

Short Note

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Short Note

Advances in Compounds Targeting Regulatory Mechanisms of Biofilm Formation in Unicellular Eukaryotes: Insights from 2024 Research and Applications in Vietnam

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Abstract: Biofilm formation by unicellular eukaryotes presents major challenges in healthcare, agriculture, and food industries, primarily due to enhanced resistance to environmental stressors and antimicrobial agents. Understanding the regulatory mechanisms of biofilm formation, such as quorum sensing (QS) and cyclic di-GMP signaling, has led to the discovery of novel compounds that can inhibit biofilm development. In 2024, significant advancements were made in identifying compounds like betulinic acid, methyl anthranilate, and pulmonarin B analogues that target these pathways. This review explores the potential applications of these compounds, especially in Vietnam's agriculture and food industries, where biofilm formation contributes to contamination and antimicrobial resistance. The findings underscore the global relevance of biofilm-disrupting technologies and their role in combating biofilm-associated infections and resistance.

Keywords: biofilm formation; quorum sensing inhibitors; cyclic di-GMP; betulinic acid; pulmonarin B analogues; antimicrobial resistance; unicellular eukaryotes; Vietnam

1. Introduction

Biofilm formation is a survival strategy utilized by unicellular eukaryotes, including fungi and protozoa, which allows them to thrive in hostile environments. Biofilms consist of microbial communities that adhere to surfaces and are embedded within an extracellular matrix of polysaccharides, proteins, and nucleic acids. This matrix serves as a protective barrier, shielding the microorganisms from antimicrobial agents and immune system attacks. Biofilm formation is a significant problem in healthcare, as it is associated with persistent infections and increased resistance to antibiotics. Additionally, biofilms contribute to contamination and spoilage in agriculture and food industries, especially in developing regions like Vietnam [1].

Understanding the molecular mechanisms that regulate biofilm formation is crucial for developing effective interventions. The two primary pathways controlling biofilm development in unicellular eukaryotes are quorum sensing (QS) and cyclic di-GMP signaling. QS enables microbial populations to communicate and regulate collective behaviors, such as virulence and biofilm formation, based on cell density. Cyclic di-GMP signaling controls the transition between motile and sessile lifestyles, with high levels of cyclic di-GMP promoting biofilm formation. Recent research has focused on compounds that disrupt these pathways, offering promising strategies to prevent and dismantle biofilms.

2. Regulatory Mechanisms of Biofilm Formation

2.1. Quorum Sensing (QS)

Quorum sensing (QS) is a cell-density-dependent signaling system that allows microorganisms to coordinate behaviors that benefit the entire population, such as biofilm formation, virulence, and resistance to antimicrobials. In gram-negative bacteria, QS signaling is mediated by the production and detection of acyl-homoserine lactones (AHLs). These molecules accumulate in the environment as cell density increases, and once a threshold concentration is reached, they activate QS-regulated gene expression, which promotes biofilm formation and the production of virulence factors.

In unicellular eukaryotes, such as *Candida albicans*, quorum sensing plays a vital role in regulating biofilm development and morphological changes that enhance survival. Compounds that inhibit QS, known as quorum sensing inhibitors (QSIs), have been identified as a promising approach to disrupt biofilm formation without inducing microbial resistance [2].

2.2. Cyclic di-GMP Signaling

Cyclic di-GMP is a second messenger that plays a central role in regulating the switch between motile and sessile states in unicellular organisms. When cyclic di-GMP levels are high, biofilm formation is promoted through the enhanced production of extracellular polymeric substances (EPS), which form the structural basis of the biofilm matrix. Lower levels of cyclic di-GMP, on the other hand, promote cell motility and biofilm dispersal. Compounds that target the cyclic di-GMP pathway have emerged as potential therapeutic agents for controlling biofilm formation by preventing the transition to the biofilm state or promoting the breakdown of established biofilms [3].

3. Recent Advances in Biofilm-Disrupting Compounds

In 2024, several compounds have been identified and studied for their ability to disrupt biofilm formation by interfering with quorum sensing and cyclic di-GMP signaling. These compounds offer promising avenues for preventing and treating biofilm-associated infections and contamination.

Table 1. Summary of Biofilm-Disrupting Compounds, Mechanisms, and Applications (2024).

Compound	Mechanism of Action	Biofilm Inhibition Effect	Applications	Reference
Betulin and Betulinic Acid	Inhibits QS, reduces exopolysaccharide production and surface hydrophobicity	Reduces biofilm formation in <i>Pseudomonas aeruginosa</i> by 80%	Healthcare, agriculture, aquaculture	[4]
Methyl Anthranilate	Inhibits QS, reduces AHL production	Reduces biofilm formation in <i>Aeromonas sobria</i> by 51.44%, motility by 74%	Aquaculture, food processing	[5]
Pulmonarin B Analogues	Disrupts cell adhesion and biofilm formation	Reduces biofilm formation in <i>Pseudomonas aeruginosa</i> by 39.8%	Industrial water systems, food processing	[3]
Cyclic di-GMP G-quadruplex inducers	Inhibits cyclic di-GMP signaling, reduces polysaccharide secretion	Inhibits biofilm formation by 62.18%, reduces virulence factors by 58%	Healthcare, industrial systems	[6]
Paerucumarin	Modulates virulence factors and biofilm-related genes in <i>Pseudomonas aeruginosa</i>	Reduces biofilm development, enhances antimicrobial susceptibility	Healthcare, hospital sanitation	[2]
Silver Nanoparticles (AgNPs)	Disrupts biofilm formation by inhibiting bacterial attachment and matrix formation	Reduces biofilm formation on dairy industry surfaces by 70%	Food processing, dairy industry sanitation	[7]

4. Biofilm Formation in Vietnam: Case Studies and Relevance

In Vietnam, biofilm formation poses significant challenges, particularly in agriculture and food processing industries. In 2024, a study focusing on *Salmonella* isolates from swine-feed mills in Vietnam found that 98.15% of the isolates were capable of forming biofilms at 28°C. This highlights

the prevalence of biofilm-related contamination in animal farming, which contributes to antimicrobial resistance and foodborne infections [1].

Additionally, research into the use of silver nanoparticles (AgNPs) synthesized from natural products, such as essential oils, has shown promise in biofilm control within Vietnam's dairy industry. These nanoparticles were found to be effective in reducing bacterial attachment and biofilm formation on processing surfaces, suggesting that AgNPs could be a viable solution for improving hygiene standards in food production [7].

5. Discussion

Despite the promising results of biofilm-disrupting compounds, challenges remain in translating these findings into practical applications. Compounds like QS inhibitors and cyclic di-GMP blockers have shown efficacy in laboratory settings, but their stability, bioavailability, and potential toxicity in real-world environments need to be addressed. Additionally, the development of resistance to these compounds is a concern that requires further investigation.

In Vietnam, the pervasiveness of biofilm formation in agriculture and food industries underscores the need for effective biofilm control strategies. The findings from swine-feed mills and dairy production facilities indicate that biofilms contribute to the persistence of pathogens and resistance to disinfection efforts, making it essential to implement new biofilm-disrupting technologies to mitigate these risks [1,7].

6. Conclusions

The discovery of biofilm-disrupting compounds, such as betulinic acid, methyl anthranilate, and pulmonarin B analogues, marks significant progress in the fight against biofilm-associated infections and contamination. These compounds target key regulatory mechanisms, including quorum sensing and cyclic di-GMP signaling, offering new opportunities for biofilm control in healthcare, agriculture, and food processing. In Vietnam, where biofilm formation is a persistent issue in animal husbandry and food industries, the application of these compounds has the potential to significantly reduce contamination and improve public health. However, further research is necessary to optimize these compounds for practical use and to address the challenges of biofilm management in real-world environments.

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