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Review Article

Streptococcus spp.: Integrating Advances in Molecular Biology, Pathogenicity, and Strategies Against Antimicrobial Resistance

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Abstract

The genus *Streptococcus* comprises Gram-positive pathogens with a high impact on public and animal health, including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus mutans*, and *Streptococcus suis*. The rise of multidrug resistance to classic antibiotics, such as beta-lactams and macrolides, drives the need for novel therapeutic approaches. This narrative review aimed to discuss virulence and antimicrobial resistance in streptococci, as well as molecular advances in the development of new therapeutic and anti-virulence strategies. The pathogenicity of *Streptococcus* species is primarily influenced by critical mechanisms such as surface proteins, biofilm formation, and the production of toxins (e.g., pneumolysin and SpeB) that facilitate immune evasion and bacterial persistence. Antimicrobial resistance in *Streptococcus* represents a global health emergency, evidenced by the reduced efficacy of beta-lactams and macrolides via mechanisms such as structural alterations and biofilm formation. This scenario is further exacerbated by severe multidrug resistance in species like *S. suis*, *S. pneumoniae*, and *S. pyogenes*, which challenge conventional therapeutic lines. Innovative strategies based on molecular biology are discussed, including the development of vaccines based on conserved proteins (such as PspA) and anti-virulence approaches that aim to "disarm" the bacteria by inhibiting adhesion and toxicity rather than focusing exclusively on cell lysis. Additionally, emerging technologies such as the use of nanocarriers, antimicrobial peptides, and combination therapies (the "Trojan Horse" strategy) are explored. It is concluded that the integration of nanotechnology and the molecular characterization of pathogenic mechanisms is crucial to overcoming the antimicrobial resistance crisis and enhancing immunoprophylaxis strategies against severe streptococcal infections.

Keywords: *One Health; Antimicrobial Resistance; Virulence Factors; Molecular Biology; Nanotechnology.*

1. Introduction

Streptococcus are Gram-positive bacteria with spherical or ovoid morphology. Widely found in the environment, these microorganisms are capable of causing severe damage to both animal and human health [1]. Currently, the genus encompasses approximately 100 species in its taxonomic classification and stands out in the context of multidrug resistance (MDR), which generates negative impacts on both public health and the global economy [2]. Among the most relevant pathogens are *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. mutans*, and *S. suis* [2–4].

These species are notable not only for their prevalence but also for the severity of the infections they cause, ranging from dental caries [5] and throat infections to lethal invasive conditions such as meningitis, pneumonia [6] and sepsis, primarily affecting pregnant women, fetuses, and infants [7]. Furthermore, the clinical management of these infections faces a growing obstacle: the global emergence of strains multidrug-resistant to conventional antimicrobials, including macrolides, tetracyclines, and fluoroquinolones [8,9]

The pathogenicity of these species is sustained by a complex arsenal of virulence factors [7,10–12]. Recent data indicate that the infectious capacity of these microorganisms is intrinsically linked to the expression of specific genes encoding surface proteins [13], immune system evasion mechanisms [14], and toxin production [15,16]. Bacterial persistence is further exacerbated by the ability to form biofilms and rapid genetic adaptation, rendering traditional treatments progressively less effective [17].

Additionally, the coordinated expression of these genes is often mediated by signal transduction systems, allowing the bacteria to respond rapidly to changes in the host microenvironment [18]. Given the selective pressure imposed by antibiotics and the consequent resistance, biomedical research has turned to molecular biology as a crucial tool for elucidating the immunology, vaccinology, and genetics of these pathogens [19–21]

In this context, the integration of these findings with emerging technologies, such as nanotechnology [22], combination therapies, and the use of antimicrobial peptides [23], presents promising results. This review aims to integrate recent advances in the molecular biology of *Streptococcus* spp., discussing how a deep understanding of their pathogenic mechanisms is paving the way for innovative therapies capable of bypassing the antimicrobial resistance crisis.

2. Steptococcus spp.

Streptococcus pneumoniae is characterized as an opportunistic pathogen that commensally inhabits the human respiratory system. However, it can become invasive and cause severe infections upon reaching the lungs, ears, or bloodstream [20]. Consequently, individuals may develop pneumococcal pneumonia, a condition that can progress to systemic sepsis. In 2019, this condition caused approximately 740,180 deaths, primarily affecting children [24,25]. his microorganism is the leading etiological agent of pneumonia among 100 pathogens analyzed, with an emphasis on community-acquired pneumonia (CAP), where the infection occurs outside the hospital environment [26].

In turn, *S. pyogenes*, known as GAS (Group A *Streptococcus*), is also responsible for various human pathologies, commensally colonizing nasopharyngeal cells and the epidermis [27]. It is a causative agent of skin infections and pharyngitis, which can evolve into severe systemic diseases such as necrotizing fasciitis and streptococcal toxic shock syndrome. Such manifestations represent one of the leading causes of mortality worldwide, especially in underdeveloped regions [28].

Another species with high infection rates and mortality risk is *S. agalactiae*, or Group B *Streptococcus* (GBS). This beta-hemolytic bacterium is known for infecting the bloodstream, presenting high morbidity rates in newborns, pregnant women, and the elderly [29]. Furthermore, it can colonize the genitourinary and gastrointestinal systems, causing bacteremia, pneumonia, meningitis, and sepsis in pregnant women [30,31]. he infection also compromises fetal development, potentially leading to premature birth, stillbirth, and chorioamnionitis [32].

S. mutans also belongs to this group of public health relevance, being associated with approximately 500,000 deaths annually worldwide [33]. Although it is capable of causing mild and superficial infections in the oral cavity [17], it can progress to bacteremia, sepsis, toxic shock syndrome, and necrotizing fasciitis, primarily affecting immunocompromised individuals or those with cardiac and rheumatic diseases [34].

Finally, the species *S. suis* stands out as a zoonotic agent, transmitting diseases between animals and humans through the digestive and respiratory tracts or via skin wounds. Clinical manifestations include arthritis, pneumonia, and meningitis [35]. This strain primarily infects swine; humans who handle these animals daily, process meat products, or consume undercooked pork are the most susceptible to systemic infections [11,36].

3. Pathogenicity and Virulence Factors

The pathogenicity of species within the genus *Streptococcus* is mediated by a complex arsenal of molecular determinants that ensure the establishment and persistence of infection. These virulence factors—ranging from surface proteins and exotoxins to regulatory and resistance genes—act in a coordinated manner to promote host colonization [12,33,37,38].

The mechanisms involved include adhesion to and invasion of biological barriers, biofilm formation, and the modulation of the immune response, which hinders phagocytosis and the efficacy of antimicrobials. Table 1 presents a synthesis of the primary strains discussed (*S. pneumoniae*, *S. agalactiae*, *S. pyogenes*, *S. mutans*, and *S. suis*), detailing their respective virulence factors, mechanisms of action, and the references supporting these interactions.

Table 1. Virulence factors associated with *S. pneumoniae*, *S. agalactiae*, *S. pyogenes*, *S. mutans*, and *S. suis* strains.

Bacterial Strain	Virulence Factor	Mechanism of Action	Reference
S. pneumoniae	PspA and PspC	Act as adhesins promoting infection and mediating immune system evasion	[13]
	Spn gene	Responsible for encoding proteins involved in adhesion and invasion of host cells.	[20,39]
	PLY	Induces apoptosis and cellular toxicity; inhibits local inflammation, increasing bacterial survival and immune evasion.	[40]
S. agalactiae	*BrpA*	Enhances antibiotic resistance and inhibits host immune defenses.	[1]
	FbsA, FbsB, FbsC	Surface and secreted proteins that mediate bacterial adhesion.	[1]
	hvgA	Facilitates bacterial adhesion and penetration of biological barriers (intestinal, blood-brain); aids migration through host systems.	[29]
	Cps	Contributes to evasion of the immune system.	[37]
	Gene *scpB* (C5a peptidase)	Facilitates invasion and infection of healthy cells.	[41]

Table 1. Continued..

S. pyogenes	*erm* gene	Modifies the antibiotic target structure (prevents 23S rRNA methylation), conferring resistance.	[8]
	ropB gene	Integrates growth/metabolism signals, senses pH, and induces protease expression.	[12,42]
	SpeB	Causes tissue damage, cleaves proteins, and neutralizes immunoglobulins.	[12,16]
	mga gene	Encodes proteins involved in adhesion and invasion.	[12]
S. mutans	KAT ActG	Biofilm formation.	[43]
S. suis	Ihk/Irr-PepO	Confer high virulence profiles and significant immune system evasion	[14]

3.1 *Streptococcus pneumoniae*

Among the primary virulence mechanisms of *Streptococcus pneumoniae*, the pneumococcal surface proteins (Psp) are of particular importance, with the PspA and PspC fractions classified as the most virulent. These proteins play a critical role in pathogenesis by acting as adhesins, facilitating attachment to the host epithelium, and as mediators of immune evasion by preventing complement system deposition and subsequent phagocytosis [13].

Furthermore, pneumococcal virulence is enhanced by the expression of several genes encoding essential surface proteins and toxins, such as pneumolysin (PLY), CbpA, LytA, and other choline-binding proteins [39,44]. These proteins exhibit diverse virulence mechanisms; for instance, the PLY protein belongs to a group of beta-hemolytic toxins whose activity induces apoptotic processes and cellular toxicity. Additionally, PLY can inhibit localized inflammation at the site of infection, thereby increasing immune evasion and bacterial survival [40].

3.2 *Streptococcus agalactiae*

S. agalactiae exhibits a diverse array of virulence factors. Among these, the biofilm regulatory protein A (BrpA) stands out, as it enhances antibiotic resistance and inhibits host defense mechanisms. The virulence arsenal also includes cell wall-anchored and secreted proteins that function as adhesins, such as the fibrinogen-binding surface proteins (FbsA, FbsB, and FbsC) and the laminin-binding protein (Lmb) [45].

Furthermore, *S. agalactiae* expresses the HvgA gene, which is crucial to its infection pathway. This gene encodes specific proteins that optimize bacterial adhesion and facilitate the crossing of the intestinal, blood-brain, and placental barriers. This cellular invasion capacity assists the microorganism's migration through host systems, significantly increasing the rates of systemic infection [38]. Another essential component is the capsular polysaccharide (CPS), which acts as a physical and chemical barrier against phagocytosis, contributing to immune system evasion [37].

The scpB gene also plays a fundamental role within the species' virulence factors. It is responsible for the expression of the C5a peptidase enzyme, which inactivates the C5a component of the complement system. This process impairs the recruitment of defense units (leucocytes) to the infection site and facilitates the invasion of healthy tissues. The relevance of this gene is underscored by its high prevalence in bacterial isolates, reaching rates of 88.8% to 100% in recent studies [41].

3.3 *Streptococcus pyogenes*

The GAS strain (*Group A Streptococcus*) is a concerning infectious agent due to the presence of genes that complicate treatment. For instance, the *erm* gene (erythromycin ribosome methylase) is capable of modifying the target structure of commonly used antibiotics; it promotes the methylation of the 23S rRNA component of the 50S ribosomal subunit, thereby preventing drug binding [8]. Among the virulence factors of GAS, the *ropB* gene is prominent, as it integrates growth signals and the bacterium's metabolic state, directly influencing its pathogenicity [42]

RopB induces the expression of proteases such as SpeB (streptococcal pyogenic exotoxin B), which causes direct damage to host tissues and promotes immune system evasion. Furthermore, this gene acts as an environmental regulator, primarily through pH sensing, allowing the bacterium to coordinate its metabolism and signal key pathways for the production of virulence factors at the infection site [12,42]. SpeB also functions in protein cleavage, being capable of neutralizing immunoglobulins (IgA, IgM, IgD, IgE, and IgG). This results in a reduction of the immune system's phagocytic efficacy [16].

Additionally, *S. pyogenes* possesses the *mga* gene (multigene activator), which participates in the development of crucial virulence pathways. It encodes essential proteins for the adhesion to and invasion of host cells, including the surface proteins Mrp and Enn (fibronectin-binding adhesins). The expression of the *mga* gene occurs primarily during the logarithmic growth phase, regulating bacterial activity to facilitate infection and evasion of host defenses [12].

3.4 *Streptococcus mutans*

The virulence of *S. mutans* depends fundamentally on the formation of cariogenic biofilms, which are structured by glucans whose synthesis is catalyzed by key enzymes known as glucosyltransferases (Gtfs) [46]. In this context, our study demonstrated that the KAT ActG induces the specific enzymatic acetylation of GtfB and GtfC. By modifying these proteins—which are essential for adhesion and the structuring of the polysaccharide matrix on dental enamel—the KAT ActG acts as a crucial regulatory mechanism, enhancing biofilm formation and, consequently, exacerbating bacterial pathogenicity [47].

3.5 *Streptococcus suis*

S. suis is described as a bacterial strain with a high virulence profile. Recently, it was discovered that this pathogen employs a sophisticated mechanism known as the Ihl/Irr-PepO axis, which triggers actin polymerization in macrophages through the activation of the p38 and ERK1/2 signaling pathways. This process results in the evasion of phagocytosis, allowing for a higher bacterial survival rate and favoring progressive colonization within the host [14].

4. Antimicrobial Resistance

Streptococcal resistance to antimicrobials is a major public health concern, as this group is classified among the nine microorganisms of highest relevance regarding antibiotic resistance globally. Commonly used drugs, including beta-lactams, macrolides, and fluoroquinolones, are showing reduced efficacy against strains of the genus *Streptococcus*. Resistance to beta-lactam antibiotics—historically the first-line therapy for streptococcal infections—represents a significant clinical challenge, especially in *S. pneumoniae* [9,48]

Unlike bacteria that produce beta-lactamases, resistance in the pneumococcus is primarily mediated by structural alterations in Penicillin-Binding Proteins (PBPs) [9]. Beyond beta-lactams, an alarming increase in macrolide resistance has been observed among beta-hemolytic streptococci, such as *S. pyogenes* and *S. agalactiae* [8].

Additionally, *S. suis* has exhibited a multidrug-resistant (MDR) profile against tetracyclines, macrolides, and lincosamides—specifically involving tetracycline, erythromycin, and chloramphenicol in clinical isolates—highlighting this strain as a superbug of global concern [49,50]. Finally, *S. mutans* exhibits resistance rates primarily due to its robust capacity for cariogenic biofilm formation, which enhances both its resistance to antimicrobial agents and its overall virulence [17].

4.1 Estratégias para Controlar a Resistencia Antimicrobiana em *Streptococcus* ssp.

In recent years, the search for novel strategies to control antimicrobial resistance in *Streptococcus* spp. has intensified [51]. Researchers have sought to overcome bacterial defense mechanisms through innovative approaches, including combination therapies [52] and the development of nanotechnology-based drugs [53] and synthetic peptides [54], as illustrated in Figure 1.

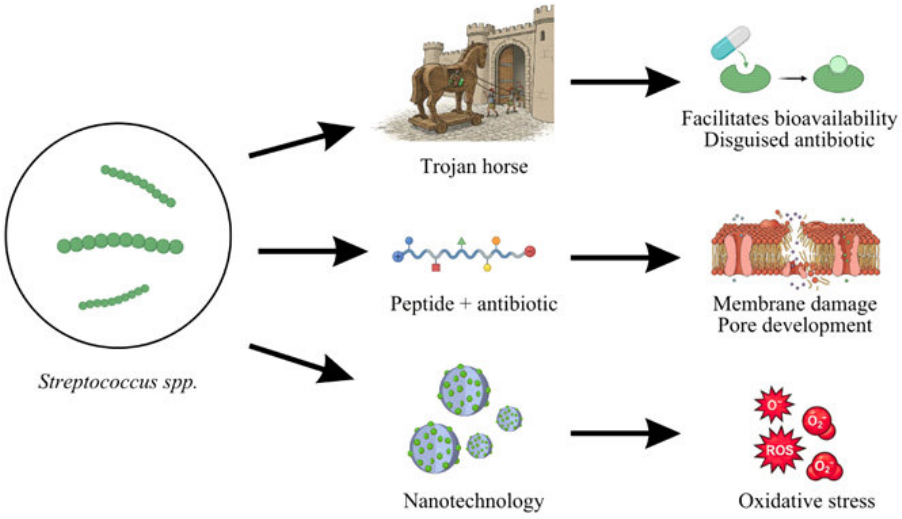

Figure 1. Molecular targets and strategies for overcoming resistance in streptococci. These strategies include: facilitation of intracellular transport via molecular mimicry ("Trojan Horse" approach), membrane permeabilization through peptide-antibiotic complexes, and nanotechnology-mediated toxicity via the production of Reactive Oxygen Species (ROS).

4.1.1 Combination Therapies

The use of combination therapies is a promising alternative for controlling bacterial resistance due to its high activity and specificity [55]. One such strategy is known as the "Trojan Horse" approach (Fig. 1), which essentially consists of camouflaging the antibiotic to bypass bacterial cellular barriers [52]. In this method, complexation occurs by linking the drug to compounds exhibiting mimetic activity, which facilitate specific transport into the cell. Thus, the technique leverages the microorganism's uptake of essential nutrients to direct the drug precisely to its intracellular target [56].

The mimicry of these conjugates typically focuses on structures recognized by bacteria, such as siderophores, carbohydrates, or peptides. This interaction results in severe damage to the microorganism, compromising vital processes such as genetic material replication, protein synthesis, and cell wall integrity. This strategy promotes the targeted activation of the antibiotic and increases selectivity for specific strains, such as those of the genus *Streptococcus*. Consequently, the technique allows for the restoration of drug efficacy and the inhibition of previously established resistance pathways [57].

4.1.2 Anti-Streptococcus Peptides

Currently, Antibiotic-Peptide Conjugates (APCs) are classified as fundamental agents in combating bacterial resistance due to their synergistic potential [58]. Peptides optimize the bioavailability and activation of the antibiotic (Fig. 1), as they possess high efficacy in penetrating the cell wall and destabilizing the cytoplasmic membrane. Obtained from natural sources—such as plants, animals, and microorganisms—these compounds have proven to be efficient therapies against resistant *Streptococcus* strains [59]

Due to their amphipathic nature, these structures interact selectively with bacterial membranes. Such interaction results in structural damage that increases cell permeability, favoring antibiotic absorption and potentiating its biological action. The formation of the conjugate occurs through covalent bonding at specific sites on the peptide, precisely at the N-terminal or C-terminal ends; this union creates a single molecule capable of hitting multiple targets simultaneously [54].

4.1.3 Applied Nanotechnology

The use of Nanoparticle-Antibiotic Conjugates (NACs) (Fig. 1) emerges as a promising frontier to overcome the limitations of conventional therapies against the genus *Streptococcus*. This hybrid platform utilizes various nanomaterials, such as metallic nanoparticles (Ag, Au), biocompatible polymers (chitosan, PLGA), and metal-organic frameworks (MOFs), to integrate antibiotics via covalent bonds or non-covalent interactions [60] The primary advantage lies in the ability of these systems to promote direct physical disruption of the bacterial membrane [61].

Additionally, the efficacy of NACs against streptococcal pathogens is enhanced by oxidative stress mechanisms and biofilm penetration. Nanomaterials such as Fe_3O_4 and Silver (Ag) induce the production of Reactive Oxygen Species (ROS) and hydroxyl radicals, overwhelming the bacterium's antioxidant defenses [51]. This oxidative attack acts in synergy with the conjugated antibiotic to disrupt cellular redox homeostasis, resulting in a drastic reduction of the MIC (Minimum Inhibitory Concentration). NACs can be designed to competitively inhibit efflux pumps or degrade resistance enzymes, such as beta-lactamases, thereby protecting the integrity of the antibiotic [53].

5. Advances In Molecular Biology

Current anti-*Streptococcus* therapies are incorporating therapeutic methods via molecular biology, particularly in parameters related to immunoprophylaxis. Among molecular techniques, the development of vaccines based on polysaccharides and choline-binding proteins stands out [62,63]. Anti-virulence treatment against *Streptococcus* spp. has been primarily focused on "disarming" the bacteria rather than directly causing cell death, targeting virulence instead of growth. This activity can prevent the infectious process and inhibit pathways, including adhesion to host tissues, bacterial toxins, and the modulation of specific gene expression that increases virulence rates [12].

5.1 Vaccines Based on Surface Proteins

Psps (Pneumococcal surface proteins) are located on the surface of bacteria of the genus *Streptococcus*, with emphasis on *S. pneumoniae*. Currently, they represent an important research avenue for controlling virulence factors, as the development of vaccines based on this strategy has shown promising results. The structure of these proteins consists of an N-terminal alpha-helical domain, a proline-rich region, and a C-terminal choline-binding domain, through which the protein binds to the host cell's lactate dehydrogenase, enhancing bacterial virulence [64].

PspA has stood out in vaccine development due to its high immunogenic potential. This activity is based on the use of monoclonal antibodies that, upon interacting with PspA, induce direct damage to the pneumococcal surface through specific protein responses. This defense mechanism is attributed to its N-terminal alpha-helical domain, which is responsible for stimulating the production of protective antibodies [65].

Furthermore, the proline-rich domain also possesses immunogenic potential, proving even more promising as it is a more conserved region, providing efficacy against the variability of bacterial strains. Given these premises, a trivalent vaccine was developed and has advanced in pre-clinical studies, including trials with primates. Currently, PspA-based vaccines are in clinical trial phases, consolidating themselves as strong candidates for controlling *S. pneumoniae* virulence [21].

5.2 Inhibition of Adhesins and Biofilms

The surface glycoprotein BrpA is essential for cellular aggregation, biofilm matrix structuring, and environmental stress tolerance in *S. agalactiae*. The functional blockade or deletion of the *brpA* gene prevents the formation of mature biofilms and reduces cellular hydrophobicity, maintaining the bacterium in an avirulent state. Consequently, strategies that inhibit BrpA destabilize the architecture of the bacterial community, making the pathogen more susceptible to phagocytosis and the action of conventional antimicrobials [66].

Currently, there are no specific commercial pharmacological inhibitors for BrpA; therefore, research is focused on immunotherapies. The most promising strategy utilizes monoclonal antibodies that block the N-terminal region of the protein, physically preventing adhesion and favoring immunological clearance [15]. Alternatively, synthetic and natural molecules capable of reducing *brpA* gene expression or destabilizing its cell wall anchoring are being investigated, resulting in biofilm degradation and bacterial resensitization to antibiotics [66].

The proteins FbsA, FbsB, and FbsC mediate initial adhesion to host cells and promote immune evasion by recruiting fibrinogen, which masks bacterial surface antigens [15]. Specifically, the neutralization of FbsC blocks cellular invasion and compromises biofilm formation, as this adhesin is crucial for cell-to-cell interaction. Therefore, inhibitors that compete for the binding sites of these proteins prevent tissue colonization and facilitate pathogen recognition and elimination by the complement system [67].

As previously described, biofilm formation is the crucial point for the high virulence and pathogenicity of *S. mutans*, with GTFs being essential for this process. The inhibition of these enzymes proves to be an important pathway for mitigating this factor. Accordingly, raffinose, an oligosaccharide found in natural products, was identified as capable of modulating the GTF pathway, inhibiting gene expression, glucan production, and, subsequently, biofilm formation [5,68].

5.3 Neutralization of Toxins and Enzymes

SpeB is a factor of great importance for *S. pyogenes* virulence, being conserved and species-specific. The search for inhibitors of these proteases is the focus of studies to control this factor; however, these inhibitors have exhibited high toxicity and damage to the immune system [69]. One notable inhibitor is L-trans-Epoxysuccinyl-leucylamido(4-guanidino)butane (E-64), which presents a broad spectrum of protease inhibition [70]. A recent study also highlighted Pentamidine as an SpeB inhibitor; it is capable of cleaving IL-1, facilitating the immunological activity responsible for killing bacterial cells [71]

6. Conclusion

The data compiled in this review indicate that the primary species of the genus *Streptococcus*, such as *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. mutans*, and *S. suis*, exhibit a complex arsenal of virulence factors and resistance mechanisms. Currently, therapeutic strategies are being revolutionized by the integration of molecular biology, particularly regarding parameters related to the immune system, vaccines, and gene expression. Among these techniques, the development of next-generation vaccines based on polysaccharides and choline-binding proteins stands out, aiming for more specific and robust protection against the characteristic immune evasion of these strains.

In parallel, a paradigm shift is emerging in the fight against these pathogens: anti-virulence treatment. Unlike conventional antibiotics, this approach focuses on "disarming" the bacteria without directly causing cell death, prioritizing the neutralization of pathogenicity over the inhibition of cellular growth. By integrating these advances with nanotechnology and the use of peptides, concrete perspectives are created to overcome the multidrug-resistance crisis and severely reduce the clinical impact of streptococcal infections.

Conflict of Interest

The authors declare no conflict of interest.

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