-target antibiotics.

VII. LIMITATIONS AND CHALLENGES

Despite the significant potential shown by plant-based compounds as quorum-sensing and biofilm-forming bacterial regulators, these compounds still suffer from several limitations that prevent them from being effectively turned into anti-virulence therapeutic agents in clinics.

7.1 Poor Bioavailability and Stability

The main limitation in the development of phytochemicals as therapeutics is the poor pharmacokinetic profile of these compounds, which results from their physical and chemical nature. Many flavonoids and phenolics, such as quercetin and naringenin, show poor aqueous solubility, rapid metabolism, and extensive metabolic turnover, so that after oral administration, these drugs do not reach the systemic level in the required amount. Also, certain such compounds get degraded chemically under the

influence of human physicochemical conditions, including pH, temperature, and even light exposure. Highly volatile terpenoids, such as carvacrol, also cause issues such as rapid evaporation and uneven distribution of molecules into body tissues. Pharmacokinetic issues are typically addressed by using modern delivery systems that can help retain drug stability and achieve the correct levels of medication at the infection site through various routes. Some of these delivery systems include nanocarriers, liposomal carriers, or polymeric carriers.

7.2 Lack of Standardization

The composition of the botanical extracts is inherently variable given the botanical species, geographical regions, agricultural conditions, harvesting periods, and also extraction methods. This is the reason why it is not easy to get the same results from different batches and why anti-QS and anti-biofilm activity reported in different works will vary. Moreover, the non-availability of standardized analytical methods for the processes of extraction, purification, and quantification of the active phytochemical components makes it really difficult to compare different studies, and it becomes impossible to establish reliable dosage-effect curves. So, regulatory approval and clinical use can be delayed.

7.3 Limited In Vivo and Clinical Data

Most of the research papers dealing with plant-derived quorum sensing and biofilm inhibitors have been done using in vitro models. These systems, although useful, are unable to completely mirror the complexity of host environments. Some of the important factors that the host environment offers, for instance, immune system activities, pharmacokinetic variability of tissues, and the nature of polymicrobial infections, are extremely hard to model through lab experiments. As a result, there is still a large gap in animal model validations, and more importantly, there is a complete absence of well-designed clinical trials testing these phytochemicals on human subjects for safety and effectiveness. The lack of sufficient translational data remains a formidable challenge to their acceptance as proper drugs.

7.4 Toxicity and Off-Target Effects

Although plant-derived compounds are frequently perceived as inherently safe due to their natural origin, this assumption does not always hold, particularly at the higher concentrations often required to achieve meaningful anti-virulence effects. Certain alkaloids and organosulfur compounds, including berberine and allicin, have been associated with cytotoxicity toward mammalian cells and potential interference with normal host-microbiome interactions at elevated doses. Additionally, the membrane-active mechanisms exhibited by terpenoids and phenolics, while effective against bacterial membranes, raise concerns regarding non-selective toxicity toward host cell membranes. A thorough evaluation of the therapeutic index and off-target pharmacological effects of these compounds is therefore essential before they can be considered for clinical use.

7.5 Complexity of Quorum Sensing Networks

A single, isolated signaling pathway rarely governs quorum sensing systems in bacteria; rather, they involve intricate, interconnected regulatory networks with considerable redundancy and cross-talk between different QS circuits, as exemplified by the Las, Rhl, and PQS systems in Pseudomonas aeruginosa. This inherent complexity means that inhibition of a single QS pathway by a phytochemical may be insufficient to achieve complete suppression of virulence and biofilm phenotypes, as compensatory signaling through alternative pathways can occur. Moreover, the specificity of many plant-derived QSIs for particular bacterial species or QS systems limits their broad-spectrum applicability, necessitating combinatorial approaches or the identification of multi-target compounds capable of simultaneously disrupting several interconnected regulatory nodes.

Collectively, these limitations underscore the need for continued interdisciplinary research integrating phytochemistry, pharmacology, and clinical microbiology to overcome the translational barriers currently preventing plant-derived anti-QS and anti-biofilm agents from reaching their full therapeutic potential.

VIII. FUTURE PERSPECTIVES

The translational gap between promising in vitro findings and clinically deployable anti-virulence therapeutics necessitates the integration of emerging technological and methodological advances. Several

converging fields offer viable pathways to overcome the limitations discussed above.

8.1 Nanotechnology-Based Delivery

Nanocarrier systems represent one of the most direct solutions to the pharmacokinetic shortcomings of plant-derived quorum sensing inhibitors (QSIs). Encapsulation of poorly soluble flavonoids and terpenoids within liposomes, polymeric nanoparticles, solid lipid nanoparticles, or cyclodextrin inclusion complexes can substantially improve aqueous solubility, protect labile compounds from premature degradation, and enable sustained, targeted release at infection sites. Beyond simple protection, nanoformulations can be engineered for biofilm-penetrating properties, allowing active compounds to bypass the diffusion barrier imposed by the EPS matrix rather than relying on passive permeation. Surface functionalization with targeting ligands further raises the possibility of selectively concentrating phytochemical QSIs at sites of biofilm-associated infection, minimizing systemic exposure and off-target toxicity while maximizing local efficacy.

8.2 AI and Molecular Docking Approaches

Computational methods are increasingly central to accelerating the identification and optimization of novel anti-QS phytochemicals. Molecular docking and molecular dynamics simulations allow researchers to predict binding affinities between candidate compounds and QS receptor proteins such as LasR, RhlR, and AgrC prior to costly experimental validation, enabling rational prioritization of promising scaffolds. Machine learning and deep learning models trained on existing structure–activity relationship data can extend this further, predicting novel bioactive candidates from large phytochemical libraries and guiding synthetic modification of natural scaffolds to enhance receptor affinity or membrane permeability. Integration of artificial intelligence-driven virtual screening with high-throughput experimental validation pipelines has the potential to substantially compress the discovery timeline for next-generation, multi-target anti-virulence agents.

8.3 Multi-Omics Integration

Given the redundancy and cross-talk inherent to bacterial quorum sensing networks, a systems-level understanding of phytochemical activity is essential for designing effective interventions. Transcriptomic, proteomic, and metabolomic profiling of bacterial cells exposed to plant-derived QSIs can reveal not only the primary molecular targets of a given compound but also secondary and compensatory regulatory responses that may underlie treatment failure or reduced efficacy. Integrating these multi-omics datasets with computational network modeling could help identify combinatorial treatment strategies that simultaneously target multiple interconnected QS circuits, thereby reducing the likelihood of compensatory pathway activation and improving the durability of anti-virulence effects.

8.4 Clinical Translation and Trials

Progression beyond preclinical models requires a structured translational pipeline, beginning with validated animal models of biofilm-associated infection and progressing toward carefully designed human clinical trials. Given that anti-virulence agents do not exert direct bactericidal pressure, appropriate clinical endpoints such as reduction in biofilm burden, virulence factor expression, or adjunctive improvement in antibiotic efficacy must be clearly defined and distinguished from traditional measures of bacterial killing. Early-phase trials evaluating plant-derived QSIs as adjuvants to existing antibiotic regimens, rather than as standalone therapies, represent a pragmatic entry point for clinical validation, particularly in chronic biofilm-associated conditions such as cystic fibrosis-associated pulmonary infections, chronic wounds, and medical device-associated infections.

8.5 Standardization and Regulatory Frameworks

The lack of standardized extraction, purification, and quantification protocols remains a fundamental obstacle to regulatory approval. Establishing consensus guidelines for phytochemical characterization, purity thresholds, and dose–response reporting would greatly enhance reproducibility across studies and facilitate meaningful comparison between candidate compounds. Regulatory agencies will likely need to develop dedicated frameworks for anti-virulence agents, distinct from those governing conventional antimicrobials, given their fundamentally different mechanism of action and the absence of direct growth inhibition as a measurable

endpoint. Collaborative efforts between academic researchers, industry stakeholders, and regulatory bodies will be essential to establish clear developmental pathways for this emerging therapeutic class.

IX. CONCLUSION

The escalating burden of antimicrobial resistance, compounded by the intrinsic protection biofilms confer against conventional antibiotics, underscores the urgent need for alternative therapeutic strategies that do not rely on direct bactericidal pressure. This review has highlighted the considerable capacity of plant-derived compounds spanning flavonoids, phenolics, terpenoids, and alkaloids to interfere with bacterial quorum sensing and biofilm development through mechanistically diverse pathways, including receptor mimicry, membrane disruption, adhesion inhibition, and covalent enzyme modification. These class-specific structure–activity relationships offer a rational foundation for the targeted design and optimization of future anti-virulence agents.

Anti-virulence strategies, by disarming rather than killing bacteria, offer a fundamentally distinct advantage over conventional antibiotics: reduced selective pressure that drives the emergence and spread of resistance. By targeting the regulatory and structural infrastructure underlying biofilm persistence and pathogenicity, quorum quenching approaches hold the potential to restore the efficacy of existing antibiotics when used adjunctively, while simultaneously reducing the evolutionary pressure that accelerates resistance development.

Nonetheless, translating plant-derived QSIs from laboratory findings to clinical reality remains hindered by poor bioavailability, lack of standardization, insufficient in vivo and clinical data, potential toxicity, and the inherent complexity of bacterial signaling networks. Addressing these challenges will require a concerted, interdisciplinary effort integrating advances in nanotechnology-based delivery, computational drug discovery, multi-omics network analysis, and rigorous clinical evaluation. With continued investment in these areas, phytochemicals are well positioned to emerge as valuable components of the broader antimicrobial resistance control arsenal, offering a complementary, lower-resistance-pressure alternative to conventional antibiotic therapy.

REFERENCES

[1] Borges, A., A. C. Abreu, C. Dias, M. J. Saavedra, F. Borges, and M. Simões, “New perspectives on the use of phytochemicals as an emergent strategy to control bacterial infections including biofilms,” *Molecules*, vol. 21, no. 7, p. 877, 2016.

[2] Brackman, G., and T. Coenye, “Current Pharmaceutical Design,” *Current Pharmaceutical Design*, vol. 21, pp. 5–11, 2015.

[3] Costerton, J. W., P. S. Stewart, and E. P. Greenberg, “Bacterial biofilms: A common cause of persistent infections,” *Science*, vol. 284, no. 5418, pp. 1318–1322, 1999.

[4] Daglia, M., “Polyphenols as antimicrobial agents,” *Current Opinion in Biotechnology*, vol. 23, no. 2, pp. 174–181, 2012.

[5] Flemming, H.-C., J. Wingender, U. Szewzyk, P. Steinberg, S. A. Rice, and S. Kjelleberg, “Biofilms: An emergent form of bacterial life,” *Nature Reviews Microbiology*, vol. 14, no. 9, pp. 563–575, 2016.

[6] Gutiérrez-Barranquero, J. A., F. J. Reen, R. R. McCarthy, and F. O’Gara, *Frontiers in Microbiology*, vol. 6, p. 20, 2015.

[7] Hall-Stoodley, L., J. W. Costerton, and P. Stoodley, “Bacterial biofilms: From the natural environment to infectious diseases,” *Nature Reviews Microbiology*, vol. 2, no. 2, pp. 95–108, 2004.

[8] Høiby, N., T. Bjarnsholt, M. Givskov, S. Molin, and O. Ciofu, “Antibiotic resistance of bacterial biofilms,” *International Journal of Antimicrobial Agents*, vol. 35, no. 4, pp. 322–332, 2010.

[9] Jamal, M., W. Ahmad, S. Andleeb, F. Jalil, M. Imran, M. A. Nawaz, T. Hussain, M. Ali, M. Rafiq, and M. A. Kamil, “Bacterial biofilm and associated infections,” *Journal of the Chinese Medical Association*, vol. 81, no. 1, pp. 7–11, 2018.

[10] Kalia, V. C., “Quorum sensing inhibitors: An overview,” *Biotechnology Advances*, vol. 31, no. 2, pp. 224–245, 2013.

[11] Karygianni, L., Z. Ren, H. Koo, and T. Thurnheer, “Biofilm matrixome: Extracellular components in structured microbial communities,” *Trends in Microbiology*, vol. 28, no. 8, pp. 668–681, 2020.

[12] Lee, J. H., S. C. Regmi, J. A. Kim, M. H. Cho, H. Yun, C. S. Lee, and J. Lee, "Apple flavonoid phloretin inhibits *Escherichia coli* O157:H7 biofilm formation and ameliorates colon inflammation," *Infection and Immunity*, vol. 82, no. 11, pp. 4814–4827, 2014.

[13] Lewis, K., "Persister cells," *Annual Review of Microbiology*, vol. 64, pp. 357–372, 2010.

[14] Lu, L., W. Hu, Z. Tian, D. Yuan, G. Yi, Y. Zhou, Q. Cheng, J. Zhu, and M. Li, "Developing natural products as potential anti-biofilm agents," *Chinese Medicine*, vol. 14, p. 11, 2019.

[15] Luo, J., J. L. Kong, B. Y. Dong, H. Huang, K. Wang, L. H. Wu, C. C. Hou, Y. H. Liang, and B. Li, "Baicalin inhibits biofilm formation and the quorum-sensing system in *Pseudomonas aeruginosa*," *Journal of Functional Foods*, vol. 40, pp. 324–333, 2017.

[16] Madsen, J. S., M. Burmølle, L. H. Hansen, and S. J. Sørensen, "The interconnection between biofilm formation and horizontal gene transfer," *FEMS Immunology & Medical Microbiology*, vol. 65, no. 2, pp. 183–195, 2012.

[17] Mah, T.-F. C., and G. A. O'Toole, "Mechanisms of biofilm resistance to antimicrobial agents," *Trends in Microbiology*, vol. 9, no. 1, pp. 34–39, 2001.

[18] Marchese, A., R. Barbieri, E. Coppo, I. E. Orhan, M. Daglia, S. F. Nabavi, M. Izadi, M. Abdollahi, S. M. Nabavi, and M. Ajami, "Antimicrobial activity of Eugenol and essential oils containing Eugenol: A mechanistic viewpoint," *Molecules*, vol. 22, no. 8, p. 1351, 2017.

[19] Miller, M. B., and B. L. Bassler, "Quorum sensing in bacteria," *Annual Review of Microbiology*, vol. 55, pp. 165–199, 2001.

[20] Niu, C., and E. S. Gilbert, "Colorimetric method for identifying plant essential oil components that affect biofilm formation and quorum sensing," *Applied and Environmental Microbiology*, vol. 70, no. 12, pp. 6951–6956, 2004.

[21] Novick, R. P., and E. Geisinger, "Quorum sensing in staphylococci," *Annual Review of Genetics*, vol. 42, pp. 541–564, 2008.

[22] O'Toole, G., H. B. Kaplan, and R. Kolter, "Biofilm formation as microbial development," *Annual Review of Microbiology*, vol. 54, pp. 49–79, 2000.

[23] O'Neill, J., *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. Review on Antimicrobial Resistance, 2016.

[24] Packiavathy, I. A. S. V., S. Priya, S. K. Pandian, and A. V. Ravi, "Inhibition of biofilm development of uropathogens by curcumin: An anti-quorum sensing agent from *Curcuma longa*," *Food Chemistry*, vol. 148, pp. 453–460, 2014.

[25] Papenfort, K., and B. L. Bassler, "Quorum sensing signal–response systems in Gram-negative bacteria," *Nature Reviews Microbiology*, vol. 14, no. 9, pp. 576–588, 2016.

[26] Pereira, C. S., J. A. Thompson, and K. B. Xavier, "AI-2-mediated signalling in bacteria," *FEMS Microbiology Reviews*, vol. 37, no. 2, pp. 156–181, 2013.

[27] Rasko, D. A., and V. Sperandio, "Anti-virulence strategies to combat bacteria-mediated disease," *Nature Reviews Drug Discovery*, vol. 9, no. 2, pp. 117–128, 2010.

[28] Rice, L. B., "Federal funding for the study of antimicrobial resistance in nosocomial pathogens: No ESKAPE," *Journal of Infectious Diseases*, vol. 197, no. 8, pp. 1079–1081, 2008.

[29] Steinmann, J., J. Buer, T. Pietschmann, and E. Steinmann, "Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea," *British Journal of Pharmacology*, vol. 168, no. 5, pp. 1059–1073, 2013.

[30] Stewart, P. S., and J. W. Costerton, "Antibiotic resistance of bacteria in biofilms," *The Lancet*, vol. 358, no. 9276, pp. 135–138, 2001.

[31] Sun, D., S. N. Abraham, and E. H. Beachey, "Influence of berberine sulfate on synthesis and expression of Pap fimbrial adhesin in uropathogenic *Escherichia coli*," *Antimicrobial Agents and Chemotherapy*, vol. 32, no. 8, pp. 1274–1277, 1988.

[32] Vandeputte, O. M., M. Kiendrebeogo, T. Rasamiravaka, C. Stévigny, P. Duez, S. Rajaonson, B. Diallo, A. Mol, M. El Jaziri, and M. Baucher, "The flavanone naringenin reduces the production of quorum sensing-controlled virulence factors in *Pseudomonas aeruginosa* PAO1," *Applied and Environmental Microbiology*, vol. 77, no. 21, pp. 7575–7577, 2011.

[33] Vattem, D. A., K. Mihalik, S. H. Crixell, and R. J. C. McLean, "Dietary phytochemicals as quorum sensing inhibitors," *Fitoterapia*, vol. 78, no. 4, pp. 302–310, 2007.
[34] Ventola, C. L., "The antibiotic resistance crisis: Part 1: Causes and threats," *P&T*, vol. 40, no. 4, pp. 277–283, 2015.
[35] World Health Organization, *Antimicrobial Resistance*. Geneva, Switzerland: World Health Organization, 2023.
[36] Zhou, J. W., H. Z. Luo, H. Jiang, T. K. Jian, Z. Q. Chen, and A. Q. Jia, "Hordenine: A novel quorum sensing inhibitor and anti-biofilm agent against *Pseudomonas aeruginosa*," *Microbial Pathogenesis*, vol. 146, Art. no. 104262, 2020.