



Review



# Plant-Derived Natural Products for Treating *Staphylococcus aureus* Skin Infections: An Update

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**Abstract:** *Staphylococcus aureus* causes recurrent skin and soft tissue infections that are increasingly difficult to treat because antimicrobial resistance reduces therapeutic success. Biofilm matrices restrict antimicrobial penetration and maintain persister cells within superficial lesions, which promotes relapse after apparently adequate therapy. Persistent colonization within hair follicles and damaged epidermis further supports survival in cutaneous niches. Adhesin driven attachment and quorum-sensing regulation stabilize early biofilm development *in vivo*. Plant derived natural products provide membrane active and anti-virulence compounds that are suitable for topical use. Flavonoids, terpenoids and phenolic acids disrupt membrane structure and interfere with quorum-sensing networks. Several phytochemicals reduce adhesion to extracellular matrix proteins and limit early biofilm formation *in vitro* and *in vivo*. Volatile constituents show rapid evaporation and limited residence time at infected sites, while poor aqueous solubility and chemical instability restrict penetration into deeper epidermal layers. Lipid nanoparticles, nanoemulsions and hydrogel systems improve retention and local bioavailability of encapsulated phytochemicals. Microneedle assisted delivery increases localization within viable epidermis without producing systemic exposure. This review evaluates plant derived natural products relevant to topical management of antimicrobial resistant *S. aureus* skin infections.

**Keywords:** *Staphylococcus aureus*; natural products; anti-virulence; biofilm inhibition; topical delivery; nanotechnology

## 1. Introduction

Skin and subcutaneous diseases remain major non-fatal causes of morbidity worldwide and continue to impose significant clinical and socioeconomic burdens. Viral and allergic skin conditions contribute substantially to this burden, with high global prevalence and persistent disparities in access to prevention, diagnosis, and treatment [1–3]. These broader epidemiological patterns provide context for the dermatologic landscape but remain secondary to bacterial skin infections.

Bacterial infections form a major component of the global skin disease burden. Bacterial skin diseases produced the highest number of deaths within this category in 2019 and remain a significant cause of morbidity in settings with limited healthcare capacity [4]. Rising antimicrobial resistance complicates management and increases risks of recurrence, chronicity, and treatment failure. Health systems with restricted antimicrobial formularies or absent culture-based diagnostics experience greater challenges, particularly in communities with high transmission rates and limited follow-up opportunities [5].

Antimicrobial-resistant *Staphylococcus aureus* is a major contributor to global skin and soft tissue infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) and community-acquired MRSA (CA-MRSA) are associated with prolonged infection duration, reduced therapeutic success, and increased risks of persistent or



deep-seated disease. Resistance to  $\beta$ -lactams, macrolides, fluoroquinolones, and other frontline antibiotics underscores the need for adjunctive approaches that reduce microbial load, disrupt biofilm-associated tolerance, and improve treatment responsiveness in chronic or recurrent cutaneous lesions [2,4,5].

Plant-derived bioactive compounds represent a structurally diverse reservoir of agents relevant to the topical management of *Staphylococcus aureus* infections. Numerous phytochemicals exhibit membrane-disruptive, quorum-sensing-inhibitory, and antibiofilm actions that weaken structural and regulatory pathways required for *S. aureus* persistence [1]. Their multi-target properties and chemical diversity support development of adjunctive or alternative strategies capable of addressing antimicrobial resistance, chronic wound colonization, and biofilm-embedded infections. This review evaluates plant-derived compounds as supportive interventions for resistant *S. aureus* skin infections and examines delivery platforms designed to optimize their cutaneous bioavailability and clinical applicability.

## 2. *Staphylococcus aureus* and Skin Pathogenesis

*S. aureus* colonizes keratinized and damaged epidermal surfaces through coordinated expression of surface-associated adhesins that mediate attachment to host proteins within the stratum corneum. These adhesins recognize fibronectin-, fibrinogen- and cytokeratin-rich structures and stabilize early attachment within superficial cutaneous layers, enabling persistence on intact and compromised skin [6]. Bap-associated amyloid fibers reinforce early microcolony formation by promoting proteinaceous scaffolding and enhancing structural resilience under low pH and low calcium conditions [7]. These early colonization processes establish the spatial organization required for subsequent biofilm maturation.

Secreted toxins contribute to epithelial injury, barrier disruption, and cutaneous inflammation. Pore-forming cytotoxins, including  $\alpha$ -toxin and leukocidins, compromise keratinocyte integrity and promote immune infiltration, enabling *S. aureus* expansion into superficial and deeper epidermal environments [6]. Proteases and lipases further degrade extracellular components and increase damage within the epidermal barrier. These virulence determinants support transitions from asymptomatic colonization to active infection when mechanical, immunological, or microbiome-derived defenses weaken.

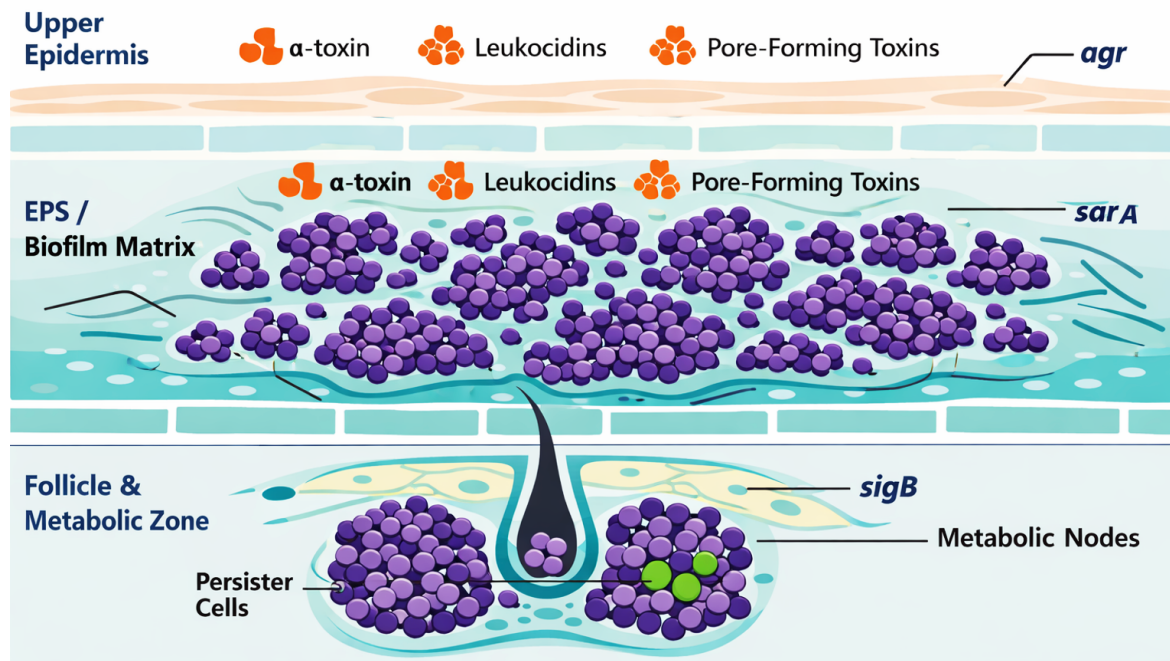
Regulatory loci govern coordinated expression of adhesion proteins, matrix-associated enzymes, and secreted toxins required for sustained cutaneous persistence. Suppression of *sarA* reduces matrix accumulation and increases susceptibility to antimicrobials, demonstrating its central role in maintaining biofilm integrity [8]. Hormonal cues also influence quorum-sensing dynamics, with androgens enhancing *agr* activity and increasing expression of virulence factors within skin environments [9]. Additional transcriptional regulators, including *sigB* and metabolic control elements, coordinate stress responses, surface protein expression, and metabolic adaptation during colonization [10]. These systems enable *S. aureus* to withstand osmotic stress, antimicrobial peptides, and lipid-rich environments.

Biofilm formation supports persistence by increasing tolerance to host defenses and restricting antimicrobial penetration. Polysaccharide intercellular adhesin contributes to matrix cohesion and protects embedded communities from environmental fluctuations, while amyloid fibers and extracellular DNA reinforce matrix rigidity [11]. Phenolic metabolites reduce polymer accumulation by interfering with polysaccharide and protein synthesis, underscoring the importance of matrix composition in resistance traits [12]. Biofilm architecture creates protective microenvironments that concentrate nutrients, retain moisture, and shield bacteria from reactive oxygen species and antimicrobial agents.

Redox imbalance and altered metabolic profiles further sustain cutaneous persistence. Membrane modulation by natural metabolites alters surface dynamics and influences biofilm cohesion [12]. Quinone exposure disrupts extracellular DNA interactions and weakens matrix density, demonstrating the structural contribution of eDNA to biofilm integrity [13]. Modifications to cell-surface hydrophobicity and charge influence adhesion strength and biofilm cohesion. Regulatory adaptation alters surface protein expression and metabolic responses, supporting survival under nutrient-limited and stress conditions [14]. These adaptations support persistence within follicular niches, where oxygen gradients and lipid-rich secretions shape bacterial metabolism. These adaptations support persistence within follicular niches, where oxygen gradients and lipid-rich secretions shape bacterial metabolism.

Biofilm-embedded communities exhibit high intrinsic tolerance to antimicrobial therapies because of structural barriers, altered metabolic states, and heterogeneous subpopulation organization. Lower permeability, slower growth, and shifts in regulatory behavior decrease antimicrobial effectiveness and increase survival of persisted cells, reflecting the combined influence of structural barriers, metabolic dormancy, and regulatory adaptation within mature biofilms [8,10]. Adhesion-associated, regulatory, and matrix-associated factors account for *S. aureus* persistence in skin and support development of therapeutic strategies targeting biofilm stability,

virulence regulation, and metabolic resilience. Figure 1 maps the structural and regulatory targets within cutaneous *S. aureus* biofilms, highlighting adhesins, extracellular polymeric substances, amyloid fibers, quorum-sensing signals, and membrane interfaces relevant to the intervention of natural products.



**Figure 1.** Structural and regulatory targets in *S. aureus* biofilms.

### 3. Natural Products with Antibiofilm Activity

Natural compounds inhibit *S. aureus* biofilms through coordinated interference with adhesion, extracellular polymeric substances, regulatory circuits, membrane integrity, and metabolic organization. These multimodal actions weaken structural cohesion, reduce tolerance traits, and complement antimicrobial therapy. Several reviews highlight the suppression of surface attachment, disruption of extracellular polymeric substance structure, and interference with quorum-sensing networks [15], while advanced delivery systems improve the stability and penetration of bioactive compounds through nanomaterial-based formulations [16]. Systematic analyses confirm multi-target activity against resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and strains with biofilm-associated tolerance [17]. Several investigations show that phytochemicals demonstrate synergistic activity with antimicrobials, producing amplified inhibition of structural and regulatory processes [18,19].

#### 3.1. Inhibition of Early Adhesion and Surface-Associated Interactions

Early adhesion depends on microbial surface components that recognize adhesive matrix molecules. Natural compounds reduce the expression or function of these adhesins, limiting stable attachment on host or abiotic surfaces [6]. Bap-associated amyloidogenic fragments promote aggregation and surface anchoring, but phytochemicals disrupt these transitions by preventing Bap-derived fiber formation [7,11]. Phenolic and terpenoid-rich extracts alter membrane charge, reduce hydrophobicity, and impair surface-associated interactions and stability, decreasing early colonization [20]. These effects align with early-stage suppression patterns observed across resistant organisms [17].

#### 3.2. Disruption of Extracellular Polymeric Substances

Extracellular polymeric substances include polysaccharides, extracellular DNA, amyloid fibers, and matrix-associated proteins. Natural compounds weaken these structures by inhibiting polysaccharide intercellular adhesin synthesis, which reduces matrix density and weakens intercellular cohesion [11]. Quinone metabolites disrupt extracellular DNA interactions and weaken biofilm matrix stability through direct DNA intercalation [13]. Phenolic derivatives inhibit polymerization pathways and reduce biomass accumulation in resistant isolates [12,20]. These multi-component disruptions mirror patterns reported across resistant pathogens [17].

### 3.3. Inhibition of Amyloid-Mediated Matrix Reinforcement

Amyloid fibers derived from Bap form a key part of the proteinaceous scaffold supporting mature biofilms. Natural compounds interrupt amyloid assembly by preventing aggregation of amyloidogenic domains required for fiber nucleation and elongation [7]. Quinone metabolites disrupt amyloid-associated proteins through redox interactions, decreasing rigidity and weakening matrix reinforcement [14]. Reduced expression of scaffold-forming proteins further contributes to loss of matrix stability [8].

### 3.4. Modulation of Quorum Sensing and Global Regulatory Circuits

Quorum-sensing systems coordinate transitions between adhesion, proliferation, matrix accumulation, and dispersal. Phytochemicals suppress *agr* signaling and reduce RNAPIII-mediated expression of virulence factors, limiting advancement toward mature biofilms [6,9]. Regulators such as *sarA* and *sigB* control adhesin expression, autolysis, polymer synthesis, and stress tolerance, and these regulators are sensitive to phytochemical interference [8,10]. A recent review highlights broad regulatory disruption produced by natural products, including reduced virulence expression and impaired adaptive responses [19]. These findings align with multi-pathway suppression patterns in resistant infections [17].

### 3.5. Membrane Disruption and Interference with Metabolic Activity

Membrane integrity supports solute transport, redox stability, and survival of embedded cells. Natural metabolites disrupt membrane permeability and surface charge, causing leakage of intracellular contents and altering nutrient uptake [14]. Terpenoid-rich extracts interfere with membrane-linked respiratory processes, reducing redox activity and limiting energetic capacity in sessile cells [20]. Quinone-mediated disruption alters cellular functions and weakens biofilm stability [13]. These metabolic effects strengthen antibiofilm activity by targeting core biochemical processes required for long-term survival [17].

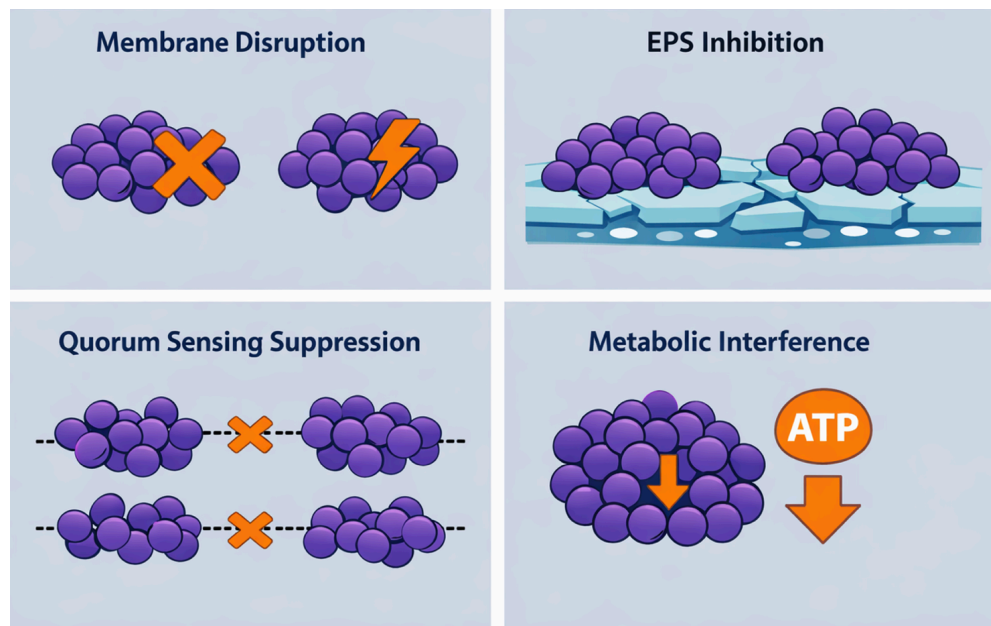
### 3.6. Multisite Disruption of Mature Biofilms

Natural compounds disrupt multiple biofilm structures simultaneously, weakening mature matrices. Quinones disrupt extracellular DNA interactions and weaken matrix integrity, contributing to the destabilization of mature biofilms [13]. Phenolic compounds interfere with polymerization and reduce the rigidity of established structures [12]. Synergistic phytochemical-antibiotic combinations reduce tolerance traits and enhance clearance of embedded cells [18,19]. These multisite disruptions reflect the multi-mechanistic antibiofilm potential documented across resistant pathogens [17].

## 4. Bioactive Compounds as Emerging Antibiofilm Interventions

Bioactive compounds inhibit the development of *S. aureus* biofilms through coordinated actions on adhesion, extracellular polymeric substances, metabolic organization, and global regulatory networks. These activities influence early and late biofilm stages, weaken structural integrity, and disrupt cooperative behaviors that support persistence in cutaneous environments. Many compounds target processes that consolidate early adhesion, interfere with proteinaceous or polysaccharide-rich scaffolds, and suppress quorum-regulated transitions required for biofilm maturation [17,21].

Flavonoids, phenolic acids, proanthocyanidins, and quinones alter physicochemical interactions at the cell surface, weaken matrix cohesion, and reduce cell-cell signaling required for spatial stability within mature structures [17,22]. Comprehensive evaluations highlight these natural compounds as contributors to multi-component antibiofilm strategies and emphasize their suitability for use against multidrug-resistant strains, including methicillin-resistant *S. aureus*. Multisite inhibition across early attachment, polymer assembly, metabolic resilience, and intercellular communication underscores the relevance of phytochemical mixtures as therapeutic adjuncts capable of reinforcing or enhancing antimicrobial outcomes. Figure 2 depicts the principal mechanisms through which plant-derived compounds disrupt *S. aureus* biofilms, including membrane damage, inhibition of extracellular polymeric substance synthesis, suppression of quorum-sensing communication, and interference with metabolic activity.



**Figure 2.** Mechanisms of natural antibiofilm compounds.

#### 4.1. Broad-Spectrum Actions of Phytochemical Mixtures

Phytochemical mixtures exert broad inhibitory effects by targeting several stages of biofilm development through combined actions of flavonoids, terpenoids, phenolic acids, and alkaloids. Many mixtures reduce adhesion strength by altering membrane charge, decreasing hydrophobicity, and impairing surface-associated interactions required for microcolony formation [20]. Several mixtures also inhibit expression or function of MSCRAMM-linked adhesins, limiting interactions with fibronectin-, collagen-, and fibrinogen-rich surfaces in early colonization zones [6].

Membrane-associated processes show pronounced sensitivity to complex extracts, which impair respiratory activity and decrease the availability of surface energy required for stable colonization [14]. These combined actions correspond to multi-target potency patterns described across resistant organisms, including strains demonstrating tolerance to conventional antibiotics [17]. The diversity of constituent compounds in crude extracts often produces improved breadth of inhibition relative to isolated molecules, supporting the rationale for harnessing synergistic interactions inherent in botanical mixtures.

#### 4.2. Interference with Quorum Sensing and Virulence Regulation

Phytochemicals disrupt quorum-sensing networks that coordinate transitions from attachment to maturation, influence virulence expression, and regulate dispersal. Many compounds suppress *agr*-linked signaling by interfering with secretion, sensing, or downstream activation of autoinducing peptides, leading to reduced activation of RNAPIII-regulated virulence determinants [6,9]. Inhibition of *agr* signaling reduces production of proteases, toxins, and extracellular enzymes required for structural remodeling and biofilm expansion.

A reduction in *sarA* activity diminishes matrix accumulation by restricting the expression of adhesins and polysaccharide intercellular adhesin, while also attenuating regulatory pathways that support biofilm stability [8]. Natural compounds also influence additional regulatory nodes, including *sigB*, autolysis regulators, and metabolic transcription factors that control stress adaptation, polymer synthesis, and surface protein expression [10]. Recent reviews highlight the broad suppression and quorum-sensing disruption across signaling networks, reflecting interactions with multiple regulons rather than isolated targets [19,21]. These regulatory effects impair biofilm formation, reduce virulence expression, and limit adaptive potential under environmental stress.

#### 4.3. Membrane Disruption and Metabolic Interference

Membrane integrity is essential for nutrient uptake, signal transduction, and maintenance of redox balance. Natural metabolites destabilize membrane function through disruption of membrane permeability, alteration of surface charge, and interference with electron transport. Membrane disruption causes leakage of intracellular constituents, collapse of membrane potential, and reduction of nutrient exchange, which impair sessile cell survival [14]. Terpenoid-rich extracts inhibit membrane-associated respiratory processes, reducing redox activity and limiting energetic capacity in

nutrient-restricted environments [20]. Quinone-mediated disruption alters cellular processes and weakens biofilm stability, particularly in deeper biofilm layers where diffusion gradients influence local activity [13]. These metabolic insults compromise the ability of sessile cells to maintain homeostasis and contribute to the weakening of mature biofilms. Such multi-component metabolic disruption aligns with the broader antibiofilm spectrum observed across natural compounds [17].

#### 4.4. Targeting Extracellular Matrix Polymers

Phytochemicals interfere with extracellular matrix components, including polysaccharides, extracellular DNA, amyloid fibers, and matrix-associated proteins. Reduced activity of the *icaADBC* operon decreases polysaccharide intercellular adhesin synthesis, reducing cohesion and decreasing matrix thickness [11]. Phenolic compounds inhibit polymerization pathways responsible for polysaccharide cross-linking and reduce biomass accumulation across resistant isolates [12].

Amyloid scaffolding formed by Bap fibers is a critical structural feature of mature biofilms, and disruption of amyloid assembly weakens mechanical integrity and decreases stability under environmental stress [7,11]. Quinones disrupt extracellular DNA interactions, lowering mechanical resistance and improving antimicrobial diffusivity within the matrix [13]. These multi-modal impediments mirror extracellular-polymer targeting patterns described in resistant pathogens and highlight the suitability of phytochemicals for weakening several structural determinants simultaneously [17,22].

#### 4.5. Synergistic Mechanisms Enhancing Antibiofilm Activity

Synergistic interactions occur when phytochemicals target multiple biofilm processes concurrently or when they enhance the activity of conventional antimicrobials. Combined inhibition of adhesion, polysaccharide production, and regulatory pathways reduces biomass stability and increases vulnerability to therapeutic intervention [6]. Synergistic phytochemical-antibiotic combinations weaken protective barriers, increase permeability and improve intracellular antibiotic accumulation, enhancing clearance of embedded cells [18].

A review emphasizes the prevalence of multisite interference patterns across natural-product strategies and supports the rationale for integrative approaches that leverage several inhibitory mechanisms simultaneously [19]. These synergistic combinations provide a basis for reducing treatment duration, lowering required antibiotic doses, and mitigating resistance development.

#### 4.6. Interference with Dispersal Pathways

Biofilm dispersal depends on coordinated activation of autolytic mechanisms, enzymatic degradation of extracellular matrix components and shifts in regulatory circuits that initiate detachment and dissemination of cells. Natural compounds impair dispersal by modulating autolysis-associated pathways, reducing controlled cell lysis and limiting the release of planktonic populations that contribute to secondary colonization events [8]. Suppression of *agr* signaling further disrupts dispersal processes by decreasing production of surfactants, proteases and extracellular enzymes required for matrix remodeling and efficient detachment [6].

#### 4.7. Enhancement of Antimicrobial Susceptibility through Matrix Weakening

Matrix weakening enhances antimicrobial penetration by reducing structural barriers and allowing deeper diffusion into mature biofilms. Reduced polysaccharide intercellular adhesin synthesis improves accessibility to deeper layers of the biofilm, increasing antimicrobial exposure [12]. Inhibition of amyloid fiber formation increases permeability and decreases rigidity of matrix frameworks [7]. Disruption of extracellular DNA interactions further lowers mechanical resistance, supporting increased penetration of therapeutic compounds [13]. Suppression of quorum-sensing signaling reduces tolerance-linked traits and improves responsiveness to antimicrobials [9]. These effects illustrate the potential for employing phytochemical interventions to sensitize resistant biofilms to treatment.

#### 4.8. Target-Based Identification of Potent Interventions

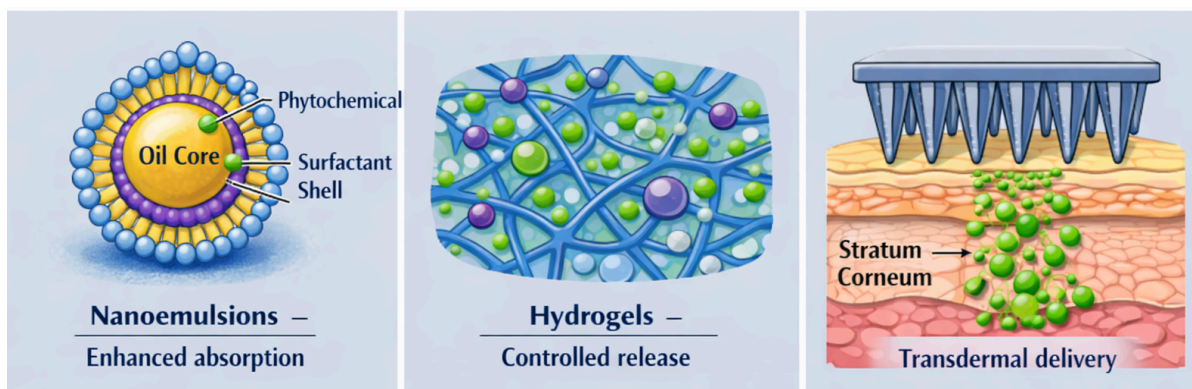
Target-based screening approaches identify phytochemicals capable of inhibiting essential determinants of biofilm survival, including adhesion proteins, extracellular-polymer enzymes, and regulatory factors. Compounds that inhibit key structural proteins or regulators provide leads for rational drug design [10]. These actions complement structural suppression across multiple biofilm determinants and reinforce the importance of combining targeted and multi-mechanistic approaches [14,17]. Identification of compounds with predictable inhibitory profiles facilitates the development of optimized scaffolds.

#### 4.9. Structural Selectivity Influencing Potency

Chemical structure influences antibiofilm interactions. Hydroxyl-rich flavonoids disrupt amyloid assembly and decrease cohesion within proteinaceous scaffolds [7]. Quinones interact with extracellular scaffold components and reduce DNA-mediated reinforcement [13]. Phenolic aldehydes inhibit polymerization pathways and decrease biomass accumulation across resistant isolates [12]. These predictable structure-activity relationships support rational design of next-generation antibiofilm agents and highlight structure-guided refinement as a promising direction for therapeutic development [6].

#### 4.10. Cross-Kingdom Activity and Polymicrobial Resilience

Multispecies biofilms often involve interactions between Gram-positive and Gram-negative organisms. Natural compounds weaken the cohesiveness of these communities by reducing adhesion strength and disrupting cross-kingdom communication pathways [14]. Disruption of interspecies signals reduces cooperative resilience and compromises structural organization within heterogeneous biofilm structures [10]. These combined effects reduce spread potential and may limit recurrent colonization in cutaneous environments. Figure 3 illustrates topical delivery platforms that enhance cutaneous localization of plant-derived compounds, including nanoemulsions, hydrogels and microneedle systems designed to improve retention and epidermal penetration.



**Figure 3.** Topical delivery systems enhancing cutaneous localization of plant-derived compounds.

#### 4.11. Enhancement of Host-Directed Clearance

Biofilm destabilization increases the susceptibility of embedded cells to host immune mechanisms. Reduced polysaccharide content improves immune penetration and access to deeper matrix layers [12]. Weakened amyloid scaffolding increases susceptibility to degradation by innate immune effectors [7]. Lower extracellular DNA reduces structural protection against phagocytic clearance [13]. Downregulated virulence signaling enhances host-mediated elimination by limiting production of immune-evasive factors [6].

### 5. Mechanisms of Action of Natural Compounds against *S.* Biofilms

Natural compounds inhibit *S.* biofilms through complementary actions on membrane integrity, adhesion pathways, extracellular polymeric substance formation, quorum-sensing circuits, and global regulatory networks. These mechanisms target structural and functional determinants required for biofilm maturation, resilience, and persistence, weakening tolerance traits associated with chronic skin infections [17].

Disruption across multiple biofilm nodes enhances susceptibility to antimicrobial exposure and reduces stability within embedded populations [8]. Systematic analyses confirm that broad multi-target activity is a distinguishing characteristic of natural compounds across resistant pathogens, including methicillin-resistant *S. aureus*, where integrated suppression of metabolic, structural, and regulatory processes contributes to meaningful antibiofilm efficacy [17].

#### 5.1. Membrane Disruption and Energetic Impairment

Natural compounds compromise membrane integrity by altering permeability, disrupting bilayer organization, and disturbing electrochemical balance. These effects cause leakage of intracellular constituents, collapse membrane potential, and inhibit nutrient exchange, impairing sessile cell survival within the biofilm [14].

Disruption of the membrane also reduces the effectiveness of proton-motive-force-dependent processes, including solute transport and ATP generation.

Terpenoid-rich extracts interfere with membrane-linked respiratory functions by suppressing electron transport and decreasing metabolic turnover, weakening viability under nutrient-limited conditions characteristic of biofilm cores [20]. Disruption of extracellular DNA interactions decreases persistence in polymicrobial environments and supports broader therapeutic relevance [13]. These assaults limit the development of metabolically active microcolonies and contribute to progressive weakening of biofilm structure [17].

### 5.2. Inhibition of Adhesion and MSCRAMM-Related Interactions

Adhesion represents the first step in establishing stable biofilms. Natural compounds inhibit adhesion by interfering with microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), reducing early binding to host tissues and abiotic substrates [6]. Reduced expression or inhibited function of MSCRAMMs lowers adhesion efficiency and diminishes the transition from reversible attachment to irreversible anchoring.

Flavonoids suppress Bap-mediated amyloid fiber formation, preventing development of the structural reinforcement required for strong adhesion and matrix consolidation [7,11]. Additional phytochemicals modulate adhesion by altering membrane charge, decreasing hydrophobicity, and reducing surface-associated interactions that promote initial aggregation [20]. These combined actions correspond to multi-target early-stage suppression patterns described across resistant organisms [17].

### 5.3. Disruption of Extracellular Polymeric Substances

Extracellular polymeric substances provide mechanical strength, nutrient retention and antimicrobial tolerance within biofilms. Natural compounds disrupt extracellular-polymeric-substance assembly by reducing icaADBC-mediated polysaccharide production and weakening intercellular cohesion [11]. Phenolic constituents interfere with polymerization pathways that contribute to polysaccharide cross-linking and reduce biomass accumulation in resistant isolates [12]. Quinones disrupt extracellular DNA interactions, a structural element that confers rigidity, promotes adhesion, and stabilizes intercellular networks within mature matrices [13].

Inhibition of Bap-associated amyloid fiber formation prevents the development of robust proteinaceous scaffolds and increases susceptibility to mechanical disruption [7]. Combined interference across polysaccharides, proteins, and extracellular DNA produces multisite destabilization patterns consistent with broad suppression profiles documented across resistant pathogens [17].

### 5.4. Modulation of Quorum Sensing and Global Regulatory Pathways

Quorum-sensing pathways regulate transitions between adhesion, proliferation, matrix accumulation, and dispersal. Many natural compounds suppress *agr* signaling by interfering with secretion, processing, or recognition of autoinducing peptides, reducing RNAPIII-dependent factors that support matrix reinforcement and virulence expression [6,9].

Reduced *sarA* activity decreases polysaccharide intercellular adhesion synthesis and suppresses stabilizing regulatory signals that maintain biofilm structure [8]. Interference with autolysis pathways limits extracellular DNA release and weakens structural persistence [10]. Additional inhibition of *sigB* and other stress-response regulators disrupts metabolic adaptation and collapses regulatory coherence essential for sustained biofilm formation [19]. These regulatory perturbations combine with structural inhibition to reduce virulence, weaken matrix formation, and impair biofilm stability.

### 5.5. Interference with Intracellular Processes Supporting Persistence

Biofilm survival depends on intracellular processes involving metabolism, transcriptional regulation, and stress adaptation. Natural compounds interrupt these processes by reducing redox activity, limiting ATP availability, and impairing metabolic pathways essential for growth under nutrient-restricted conditions. Suppressed transcription of genes involved in adhesion, polysaccharide synthesis, and stress resistance decreases production of proteins required for persistence and matrix reinforcement [8]. These intracellular disruptions synergize with membrane interference, reducing the emergence of resilient subpopulations and limiting heterogeneity within biofilm structures. Broad intracellular inhibition aligns with multi-mechanistic suppression patterns summarized across resistant organisms [17].

### 5.6. Synergy and Reduction of Intrinsic Tolerance

Weakening of extracellular polymeric substances improves antimicrobial penetration by reducing structural barriers and promoting deeper diffusion into mature matrices. Reduced polysaccharide intercellular adhesin synthesis increases access of antibiotics to deep biofilm layers [12]. Suppressed *agr* signaling reduces tolerance pathways that protect embedded cells during antimicrobial exposure [9]. Combined metabolic, regulatory, and structural inhibition enhances antibiotic efficacy and reduces intrinsic tolerance traits associated with chronic *S. aureus* infections [17].

## 6. Advanced Topical Delivery Systems for Plant-Derived Anti-Staphylococcal Agents

Topical delivery systems enhance the therapeutic potential of plant-derived antimicrobials against *S. aureus* by improving solubility, dermal retention, and penetration into biofilm-containing microenvironments. Many phytochemicals display poor aqueous solubility, rapid volatilization, susceptibility to oxidation, and inadequate permeation across the stratum corneum, resulting in sub-therapeutic concentrations at infected sites [23].

Advanced delivery systems address these limitations by increasing cutaneous deposition, sustaining local release, and facilitating deeper penetration into biofilm-embedded bacterial communities, maintaining prolonged antimicrobial exposure in infected tissue [24]. These technologies improve clinical relevance by enhancing stability, deposition, and targeting of plant-derived compounds.

### 6.1. Challenges in Topical Delivery of Plant-Derived Compounds

Hydrophobicity, volatility, and physicochemical instability represent central challenges in formulating plant-derived antimicrobials for topical delivery. Terpenoid-rich essential oils evaporate rapidly due to high vapor pressures, resulting in short residence times and reduced therapeutic contact with biofilm-laden lesions [23]. Polyphenols and antioxidant phytochemicals degrade in response to oxygen, UV light and pH fluctuations, diminishing antimicrobial potency and limiting viability as stand-alone topical agents [24].

The stratum corneum forms a dense hydrophobic barrier that restricts permeation of both hydrophilic and lipophilic phytochemicals, while chronic lesions and biofilm-rich environments further impede diffusion due to matrix density and high binding affinity for extracellular polymers [23]. These obstacles necessitate delivery systems capable of enhancing solubility, reducing volatilization, stabilizing bioactive compounds, and promoting penetration across epidermal and biofilm-associated barriers.

Advanced platforms increase solubility through surfactant-mediated emulsification, encapsulation within lipid or polymeric carriers, and sustained-release mechanisms that protect phytochemicals during cutaneous transit [24]. These advances enable topical formulations to maintain therapeutic concentrations for extended durations, increasing their potential to address persistent *S. aureus* infections.

### 6.2. Nanotechnology-Based Formulations

Nanotechnology offers strategies for improving stability, bioavailability, and dermal deposition of plant-derived antimicrobials. Lipid-based nanoparticles enhance solubility and provide sustained release, maintaining prolonged exposure at infected sites [23]. Nanoemulsions containing essential oils improve cutaneous permeation and deliver controlled-release profiles, producing stronger antibiofilm activity than unformulated oils by enhancing diffusion into biofilm matrices [24].

Encapsulation of curcumin within niosomes increases chemical stability, enhances dermal penetration, and produces improved antibiofilm activity against multidrug-resistant *S. aureus*, achieving two- to four-fold biomass reductions compared with free curcumin [25]. Nanoemulsion gels incorporating *Sophora alopecuroides* oil improve transdermal transport, increase retention of oxymatrine, and enhance inhibition of *S. aureus* and MRSA biofilms relative to free oil [26]. Optimized thymol-loaded nanoemulsions exhibit potent anti-MRSA activity by disrupting membrane potential, increasing bacterial permeability, and altering hydrophobicity, supporting multi-target mechanisms that minimize resistance development [27].

Nanoemulsion NB-201 demonstrates strong antimicrobial activity in infected porcine burn wounds and reduces inflammatory markers, underscoring translational potential for deep cutaneous infections associated with MRSA [28]. Nanotechnology platforms overcome solubility limitations and enhance retention of plant-derived antimicrobials in biofilm-dense tissue, producing stronger and more durable antimicrobial effects.

### 6.3. Vesicular and Micellar Systems

Vesicular carriers, including liposomes, ethosomes, transferosomes, and niosomes, improve solubility, protect bioactive compounds from oxidation, and enhance permeation across the stratum corneum. Their flexible, deformable membranes enable transport through narrow intercellular channels, increasing dermal deposition of encapsulated phytochemicals [29]. Encapsulation in niosomes improves curcumin's antibiofilm activity and reduces cytotoxicity compared with free curcumin, demonstrating suitability for treatment of chronic or biofilm-laden *S. aureus* wound beds [25].

Micellar platforms facilitate co-delivery of phytochemicals and antibiotics, improving cutaneous permeability and enhancing intracellular accumulation of antimicrobials within embedded cells. By reducing crystallization and improving solubilization of hydrophobic compounds, micelles extend local exposure and strengthen synergistic outcomes [23]. These vesicular and micellar carriers enhance stability, improve release kinetics, and increase biofilm penetration, enabling combined effects that exceed those of free phytochemicals [24].

### 6.4. Hydrogels, Films, and Advanced Dressings

Hydrogels create hydrated, oxygen-permeable microenvironments suitable for chronic or infected cutaneous lesions and serve as matrices for phytochemical incorporation. Thyme-oil hydrogels containing PLGA nanoparticles promote re-epithelialization, reduce microbial load, and enhance tissue regeneration in inflamed skin, supporting therapeutic use against topical *S. aureus* infections [30]. Nanogel-based formulations stabilize phytochemicals, extend retention, and enable controlled release, increasing local concentrations and improving wound-healing outcomes [23].

Thymol-loaded cationic nanoparticle hydrogels enhance MRSA inhibition and reduce *in vivo* dissemination relative to free thymol, demonstrating favorable retention and stronger wound-healing potential [31]. Plant-based films and hydrogels promote cell migration, enhance re-epithelialization, and provide intrinsic antimicrobial activity, making them suitable for long-term treatment of chronic or contaminated wounds [32]. Hydrogel dressings with intrinsic antibiofilm and antioxidant functionality accelerate healing of MRSA-infected diabetic wounds by reducing oxidative stress, enhancing clearance of embedded colonies, and improving granulation tissue quality [33]. These advanced dressings increase local phytochemical exposure, maintain hydration, and support sustained delivery within biofilm-rich microenvironments.

### 6.5. Microneedle-Assisted Delivery and Hybrid Platforms

Microneedle arrays bypass the stratum corneum barrier by creating transient microchannels that enhance penetration of phytochemical formulations into deeper epidermal and dermal tissues. These devices improve delivery to perifollicular niches, where *S. aureus* frequently persists despite topical therapy [33]. Microneedle systems increase local deposition of vesicular phytochemical carriers, enhancing antimicrobial activity and improving tissue-level targeting [34].

Hydrogel-forming microneedles maintain structural integrity upon insertion, absorb interstitial fluid, and enable extended release from swollen matrices. These platforms stabilize phytochemicals, reduce degradation, and optimize controlled release, supporting sustained therapeutic exposure in deep wound microenvironments [35]. Combined microneedle-hydrogel systems integrate deep penetration, sustained delivery, and improved deposition, offering a strategy for treating recalcitrant or biofilm-associated *S. aureus* infections [34,35].

## 7. Clinical Translation and Regulatory Considerations

Clinical translation of plant-derived anti-staphylococcal agents remains constrained by limited standardization, inconsistent formulation quality, and substantial gaps between preclinical findings and patient-level outcomes. Many experimental studies rely on *in-vitro* biofilms or small-animal wound models that do not replicate the structural, immunological, or microbiome complexities of chronic human skin infections.

The architecture, immune interface, and temporal dynamics of human cutaneous biofilms differ markedly from laboratory systems, reducing predictive value and complicating translational progression [23,24]. These differences lead to varying treatment results and emphasize the importance of developing clinical models that accurately reflect long-term infections, involve multiple species, and account for weakened barrier function as seen in actual cases.

Variability in phytochemical composition introduces further challenges during development. Differences in botanical species, chemotypes, soil composition, seasonality, harvesting practices, and extraction methods influence the identity and concentration of active constituents. This variability results in fluctuating antimicrobial potency, inconsistent antibiofilm efficacy, and uncertain reproducibility across production batches [29]. Such

fluctuations hinder cross-study comparison, complicate dose optimization, and limit regulatory evaluation of stability, safety, and therapeutic reliability.

Safety assessment of topical phytochemicals requires disciplined evaluation because plant-derived agents are not inherently innocuous [36]. Many phytochemicals produce irritant, cytotoxic, or pro-oxidant effects at concentrations required for antimicrobial action, particularly when applied to inflamed, compromised, or barrier-depleted skin. Essential oils may provoke irritant or allergic contact dermatitis and can influence barrier-lipid organization at higher concentrations.

Nanoparticles, vesicles, and microneedle platforms may alter dermal distribution and systemic absorption, necessitating toxicological evaluation under chronic-use conditions [29]. Sustained-release or deeply penetrating formulations, including lipid nanoparticles, niosomes and hydrogel-forming microneedles, increase local retention but may modify innate immune responses, keratinocyte activity or wound-healing dynamics [35]. These characteristics require a structured examination of local tolerance, potential sensitization, phototoxicity and long-term compatibility with cutaneous tissue.

Regulatory pathways for plant-based topical antimicrobials remain fragmented across jurisdictions. Herbal preparations may be evaluated as cosmetics, over-the-counter natural products, traditional medicines, or pharmaceuticals, depending on regional policies, each involving different evidence requirements for safety, manufacturing practice, and therapeutic claims. Formulations incorporating nanomaterials face additional regulatory scrutiny because particle size, polydispersity, surface chemistry, degradation by-products, and environmental accumulation influence safety and complicate approval [30,33].

Regulatory frameworks currently lack detailed guidance for hybrid systems combining natural compounds with advanced delivery technologies such as microneedles, nanogels and responsive hydrogel matrices. Microneedle-based platforms must also satisfy expectations for sterility, mechanical strength, structural uniformity and biological safety under conditions simulating clinical use [34].

Quality control represents an essential element of translation. Standardized extraction, validated quantification of active constituents, reproducible formulation parameters, and consistent physicochemical profiles are necessary to ensure predictable activity and minimize batch-to-batch variation. Delivery systems must meet stability, microbiological safety, and material-performance specifications to maintain reliability during storage, application, and clinical evaluation [23,24]. Achieving regulatory compliance requires harmonized documentation of product identity, purity, contamination limits, degradation pathways, and release kinetics.

Clinical adoption of plant-derived anti-staphylococcal agents will depend on robust human trials that evaluate meaningful endpoints, including wound-specific healing trajectories, reduction of biofilm burden, symptomatic improvement, and safety across diverse patient groups. Formulations combining phytochemical complexity with engineered delivery platforms, such as nanoemulsions, vesicular carriers, hydrogels, and microneedle systems, require integrated evaluation to determine therapeutic benefit, dermal compatibility, systemic exposure, and long-term safety [24,34,35].

These trials must also address dose-response relationships, optimal application frequency, site-specific pharmacokinetics, and the influence of lesion chronicity, microbial diversity, and host immune status. Effective translation depends on coordinated development that integrates rigorous standardization, regulatory alignment, well-designed clinical trials, and comprehensive assessment of safety, performance, and long-term outcomes [24,34,35].

## 8. Challenges and Limitations in Developing Plant-Derived Topical Therapies against *S. aureus*

Development of plant-derived topical therapies for *S. aureus* faces technological, biological and regulatory constraints. Chemical variability, unstable physicochemical profiles, limited bioavailability, and incomplete mechanistic understanding remain barriers to clinical translation [35,36]. Penetration through the stratum corneum, diffusion into biofilm-dense lesions, and persistence within wound microenvironments remain inconsistent across formulations.

Metabolic degradation at wound sites and sequestration by extracellular polymeric matrices further diminish therapeutic concentrations, particularly in chronic or exudative lesions where oxidative stress and elevated proteolytic activity degrade many phytochemicals [10]. These challenges weaken translational predictability and complicate efforts to align laboratory outcomes with patient-level responses.

### 8.1. Standardisation, Sourcing and Quality Control

Plant-derived antimicrobials exhibit compositional variability shaped by species differences, chemotype diversity, geographic origin, cultivation conditions, seasonal variation, and extraction methodology. These factors affect identity and abundance of active constituents, producing fluctuations in antimicrobial potency and antibiofilm activity [35]. Essential oils, phenolic-rich extracts, and alkaloid blends often display heterogeneous

chemical fingerprints, resulting in inconsistent inhibitory concentrations even when harvested from the same species [12]. Many bioactive compounds occur in low abundance, and reliance on wild harvesting places pressure on natural populations while limiting scalability.

Controlled cultivation, authenticated botanical sourcing, and validated extraction processes reduce variability and support sustainable production [36]. Standardization requires rigorous characterization of active constituents, defined processing conditions, and verification of bioactive markers to ensure reproducible therapeutic performance. Without systematic chemical standardization, regulatory approval becomes more difficult, and batch-to-batch variability undermines clinical reliability.

### 8.2. Formulation, Drug Metabolism, and Topical Bioavailability

Many plant-derived compounds possess unfavorable physicochemical characteristics, including high lipophilicity, low aqueous solubility, instability in the presence of oxygen or UV light, and susceptibility to pH-dependent degradation. These properties constrain penetration through the stratum corneum and reduce persistence in inflamed or exudative tissue [23]. Phenolic compounds rapidly lose potency during exposure to environmental oxidative stress, while terpenoid constituents evaporate quickly, limiting dermal contact time [24]. Hydrophobic compounds frequently display poor miscibility in aqueous formulations, restricting suitability for gels, ointments, and hydrogels.

Nanotechnology-based systems enhance solubility and protect unstable compounds but introduce complexities in manufacturing, surfactant optimization, particle-size control, and regulatory compliance [28]. Polyphenols and peptides experience rapid enzymatic degradation at wound surfaces, requiring encapsulation in vesicles, gels or nanoparticles to maintain stability and prolong cutaneous residence [24]. Achieving therapeutic concentrations within deep biofilm layers remains one of the most persistent obstacles to effective topical therapy.

### 8.3. Safety and Toxicity Considerations

The assumption that plant-derived therapies are inherently safe is not supported by available evidence. Many phytochemicals induce irritant, cytotoxic or pro-oxidant effects when applied at antibacterial concentrations, particularly on compromised or inflamed skin [35]. Essential oils may disrupt epidermal lipid structure, alter barrier function, or provoke allergic reactions. Surfactants, penetration enhancers, and nanocarriers modulate membrane integrity and may trigger local inflammatory responses, requiring careful optimization of excipient composition [28].

Biomaterial-based carriers such as hydrogels and films require evaluation of compatibility with wound microenvironments, including moisture balance, pH gradients, enzymatic activity, and immune milieu [31]. Antioxidant hydrogels and nanogels may alter redox balance or influence keratinocyte function, necessitating safety studies in reconstructed epidermis models, primary cell assays, and long-term *in vivo* systems [32]. Comprehensive toxicological evaluation remains essential for regulatory acceptance of advanced phytochemical formulations.

### 8.4. Rediscovery, Dereplication, and Innovation Gaps

Natural-product discovery is hindered by repeated isolation of known antibacterial scaffolds, consuming analytical resources and delaying identification of novel compounds. Dereplication strategies using mass spectrometry, molecular networking, and spectral libraries enable early identification of previously characterized metabolites and redirect effort toward unique chemical entities [37].

Many screening assays rely on crude extracts, small panels of *S. aureus* strains, or planktonic minimum inhibitory concentration tests, which fail to capture physiological features of biofilm-embedded cells [7]. These limitations obscure identification of compounds capable of penetrating biofilms, modulating regulatory pathways, or overcoming tolerance phenotypes [14]. Greater emphasis on mechanistically informative screening models, including *ex vivo* skin systems, biofilm-mimicking hydrogels, and multi-omics-guided assays, is required to identify interventions that target persistent biofilm states.

### 8.5. Mechanistic Gaps and Limited Potency

Many phytochemicals exhibit moderate activity in planktonic assays but reduced potency when isolated from synergistic extract matrices. Poorly defined mechanisms impede rational optimization of potency, stability, and therapeutic efficacy [11]. Integrating genomic, proteomic, and metabolomic approaches enables a deeper understanding of intracellular targets, signaling pathways, and metabolic stress responses influenced by phytochemicals [17]. Computational tools, including molecular docking and machine-learning-based structure-

activity prediction, support identification of active motifs and facilitate semi-synthetic refinement [24]. Mechanistic precision forms the foundation for rational drug discovery from natural scaffolds, improving predictability and enabling the design of next-generation antibiofilm agents [38].

### 8.6. Regulatory, Intellectual Property and Commercialisation Barriers

Plant-derived topical antibacterials occupy overlapping regulatory categories spanning cosmetics, botanical extracts, traditional medicines, and pharmaceuticals. This diversity complicates regulatory approval, as each classification demands different evidence thresholds for efficacy, safety, manufacturing practice, and quality control [23]. Evaluation is further constrained by inconsistent biofilm assay methodologies and limited regulatory guidance on natural formulations incorporating nanotechnology or microneedle platforms [24].

## 9. Conclusions

This review examines plant-derived agents with membrane-disruptive, anti-virulence, and antibiofilm actions against cutaneous *S. aureus*. These natural compounds interfere with membrane integrity, impair early adhesion, suppress quorum-sensing networks, and weaken extracellular matrix structures that support biofilm persistence. Their multi-target actions disrupt structural organization and regulatory coherence while reducing the resilience of embedded cells, providing complementary benefits alongside conventional antibiotics.

Advances in topical delivery have significantly enhanced the performance of phytochemicals by improving solubility, chemical stability, dermal retention, and penetration into biofilm-containing lesions. Nanoparticles, nanoemulsions, vesicular carriers, micelles, hydrogels, and microneedle platforms enable sustained release and deeper permeation into infected tissue. These systems increase interaction with biofilm matrices, improve antimicrobial access to protected niches, and enhance local antibacterial effects in both laboratory models and experimental wound infections.

Despite these developments, substantial barriers continue to limit translation into clinical use. Chemical variability, physicochemical instability, limited bioavailability and formulation complexity impede consistent activity. Safety considerations, including potential irritation, cytotoxicity, and risks associated with nanocarrier accumulation, require rigorous evaluation. Regulatory frameworks and intellectual-property constraints further restrict commercial investment and slow product development. The multicomponent nature of botanical extracts, coupled with a lack of standardized antibiofilm testing methodologies, complicates the demonstration of reliable performance and hinders approval pathways.

Future progress depends on integrated efforts linking natural-product chemistry, mechanistic investigation and advanced formulation engineering. Improved botanical standardization, sustainable sourcing, robust safety assessment, and harmonized regulatory guidance will be essential for enabling clinical translation. With coordinated scientific and regulatory support, plant-derived antibiofilm agents hold meaningful potential to augment treatment of *S. aureus* skin infections and address key limitations of current antibiotic-based strategies.

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