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Effects of *Candida albicans*-derived Farnesol and Tyrosol on Quorum-Sensing Pathways in Pseudomonas aeruginosa Biofilms: Implication for Antimicrobial Resistance

Abstract

In 2017, amid an antimicrobial crisis, the World Health Organization classified *Pseudomonas aeruginosa* as a priority pathogen for the Research and Development of new antibiotics. *P. aeruginosa*'s ability to form biofilms–structured aggregation of microcolonies embedded in a self-generated matrix–and regulate virulence through quorum-sensing (QS) often results in antibiotic failure, especially in nosocomial settings. As synthetic antibiotics have become increasingly ineffective in eradicating *P. aeruginosa* biofilm, chronic infections persist in cystic fibrosis and burn wound patients. This review investigates *C. albicans*-derived molecules, tyrosol, and farnesol, as potential quorum-sensing inhibitors (QSIs) of *P. aeruginosa* QS circuits (LasI/LasR, RhlI/RhlR, and PQS) in single-species biofilms. These fungal-derived compounds have been shown to have anti-biofilm and antibacterial activity by disrupting *P. aeruginosa* QS pathways and modulating virulence factor expression. In combinatorial therapeutics, tyrosol and farnesol have been demonstrated to facilitate certain antibiotic activity, suggesting potential for clinical implementation. Unlike traditional antibiotics, *C. albicans* QSIs have co-evolved with *P. aeruginosa* and developed inhibition mechanisms that minimize the selective pressures driving antimicrobial resistance. By targeting cell-to-cell communication rather than bacterial growth, tyrosol and farnesol offer a propitious avenue for *P. aeruginosa* biofilms-associated infections. However, as this remains an emerging field of research in the context of *P. aeruginosa*-driven infections, further research is needed to determine clinical plausibility, especially in *in vivo* models, to understand specific mechanisms of action, dosage optimization and potential undesirable off-target interactions.

Introduction

In hospital settings, 80% of microbial infections are associated with biofilms, which are 1000-fold more tolerant to antibiotic exposure than their planktonic counterparts[1, 2, 3, 4]. Amid an antimicrobial resistance crisis, *Pseudomonas aeruginosa*, a gram-negative bacterium, has become increasingly challenging to treat with conventional therapeutics, often leading to antibiotic failure[3]. In nosocomial settings, its ability to form biofilms results in chronic infections in patients with cystic fibrosis, burn wounds, and medical devices (e.g., urinary catheters and implants)[1, 4, 5, 6, 7]. A biofilm is a complex, compact community of bacteria embedded in a self-produced extracellular matrix (EPS) made of polysaccharides, extracellular DNA, proteins, and lipids[1, 3, 4]. Constituting 90% of the biofilm mass, the matrix acts as a protective barrier for microcolonies against environmental stresses, allowing the adaptation of *P. aeruginosa* to extreme niches[3]. Internally, EPS facilitates nutrient flow, antibiotic tolerance, and cell-to-cell communication[1]. Historically, planktonic bacteria have been studied as primitive, solitary organisms lacking the social and behavioral mechanisms observed in eukaryotes. However, in recent decades, research has redefined them as complex social communities that interact, coordinate, and communicate through systems known as quorum-sensing (QS)[8, 9]. QS systems are concentration-dependent mechanisms that operate through small molecules called autoinducers to regulate gene expression, antibiotic production, virulence factors, and biofilm formation[1, 2, 8]. In *P. aeruginosa*, three distinct QS systems, LasI/LasR, RhlI/RhIR, and PQS, are utilized by bacteria to evade the host immune system and produce public goods (e.g., virulence factors) that increase antibiotic tolerance[3, 4, 9].

As the failure of synthetic antibiotics has become increasingly common, researchers are turning to natural compounds as promising alternatives. Due to the coevolution of bacteria and fungi in their ecological niche, fungi like *C. albicans* have been able to produce quorum-sensing molecules that may interfere with *P. aeruginosa* quorum-sensing pathways[10]. Among these, tyrosol and farnesol have emerged as potential quorum-sensing inhibitors (QSIs) with implications for antibiotic stewardship. While tyrosol and farnesol have been extensively investigated in the context of *C. albicans* biofilm formation, little research has studied their effects on other microorganisms and their potential therapeutic applications. This review demonstrates that tyrosol and farnesol have significant clinical potential as adjuncts to conventional antibiotics. By modulating quorum-sensing pathways and virulence factors expression rather than bacterial growth, they enhance antibiotic susceptibility while minimizing selective pressures for resistance development. As this avenue remains largely unexplored, we will critically analyze current limitations and propose future research directions.

2. Methodology

A literature search was conducted using Pubmed, and Scopus. Search terms included "farnesol", "tyrosol", "quorum-sensing", "quorum-quenching", "*Pseudomonas aeruginosas*" and "*Candida albicans*", among others. Articles published in the last 20 years were considered. Titles were screened for relevance and studies focused on investigating the effect of farnesol and tyrosol on *P. aeruginosa* biofilm formation, virulence factors, and combinatorial therapeutics were included. Papers published in another language than English were excluded. A total of 27 papers were included, with 16

primary studies, 10 reviews, and 1 book chapter.

3. Quorum-Sensing Systems in *P. aeruginosa*

Quorum-sensing is a density-dependent mechanism that uses chemical signals to enable the coordination of social behaviors within bacterial communities. The *P. aeruginosa* QS system contains three interdependent circuits–LasI/LasR, RhlI/RhIR, and PQS–with LasI and RhlI approximately regulating 10% of *P. aeruginosa* genome[3, 4, 9, 11]. The LasI/LasR system typically regulates the RhlI/RhIR, which then influences PQS production, while PQS is an intermediary that modulates both AHL-mediated systems[12]. The LasI/LasR and RhlI/RhIR use acyl-homoserine lactone signals, whereas the PQS system operates with quinolone signaling[3, 4, 9]. Relevant to this review is the contribution of QS to biofilm formation in *P. aeruginosa*, including the expression of genes encoding for proteases, toxins, and virulence factors at bacterial quorum size. QS-regulated products can influence group behaviors like nutrient acquisition, microbial competition, antibiotic tolerance, cytotoxicity, and pathogenicity[4]. This enables the biofilm to persist in a sessile stage, exhibiting a 1000-fold more tolerance to current antibiotic treatment than planktonic bacteria[2, 3, 4].

3.1 AHLs System

The AHL-mediated quorum-sensing systems in *P. aeruginosa* consist of two circuits: LasI/LasR and RhlI/RhIR, both regulated by LuxI-like synthases, LasI and RhlI, respectively[3, 4, 9]. LasI synthase produces the signal molecule 3OC12-HSL (N-3-oxo-dodecanoyl homoserine lactone), which binds to the transcriptional regulator LasR at quorum-sensing threshold levels. Similarly, RhlI synthase produces C4-HSL (N-butyryl homoserine lactone), which binds to RhIR[34, 11]. These interactions result in the production of LuxR-like transcription factors, functioning mainly as activators of QS-regulated genes[9]. The LasI/LasR and RhlI/RhIR systems regulate the expression of virulence factors in distinct and independent ways, including protease elastase (*lasB* gene) and rhamnolipids, respectively[3]. Rhamnolipids, a biosurfactant, preserves mature biofilm architecture by maintaining pores and channels between microcolonies, facilitating nutrient and liquid flow within the matrix[9]. Additionally, they contribute to immune evasion by inducing lytic necrosis in polymorphonuclear neutrophils (PMNs) and macrophages[3, 4]. It is worth noting that QS-regulated genes can rely on either LasR or RhlR, while others, like *lasB*, rely on both circuits[9].

3.2 PQS System

The PQS system, the most recently discovered, utilizes two signaling molecules: high-affinity PQS (2-heptyl-3-hydroxy-4-quinolone) and low-affinity HHQ (2-heptyl-4-hydroxyquinoline)[3, 4]. These chemical signals activate the transcriptional regulator *PqsR*, leading to the expression of the *pgsABCDE* operon. PQS operates through a self-reinforcing feedback loop, similar to the LasR-LasI AHL system[4, 9]. Acting as an intermediary system in the quorum-sensing hierarchy of *P. aeruginosa*, PQS is activated by LasR but inhibited by RhlR. Work has also shown that the gene product of *pqsE*, while not directly involved in PQS, can regulate RhlR activity, but its mechanistic inhibition remains unclear[9]. The QS-regulated products of the PQS system are lectin A, hydrogen cyanide, and pyocyanin[3]. Pyocyanin is of particular interest as it is responsible for approximately 95% of *P. aeruginosa* antimicrobial properties and promotes biofilm formation[13].

4. Effect of Tyrosol and Farnesol in *P. aeruginosa*

Farnesol and tyrosol, *C. albicans*-derived compounds, are potential QSIs that can disrupt quorum-sensing pathways in *P. aeruginosa*. In *C. albicans*, they have been shown to work in tandem during biofilm formation and morphological growth; tyrosol promotes the transition from yeast to hyphae while farnesol inhibits this shift at high cell densities[2, 10, 14, 15]. This dynamic regulates *C. albicans* pathogenicity and biofilm structure, shaping its response to different ecological niches and natural competitors like *P. aeruginosa*[10]. In polymicrobial infections, *C. albicans* and *P. aeruginosa* not only co-exist but also engage in bidirectional communication. Research has shown that *P. aeruginosa* can impede fungal growth through 3OC12-HSL, a QS signaling molecule, while *C. albicans* can disrupt PQS signal and associated virulence factor (e.g. pyocyanin) through farnesol[11, 12, 14, 16, 17]. In *Pseudomonas aeruginosa*-driven chronic infections, tyrosol and farnesol are promising therapeutics, either in isolation or combined with antimicrobials. For example, in PAO1 biofilms, farnesol emulsion of 3mg/ml not only disrupted biofilm formation, but it also preserved lung cell viability more effectively than the antibiotic ciprofloxacin[18]

4.1 Disruption of Quorum-Sensing Pathways

QPCR analysis of non-mucoid (NCTC 10,662), mucoid (PAO1), and heavily mucoid (RBHi) strains of *Pseudomonas aeruginosa* demonstrates that *C. albicans*-derived compounds, farnesol, and tyrosol, decrease the expression of LasI and *RhlL*[10, 19]. In turn, this downregulates the production of AHLs signal molecules, 3OC12-HSL and C4-HSL. Furthermore, at α=0.05, farnesol appears to have a stronger effect on the inhibiting of LasI compared to tyrosol[10]. This suggests that farnesol may be more effective in disrupting the LasI/LasR. However, farnesol shows to up-regulate LasR activity in both strains NCTC 10,622, and PAO1, whereas tyrosol only increased LasR activity in the latter[10]. This finding highlights the strain specificity of quorum sensing modulators. Another study demonstrates that tyrosol decreased C4-HSL and 3OC12-HSL by 72%, and 75% at 1/4x MIC, respectively in *P. aeruginosa*[19]. The interactions of farnesol and tyrosol with the QS-system in *P. aeruginosa* warrants further investigation, as the mechanisms of actions under those compounds operating in various bacterial strains remain unclear. While these compounds can be beneficial, they can have inadvertent effects in specific contexts, such as enhancing biofilm persistence or virulence, which makes their use in treatment strategies rather unpredictable.

4.2 Regulation of virulence factors and growth

In recent years, it has been shown that compounds like farnesol exhibit anti-biofilm properties, whereas tyrosol possess antibacterial activity, although some studies suggest that farnesol does exhibit antibacterial activity as well[8, 10, 19, 20, 21, 22, 23, 24]. These properties, respectively, halt or slow the progression of the biofilm and limit the growth and viability of bacteria. Additional research has indicated that farnesol disrupts the PQS system of *P. aeruginosa* by inhibiting 2-heptyl-3-hydroxy-4-quinolone[2] and represses *pqsA* transcription, first gene of the PQS operon, in a dose-dependent manner[14]. This leads to a reduction in the production of pyocyanin, a PQS-regulated virulence factor, that decreases bacteria's swarming motility by lowering haemolysin production[2, 16]. It is worth noting that, as well as inhibiting protease production and impacting swarming motility, tyrosol inhibits heamolysin production to a greater degree than farnesol[2, 8, 19]. Specifically, testing on 20 *P. aeruginosa* isolates at α=0.001, 1.2 μM tyrosol significantly decreases both heamolysin and protease production whereas 10 μM farnesol only affects heamolysin production[8]. Furthermore, tyrosol at 10 μM inhibited >50% of *P. aeruginosa* growth after a 16h cultivation, whereas farnesol concentrations of 200 μM inhibited >30% growth[8]. It is important to note that anti-resistance advantages are solely present when QSIs are used at their sub-inhibitory concentrations, which disrupt QS signaling pathways without affecting cell viability. Concentrations lower than 1.2 μM tyrosol and 10 μM farnesol have little to no effect on *P. aeruginosa* growth[8]. However, farnesol concentrations of 25 μM effectively disrupt the PQS system[14]. Further research by Cugini *et al.* demonstrates that farnesol can stimulate PQS production in *P. aeruginosa* LasR-defective mutants,

Table 1. Summarizing key studies evaluating the effects of farnesol and tyrosol on P. aeruginosa strains

Strain Type	Experimental Model	Treatment	Key Findings	Study
PAO1	In vitro single-species biofilms of *P. aeruginosa*	Farnesol/ tyrosol	Farnesol showed stronger antibiofilm activity	(Hacioglu *et al.*, 2024)
	In vitro dual-species biofilms (*C. albicans* + *P. aeruginosa*)	Farnesol/ tyrosol	Both reduced biofilm counts, especially farnesol	
Clinical isolates	*In vitro*	Farnesol/ tyrosol	Growth inhibition and reduced haemolysin and protease production at certain concentrations	(Abdel-Rhman *et al.*, 2015)
NCTC 10,662 PAO1 RBHi	*In vitro*	Tyrosol and farnesol with furanone treatment	Up-regulation of LasR with farnesol Up-regulation of LasR with tyrosol and farnesol Up-regulation of RhlR receptor with tyrosol Shared results included: • Significant reduction in LasI protein with farnesol > tyrosol; • Reductions in mRNA expression for RhlI protein; • Down-regulation of toxA, aprA, rhlAB and LasB	(Kalgudi *et al.*, 2022)
PA14	*In vitro*	Farnesol	Reduction in pyocyanin production and dose-dependent reduction in PQS production by inhibition of *pqsA*	(Cugini, 2007)
	In vitro C. albicans and *P. aeruginosa* co-cultures	Farnesol	Reduction in pyocyanin and PQS production	
PAO1	*In vitro*	Farnesol	Reduction in pyocyanin production	
ΔLasR	*In vitro*	Farnesol	Stimulation of PQS production	(Cugini *et al.*, 2010)

which are frequently observed in cystic fibrosis infections[25]. This finding further underscores that QSIs may exhibit strain-specific effects which requires extensive investigation when developing targeted therapeutic interventions. Another study demonstrates that farnesol and tyrosol can down-regulate virulence-related genes that code for the proteins toxA, aprA, LasB, and rhlAB, which are key to the production of rhamnolipids[10]. Findings are summarized in Table 1.

5. Implications for Antimicrobial Resistance

In the past decades, *P. aeruginosa* has become increasingly resistant to many classes of antibiotics due to its high versatility and ability to form persistent biofilms[3]. In nosocomial infections, broad spectrum antibiotics result in antibiotic failure, often giving rise to chronic diseases. This can lead to more invasive procedures such as surgical debridement, a standard method for treating chronic wounds[5, 6, 7, 20]. However, natural QS-agents like farnesol and tyrosol offer a promising avenue that can co-evolve with *P. aeruginosa* in their ecological niche[10]. Evidence suggests that *C. albicans* and *P. aeruginosa* have mutually antagonistic effects that ultimately increase mutability rates in both species, favoring constant evolution[16, 17] .

Contrary to synthetic antibiotics, compounds like farnesol and tyrosol can naturally develop counter-adaptations to *P. aeruginosa* resistance mechanisms, and if harnessed, can provide novel therapeutics. If combined with other pharmacological products, QS-agents, including farnesol and tyrosol, might enhance antibiotic susceptibility by disrupting quorum-sensing pathways and regulating virulence factors. This facilitates the penetration of antibiotics through the biofilm's extracellular matrix. It is widely believed that QS-agents, farnesol and tyrosol, do not interfere with the growth of the biofilm when used at their sub-inhibitory concentrations. This minimizes the selective pressures for resistance[14], slowing down the emergence of multi-drug-resistant strains of *P. aeruginosa*[4]. While QS-agents present a propitious strategy, considerations concerning their long-term efficacy, potential bacterial interactions and clinical implementation warrant further investigation (discussed in a later section).

5.1 Combination therapeutics

Combination therapeutics involve the use of several drugs that synergistically interact to target different biological pathways or mechanisms. By combining natural compounds such as farnesol and tyrosol with antibiotics, we can potentially minimize the occurrence of invasive procedures while mitigating the selective pressures of antimicrobial resistance on bacterial strains. Additionally, natural compounds can have synergistic effects with conventional antibiotics, which can mitigate the dosage of antibiotics, preventing their overuse in medical settings. Multiple studies have demonstrated that those compounds enhance antibiotic susceptibility in organisms such as *E. coli*, *S. aureus* and *P. aeruginosa*[12, 21, 26].

Hacioglu *et al.* in-vitro study demonstrates that the combination of farnesol with antibiotics, particularly colistin (200 mg/L), produced a statistically significant effect at α=0.05, whereas tyrosol combinations did not yield significant results in single-species *P. aeruginosa* biofilms[2]. However, Abdel-Rhman S.H. *et al.* reported that tyrosol and farnesol, when used at their subinhibitory concentrations, did not have a significant effect on the antibacterial activity of ceftriaxone, ciprofloxacin, and gentamicin on *P. aeruginosa* at concentrations of 64000-0.12, 4000-0.004, and 2000-0.002 μg/mL respectively[8]. Taking it a step further, Bandara *et al.* demonstrated that liposomal ciprofloxacin combined with farnesol disrupted extensively the biofilm's structure and lowered metabolic activity. This resulted in a significant decrease in viability[27]. Using the *P. aeruginosa* TL2314 strain in *G. mellonella*, Han *et al.* (2023) shows in-vitro and *in vivo* synergistic antibacterial effects between colistin and farnesol. While this review focuses on single-species *P. aeruginosa* biofilms, an *in vivo* study using *C. elegans* model shows that the combination of tyrosol or farnesol with colistin is statistically significant, at α=0.05 in dual-species *C. albicans*-*P. aeruginosa* biofilms[2]. Specifically, the combination of farnesol and colistin was most effective, which supports in vitro results in single-species *P. aeruginosa* biofilms[2]. Additionally, combinations of farnesol and tyrosol with fluconazole (10 mg/L) increased *C. elegans* viability and proved to be more effective than isolated QQMs[2]. To date, few *in vivo* studies have tested farnesol and tyrosol with antibiotics in single-species biofilms. Nonetheless, further investigation would be relevant based on the *in vivo* findings in dual-species biofilms. Along with the previous studies, this suggests that

Table 2. Summarizing key studies evaluating the effect of combinatorial therapeutics on P. aeruginosa strains

Strain Type	Experimental Model	Treatment	Key Outcomes	Study
PAO1	*In vitro* single-species biofilms	Tyrosol/ Farnesol; Fluconazole/ amphotericin/ caspofungin/ aztreonam/ colistin/ tobramycin	Farnesol-colistin combination is most effective; all antibiotic and farnesol are statistically significant	(Hacioglu *et al.*, 2024)
	In vitro dual-species biofilms (*C. albicans* + *P. aeruginosa*)	Tyrosol/ Farnesol; Fluconazole/ amphotericin/ caspofungin/ aztreonam/ colistin/ tobramycin	Farnesol-colistin combination is most effective; all combinations are statistically significant	
	In vivo C. elegans models (*C. albicans* + *P. aeruginosa*)	Tyrosol/ Farnesol; Colistin/ Fluconazole	Increased survival for any combinations; Farnesol-colistin combination was more effective than tyrosol combinations against *P. aeruginosa*	
Clinical isolates	*In vitro*	Farnesol/ Tyrosol; Ceftriaxone/ Ciprofloxacin/ Gentamicin	No significant effect on the antibacterial activity of tested antibiotics when used at their sub-inhibitory concentrations	(Abdel-Rhman *et al.*, 2015)
PAO1	*In vitro*	Farnesol; Liposomal ciprofloxacin	Biofilm disruption and lower live/dead cell ratio	(Bandara *et al.*, 2016)
TL2314	*In vitro* and *in vivo G.mellonella* models	Farnesol; colistin	Synergistic antibacterial effect between farnesol and colistin	(Han *et al.*, 2023)

tyrosol and farnesol may act synergistically with the tested antibiotics, enabling reduced antibiotic doses without promoting resistance or tolerance in *P. aeruginosa* strains at their specific concentrations[2, 8, 27].

For clinical use, it will be crucial to use effective detection methods of early-stages biofilms to ensure appropriate treatment as the effectiveness of combinatorial therapeutics can depend on the maturation stages of biofilms. Therefore, treatments applied during the early stages of biofilm formation are usually more effective than those applied to mature biofilms. Immature biofilms usually exhibit greater susceptibility to antibiotics, whereas mature biofilms tend to be more resistant due to structural and physiological changes, such as the development of the extracellular matrix[5, 6]. Findings are summarized in Table 2.

6. Future Direction and Research Gaps

The research of natural compounds as potential modulators of the quorum-sensing system is a growing and active field of research. Yet, there are many research gaps that need to be addressed, ultimately informing the research processes.

Since very few studies have been conducted on *in vivo* models, there is a lack of knowledge on the biological plausibility of farnesol and tyrosol in a medical setting. *In vivo* studies will be useful in examining fully the phenotypic and genotypic complexity of biofilm growth in diverse micro-environment[7]. Therefore, they will be key in determining the mechanisms of actions of quorum-sensing inhibitors, dose-response, and potential off-target interactions, all of which remain unclear. Although not in the scope of this mini-review, it is also worth noting that future research on dual-species biofilms would be relevant to understanding potential undesirable off-target synergistic effects at play between *C. albicans* and *P. aeruginosa*. There is also a need to assess the stability and bioavailability of farnesol and tyrosol to determine if pharmaceutical production is plausible and possible at the global stage. Furthermore, there is the possibility that *P. aeruginosa* strains develop resistance to QS-interfering agents themselves. However, this is a challenge pertinent to any new and current compounds, synthetic or natural. The development of resistance is an evolutionary process that cannot be evaded but slowed down by a smart distribution and usage of antimicrobials as well as diversification of treatments.

As discussed in a previous section, combination therapeutics may be used adjunctively with standard care to develop targeted interventions that could minimize invasive procedures when infections are detected at an early stage[5, 7]. However, within the scope of this review, *in vivo* and *in-vitro* studies on the effect of tyrosol and farnesol used conjointly with antibiotics in single-species *P. aeruginosa* biofilms were sparse. To investigate the role of QSIs in antimicrobial stewardship, we need to explore the potential for combinatorial therapies and determine the most effective combinations specific to *P. aeruginosa* strains[2]. Kalgudi *et al.* show that, mucoid, non-mucoid, and heavily mucoid *P. aeruginosa* strains responded differently to various combinations. This highlights the need for testing the strain-specific effect of farnesol and tyrosol as *Pseudomonas aeruginosa* is an extremely versatile and adaptive organism that can express different phenotypes.

In retrospect, natural compounds like tyrosol and farnesol have demonstrated anti-biofilm and anti-bacterial activity in single-species *P. aeruginosa* biofilms, primarily through the quorum-sensing dysregulation and the regulation of the expression of virulence factors. As antimicrobial resistance continues to rise, quorum-sensing inhibitors could open a new niche within antibiotic stewardship, offering dynamic alternative treatments.

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