

Supplementary Table S1: Comprehensive summary of antivirulence factors: efficacy, advantages, and limitations against *Staphylococcus aureus*

Antivirulence Factor	Efficacy	Advantage	Disadvantages
10-Hydroxy-2-decenoic acid	41.9–72.9% biofilm biomass reduction; inhibits α -hemolysin	Natural compound; dual anti-biofilm and anti-virulence	Sub-MICs required; limited direct bactericidal activity
2B4 receptor blockade	Reduces SEB-induced eosinophil activation and inflammation	Novel target; mitigates allergic inflammation	Specific to SEB-2B4 interaction; untested in humans
2R,3R-Dihydromyricetin	IC ₅₀ : 73.43 μ M (SrtA); reduces adhesion by 1.14–1.75 log CFU/cm ²	Safe for food applications; binds SrtA catalytic pocket	Moderate potency compared to other SrtA inhibitors
3,2'-Dihydroxyflavone	MIC 75 μ g/mL; inhibits polymicrobial biofilms	Targets dual-species infections	Not specified
3,4'-DMF, HPC	Reduced MRSA virulence in murine skin infection; prevented dermonecrosis.	Targets quorum sensing without affecting bacterial growth.	Mechanism of HPC not fully elucidated.
5-Fluorouracil	Reduces AI-2; enhances daptomycin efficacy <i>in vivo</i> .	Synergizes with antibiotics; prevents resistance.	Potential off-target effects (originally an oncology drug).
7,8-Dihydroxyflavone	32 μ g/mL inhibits Hla; synergizes with vancomycin <i>in vivo</i>	No host cytotoxicity	Not specified
Actinomycetales metabolites	Phenalinolactones A–D inhibit AgrA ATP site; suppress hemolysis.	Dual <i>agr</i> and <i>fsr</i> inhibition (Synerazol).	Synergistic effects with antibiotics not tested.
Ag@Glu/Tsc Nanoparticles	Reduces biofilm biomass by 76.7%; downregulates <i>icaA/icaD</i> by 60–67%	Functionalized for targeted delivery; induces oxidative stress in biofilms	Risk of silver resistance; nanoparticle aggregation in biological environments
Ag-Au-Pd Nanoapatites	MIC: 128 μ g/mL; inhibits MRSA/VRE biofilms	Low cytotoxicity; promotes fibroblast survival in biofilm-infected conditions	Complex synthesis process; potential long-term biocompatibility concerns
AgNPs (<i>H. speciosa</i>)	92.41% biofilm eradication (0–25 μ g/mL)	Green synthesis; broad anti-biofilm activity	Potential cytotoxicity of silver nanoparticles

Allantodapsone	IC50: 21.3 mM (fibrinogen); inhibits ClfA/ClfB	First MSCRAMM inhibitor; prevents colonization	High IC50 may limit therapeutic utility
Ambuic acid	Suppress <i>agr</i> and <i>fsr</i> systems; reduce hemolysin and biofilm.	Broad-spectrum QS inhibition.	Epoxide reactivity may cause off-target effects.
AMPT (Thiazole Derivative)	MIC lower than vancomycin; inhibits biofilm and virulence.	Superior bactericidal activity; targets AgrA/SarA.	Stability and delivery challenges.
Anandamide	Reduces SEB-induced ARDS via miRNA modulation and Treg/MDSC expansion	Immunomodulatory; natural endocannabinoid	Psychoactive potential (if THC-derived); route-specific efficacy
Anti-SraP L-lectin mAb	Reduces bacterial load in bloodstream; blocks adhesion	Targets key adhesin; passive immunization strategy	Requires antibody administration; no active immunity
Apigenin-7-O-glucoside	MBIC 0.20 mg/mL; reduces biofilm by 88.9%.	Natural compound; reduces hydrophobicity and EPS.	Limited to <i>S. aureus</i> and <i>E. coli</i> .
<i>Artemisia dracunculus</i> EOs	MIC 1.25 μ L/mL; inhibits biofilm and QS genes.	Natural source; disrupts pre-formed biofilms.	Estragole (main compound) may have toxicity concerns.
Artesunate	Sub-MIC reduces adhesion and biofilm	Targets quorum sensing	Not specified
Avacopan	Reduces PVL EC50, suppresses IL-1 β	Repurposed drug; adjunctive therapy	Some compounds (e.g., BM213) enhance cytotoxicity
Ayanin	Inhibits ClpP (IC50: 19.63 μ M); reduces virulence factors (e.g., <i>hla</i>)	Synergizes with vancomycin; targets multiple virulence pathways	Moderate IC50
Azan-7	Inhibits AgrA; enhances clindamycin susceptibility.	No resistance development; stable long-term.	Requires adjunct therapy; bioavailability issues.
Azithromycin	Reduces hemolytic activity at sub-MIC	Reduces inflammatory damage (e.g., ocular)	Mechanism not fully elucidated
<i>B. subtilis</i> Peptides	Disrupts biofilms across <i>agr</i> types; enhances antibiotic susceptibility.	Probiotic-derived; protects host cells.	Unidentified peptide components; requires formulation.
Baicalein	Inhibits vWbp; improves survival in pneumonia model	Enhances penicillin G efficacy	Herbal extraction complexity

Bicyclomycin	Increased dependent factors. SaeRS-virulence	N/A (study highlights risk).	Paradoxically enhances virulence; not recommended.
Biochanin A	32 µg/mL inhibits Hla; reduces lung bacterial load	Improves survival in lethal MRSA model	Not specified
Bisdemethoxycurcumin	Downregulates agrA; inhibits biofilm formation	Natural compound, targets quorum sensing	Not specified
Bispecific scFV antibody (MB102a)	Allosterically blocks SEB-TCR binding; prevents immune activation	Dual targeting; computationally optimized	Complex production; stability <i>in vivo</i> uncertain
BLS P34	Reduces <i>S. aureus</i> biofilm metabolism by 41-95%	Food-safe bacteriocin-like peptide	Ineffective against preformed biofilms; stimulates <i>E. faecalis</i> metabolism
Bumetanide	70% AgrA inhibition at 0.1 µM; reduces ulceration <i>in vivo</i> .	Repurposed drug; no resistance or toxicity observed.	Off-target diuretic effects in systemic use.
C1/C2 (<i>L. plantarum</i>)	Reduces biofilm formation; downregulates <i>icaC/D</i>	Novel compounds; effective against MRSA	Uncharacterized long-term safety
Candesartan, Domperidone, Miconazole	Sub-MIC inhibition of virulence factors; candesartan downregulates <i>icaA</i> , <i>hla</i> , <i>crtM</i>	FDA-approved, reduces resistance pressure	Not specified
Carboxypyrananthocyanins	Reduces <i>S. aureus</i> biofilm; downregulates <i>agrA</i> .	Non-toxic; synergizes with antibiotics.	Ineffective against <i>P. aeruginosa</i> biofilm.
Celastrol	Inhibits CrtM; reduces STX and biofilm	Multi-targeted; enhances oxidative stress susceptibility	Potential toxicity from plant source (<i>Tripterygium</i>)
Chitosan-coated Surfaces	Reduces <i>S. aureus</i> biofilm by 79%	Biocompatible; reduces viable but nonculturable (VBNC) cells	Lower efficacy against <i>P. aeruginosa</i> (66%)
Chlorothymol	MIC: 32 µg/ml; inhibits biofilm/motility at 8 µg/ml	Synergizes with oxacillin (FIC: 0.3125); membrane disruption	High MIC for clinical use
Chrysanthemum EOs	Inhibits MRSA growth, biofilm, and virulence genes (<i>mecA</i> , <i>sea</i> , <i>agrA</i>)	Natural antimicrobial; combats antibiotic resistance	Concentration-dependent efficacy; unstandardized extracts

CHX-loaded nanoHA	Dose-dependent bacterial inhibition; biocompatible at low doses	Controlled release; medical device coating	Cytotoxic at high CHX concentrations
Citral	MIC 5–40 mg/mL; reduces early-stage biofilm	Adjunct to conventional therapies	High concentrations required
Compound 5, N1, N3, N9, N10 (VraSR inhibitor)	Inhibited VraS ATP-binding (ΔG_{bind} -294.32 kJ/mol); disrupted VraR-DNA binding.	Reduces antibiotic resistance mechanisms.	Requires validation in clinical isolates.
Coptisine	Inhibits SrtB; protects lung epithelial cells	Avoids antibiotic resistance; targets adhesion	Indirect mechanism; no direct antibacterial activity
Coumarin-chalcone conjugate	Reduces biofilm biomass (30%); downregulates <i>lasI/R</i> , <i>rhII/A</i> .	Broad-spectrum QS inhibition; sensitizes biofilms to antibiotics.	Mechanism of cyclic-di-GMP modulation unclear.
Daphnetin	IC ₅₀ : 25.98 $\mu\text{g/mL}$ (SrtA); suppresses hemolysis and motility	Dual targeting of SrtA and α -hemolysin; protects against pneumonia <i>in vivo</i>	Binding affinity may vary across strains
D-Asp/D-Glu + Ciprofloxacin	97% biofilm inhibition/dispersal at 40 mM	Disrupts eDNA; enhances antibiotic efficacy	High amino acid concentration required
Delta-9-THC	Prevents SEB-induced ARDS mortality; suppresses cytokines via CB2 receptor	Effective post-exposure; promotes anti-inflammatory response	Psychoactive side effects; regulatory hurdles
Diclofenac, Meloxicam	47–59 $\mu\text{g/mL}$ inhibits STX by 79–98%	Binds CrtM, adjuvant potential	Not specified
DLL37-1/LL37-1	52-58% biofilm inhibition at 5 μM	No hemolysis/cytotoxicity up to 5 μM ; targets MSCRAMM proteins	Limited data on <i>in vivo</i> efficacy
DPTM (pleuromutilin derivative)	Dose-dependent Hla/agrA downregulation; reduces inflammation	Anti-inflammatory, protects host cells	Not specified
D-Serine	Reduces MRSA adhesion and biofilm genes (<i>agrA</i> , <i>sarS</i>)	Non-antibiotic; specific to biofilm inhibition	Efficacy in complex <i>in vivo</i> models requires validation

DSS (SaeR inhibitors)	Inhibited biofilm attachment via secreted protein.	Species-specific biofilm control.	Inhibitory protein identity remains unknown.
DSS and I-modulia®	Suppressed δ -toxin and SaeRS-regulated genes.	Synergistic effect; safe for skin microbiota.	Limited to topical applications (e.g., dermatitis).
EGCG and NOL polyphenols	Suppress SEA production and biofilm-related genes in MVs	Natural compounds; dual anti-inflammatory and antibiofilm effects	Variable potency (EGCG > NOL); limited <i>in vivo</i> data
EGCG-functionalized p(HEMA-co-GMA)	71% reduction in <i>S. aureus</i> adhesion (1000 μ g/mL, 4h)	Prevents contamination in biomedical devices and food packaging	Dose-dependent efficacy; high concentrations required
Engineered chromones	Inhibit TSST-1 via high-affinity binding; optimized drug-like properties	Targets antibiotic-resistant strains; good solubility and permeation	Early-stage design; untested in animal models
Ensifentrine	Preserves lung barrier function; reduces IL-6/IL-8 and endothelial leakage	Mitigates MRSA-induced ARDS; EPAC-mediated anti-inflammatory effects	Does not directly target bacterial viability
Eugenol	Inhibits AgrA phosphorylation; reduces ATP and enterotoxin production.	Natural compound; effective in food safety applications.	High concentrations may affect host cells.
Fenoprofen	Attenuated biofilm pathogenicity in implant models.	FDA-approved repurposing; no resistance induction.	NSAID side effects in chronic use.
Flavone derivatives	Reduced oxacillin resistance in MRSA.	Dual antivirulence and resistance modulation.	Mechanism via GraRS or mecA-PBP2a remains unclear.
Flavuside B	Suppresses <i>agrA</i> (1.7-fold); promotes wound healing.	Dual antioxidant and anti-QS effects; in vitro wound model.	Marine-derived; scalability challenges.
Fmoc-F	Inhibits biofilm ECM components; synergizes with antibiotics	Effective as a coating material; targets multiple ECM components	Mechanism of ECM interaction not fully elucidated
Forsythiaside	Inhibits adhesion (>30 mg/mL); attenuates NF- κ B	Dual antibacterial and anti-inflammatory activity	High concentrations needed for biofilm prevention
G5-QQ3 Dendrimer	Biofilm inhibition (60–72%); MIC ₅₀ 18 μ M.	Enhanced peptide stability; penetrates biofilms.	Complex synthesis; untested <i>in vivo</i> .

GA, NGA (SaeR inhibitors)	Inhibited biofilm formation and virulence gene expression <i>in vitro</i> and <i>in vivo</i> .	Dual activity against planktonic and biofilm-associated MRSA.	Potential off-target effects due to broad transcriptomic changes.
Galangin	Inhibits vWbp; reduces bacterial load <i>in vivo</i>	Enhances latamoxef; binds directly to vWbp	Mechanism specificity
Gallic Acid	MIC: 32 µg/mL; inhibits biofilms at 8 µg/mL	Reduces PIA production; downregulates <i>sarA/icaA/icaD</i>	Limited efficacy against mature biofilms at low concentrations
GW3965-HCl (FeoB Inhibition)	Reduces FeoB activity, staphyloxanthin, and bacterial growth	Synergistic with host oxidative stress; low resistance development	Specificity and pharmacokinetics not fully characterized
Hexestrol	MIC: 16 µg/mL; reduces EPS and biofilm-related genes	Synergistic with aminoglycosides; targets MRSA	Synthetic estrogen may have off-target effects
Hibifolin	IC50: 31.20 mg/mL for SrtA; enhances cefotaxime efficacy	Adjuvant therapy; reduces antibiotic resistance risk	High IC50 limits standalone use
HR3744, SAV13 (SaeR inhibitors)	Reduced α-toxin and PVL expression; effective in murine models.	High specificity; no selective pressure.	SAV13 potency requires toxicity evaluation.
HSGN-220, HSGN-218	MIC = 0.06–0.5 µg/mL against MRSA; disrupts DNA replication, iron starvation, and membrane potential	Multi-target action; low resistance propensity	Complex synthesis; potential off-target effects in hosts
Ibuprofen	Synergy with vancomycin enhances wound healing in rats	Enhances traditional antibiotics	Not specified
Iclaprim	Strain-dependent Hla reduction; depolymerizes biofilms at 1 MIC	Improves survival in <i>Galleria</i> model	Strain-dependent efficacy
Isoquercitrin	Inhibits Coa (binds Asp-181/Tyr-188); reduces bacterial load <i>in vivo</i>	Improves survival in pneumonia; non-bactericidal	Limited to Coa-targeted therapy
Isorhapontigenin	Inhibits MgrA; synergizes with vancomycin in murine pneumonia	Reduces virulence gene expression; enhances immune response	No direct bactericidal activity
Isosakuranetin	IC50: 21.20 µg/mL for SrtA; reduces lung damage <i>in vivo</i>	Dual inhibition of SrtA and Hla; anti-inflammatory	Low IC50 requires further validation

Isovitexin	Inhibits Coa activity; prevents fibrin formation	No impact on bacterial growth	Specific to Coa; limited broad-spectrum applicability
Iturins (<i>Bacillus velezensis</i>)	76% hemolysis reduction	No resistance pressure, livestock applications	Not specified
Kaempferol	32 µg/mL inhibits Hla; improves survival in pneumonia model	Protects lung tissue	Not specified
<i>L. helveticus</i> Biosurfactants	Inhibits quorum sensing via AI-2; reduces <i>icaA/sarA/agrA</i> expression	Safe, natural alternative; prevents host cell invasion	Strain-dependent efficacy (e.g., 27170 > 27058)
<i>Lactobacillus</i> strains	Moderate inhibition of <i>S. aureus</i> adhesion	Safe for food/pharmaceutical use; natural origin	Variable strain efficacy; live cells required for optimal effect
Lignin-capped AgNPs	MIC 10 µg/mL; downregulates <i>luxR</i> , biofilm genes.	Non-toxic to human cells; QS and biofilm dual targeting.	Risk of metal resistance gene upregulation.
LL-37	MIC: 0.62 mM; reduces adhesion at ≥0.16 mM; disrupts biofilms at 5 mM	Potent anti-biofilm activity; targets titanium implant infections	High concentration required for mature biofilms
Lysine	Reduces hemolysis; protects intestinal mucosa in mice	Food-safe, biocompatible	Not specified
MA01 rhamnolipid	70% reduction in MRSA viability; inhibits biofilm via <i>agrA</i> , <i>agrC</i> , <i>icaA/D</i> downregulation.	Natural biosurfactant; dual QS and biofilm inhibition.	High effective concentrations (30–120 mg/mL).
mAbs (Hla, Luk, ClfA)	69% survival improvement in septic shock model	Multi-toxin targeting	Not specified
Macrocyclic QQ peptides	IC ₅₀ ~1 nM; blocks AgrC activation.	High affinity; resistance unlikely due to non-bactericidal action.	Peptide stability and delivery challenges.
Maleimide-diselenide	Inhibits biofilm via <i>sarX</i> suppression; reduces nasal colonization	Low resistance risk; <i>in vivo</i> efficacy	Early-stage research; limited toxicity data
MAS-19/MAS-30 (phenyl esters)	>60% inhibition of ClpXP; reduces hemolysis	High stability, minimal cytotoxicity	Not specified
Metal Oxide Nanoparticles	Biofilm disruption (80–88%); MIC 0.63 mg/mL (ZnO).	Broad-spectrum; durable.	No QS inhibition; bactericidal mechanism only.

Microalgal EPS (<i>T. suecica</i>)	Reduces adhesion via surface hydrophilicity	Sustainable; non-toxic coating for food surfaces	Limited to specific surfaces (e.g., polystyrene)
Monoclonal antibody Hm0487	Neutralizes SEB by blocking TCR/MHC-II interaction; improves survival in mice	High affinity; targets novel epitope distant from TCR/MHC-II sites	Requires cold storage; high production costs
Monoclonal antibody LXY8	Neutralizes SEB with 0.525 nM affinity; protects against toxic shock	High potency; human-derived for reduced immunogenicity	Requires parenteral administration; costly production
Monoclonal antibody YG1	Neutralizes Hla; protects against bacteremia/pneumonia	Specific epitope targeting	Not specified
Morin	Inhibits biofilm (sub-MIC); disrupts EPS production.	Non-bactericidal (reduces resistance risk); targets SarA protein.	Negligible direct antibacterial activity.
MPDA-LUT@CaP implant coating	95.59% antibacterial rate; 90.3% biofilm elimination.	Dual PTT-QSI action; promotes osseointegration.	Requires NIR activation; acidic microenvironment dependency.
mRNA-based SEB vaccines/mAbs	Induces robust immune responses; superior to protein-based vaccines	Rapid development; long-lasting immunity	Requires cold chain storage; potential mRNA instability
MSI-1 peptide	Bacteriostatic/bactericidal; inhibits STX, synergizes with vancomycin	Targets LTA and CrtN; effective against MRSA/VRSA	Toxicity not fully assessed
Multicomponent toxoid vaccine (IBT-V02)	Generates neutralizing antibodies against Hla, PVL, LukAB, SEB, SEA, TSST-1	Broad protection; effective in pre-exposed hosts	Complex formulation; potential antigen competition
Myricetin	Reduces lung injury in mice; inhibits biofilm	Dietary flavonoid, adjunctive therapy	Not specified
Naphto-γ-pyrones (NGPs)	Inhibits biofilm/hemolysis (80%); enhances vancomycin efficacy	Non-bactericidal; marine fungal origin	Production scalability from marine fungi
Naringenin (Hass avocado extract)	Binds SEIX; inhibits MRSA biofilm and toxin production	Natural compound; dual antimicrobial and antivirulence effects	Variable bioavailability; unoptimized dosing
NH125 (VraSR inhibitor)	Sensitized MRSA to carbenicillin/vancomycin.	Noncompetitive kinase inhibition; combinatorial potential.	High concentrations required for efficacy.

Non-digestible oligosaccharides	Inhibit bacterial adherence, biofilm formation, and toxin receptor mimicry	Broad-spectrum; prebiotic benefits for gut microbiota	Efficacy dependent on gut microbiota composition
Norlichexanthone	Reduced toxins and biofilm formation.	Dual targeting of Agr and SaeRS.	Fungal-derived compound; scalability concerns.
Nusbiarylins	Reduces toxin production at sub-MIC	Targets transcription, avoids resistance	Not specified
PASP and EO@PASP/HACCNP_s	1.20–1.68 log CFU/mL biofilm reduction; 97.35% inhibition rate	Enhances food safety; preserves sensory properties	Complex nanoparticle synthesis
Patuletin	Reduces biofilm (27-23%) and staphyloxanthin (53-46%) at 1/4 MIC	Synergizes with antibiotics; stable CrtM binding	Sub-inhibitory concentrations may not kill bacteria
PEINF Nanoparticles	Inhibits biofilm and motility; QS inhibition in <i>C. violaceum</i> .	Broad activity (bacteria and fungi); durable effects.	No direct QS inhibition in <i>S. aureus</i> .
Petroselinic acid	Inhibits biofilm on abiotic/skin surfaces; downregulates agrA, RNAIII	Non-toxic, targets quorum sensing	Not specified
Phenazopyridine HCl	Inhibits TSST-1 via SaeRS TCS suppression; spares microbiota	Targets virulence without affecting growth; preserves vaginal microbiota	Narrow focus on TSST-1; unconfirmed efficacy against other toxins
Photoactivated Ga³⁺CHP	Reduces SEC/TSST-1 production via ROS generation; lowers cytotoxicity	Non-antibiotic; targets skin colonization; safer for human cells	Requires light activation; limited to topical applications
PhPr(3Br)-Bnc3 peptidomimetics	Sub-nanomolar IC ₅₀ across all <i>agr</i> groups.	Pan- <i>agr</i> inhibition; structural tunability.	Synthetic complexity and cost.
PHT-427 (FeoB Inhibition)	Reduces staphyloxanthin, biofilm, and enhances antibiotic susceptibility	Safe in animal models; broad Gram-positive activity	Limited to bovine mastitis model; no human trial data
Physalins	Block AgrA-DNA binding; reduce hemolytic toxin production.	Plant-derived; target DNA-binding site.	Limited solubility or bioavailability data.
Piceatannol	Binds Hla; disrupts pore formation	Direct toxin interaction	Not specified

Plantamajoside	IC50: 22.93 µg/mL (SrtA); synergizes with vancomycin	Reduces immune evasion; effective in murine and <i>Galleria</i> models	Requires combination therapy for optimal MRSA eradication
PMI-5	Reduced hemolysis by 65%; decreased lesion size in murine models.	Broad inhibition of virulence-associated TCSs.	Requires further pharmacokinetic studies.
Pomegranate/persimmon extracts	PoPE reduces QS pigments; GrPE disrupts biofilms.	Food waste utilization; multi-pathogen activity.	Variable efficacy across extracts.
PP-HCl (SaeR inhibitors)	Downregulated TSST-1; mitigated T-cell activation.	Preserves vaginal microbiota; non-bactericidal.	Specific to toxin-mediated infections (e.g., menstrual TSS).
Probiotic Metabolites	Downregulates <i>agrA</i> ; enhances oxidative stress susceptibility.	Non-antibiotic strategy; safe for host.	Strain-specific effects; requires co-administration.
Propolis Triterpenoids	18–40% biofilm inhibition at MIC.	Natural product; targets QS and virulence.	Moderate efficacy; limited to <i>S. aureus</i> .
Pyocyanin	MIC 8 µg/mL; eradicates 83–88% biofilms.	Targets AgrA; inhibits motility and virulence.	Potential cytotoxicity at higher doses.
Pyrazolopyrimidine	Suppresses PSMs; no growth inhibition.	High-throughput screening validated; specific <i>agr</i> targeting.	Limited <i>in vivo</i> efficacy data.
Quebrachitol	Inhibits biofilm without affecting growth; downregulates <i>sarA/agr/ica</i>	Broad-spectrum anti-adhesive activity; natural compound	No direct bactericidal effect
Quercetin	Prevents αHL-induced hemolysis at sub-MIC	Protects host membranes	Does not inhibit toxin production
Quercetin + antibiotics	Enhances ROS production; disrupts biofilm	Broad-spectrum, amplifies antibiotic effects	Host membrane modulation (indirect)
Resveratrol	Binds AgrC (−8.9 kcal/mol); stable in MD simulations.	Superior pharmacokinetics vs. penicillin; natural origin.	Limited <i>in vivo</i> validation.
Rhodionin	IC50: 22.85 µg/mL for SrtA; improves survival in pneumonia model	Targets virulence without affecting growth; <i>in vivo</i> efficacy	Moderate potency
Robusta Coffee Extracts	39.69% biofilm inhibition at ½ MIC.	Natural source; inhibits mature biofilms.	Moderate activity; limited to in vitro models.

Rosemary extracts (carnosic acid)	Inhibits <i>agr</i> at 5 μ M; reduces PSMs and α -hemolysin.	Natural source; anti-inflammatory potential.	Variable potency between compounds (carnosol vs. rosmarinic acid).
Rosemary/Myrtle EOs	Reduces biofilm (74%); inhibits hemolysin/DNase	Natural combination; ROS-mediated oxidative stress	Variable MICs (0.7–11.25 mg/mL)
Rutin-loaded chitosan NPs	Reduces staphyloxanthin; inhibits biofilm (22.5–37.5%)	Multi-mechanistic; enhances H ₂ O ₂ susceptibility	Nanoparticle delivery challenges
<i>S. simulans</i> AIP-I	Nanomolar inhibition of all MRSA <i>agr</i> types; reduces dermonecrosis <i>in vivo</i> .	Broad-spectrum <i>agr</i> suppression; non-antibiotic.	Limited clinical validation.
<i>S. warneri</i> AIPs	Dose-dependent <i>agr</i> inhibition; reduces MRSA skin damage <i>in vivo</i> .	Commensal-derived; topical applicability.	Variability in AIP potency (AIP-II > AIP-I).
S-342-3	Reduces biofilm mass by 25–57% at 4 μ g/mL	Non-toxic to human cells and <i>Galleria</i> ; downregulates <i>agrA/sarA</i>	Sub-MIC use limits bactericidal activity
Saikosaponin A	Reduces TNF- α , IL-1 β , and ferroptosis markers (e.g., MDA, GPX4)	Modulates host inflammation and iron metabolism	Indirect antibacterial effect; requires host cooperation
scFv MS473	100% survival in TSST-1-induced shock; prevents organ damage	Fully human; effective post-exposure therapy	Limited to TSST-1; requires early administration
SEA-specific aptamer (Apt5)	Detects SEA at 100 ng (food poisoning threshold)	Rapid lateral flow assay compatibility; no antibodies required	Limited to diagnostic applications
SEB mimetic peptide (pSEB116-132)	Blocks SEB-CD28 binding, reduces cytokine production, restores barrier integrity	Specific targeting; mitigates intestinal dysfunction	Limited to SEB; potential delivery challenges
SEB-targeting nanobody (Nb8)	Inhibits SEB-MHC-II interaction; blocks inflammatory responses	Small size; high stability; engineered for specificity	Potential immunogenicity; unproven in human trials
SED-specific aptamer (Aptamer 1)	Detects SED with high sensitivity (LOD: 45 nM)	Cost-effective; reproducible alternative to antibodies	Diagnostic use only; limited therapeutic application

Shikonin	Downregulates <i>agrA</i> , <i>RNAIII</i> ; 70% biofilm inhibition; promotes wound healing.	Dual antimicrobial and tissue-regenerating effects.	Polymicrobial biofilm efficacy requires further validation.
Short-chain fatty acids (SCFAs)	Modulate intestinal environment; inhibit pathogen growth and toxin activity	Naturally derived; enhances commensal microbiota	Variable concentration in gut; indirect action
Sidr Honey	MIC 50–400 mg/mL; inhibits biofilm (70.88%).	Broad-spectrum; antioxidant properties.	High MIC limits practical use.
Silver nanoparticles	Downregulates <i>ica</i> , <i>agr</i> , and virulence genes	Broad-spectrum; disrupts biofilm architecture	Risk of silver resistance; cytotoxic at high doses
Sinensetin	Inhibits Coa (128 µg/mL); reduces biofilm	<i>In vivo</i> efficacy; synergizes with oxacillin	High concentration required
Siphonocholin	60% biofilm inhibition; binds BfmR QS regulator.	Marine-derived; dual QS and biofilm suppression.	Limited mechanistic studies in MRSA.
Sitagliptin	Inhibits biofilm (both <i>S. aureus</i> and <i>P. aeruginosa</i>); protects mice.	Repurposed drug with known safety; downregulates multiple QS genes.	Limited to specific QS pathways; requires clinical validation.
SKKUCS (SaeR inhibitors)	Reduced bacterial burden in murine models; no growth impact.	High-throughput validated; low resistance risk.	Mechanism limited to kinase ATP-binding site.
Snail mucus fractions	MIC20 reduces virulence factors	Natural source, antibiofilm activity	Source availability challenges
Staquorsin	Inhibits AgrA binding; reduces RNA III, hemolysins, lipases; <i>in vivo</i> reduction of bacterial burden.	Minimal impact on viability; no resistance observed.	Long-term safety profile not fully established.
Sumra Honey	Inhibits biofilm (48%) and QS (68.7%).	Rich in bioactive compounds; natural.	High MIC (300 mg/mL); impractical for clinical use.
Surfactin	Inhibits biofilm formation on multiple surfaces	Natural biosurfactant; modulates quorum sensing	Stability in practical applications unclear
SYG-180-2-2	Reduces abscess formation in mice; sensitizes to oxidative stress	No growth inhibition, <i>in vivo</i> efficacy	Not specified
Synthetic Gallotannins	Sub-MIC biofilm inhibition; disrupts quorum sensing	Effective against MRSA biofilms; antioxidant properties	Moderate direct antibacterial activity (MICs not specified)

Tamarixetin	Inhibits ClpP (IC50: 49.73 μ M); suppresses <i>hla</i> , <i>agr</i> transcription	Non-cytotoxic; enhances cefotaxime efficacy	Higher IC50 compared to ayanin
Terbinafine	Inhibits CrtN; reduces staphyloxanthin, enhances antibiotic susceptibility	Synergizes with ampicillin/cefotaxime; reduces biofilm	Antifungal repurposing may have off-target effects
Theaflavin 3,3'-digallate	50 μ g/mL inhibits Hla; preserves skin barrier	Anti-inflammatory, no resistance risk	Not specified
Thymol-isatin hybrid	MIC: 1.9 μ M; inhibits biofilm and staphyloxanthin	Low toxicity in <i>Galleria mellonella</i> ; modulates immune response	Early-stage research
Tilmicosin	Reduced biofilm formation; synergistic with oxacillin.	Macrolide repurposing; targets mature biofilms.	Potential off-target effects due to antibiotic class.
Trehalose-functionalized AuNPs	Reduces bacterial binding to HUVECs	Non-toxic; targets bacterial-specific metabolism	Limited to in vitro models
Triterpenoid acids	Inhibits <i>agr</i> system; reduces dermonecrotic lesions (murine model)	Targets quorum sensing; no resistance pressure	Not specified
Truncated SEA aptamers	Enhanced binding specificity (lower Kd) for SEA detection	Reduced production time/cost compared to full-length aptamers	Requires validation in complex matrices (e.g., food)
TST1N-224 (VraRC inhibitor)	Restored vancomycin/methicillin susceptibility in VISA (IC50 = 60.2 μ M).	Adjuvant potential with antibiotics.	Moderate binding affinity (KD = 23.4 μ M).
Vaccenic Acid	Inhibits biofilm (40–60%) and virulence factors at sub-MIC.	Broad-spectrum (MRSA and <i>C. violaceum</i>); targets QS genes.	Limited <i>in vivo</i> data; moderate efficacy.
Vancomycin-grafted Implants	20-fold reduction in bacterial attachment <i>in vivo</i>	Long-term prevention of colonization; mitigates systemic inflammation	Residual bacteria persist on bone surfaces
Vc-EAF	MIC: 625 μ g/mL (standard strains); synergistic with ampicillin	Natural origin; disrupts membrane permeability	High MIC (>2500 μ g/mL) for some MRSA strains

Verbascoside	Inhibits SrtA-mediated adhesion; protects <i>Galleria</i> and murine models	Targets virulence without bactericidal pressure; strong SrtA binding affinity	Narrow focus on SrtA pathway
Verteporfin	Reduced bacterial load in murine wound infection; enhanced PMN killing.	Repurposed drug; targets redox sensing.	Limited data on long-term efficacy.
Visomitin	Bactericidal at >MIC; QS inhibition at sub-MIC; reduces hemolysin, biofilm.	Dual action (bactericidal + anti-QS); targets Agr system.	Higher concentrations needed for bactericidal effect.
Xanthoangelol B, PM-56 (SaeR inhibitors)	Suppressed hemolysins; improved survival in <i>Galleria mellonella</i> models.	Direct binding to SaeS; no growth inhibition.	Limited <i>in vivo</i> mammalian data.
YycFG antisense RNA	Reduced biofilm formation; increased cefoxitin susceptibility.	Enhances antibiotic efficacy; targets chronic infections.	Delivery challenges for antisense RNA <i>in vivo</i> .
Zinc sulfate	Synergy with antibiotics; downregulates <i>icaA</i> , <i>icaD</i> , <i>fnbA</i>	Enhances antibiotic efficacy, combats resistant strains	Not specified

Legend

AgNPs: Silver Nanoparticles; AgrA: Accessory gene regulator A; AI-2: Autoinducer-2; ARDS: Acute Respiratory Distress Syndrome; AuNPs: Gold Nanoparticles; *BfmR*: Biofilm regulatory protein; CFU: Colony Forming Units; ClfA/B: Clumping factors A and B; ClpP: Caseinolytic protease P; Coa: Coagulase; CrtM/N: Carotenoid biosynthesis enzymes; ΔG_{bind} : Gibbs free energy change of binding; DNase: Deoxyribonuclease; eDNA: Extracellular DNA; EC50: Half Maximal Effective Concentration; EGCG: Epigallocatechin gallate; EPS: Extracellular Polymeric Substances; FIC: Fractional Inhibitory Concentration; FeoB: Ferrous iron transporter B; Fmoc-F: Fluorenylmethyloxycarbonyl-phenylalanine; GPX4: Glutathione Peroxidase 4; GrPE: Persimmon extract; Hla: Alpha-hemolysin; HPC: Hydroxypropyl Cellulose; HUVECs: Human Umbilical Vein Endothelial Cells; IC50: Half Maximal Inhibitory Concentration; ICA: Intercellular adhesion (*icaA/icaD* genes encode biofilm components); IL-1 β /IL-6/IL-8: Interleukin-1 beta, Interleukin-6, Interleukin-8; LTA: Lipoteichoic Acid; LukAB: Leukocidin AB; MBIC: Minimum Biofilm Inhibitory Concentration; MDA: Malondialdehyde; MHC-II: Major Histocompatibility Complex class II; MIC: Minimum Inhibitory Concentration; MSCRAMM: Microbial Surface Components Recognizing Adhesive Matrix Molecules; MRSA: Methicillin-Resistant *S. aureus*; mAb: Monoclonal antibody; MD simulations: Molecular Dynamics simulations; NF- κ B: Nuclear Factor kappa-light-chain-enhancer of activated B cells; NIR: Near-Infrared; PIA: Polysaccharide Intercellular Adhesin; PMN: Polymorphonuclear leukocytes; PoPE: Pomegranate extract; PSMs: Phenol-soluble modulins; PTT: Photothermal Therapy; PVL: Pantone-Valentine Leukocidin; QS: Quorum Sensing; QSI: Quorum Sensing Inhibition; RNAIII: RNA molecule regulating virulence in *S. aureus*; ROS: Reactive Oxygen

Species; SarA: Staphylococcal accessory regulator A; SaeRS: Two-component system regulating virulence in *S. aureus*; scFv: Single-chain variable fragment (antibody fragment); SEA/SED/SEB: Staphylococcal Enterotoxins A, D, B; STX: Staphylococcal Toxin; SrtA/B: Sortase A/B; TCR: T-Cell Receptor; THC: Delta-9-Tetrahydrocannabinol; TNF- α : Tumor Necrosis Factor alpha; TSST-1: Toxic Shock Syndrome Toxin-1; VBNC: Viable But Non-Culturable; VISA: Vancomycin-Intermediate *S. aureus*; VRE: Vancomycin-Resistant Enterococci; VraS/R: Two-component system involved in cell wall stress response; vWbp: von Willebrand factor-binding protein.