Infection and Drug Resistance

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REVIEW

Research Progress on Antivirulence Agents Targeting the Accessory Gene Regulator (Agr) System of *Staphylococcus Aureus*

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Abstract: With global spread of drug-resistant strains such as methicillin-resistant *Staphylococcus aureus*, conventional antimicrobial strategies face significant challenges, which prompt the development of antiinfective agents with alternative strategies. The anti-virulence approach targets bacterial virulence factors without directly killing the bacteria. The accessory gene regulator (Agr) system, a central quorum-sensing pathway in *S. aureus*, represents a primary target for such therapies. However, inhibition of the Agr system presents a dual nature: while it attenuates acute virulence, it may inadvertently promote biofilm formation and poses potential therapeutic trade-offs. This review provides an overview of the Agr system structure and functional mechanisms alongside recent advances in synthetic and natural quorum sensing inhibitors targeting the Agr system in *S. aureus*. By regulating primary virulence factors, this system serves as an ideal target for antivirulence therapies. Disrupting Agr can reduce pathogenicity without affecting bacterial growth. Current researches suggest that the Agr inhibitors hold significant potential as novel therapeutics, though their clinical application requires careful consideration of the dual effects.

Keywords: quorum sensing, Agr system, antivirulence, Agr inhibitors, quenching antibodies

Introduction

Staphylococcus aureus is a leading pathogen responsible for a wide range of infections from skin/soft tissue infections to life-threatening conditions such as pneumonia and sepsis.[1] Over the past several decades, global spread of multidrug resistant strains, particularly methicillin-resistant *S. aureus* (MRSA), has posed significant challenges in the clinical treatment of infections caused by multidrug resistant *S. aureus*.[1,2] MRSA infections cause over 100,000 deaths annually worldwide.[3] Despite the development of novel antibiotics, the rapid evolution of drug resistance has significantly diminished the efficacy of traditional bactericidal strategies.[4] Therefore, there is an urgent need to develop new antimicrobial approaches.

Quorum sensing (QS) is a crucial regulatory mechanism through which bacteria coordinate group behaviors by secreting and sensing signaling molecules.[5] In *S. aureus*, QS plays a critical role in regulating the expression of virulence factors and biofilm formation, which are essential for establishing and maintaining infections.[6,7] Interference with QS can markedly attenuate pathogenicity without inhibiting growth, thereby reducing selective pressure and delays resistance development.[8] Unlike many Gram-negative bacteria that possess multiple QS circuits, *S. aureus* relies on a single system, the accessory gene regulator (Agr), which detects autoinducing peptide (AIP) gradients and dynamically modulates virulence gene expression.[9,10] By contrast, Gram-negative pathogens, such as *Pseudomonas aeruginosa*, employ multiple interconnected QS systems (eg., *las, rhl*, and *pqs* systems), which complicate inhibitor design and may allow compensatory pathway activation upon single-target inhibition.[11,12] The structural simplicity of the Agr system thus offers a more straightforward target for

https://doi.org/10.2147/IDR.S594449
Received: 7 January 2026
Accepted: 13 March 2026
Published: 24 March 2026

therapeutic intervention, with reduced risk of resistance bypass mechanisms. These characteristics make the Agr system a promising target for antivirulence therapy.

Compared with traditional bactericidal strategies, antivirulence approaches possess unique advantages.[13] First, these approaches alleviate collateral damage to host tissues by inhibiting virulence factor rather than directly killing bacteria. Second, this disarmament strategy exerts lower selection pressure, and delays resistance emergence. Finally, Agr inhibitors may synergize with existing antibiotics to enhance their therapeutic efficacy.[14] Among antivirulence targets, the Agr-targeted therapy occupies a distinctive position among antivirulence strategies: unlike direct virulence factor neutralization or *ica*-targeted anti-biofilm approaches that address single phenotypes, Agr inhibition offers broad-spectrum virulence suppression at the cost of potential biofilm enhancement;[13,15] Conversely, alternative quorum sensing targets such as the *sae* system yield more modest effects due to their less central regulatory roles.[16] The present article reviews the components and functions of the Agr system as well as recent advances in *S. aureus* quorum sensing inhibitors (QSIs), and provides perspectives on future development in this area.

Structure and Function of the Agr System

The *agr* gene cluster in *S. aureus* comprises two transcriptional units: RNAII and RNAIII. The RNAII operon consists of four genes (*agrA, agrB, agrC*, and *agrD*), which encode the core components of the Agr system. Specifically, *agrD* encodes the precursor of the autoinducing peptide; *agrB* encodes a membrane-bound protease responsible for processing and secreting the AIP precursor; while *agrC* and *agrA* encode a histidine kinase and a response regulator protein, respectively, which form a two-component signal transduction system. RNAIII serves as the primary effector molecule, which regulates the expression of target genes including those encoding virulence factors.[5,9,10,17]

AIP biosynthesis begins with the precursor peptide encoded by *agrD*, which is processed by AgrB and MroQ to produce a mature cyclic peptide.[18] When AIP concentrations reach a threshold level, AIP binds to the transmembrane receptor AgrC, and triggers its autophosphorylation and subsequent transfer of the phosphate group to AgrA.[19] Activated AgrA acts as a transcription factor that promotes the transcription of both RNAII and RNAIII, thereby establishing a positive feedback loop that amplifies the signal cascade[20] (Figure 1).

The Agr system regulates the expression of associated genes through RNAIII. During the early stages of infection, when Agr activity is low, surface proteins such as Protein A and fibronectin-binding proteins are expressed and facilitate bacterial adhesion and colonization.[21] As AIP concentrations increase, the activated Agr system upregulates secreted virulence factors like α-hemolysin and phenol-soluble modulins (PSMs), which promote tissue invasion and immune evasion.[22,23] Simultaneously, the Agr system dynamically controls biofilm formation and dispersal by modulating the *ica* operon and protease expression. This temporal regulation mechanism enables *S. aureus* to adaptively adjust its behavior across different infection stages and microenvironments.[14,24]

Given the central role of the Agr system in modulating *S. aureus* virulence, its genetic or pharmacological inactivation generally attenuates toxin production and lessens tissue damage in multiple animal models.[25] However, the same mutation frequently enhances biofilm formation, which impairs neutrophil-mediated clearance and leads to persistent colonization or chronic infection. Moreover, rapid compensatory up-regulation of non-Agr virulence determinants and the possible selection of Agr-negative strains have been observed in patients receiving long-term intensive care.[16] These contradictory outcomes underscore that Agr inhibition is not a universally beneficial intervention and highlight the need for carefully timed or combination therapy.

Research Progress on Agr System Inhibitors

Synthetic Quorum Sensing Inhibitors

AIP Analogs

The discovery of AIP analogs as QSIs can be traced back to 1997, when cross-inhibiting AIPs were first shown to antagonize AgrC by interfering with AIP recognition.[26] This finding established competitive receptor binding as a viable strategy for blocking QS signaling. Although rapidly cleared in vivo, AIP-2 was found to prevent abscess formation by disrupting the transient Agr-dependent initiation window.[27,28]

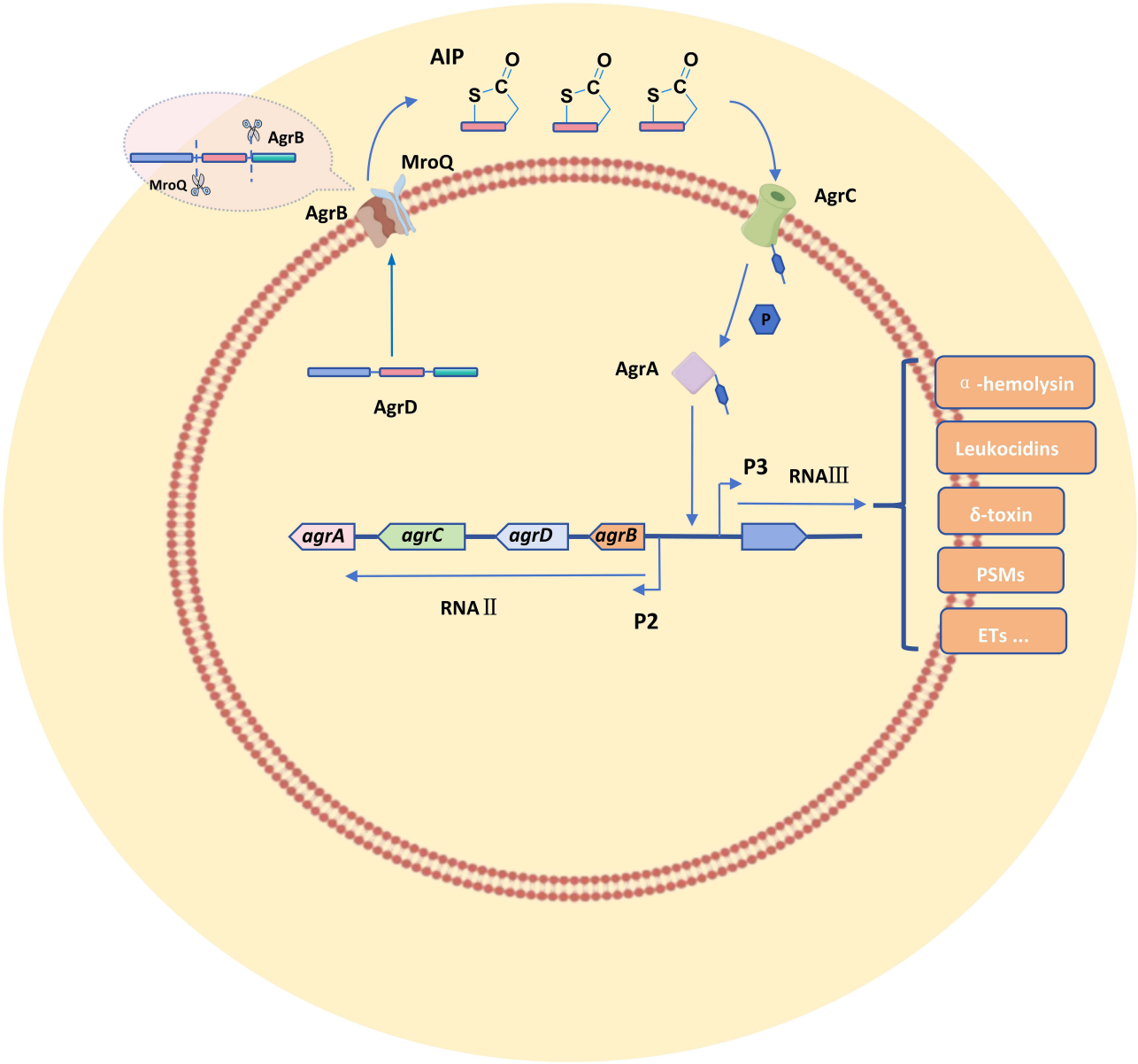

Figure 1 Regulatory mechanism of the Agr system in *Staphylococcus aureus*. The RNAII operon includes four genes: *agrA*, *agrB*, *agrC*, and *agrD*. The *agrD* gene encodes the AIP precursor (AgrD), which is processed by AgrB (the membrane-bound protease encoded by *agrB*) and MroQ to generate mature AIP. Upon reaching a threshold concentration, AIP activates the AgrC-AgrA two-component signal transduction system and drives positive feedback in RNAII transcription and RNAIII-mediated regulation of virulence genes such as α-hemolysin, leukocidins, δ-toxin, pore-forming small molecules (PSMs), and enterotoxins (ETs).

However, peptide-based QSIs face inherent pharmacokinetic limitations with susceptibility to proteolytic degradation and poor metabolic stability. To overcome these challenges, Tal-Gan et al undertook a systematic synthetic study of AIP-III analogs. Among them, four lead AgrC inhibitors (AIP-III D4A, tAIP-III D2A, AIP-III N2A/D4A, and AIP-III I1A/N2A/D4A) reduced the production of toxic shock syndrome toxin-1, a QS-regulated virulence factor, by over 80% at nanomolar concentrations. Recognizing that the thioester linkage in native AIPs is prone to hydrolysis, they subsequently developed amide-linked derivatives to enhance stability and solubility while retaining potent inhibitory activity against the AgrC receptor in *S. aureus*.[29,30] Starting with t-AIP-II, they identified a peptidomimetic compound, n7OFF, which shares amphiphilic characteristics with native AIP-II and AIP-III D4A.[31] Through further replacement of labile peptide bonds with non-hydrolyzable linkages, subsequent structural modifications of n7OFF yielded the highly active Agr

https://doi.org/10.2147/IDR.S594449

inhibitor PhPr(3Br)-Bnc3, which represents the most potent peptidomimetic-type Agr inhibitor across all four *S. aureus* groups reported to date.[32,33]

RNAIII Inhibiting Peptide (RIP) Analogs

The RIP is produced by coagulase negative *Staphylococcus* with characteristic sequence YSPXTNF, where X can be a cysteine, a tryptophan, or a modified amino acid. RIP and its derivatives suppress RNAIII transcription, which in turn inhibits the production of QS-regulated toxins. Synthetic RIP analogs serve as potent suppressors of Agr-regulated exotoxin production in *S. aureus* in vitro.[34,35] RIP had been demonstrated efficacy in treating various animal infection models including cellulitis in mice, keratitis in rabbits, osteomyelitis in rabbits, mastitis in cows, and septic arthritis in mice.[36,37] The RIP treatment significantly reduced bacterial pathology and delayed the onset of disease symptoms.

Cirioni, Simonetti et al synthesized novel RIP derivatives including FS3, FS8, and FS10, which effectively inhibit the QS system of *S. aureus*. In a rat vascular graft infection model, the heptapeptide FS3 significantly enhanced *S. aureus* susceptibility to daptomycin.[38] In a murine wound infection model, the tetrapeptide FS10 markedly increased MRSA susceptibility to tigecycline.[39] These data indicated the potential of these RIP derivatives as antibiotic enhancers against MRSA infections.

Active Molecules from Compound Library Screening

High-throughput screening of compound libraries is a widely adopted strategy for drug discovery. This approach encompasses diverse methodologies including FDA-approved drug repurposing, combinatorial synthesis, phytochemical screening, and innovative display technologies.

FDA-Approved Drug Repurposing

Palaniappan et al performed in silico molecular docking with the C-LytTR domain of AgrA to screen an FDA-approved drug library. They identified the diuretic bumetanide with binding ability to AgrA. Bumetanide suppressed the expression of α-hemolysin, phenol-soluble modulins, and Panton-Valentine leukocidin. Animal studies demonstrated its efficacy in controlling ulcer progression and promoting wound healing.[40]

Salicylic acid (SAL), the primary metabolite of aspirin, was shown to bind to AgrA, thereby downregulating Agr-associated genes including *agrA, agrC, rnaIII*, and *psmα*/*psmβ*.[41] However, SAL stabilized the mature biofilms of *S. aureus*, which may facilitate the bacterial persistence leading to therapeutic failure.[42] Subinhibitory visomitin, a small-molecule antioxidant, reduces hemolysis, staphylococcal toxins, and colony spreading.[43] Gliptins, a novel class of antidiabetics that are dipeptidyl peptidase-4 inhibitors (DPP-4) used to improve β-cell health and control blood glucose levels in type 2 diabetes mellitus, have been identified by Khayat et al as possessing antivirulence and anti-QS activity against *S. aureus* and *P. aeruginosa*.[44]

Synthetic and Natural Product Libraries

Sully et al identified the small-molecule inhibitor savirin via high-throughput screening. Savirin suppresses QS by targeting AgrA and leads to reduced tissue damage and enhanced bacterial clearance in two murine skin infection models. Notably, long-term in vitro passaging and in vivo studies revealed no resistance or tolerance to savirin in *S. aureus*, highlighting its stable anti-QS activity.[14]

Yu et al constructed a 148-member biarylhydroxyketone library via combinatorial synthesis and identified the bioactive compound 4f-12, which inhibits AgrA-DNA binding in electrophoretic mobility shift assays. The compound 4f-12 reduced rabbit erythrocyte hemolysis by 98.1 ± 0.1% compared to control without the 4f-12 treatment.[45] Kuo et al demonstrated that three biarylhydroxyketone compounds (F1, F12, F19) act as QS inhibitors by targeting the AgrA response regulator. In an MRSA murine wound model, these compounds accelerated wound healing via suppression of virulence factor expression. In a *Galleria mellonella* infection model, they prolonged host survival and restored MRSA susceptibility to β-lactam antibiotics.[46]

Yamaguchi et al screened 577 phytochemicals and identified physalin H, physalin B, and isophysalin B as novel Agr-QS modulators. These compounds inhibit *S. aureus* QS by binding to the DNA-binding domain of AgrA, thereby blocking its interaction with the P3 promoter region.[47] Khodaverdian et al screened 90,000 small molecules from the National Cancer Institute library and identified biaryl compounds that block AgrA's phosphate-binding site. These compounds dose-

dependently inhibit α-hemolysin and PSMα production without affecting bacterial growth.[48] Todd et al demonstrated that succinic acid reduces MRSA-induced abscess formation in mice and validated its in vivo QS inhibitory activity.[49]

Structure-Based and Display Technologies

Kim et al employed click chemistry to covalently link QS modulators to surfaces. The surface-PEG10000-triazole-TrAIP-II competitively inhibited QS responses.[50] Xie et al utilized the RaPID system with lipid nanodiscs to screen $>10^{12}$ cyclic peptides and identified QQ-1 to QQ-4 as AgrC-binding inhibitors. QQ-3 and QQ-5 (a desulfurized analog) effectively suppressed *S. aureus*-induced hemolysis and demonstrated strong antivirulence potential. Although these cyclic peptides lack the thiolactone scaffold characteristic of native AIPs, they still dock into the AgrC ligand-binding pocket, competitively displace AIP and silence AgrC-mediated quorum sensing.[51]

Fatty Acids and Halogenated Scaffolds

Among the C18 unsaturated fatty acids tested (petroselinic, vaccenic, and oleic acids), petroselinic acid markedly suppresses the production of toxins, lipase, and α-hemolysin by downregulating *agrA, rnaIII, hla, nuc1/nuc2*, and *saeR*.[52] The halogenated pyrimidine 2,4-dichloro-5-fluoropyrimidine (24DC5FP) inhibits *agrA, rnaIII*, *hla, nuc1*, and *saeR* expression.[53]

Despite promising in vitro activity, these synthetic QSIs generally lack human pharmacokinetic characterization and long-term toxicity evaluation, limiting their translational readiness.

Nanomaterial Applications for QSIs

Although a large number of studies have shown that QSIs have promising application potential in antiinfective therapy, they still face limitations in safety, solubility, and stability. Researchers have enhanced their performance through structural optimization and the integration of nanotechnology.[29,30] For example, Kratochvil et al developed nanoporous, polymer-based superhydrophobic coatings as a reservoir for water-sensitive peptide QSIs, and enabled their prolonged release. These QSIs were continuously released into the surrounding medium for more than 8 mouths and potently inhibited the Agr quorum-sensing system in *S. aureus* for at least 40 days.[54] Chen et al developed nanocomposite coatings with dihydropyrrol-2-ones (DHP) analogues, which can be applied to surfaces of any length scale and abolish *S. aureus*'s adhesion[55] (Table 1).

Nanomaterial-based delivery systems, while addressing solubility and stability limitations, introduce additional safety considerations regarding biodistribution, clearance, and potential inflammatory responses that remain incompletely characterized.

Natural Product-Derived QSIs

Evolutionary pressures from plant-microbe, microbe-microbe and animal-microbe interactions have driven the emergence of QSIs, which makes natural products a rich resource for the discovery of novel QSIs.

Microbial QSIs

A marine luminescent bacterium produces solonamides A and B, cyclic depsipeptides that interfere with the *S. aureus* Agr system and suppress QS-related genes including *hla, rnaIII*, and *spa*.[58] *Lactobacillus reuteri* synthesizes cyclo (L-Phe-L-Pro) and cyclo (L-Tyr-L-Pro), both of which inhibit toxic shock syndrome toxin-1 (TSST-1) expression via Agr interference.[59] An *Arthrobacter* strain, isolated from sandstone, produces arthroamide and turnagainlide A, both of which inhibit QS at submicromolar to micromolar concentrations.[60]

Desouky et al screened 54 actinomycete metabolites and identified phenalinolactones A-D, BU-4664LMe, 4,5-dehydrogeldamycin, and questinomycin A as inhibitors of QS and hemolysis.[61] Bioactive peptides from *Lactobacillus* strains downregulate QS-controlled virulence mechanisms and restore MRSA sensitivity to cefoxitin when combined with β-lactams.[62] Fungal cerebroside flavuside B reduces *agrA* expression in *S. aureus* and exhibits antioxidant and anti-inflammatory properties in *S. aureus*-infected skin wounds.[63] The cyclodepsipeptide WS9326B, which is isolated from actinomycetes, suppresses *S. aureus* Agr activity and reduces corneal epithelial cell toxicity.[64]

Apicidin, a fungal metabolite, functions as a quorum-sensing inhibitor by directly antagonizing the AgrA response regulator of the *S. aureus* Agr system. This QS blockade suppresses the expression of major virulence

Table 1 Synthetic QS Inhibitors and Quorum Quenching Antibodies Targeting the *S. aureus* Agr System

Category	Inhibitor	Target/Mechanism	Effects on QS System	Reference
AIP analogs	AIP-III D4A, tAIP-III D2A, etc.	Competitive antagonism of AgrC receptor	Reducing TSST-1production by > 80% at nanomolar concentrations	[29, 30]
	n7OFF, PhPr(3Br)-Bnc3	AgrC receptor (non-hydrolyzable scaffold)	Stable peptide bond mimics, potent AgrC inhibition	[31–33]
RIP analogs	RIP (YSPXTNF)	RNAIII transcription inhibition	Suppress Agr-regulated exotoxin production	[34–37]
	FS3, FS8, FS10	RNAIII transcription inhibition	Enhance antibiotic susceptibility	[38, 39]
Compound libraeniry screng	Bumetanide	AgrA C-LytTR domain	Suppress α-hemolysin, PSM, PVL expression	[40]
	Salicylic acid (SAL)	Binding to AgrA	Downregulating *agrA, agrC, rnaIII*, and *psmα/psmβ*	[41]
	Subinhibitory visomitin	Interfering with Agr system	Reducing hemolysis, staphylococcal toxins, and colony spreading	[43]
	Gliptins (DPP-4 inhibitors)	Targeting QS regulatory components (in silico)	Exhibiting antivirulence and anti-QS activity against *S. aureus* and *P. aeruginosa*	[44]
	Savirin	Targeting AgrA	Reducing tissue damage,enhancing bacterial clearance without resistance	[14]
	4f-12	Inhibiting AgrA-DNA binding	Reducing hemolysis by 98.1%, restoring β-lactam susceptibility	[45]
	F1, F12, F19	Targeting AgrA response regulator	Suppressing virulence factors, restoring MRSA susceptibility to β-lactams	[46]
	Physalin H, Physalin B, Isophysalin B	Binding to AgrA DNA-binding domain	Blocking AgrA-P3 promoter interaction	[47]
	Biaryl compounds (NCI library)	Blocking AgrA phosphate-binding site	Inhibiting α-hemolysin and PSMα production dose-dependently	[48]
	Succinic acid	Targeting AgrA	Reducing abscess formation, validating in vivo QS inhibition	[49]
	Surface-PEG10000-triazole-TrAIP-II	Binding to AgrC	Competitively inhibiting QS responses via surface-immobilized modulators	[50]
	QQ-3, QQ-5	Docking into AgrC ligand-binding pocket	Competitively displacing AIP, silencing AgrC-mediated QS	[51]
	Petroselinic acid (C18)	Downregulating *agrA, rnaIII, hla, nuc1/nuc2, saeR*	Suppressing toxins, lipase, and α-hemolysin production	[52]
	24DC5FP (2,4-dichloro-5-fluoropyrimidine)	Inhibiting *agrA, rnaIII, hla, nuc1, saeR* expression	Inhibiting virulence factor production	[53]
Nanomaterials	Nanoporous polymer superhydrophobic coatings	Sustained release of water-sensitive peptide QSIs	Releasing >8 months, inhibiting Agr QS ≥40 days	[54]
	DHP nanocomposite coatings	Surface anti-adhesion	Abolishing *S. aureus* adhesion (physical antibiofilm)	[55]
Quenching antibodies	Anti-AIP-4 mAb (AP4-24H11)	Binding and neutralizing AIP-4 autoinducer	Blocking QS signal propagation, protecting mice from lethal infection	[56, 57]
	Anti-TRAP mAbs	Targeting TRAP receptor	Inhibiting Agr-regulated toxin production	[34]

Abbreviations: AIP, autoinducing peptide; PSM, phenol-soluble modulin; TSST-1, toxic shock syndrome toxin-1; mAb, monoclonal antibody; DPP-4, dipeptidyl peptidase-4.

determinants, thereby reduces bacterial pathogenicity in vivo. Consistently, apicidin treatment significantly decreased ulcer size and weight loss in murine MRSA skin infection models.[65] *Penicillium restrictum* produces ω-hydroxyemodin (OHM), a polyhydroxyanthraquinone that binds AgrA to block its interaction with the P2 promoter. OHM treatment reduced skin necrosis, enhanced bacterial clearance, and lowered inflammatory cytokine levels in murine soft tissue infection models.[66] The cyclic peptide avellanin C, derived from *Hamigera ingelheimensis*, inhibits QS signaling in *S. aureus* by targeting the *agr* P3 promoter, and potentially reduces the expression of Agr-regulated virulence factors.[67]

Plant-Derived QSIs

Medicinal plants are rich sources of QSIs. Echinatin, a natural compound derived from licorice, suppresses MRSA hemolysis via transcriptional regulation.[68] Tanshinone IIB, a major bioactive compound extracted from the roots of *Salvia miltiorrhiza*, exhibits potent anti-virulence activity both in vitro and in vivo by reducing the expression of *rnaIII* and *psmα*.[69] Thymol (2-isopropyl-5-methylphenol), a major constituent of thyme herb (*Thymus vulgaris* L.), possesses a wide spectrum of antimicrobial activity. Specifically, thymol reduces the production of PSMα and

δ-toxin in *S. aureus*, and molecular docking studies indicate that thymol has binding affinity for the AgrA and AgrC receptors.[70] Hamamelitannin, a polyphenol from *Hamamelis virginiana* bark, exerts anti-QS effects by inhibiting RNAIII without affecting bacterial growth. In rat graft models, it prevented device-related infections caused by MRSA and *Staphylococcus epidermidis*.[71] Vermote et al demonstrated that hamamelitannin analogs increase the antibiotic susceptibility of *S. aureus* in both *Caenorhabditis elegans* and murine mammary infection models. These findings support their potential as antibiotic adjuvants.[72,73]

Hydrastis canadensis L. extract exhibits quorum quenching by suppressing the AgrC-AgrA two-component system, and reduces α-hemolysin production and MRSA-induced keratinocyte damage.[74] The flavonoid-rich extract 430D-F5 from *Schinus terebinthifolia* (Brazilian Peppertree) inhibits Agr activity of *S. aureus* without growth suppression and reduces skin necrosis in murine models.[75] Carnosic acid derived from *Rosmarinus officinalis* L. leaves suppresses *agr* expression.[76]

Hispidulin, a natural flavone, has been identified through a hemolysis activity assay as an inhibitor of hemolysis and *hla* transcription by binding to AgrC-AgrA. This action alleviates *S. aureus*-induced damage to A549 cells and reduces lactate dehydrogenase (LDH) release.[77] Ajoene, a sulfur-rich garlic compound derived from allicin, suppresses QS in *S. aureus* and *P. aeruginosa* via inhibiting small RNA (sRNA).[78]

Animal-Derived QSIs

In addition to plant-derived and microbe-derived inhibitors, animals have co-evolved molecules capable of interfering with the staphylococcal Agr system. Li et al identified the milk-derived antimicrobial peptide BCp12, which down-regulates *agrA, agrB, agrC* and *psmβ*, as well as markedly reduces MRSA α-hemolysin and phenol-soluble modulin (PSM) production.[79] Notably, BCp12 acts upstream of the AgrC-AgrA two-component system, offering a complementary mode of action to RIP derivatives and flavonoids, making it a valuable partner for combination regimens. Colostrum oligosaccharides and lactoferrin hydrolysates have also been reported to possess quorum-quenching potential, indicating that the animal-derived bioactive library remains largely unexplored.[80] Future efforts should integrate multi-omics screening, synthetic-biology expression and formulation protection to expand the structural diversity and in-vivo stability of such peptides (Table 2).

Table 2 Natural Product-Derived QSIs Targeting the *S. aureus* Agr System

Category	Inhibitor	Target/Mechanism	Effects on QS system	Reference
Microbial-Derived	Solonamides A and B	Interfering with Agr system	Suppressing *hla, rnaIII*, and *spa* expression	[58]
	Cyclo(L-Phe-L-Pro), Cyclo(L-Tyr-L-Pro) (L. reuteri)	Interfering with Agr signaling	Inhibiting TSST-1 expression	[59]
	Arthroamide, Turnagainlide A (*Arthrobacter*)	Inhibiting QS	Inhibiting QS at submicromolar to micromolar concentrations	[60]
	Phenalinolactones A-D, BU-4664LMe, 4,5-dehydrogeldamycin, Questinomycin A	Binding to AgrA ATP active site	Inhibiting Agr QS and hemolysis (in vitro and in silico)	[61]
	Bioactive peptides from *Lactobacillus* strains	Downregulating QS-controlled virulence	Restoring MRSA sensitivity to cefoxitin when combined with β-lactams	[62]
	Flavuside B (fungal cerebroside)	Reducing *agrA* expression	Exhibiting antioxidant and anti-inflammatory properties	[63]
	WS9326B (actinomycete cyclodepsipeptide)	Suppressing Agr activity	Reducing corneal epithelial cell toxicity	[64]
	Apicidin (fungal metabolite)	Antagonizing AgrA response regulator	Reducing virulence determinants, decreasing ulcer size and weight loss	[65]
	ω-Hydroxyemodin (OHM, *P. restrictum*)	Blocking AgrA-P2 promoter interaction	Reducing skin necrosis, enhancing bacterial clearance, lowering inflammatory cytokines	[66]
	Avellanin C (*H. ingelheimensis*)	Targeting *agr* P3 promoter	Inhibiting QS signaling, reducing *agr*-regulated virulence factors	[67]

(*Continued*)

https://doi.org/10.2147/IDR.S594449

Table 2 (Continued).

Category	Inhibitor	Target/Mechanism	Effects on QS system	Reference
Plant-**Derived**	Echinatin (licorice)	Regulating transcription	Suppressing MRSA hemolysis via transcriptional regulation	[68]
	Tanshinone IIB (*Salvia miltiorrhiza*)	Attenuating Agr system	Reducing *rnaIII* and *psmα* expression, exhibiting in vitro and in vivo antivirulence	[69]
	Thymol (*Thymus vulgaris*)	Binding to AgrA and AgrC receptors	Reducing PSMα and δ-toxin production	[70]
	Hamamelitannin (*Hamamelis virginiana*)	Inhibiting RNAIII	Inhibiting RNAIII without affecting bacterial growth; preventing device-related infections	[71]
	Hamamelitannin analogs	Modulating QS	Increasing antibiotic susceptibility in C. elegans and murine models	[72, 73]
	Hydrastis canadensis extract (goldenseal)	Suppressing AgrC-AgrA two-component system	Suppressing QS, reducing α-hemolysin and MRSA-induced keratinocyte damage	[74]
	430D-F5 extract (*Schinus terebinthifolia*)	Inhibiting Agr activity	Inhibiting Agr activity without growth suppression, reducing skin necrosis	[75]
	Carnosic acid (*Rosmarinus officinalis*)	Suppressing *agr* expression	Suppressing *agr* expression	[76]
	Hispidulin (natural flavone)	Binding to AgrC-AgrA	Inhibiting hemolysis and *hla* transcription, reducing A549 cell damage and LDH release	[77]
	Ajoene (garlic-derived)	Inhibiting sRNA	Suppressing QS in *S. aureus* and *P. aeruginosa* via sRNA inhibition	[78]
Animal-**Derived**	BCp12 (milk-derived antimicrobial peptide)	Acting upstream of AgrC-AgrA	Downregulating *agrA, agrB, agrC* and *psmβ*; reducing α-hemolysin and PSM production	[79]
	Colostrum oligosaccharides, lactoferrin hydrolysates	Quenching QS	Possessing quorum-quenching potential	[80]

Abbreviations: TSST-1, toxic shock syndrome toxin-1; sRNA, small RNA; PSM, phenol-soluble modulin; OHM, ω-hydroxyemodin.

Quenching Antibodies

Quorum quenching antibodies specifically bind to and neutralize QS autoinducers (AIs), and block signal propagation. Park et al developed the anti-AIP-4 monoclonal antibody AP4-24H11, which inhibits *S. aureus* QS in vitro and protects mice from lethal infections in abscess models.[56,57] Beyond targeting AIs directly, antibodies can also suppress QS by interfering with signal transduction components. For instance, anti-TRAP monoclonal antibodies inhibit Agr-regulated toxin production by targeting the TRAP receptor, which mediates RIP protein-dependent Agr suppression[34] (Table 1).

Compared to small-molecule inhibitors, antibody-based approaches offer distinct pharmacological advantages. Monoclonal antibodies exhibit extended serum half-lives, enabling prolonged therapeutic coverage and less frequent dosing.[81,82] Their high target specificity minimizes off-target effects and reduces resistance selection pressure, while the ability to provide immediate protection without invoking host immune responses renders them particularly attractive for passive immunization strategies, especially in immunocompromised patients who respond poorly to active vaccines.[15,81,83]

Challenges in Agr-Targeted Antivirulence Research

Despite over two decades of research on quorum sensing inhibition of *S. aureus*, no Agr-targeted antivirulence inhibitors have advanced to clinical application. This stagnation in clinical translation stems from three interconnected challenges, each defining specific research priorities grounded in current evidence:

First, robust in vivo efficacy data remain scarce, particularly from infection models that rigorously distinguish antivirulence effects from growth inhibition. While numerous Agr inhibitors exhibit potent activity at nanomolar concentrations in vitro, their protective efficacy in vivo is inconclusive. The predominant reliance on acute topical infection models or simple co-incubation assays fails to exclude confounding by nonspecific antibacterial activity, leaving the mechanism of protection ambiguous. Addressing this limitation necessitates prioritizing chronic and device-associated infection models—contexts where Agr exhibits its most complex and clinically relevant regulatory behavior—complemented by isogenic Agr-mutant controls and transcriptomic validation of on-target activity to establish mechanism-specific efficacy.

Second, the pleiotropic and context-dependent nature of Agr regulation creates inherent therapeutic trade-offs. Although Agr upregulates secreted toxins and immune evasion factors, it concurrently suppresses biofilm formation and promotes bacterial dissemination.[23] Consequently, Agr inhibition risks exacerbating biofilm persistence, particularly in chronic and device-associated infections, thereby constraining its therapeutic utility. The most viable strategy emerging from existing data is the dual-activity design principle: selection of candidates that simultaneously inhibit Agr signaling and prevent biofilm formation. Current literature identifies three promising chemical classes: RIP derivatives (exemplified by FS8, which inhibits Agr signaling at nanomolar concentrations and synergizes with tigecycline to attenuate biofilm formation);[84] natural flavonoids (luteolin, quercetin, and baicalein, which concurrently suppress Agr-regulated virulence factors and biofilm development at sub-inhibitory concentrations);[85–87] and multifunctional natural products (carboxypyranoanthocyanins, baohuoside I, and cinnamaldehyde, which attenuate virulence without inducing biofilm rebound).[88–92] These scaffolds constitute rational starting points for lead optimization and translational development.

Third, the clinical and regulatory pathway for non-bactericidal antivirulence agents remains ill-defined. The absence of rapid bactericidal activity complicates efficacy assessment and may deter commercial investment. To navigate these barriers, future efforts should prioritize combination therapeutic strategies that pair Agr inhibitors with conventional antibiotics or anti-biofilm agents—leveraging the documented synergy between FS8 and tigecycline as proof-of-concept. Beyond small-molecule approaches, nanomaterial-based delivery systems (eg, liposomal encapsulation, polymeric nanoparticles) offer promising avenues to enhance inhibitor stability, achieve sustained release at infection sites, and improve penetration of biofilm matrices. Additionally, biologic modalities including anti-AgrA monoclonal antibodies and AIP-targeted aptamers provide alternative targeting strategies with potentially superior specificity compared to small molecules. These technological innovations, integrated with the dual-activity scaffolds identified above, represent the most promising path toward overcoming current translational bottlenecks.

Conclusions and Future Directions

As the primary quorum sensing system in *S. aureus*, AgrA regulates the majority of virulence factors in this pathogen. This characteristic makes it an attractive target for screening anti-virulence drugs. To date, numerous candidate compounds targeting AgrA have been identified. These compounds not only exhibit significant inhibition of AgrA activity in vitro but have also demonstrated effective antiinfective effects in vivo in animal experiments, suggesting their potential for further development. However, since anti-AgrA compounds often simultaneously promote biofilm formation, a comprehensive and cautious evaluation of their potential side effects in vivo is necessary. Future efforts should focus on screening anti-virulence drugs that possess both anti-AgrA and biofilm inhibition properties. Further research should be conducted on the pharmacokinetics, toxicology, stability, and other characteristics of candidate drugs. Based on these findings, additional modifications, such as chemical stabilization through structural modification or the application of nanotechnology for controlled release, are essential to ultimately facilitate the practical application of these potential anti-virulence drugs against *S. aureus*.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Dongguan Key Laboratory for Pathogenesis and Experimental Diagnosis of Infectious Diseases (20231600400762). Talent Development Foundation of The First Dongguan Affiliated Hospital of Guangdong Medical University (GCC2023002).

Disclosure

The authors declare that they have no conflict of financial interests.

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