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Insights into quorum quenching as an alternative to face the risk of infections in biomedical applications: A review of design strategies

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ABSTRACT

Bacterial infections associated with biomedical devices pose significant challenges, often leading to implant failure and severe health complications. Traditional antimicrobial strategies, primarily based on antibiotics and biocidal agents, contribute to the emergence of resistant bacterial strains. In this context, quorum quenching (QQ) has emerged as a promising, non-biocidal approach to mitigate infections by disrupting bacterial communication systems, thus without promoting the development of drug resistance mechanisms. In this perspective, this review provides a comprehensive analysis of the latest advances in QQ-functionalized biomaterials designed for biomedical applications. We explore various QQ mechanisms, including enzymatic degradation of signalling molecules, molecular inhibition strategies, and their integration into biomaterials. Furthermore, we discuss the effectiveness of these strategies in preventing biofilm formation, their biocompatibility, and challenges related to stability and long-term performance. By highlighting innovative design strategies and potential clinical implications, this review underscores the role of QQ in the next-generation biomaterials aimed at reducing infection risks in medical settings.

1. Introduction

Bacterial infections pose a significant risk to human health, a problem worsened by the growing issue of antibiotic resistance [1]. These infections occur in most cases through exogenous contamination by pathogenic microorganisms from the surgical environment; seldom, the translocation of endogenous microorganisms, including commensal and opportunistic members of the patient's physiological microbiota, can occur from normally colonized sites such as the mucosal linings of the nose, mouth, intestine, and urethra to normally sterile tissues, including the lungs, pancreas, bloodstream, brain, bladder, or kidneys [2]. Medical devices, both short-term (e.g., temporary fracture fixators, urinary catheters, intubation tubes, central lines, and needles) and long-term (e.g., cardiac implants, joint replacements, and dental screws), can act as carriers for this bacterial migration. Advances in orthopaedic and trauma care, including modern imaging technologies, enhanced surgical methods, and improved implant designs and materials, have significantly improved patient outcomes [3]. However, infections remain a challenging complication despite these developments. Common infections in dental, orthopaedic, and trauma surgery include Surgical Site Infections (SSIs), Periprosthetic Joint Infections (PJIs), Fracture-Related Infections (FRIs), and infections associated with biomaterials or implants (BAIs/IAIs) [4,5]. Although PJI is relatively rare, it has a profound impact on patients' health and quality of life [6]. In fact, it is notoriously difficult to eradicate without compromising the medical device's integrity and functionality, making it a serious complication with substantial clinical and economic consequences. The likelihood of FRI depends on the extent of the trauma and the associated tissue damage. In open fractures treated with systemic antibiotics, the risk can reach up to 31%, but it can be reduced to 9% when supplemented with local antibiotic treatment [7]. The incidence of BAI varies widely, ranging from 0.1% in cases like intraocular lenses to as high as 33% for urinary tract catheters, with prostheses or nails falling between 1% and 7%. This variability arises from the propensity of bacteria to adhere and colonize material surfaces and the compromised immune response in injured tissues [8].

This discussion focuses on the fundamentals of quorum sensing (QS) and QQ in relation to biofilm formation and biomedical applications. The study also considers relevant bacterial strains and materials

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List of Acronyms

2-MAMP	2-[(methylamino)methylphenol
6-MC	6-Methylcoumarine
AGR	Accessory gene regulator
AHL	N-acyl-homoserine lactone
AI	Autoinducer
AIP	Autoinducing peptide
AL	Alginate lyase
AMP	Antimicrobial peptide
BAI	Biomaterials associated infection
BBF	(Z-)-4- bromo-5-(bromomethylene)-2(5 H)-furanone
BHL	N-butanoyl L-homoserine lactone
CuAAC	Copper-catalysed azide-alkyne 1,3-dipolar cycloaddition
CS	Chitosan
DHP	2,5-dihydro-2H-pyrrole
EPM	Extracellular polymeric matrix
EPS	Extracellular polymeric substance
FEP	Fluorinated ethylene propylene
FRI	Fracture-related infection
FU	Furanone
GMA	Glycidyl methacrylate
HA	Hyaluronic acid
HHQ	2-heptyl-4-hydroxyquinoline
HSL	1-homoserine lactone
IAI	Implant associated infection
LbL	Layer-by-layer
LUT	Luteolin
MIP	Molecular imprinted polymer
MPDA	Mesoporous polydopamine
NO	Nitric oxide
NP	Nanoparticle
PAMP	Pathogen-associated molecular patterns
PCL	Polycaprolactone
PEG	Polyethylene glycol
PEI	Polyethyleneimine
PJI	Periprosthetic joint infection
PLLA	Poly-L-lactic acid
PP	Polypropylene
PQS	2-heptyl-3-hydroxy-4-quinolone
PS	Polystyrene
PU	Polyurethane
PVC	Polyvinyl chloride
PVDMA	Poly(4,4-vinyldimethylazlactone)
QS	Quorum sensing
QSI	Quorum sensing inhibitor
QSM	Quorum sensing molecule
QQ	Quorum quenching
QQE	Quorum quenching enzyme
SAM	S-adenosylmethionine
SLN	Solid lipid nanoparticle
SSI	Surgical site infection
UF	Ultrafiltration

associated with QS and QQ. To provide a comprehensive overview, almost 100 scientific articles published during the last 10 years were reviewed. By detailing the literature, the discussion ensures a well-rounded understanding of QS and QQ, emphasizing their importance in biofilm control and potential biomedical applications, such as antimicrobial treatments and medical device coatings.

2. Quorum sensing (QS) and fundamentals of biofilm formation

QS is a microbial communication mechanism in which the release of signalling molecules allows cells to detect their population density [9]. This process influences key microbial traits, including antibiotic resistance, bioluminescence, virulence, and sporulation. It depends on the density of microbial cells and involves small, low-molecular-weight signalling molecules called autoinducers (AIs). These AIs interact with transcriptional activator regions to regulate gene expression, controlling the pathogenic behaviour of microorganisms [10]. Once the concentration of AIs surpasses a certain threshold, it triggers changes in gene expression [11]. The release and detection of QS signals lead to two primary outcomes. First, they control the production of various extracellular substances released by cells, which serve multiple purposes, such as nutrient scavenging, increasing virulence, suppressing the immune system, providing structural support for biofilms on surfaces, and enhancing mobility [12]. These substances benefit the surrounding cell population; therefore, QS enables individual cells to monitor and assess the size of their community, allowing them to manage and regulate resource-intensive traits based on cell density and signal concentration in the surrounding environment [13]. This coordination allows bacteria to perform cooperative behaviour that single cells could not achieve on their own [14].

Gram-negative and Gram-positive bacteria employ distinct QS systems, as detailed in the following sub-paragraphs and summarized in Fig. 1:

2.1. QS system in gram-negative bacteria

Most Gram-negative bacteria utilise small molecules as AIs, such as *N*-acyl-homoserine lactones (AHLs) or other molecules derived from S-adenosylmethionine (SAM), such as autoinducer-2 (AI-2) [15] as reported in Fig. 1**a**. These AIs are synthesised inside the cell and diffuse across the inner and outer membranes freely or by active transport [16]. When AI concentrations reach a threshold at high cell density, they bind to cytoplasmic receptors and activate transcription factors related to virulence gene regulation. The main AHLs in biofilms are C8-HSL, C10-HSL, C12-HSL, and 3-oxo-C10-HSL [17]. C8-HSL is the main AHL causing membrane biofouling. C10-HSL and C12-HSL are significantly correlated with biofilm adhesion activity [18].

AIs are typically synthesised using SAM as a precursor. The most common class of AIs in Gram-negative bacteria is AHLs, which consist of an N-acylated homoserine-lactone ring attached to a 4–18 carbon acyl chain. The length and modifications of the acyl chain influence its stability. LuxI-type enzymes are the major producers of AHLs, but they are not the only ones. A LuxM synthase found in *Vibrio harveyi*, which is not a homolog of LuxI, can produce AHLs for their intra-species communication. LuxR-type receptors, which act as cytoplasmic transcription factors, bind freely diffusible AHLs within the cytoplasm. Once bound to AHLs, stable LuxR-AHL complexes can attach to DNA and regulate gene expression. In contrast, unbound LuxR proteins degrade rapidly [16]. Receptors for QS molecules act as transcription factors that regulate numerous genes involved in biofilm formation, virulence, and other processes. These receptors establish a feedback mechanism known as autoinduction, where increased synthesis of AIs promotes synchronised gene expression across the bacterial population [19]. This coordination system enables bacteria to effectively adapt to new environments, such as the surface of a medical device, and promotes crosstalk between the multispecies community populating the biofilm, improving their survival and resistance to external attacks such as antibiotic administration.

Similar LuxI/LuxR-type homologues have been identified in other Gram-negative bacterial species: two AHL-dependent systems, namely

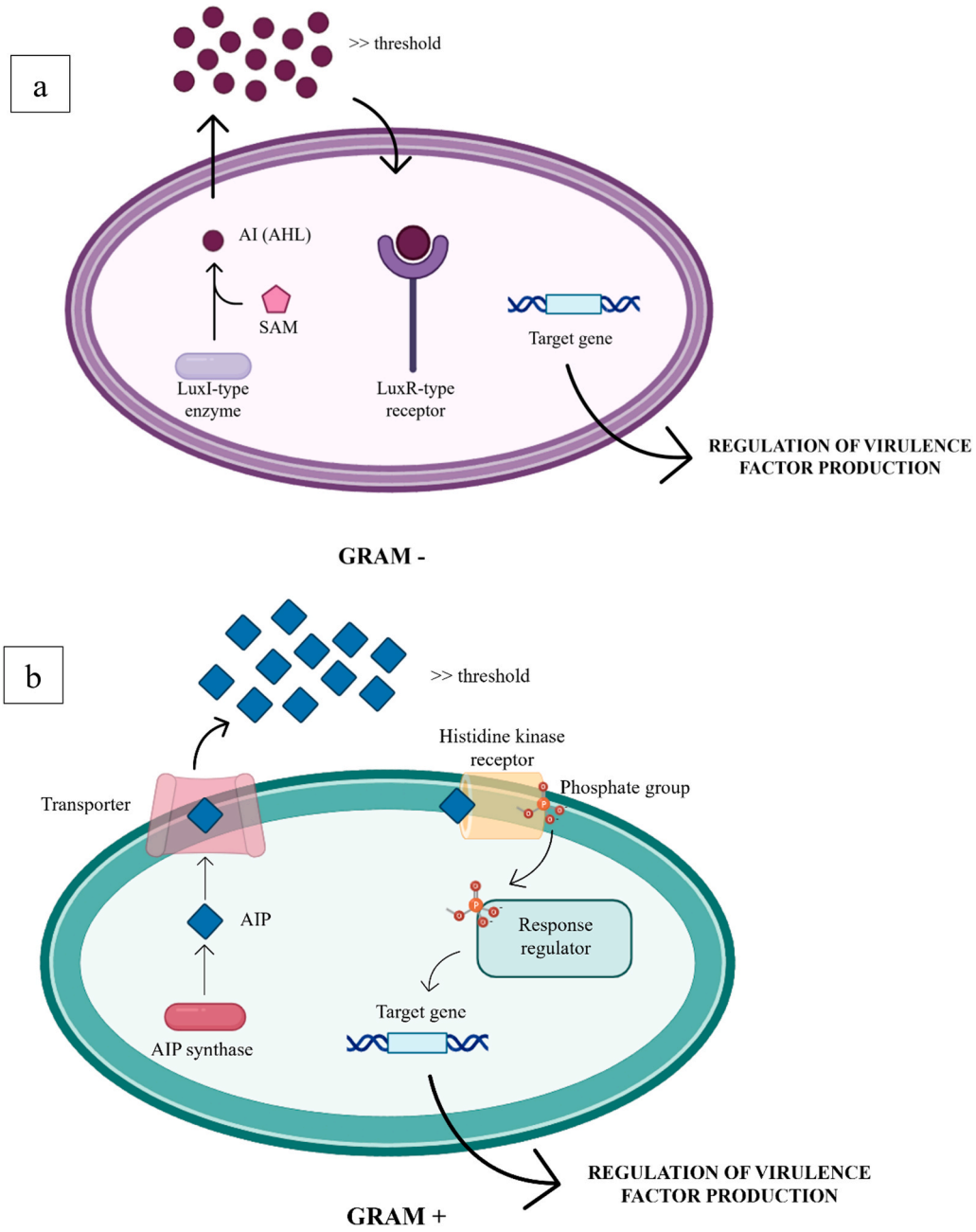


Fig. 1. AI-based QS main mechanisms. (a) Gram-negative bacteria's communication relies mostly on the release of small molecules such as the acyl-homoserine lactones (AHLs) that are synthesized from S-adenosylmethionine (SAM) by LuxI-type enzymes; alternatively, AHLs can directly bind to LuxR-type receptors, influencing virulence gene expression. (b) In Gram-positive bacteria, the accumulation of autoinducing peptides (AIPs) leads to the binding with histidine kinase receptors, releasing intracellular phosphate groups upon phosphorylation: such phosphates are then linked by cytoplasmic regulators influencing virulence gene expression.

LasR/LasI and RhlR/RhlI, are responsible for the synthesis of the N-(3-oxo-dodecanoyl)-L-homoserine lactone (3OC12-HSL) and N-butanoyl-L-homoserine lactone (C4-AHL) [20]. In addition to the Las and Rhl systems, *P. aeruginosa* possesses another QS system known as the Pseudomonas quinolone signal (Pqs) system, which relies on 2-heptyl-3-hydroxy-4-quinolone (PQS) and its precursor 4-hydroxy-2--heptylquinoline (HHQ) rather than AHLs [21]. PQS is synthesized through the *pqsABCDE* operon and subsequently binds to the transcriptional regulator PqsR (also known as MvfR), activating the expression of numerous genes involved in virulence, including those responsible for pyocyanin, rhamnolipid, elastase, siderophore production, oxidative stress response, and biofilm development [22]. Moreover, the Pqs system is tightly interconnected with the Las and Rhl regulatory networks, forming a highly integrated QS hierarchy. Pqs signalling also promotes extracellular DNA (eDNA) release through controlled autolysis and stimulates the production of outer membrane vesicles (OMVs), which facilitate the transport of hydrophobic PQS molecules and contribute to biofilm maturation and dispersion [23].

In some Gram-negative systems, AIs are detected by two-component histidine kinase receptors, similarly to Gram-positive QS systems (see below).

2.2. QS system in gram-positive bacteria

In most Gram-positive bacteria, peptides known as autoinducing peptides (AIPs) act as signalling molecules (Fig. 1**b**). As well as in Gram-

negative bacteria, AI-2 is one of the main signalling molecules. AI-2 can enhance interspecific bacterial communication, regulate microbial physiological properties such as EPS secretion and flagellar activity, and promote bacterial growth from floating to attached growth [16]. These properties are closely related to biofilm formation. The concentration of AI-2 is lowest in loosely bound biofilms and highest on the membrane surface. AI-2 can enhance interspecific bacterial communication, induce the expression of related genes, and promote bacterial growth from floating to attached growth. Without AI-2, biofilm growth is impeded or even stalled [24]. These peptides are synthesised within the cell and then secreted as activators of the pro-virulence cascade. At high cell densities, when the extracellular concentration of AIPs becomes elevated, they bind to specific membrane-bound two-component histidine kinase receptors [16]. This interaction typically activates the receptor's kinase function, leading to autophosphorylation and transfer of a phosphate group to a corresponding cytoplasmic response regulator. The phosphorylated regulator then promotes the transcription of genes within the QS regulon. Additionally, in certain Gram-positive systems, AIPs are transported back into the cell cytoplasm, where they directly interact with transcription factors, influencing their activity and modulating gene expression.

There are two primary types of canonical AIP-based QS systems. In one class, AIPs are synthesised as precursors encoded within the QS operon, then processed and secreted outside the cell by specialised transporters. These AIPs, typically composed of 5–17 amino acids, may exist in either linear or cyclized forms. Membrane-bound two-component sensor histidine kinases function as receptors for these AIPs [25]. In the second class of AIP-QS systems, pre-AIPs are secreted via the secretory system and subsequently processed by extracellular proteases, such as secreted neutral protease B. The processed AIPs are then transported into the cell through the oligopeptide permease system, where they bind to transcription factors to regulate DNA expression. This autoinduction mechanism ensures the synchronisation of the QS response across the bacterial population [26].

The most typical example of AIP-mediated QS is the *agr* system in *S. aureus:* The agr system is highly conserved among several Gram-positive species, including *Clostridium botulinum*, *Clostridium perfringens, Clostridioides difficile, Listeria monocytogenes, Enterococcus faecalis,* and *Lactiplantibacillus plantarum*. In *S. aureus*, the agr locus comprises the agrBDCA operon, whose expression is controlled by the P2 and P3 promoters [27]. The precursor peptide AgrD is processed and cyclized by AgrB to generate the mature AIP, which is secreted into the extracellular environment. Once a threshold concentration is reached, AIP binds to the membrane-bound histidine kinase AgrC, triggering its autophosphorylation and the subsequent activation of the response regulator AgrA. Activated AgrA promotes the transcription of target genes involved in virulence and biofilm regulation, while simultaneously amplifying agr expression through a positive feedback loop [28].

2.3. Biofilm formation through the QS system

Biofilm formation is a complex multi-step process in which the multispecies bacterial community is finely orchestrated by QS signalling, relying on strongly communication-mediated phenotypes. Among the best-characterized QS signalling molecules are N-acyl homoserine lactones (AHLs), predominantly used by Gram-negative bacteria, and autoinducing peptides (AIPs), which mediate communication in Gram-positive bacteria. These structurally distinct molecules generally enable species-specific or closely related bacterial communication. In contrast, autoinducer-2 (AI-2) functions as a universal interspecies signalling molecule, facilitating communication among phylogenetically diverse bacteria within polymicrobial communities. AI-2 exists in different furanone-derived forms depending on the surrounding chemical environment. Additional signalling molecules, including indole and diffusible signal factors (DSFs), also contribute to bacterial population sensing through mechanisms distinct from the classical AI-based QS systems [29] [30]. Growing evidence has demonstrated that QS is a central regulator of biofilm development, coordinating the different stages of biofilm formation, maturation, and dispersal, while simultaneously controlling the expression of numerous virulence-associated genes [31–33]. Since microbial infections are frequently associated with QS-regulated biofilms, interfering with bacterial communication has emerged as an attractive anti-virulence strategy: rather than directly inhibiting bacterial growth, the aim is to disrupt QS signalling through different mechanisms, including the use of QSIs, thereby preventing biofilm formation and reducing bacterial pathogenicity [34,35].

Despite its considerable therapeutic potential as an alternative or complementary approach to conventional antibiotics, the development of effective QS-targeting strategies remains challenging because bacterial communication networks are highly complex, involving multiple interconnected signalling pathways, regulatory genes, and species-specific communication systems.

3. Quorum quenching (QQ) and biofilm formation inhibition

The growing threat of antibiotic-resistant bacterial pathogens has highlighted the urgent need for alternative strategies to replace current antibiotics and reduce the development of resistance mechanisms. One promising approach involves disrupting bacterial signalling pathways that regulate multispecies community cell-to-cell crosstalk for pathogenesis and the development of drug-resistant mechanisms [34]. As previously discussed, microbial communities exhibit regulatory mechanisms that can be compared to social behaviour, and such complex communication is managed through QS [35], a process that has been identified as a new target for innovative infection control methods.

QQ refers to the mechanism that disrupts QS-mediated activities. By interfering with QS, QQ can prevent bacteria from expressing specific phenotypes without promoting the development of new drug-resistance mechanisms. Since QS-regulated biological functions, such as biofilm formation and virulence, are not essential bacterial housekeeping processes, these traits can be effectively controlled using QQ strategies [36].

QS inhibition can generally be achieved through three primary strategies.

Blocking Receptors with QS Signal Molecule (QSM) Analogues: in this approach, compounds structurally like the natural QS molecules are used as QSIs to compete for receptor binding (*First Strategy*) [37,38].

Delaying or Blocking the Production of QSMs: this involves using QSIs to interfere with the synthesis of AIs, preventing QS from initiating (*Second Strategy*).

Enzymatic Degradation of QSMs: enzymes such as acylase and lactonase can degrade AHL-like QS signals, a process that is particularly effective under oxidative stress conditions (*Third Strategy*) [39].

These strategies have demonstrated effectiveness in reducing bacterial pathogenicity and biofilm formation, potentially enhancing bacterial susceptibility to antimicrobial agents, including antibiotics and bacteriophages [40].

QSIs can be classified into three major categories from the chemical standpoint; a summary diagram of the different strategies and molecules involved is shown in Table 1.

The first one includes natural and synthetic non-peptide small molecules, involved in the first two strategies. Natural non-peptide QSIs consist, for instance, of brominated furanones from marine *Delisea pulchra*, which mimic L-homoserine lactone (HSL- a simple lactone without the acyl chain, with metabolic functions rather than signalling) and disrupt AHL signalling, interfering with the stability and function of QS receptors in bacteria (according to the *first strategy*). Furanones can be used to avoid bacterial biofilm formation on implants; research is ongoing to improve stability using covalently bound furanone polymers [48]. Moreover, Urolithin A [49] and furanone C-30 [50] effectively inhibit biofouling. Flavonoids extracted from hyacinth, aspergillin, and penicillic acid from *Penicillium* secondary metabolites, and phenylethyl

Table 1
QQ mechanisms of action.

QUORUM QUENCHING		
QQ STRATEGY	**MECHANISM**	**MOLECULES**
QSM analogues	Compounds like natural QSM compete for receptor binding, preventing QS from developing [37,38].	**Non-peptide small molecules** *Natural* (brominated furanones) [41]. *Synthetic* (AHL analogues). **Peptide compounds** AIP analogues (TrAIP-II and RNAIII-RIP).
Blocking QSM production	QSIs interfere with AIs' synthesis, preventing QS from initiating [42].	**Non-peptide small molecules** *Natural* (flavonoids, aspergillin and penicillic acid, phenyl ethyl acetate) [43] *Synthetic* (AHL analogues). **Peptide compounds** AIP analogues (Solonamide A and B) [44].
Degradation of QSM	Acylase or lactonase degrade AHL-like QS signals, preventing QS from developing [40].	**Lactonases** hydrolyse the lactone ring, with broad substrate specificity, and make inactive AHL (reversible) [45]. **Acylases** hydrolyse the bond between the lactone ring and the acyl side chain (longer than 10 carbons), with irreversible inactivation [46, 47].

acetate from *Bacillus halophilus* fermentation broth are other examples that interfere with AI synthesis (*second strategy*). Some examples are luteolin (LUT), vanillin, and quercetin (Qe), which selectively act on pathogenic bacteria/biofilm, hindering the communication of bacterial QS signals and putting them in a quiescent state [51]. Synthetic non-peptide QSIs primarily include AHL analogues (first strategy) [52]: for example, in this category we can find (Z-)-4- bromo-5-(bromomethylene)-2(5 H)-furanone (BBF), 3-(10-bromohexyl)-5-dibromomethylene-2(5 H)-furanone), or 2,5-dihydro-2H-pyrrole (DHP) which have a mechanism similar to that of AHLs to inhibit QS in *S. aureus* and *P. aeruginosa*, displacing the AHL signal from the receptor site without affecting bacterial growth [53], interacting directly with the bacterial cell membrane [54]. Additionally, AHL with a long acyl chain (C18-HSL) originating from *Delftia tsuruhatensis* is recognised as an antagonist of *P. aeruginosa* QS (*first strategy*) [55]. Moreover, 2-MAMP (2-[(methylamino)methylphenol), a compound known for its anti-biofilm and anti-virulence properties [56].

The second category involves peptides that are primarily AIP analogues (*first strategy*), such as spectral inhibitors TrAIP-II and RNAIII inhibitory peptides. Additionally, deep-sea peptides (such as solonamide A and B), derived from Gram-positive marine luminous bacteria, inhibit the *agr* QS system in highly virulent strains like USA300 and *S. aureus* (*second strategy*). These are the first reported *agr* QSIs sourced from marine bacteria [44].

Finally, the last category includes proteins such as QQ enzymes and QQ antibodies, which are mainly used in the *third strategy*, targeting fatty acid and SAM biosynthesis. The two most extensively studied types of QQ enzymes are lactonases and acylases, both of which target AHLs. Lactonases and acylases employ distinct mechanisms to inactivate AHLs. Lactonases hydrolyse the ester bond within the lactone ring, yielding acyL-homoserine, and exhibit broad substrate specificity, acting on both short- and long-chain AHLs [46]. Conversely, acylases primarily target AHLs with side chains longer than 10 carbons, hydrolyse the amide bonds that connect the lactone moiety to the acyl side chain, and produce homoserine lactone and a fatty acid. While both enzymatic reactions render AHLs inactive, only the acylase-mediated process is irreversible. The product of the lactonase reaction can re-form the active lactone ring in acidic environments, restoring its QS activity.

3.1. Lactonase

QQ lactonases are classified into three structurally distinct families: phosphotriesterase-like lactonases, metallo-β-lactamase-like lactonases, and serum paraoxonases [57]. These families exhibit unique structural and functional characteristics, with representatives extensively studied for their sequences, structures, and enzymatic activities. Consequently, lactonases from these families have frequently served as templates for protein engineering, enabling researchers to enhance their stability, catalytic efficiency, and substrate specificity [58]. Lactonases are the most investigated QQ enzymes, and they originate from various organisms, including bacteria, archaea, plants, fungi and mammals [45, 59–61].

3.2. Acylase

AHL acylases represent the second major class of QQ enzymes. Unlike lactonases, most AHL acylases belong to a single protein family: the N-terminal nucleophile family [62]. These structural insights have been instrumental in guiding rational protein engineering efforts to modify and enhance the substrate specificity of AHL acylases. Such advancements aim to expand their potential applications in QS disruption and infection control [63].

In Fig. 2 are schematically summarized the three QQ strategies:

4. QS and QQ mechanisms of the main pathogens responsible for biomedical device failure

4.1. Pseudomonas aeruginosa

It plays a major role in infections caused by Gram-negative bacteria, particularly among immunocompromised patients. The rise of multimechanism antimicrobial resistance has drastically reduced treatment options for *P. aeruginosa* infections, making it a critical and potentially fatal issue, with approximately 51,000 healthcare-associated infections reported annually in the United States [64,65]. *P. aeruginosa* is a highly adaptable pathogen with a large genome capable of developing resistance to nearly all antibiotic classes. Key infections caused by this organism include bloodstream infections, ventilator-associated pneumonia, urinary tract infections, chronic osteomyelitis, diabetic foot infections, and skin and soft-tissue infections. Resistance mechanisms in *P. aeruginosa* include reduced membrane permeability, activation of efflux pumps, production of antibiotic-inactivating enzymes, and modifications to drug-specific binding sites. Often acting simultaneously, these mechanisms enable the bacterium to withstand multiple antibiotic classes.

P. aeruginosa possesses the most complex and most widely explored QS network described so far. In this bacterium, QS operates through three primary systems. Two of these, the *las* and *rhl* systems, utilise AHLs as signalling molecules [66]. The third system, known as the *pqs* system, interacts with and is interconnected to the other two systems. These three QS systems are intricately correlated and function as a unified network rather than independently. Together, they create a complex hierarchical QS circuitry [67]. At the top of this hierarchy is the *las* system, which plays a crucial role in optimally activating both the *rhl* and *pqs* systems [56].

The *las* system plays a pivotal role in regulating the QS network of *P. aeruginosa* and its signalling molecule is N-(3-oxo-dodecanoyl)-L-homoserine lactone (3-oxo-C12-HSL, OdDHL). The *las* signalling pathway controls key virulence factors, including exotoxin A, as well as enzymes like LasA staphylolytic protease, LasB elastase, and Apr alkaline protease, all of which are critical for biofilm formation [68]. LasA and LasB are essential in protease regulation, facilitating the degradation of elastin, fibrin, complement, interferon, and collagen during

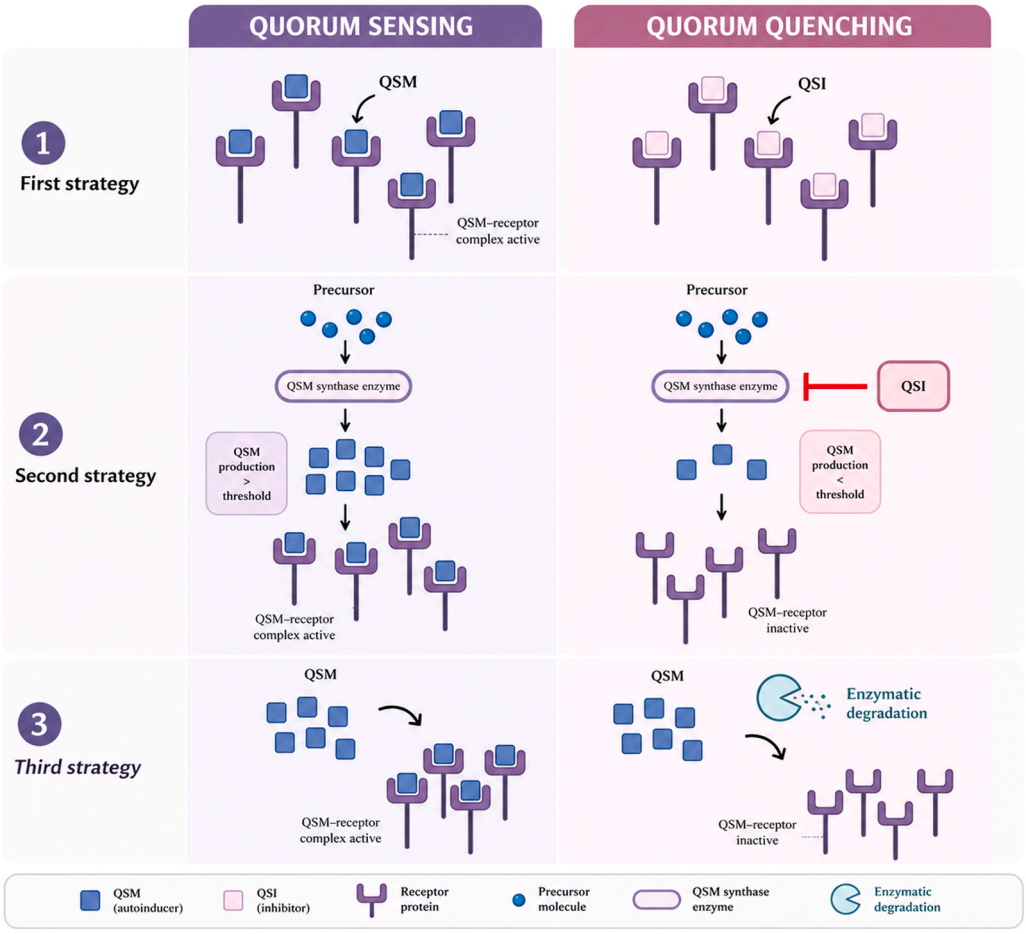


Fig. 2. Schematic representation of QQ different strategies: (i) competitive inhibition of receptor binding by QSIs, (ii) suppression of QSM biosynthesis through inhibition of the synthase enzyme, reducing signal production below the activation threshold, and (iii) enzymatic degradation of QSMs, preventing the formation of the QSM–receptor complex and, consequently, the activation of quorum sensing-regulated responses.

infections, and influencing toxin production [69]. Given its central role in QS and pathogenicity, targeting the *las* system is an effective strategy to disrupt the QS network.

Another system in the QS network of *P. aeruginosa* is the *rhl* system, which is similar to the *las* system. The key distinction lies in the signalling molecule, N-butanoyl-L-homoserine lactone (BHL or C4-HSL). This molecule binds to the rhlR receptor, activating its role as a transcriptional regulator [70]. The *rhl* system is associated with the production of various virulence factors, including rhamnolipids, LasA elastase, and toxic extracellular factors, such as hydrogen cyanide and pyocyanin [71]. Rhamnolipids, biodegradable surfactants composed of two fatty acid molecules and rhamnose residues [72], are crucial for protecting cells from oxidative stress and facilitating biofilm growth and maturation. Meanwhile, pyocyanin, a greenish pigment secreted by *P. aeruginosa*, exhibits significant toxicity to host cells. Thus, targeting the *rhl* system offers a promising approach for managing QS-related infections [73].

The third QS system in *P. aeruginosa* is *pqs* and is closely linked to the two AHL-based systems. Signalling molecules are 2-heptyl-3-hydroxy-4-quinolone (PQS) and its precursor, 2-heptyl-4-hydroxyquinoline (HHQ), which is commonly associated with QS and the *pqs* system [74]. PqsR is a transcriptional regulator and is central to the *pqs* system, regulating the expression of rhlI and several virulence-related processes, including hydrogen cyanide and pyocyanin production, bacterial motility, and biofilm formation [75]. While lasR activates these functions, rhlR inhibits their expression. Due to its critical role, pqsR is a promising target for developing novel QSIs.

As already discussed in Section 3, the *first* QQ *strategy* against *P. aeruginosa* can be achieved using natural compounds such as flavonoids, phenolics, and terpenoids. These molecules primarily target LasI/RhlI, leading to a reduction in AHL production and, consequently, in AHL-regulated phenotypes [76]. Alternatively, the *second strategy* involves inhibiting HHQ and PQS biosynthesis by targeting different enzymes within the quinolone signalling pathway. In this context, PqsA, which catalyzes the first step of PQS biosynthesis, represents a particularly attractive target for disrupting quinolone-mediated signalling. Several inhibitors, including halogenated anthranilic acid analogues and anthraniloyl-AMP derivatives, have been shown to reduce HHQ and PQS production. However, their therapeutic potential remains limited due to poor cellular permeability, suboptimal target specificity, and the lack of robust in vivo validation, making effective pharmacological inhibition of PqsA challenging [77]

PqsD, a key condensation enzyme involved in the early stages of PQS biosynthesis, has also been extensively studied as a potential therapeutic target. Various classes of inhibitors, including transition-state analogues, 2-benzamidobenzoic acid derivatives, and ureidothiophene carboxylic scaffolds, have demonstrated the ability to reduce HHQ and PQS levels and partially inhibit biofilm formation. Despite promising in vitro results, their further development is hindered by limited cellular uptake, active efflux, and the absence of validation in relevant in vivo infection models [78].

Finally, PqsH, a FAD-dependent monooxygenase that catalyses the conversion of HHQ into the active signalling molecule PQS, represents a promising but still underexplored therapeutic target. To date, only in

silico studies have identified potential PqsH inhibitors, with no experimental validation or in vivo evidence of efficacy [79].

Regarding the *third strategy,* the best-characterized QQ enzymes are lactonases: engineered variant f the archaeal lactonase SsoPox (e.g., SsoPox-W263I) have shown strong efficacy in quenching virulence in clinical isolates and can also influence the expression of bacterial CRISPR-Cas systems. In addition, enzymes such as the YtnP family [45, 80] and the marine-derived RmmLII have demonstrated potent biofilm inhibition and increased antibiotic synergy in in vivo murine models, including against multidrug-resistant (MDR) strains [81].

4.2. *Escherichia coli*

It is a Gram-negative bacterium commonly found in various districts, including the gastrointestinal tracts of humans and warm-blooded animals, where it plays a role in the gut microbiota. Certain strains of *E. coli* are used as probiotics and are beneficial to host health. Conversely, other strains can be pathogenic, leading to intestinal and extraintestinal infections in both humans and animals. Thus*, E. coli* encompasses a diverse array of strains, each characterised by unique traits [82]. Certain *E. coli* strains are notable for their role in mediating various diseases, including intestinal and extraintestinal disorders in humans. *E. coli* is a common cause of spinal infections (vertebral osteomyelitis), often originating from bacteremia due to urinary tract infections or surgical procedures, diabetic foot osteomyelitis, and post-traumatic osteomyelitis. Enteric *E. coli* pathotypes contribute to a wide range of diseases through diverse mechanisms of pathogenesis, with the expression of virulence factor-encoding genes that enable the pathogen to infect and damage the host [83]. In *E. coli*, QS primarily depends on the AI-2 system, mediated by the LuxS enzyme, which regulates biofilm formation, motility, and virulence gene expression in response to population density and environmental conditions. Although *E. coli* does not produce AHLs, it is sensitive to these molecules in the environment, even if synthesised by other bacterial species [84].

Several natural compounds have shown QQ activity against *E. coli*, following the *first strategy* primarily by interfering with AI-2 signalling. Plant-derived extracts, including those from Cypriot medicinal plants, broccoli, and grapefruit, reduce biofilm formation, motility, and AI-2 production without affecting bacterial growth [85,86]. Similarly, the flavonoid echinatin suppresses QS-regulated phenotypes and enhances the activity of colistin against antibiotic-resistant *E. coli* by down-regulating AI-2-related genes. Marine-derived compounds have also demonstrated anti-QS and antibiofilm activity, further highlighting the potential of natural products as antivirulence agents [81,87].

Furthermore, the synthetic compound (*Z*)-4-bromo-5-(bromomethylene)-3-methylfuran-2(5 H)-one (BF8) can block AI-2 synthesis, following the *second strategy*, while lactonases enzymes like Aii20J lactonase have also shown promising antivirulence and biofilm activities against *E. coli* (*third strategy)*[88].

4.3. *Staphylococcus aureus*

It is a Gram-positive bacterium responsible for infections acquired mostly in hospitals. *S. aureus* infections can vary from mild skin and soft tissue infections to more severe conditions, such as bloodstream infections, sepsis, and bone infections. Research has shown that many bacteria, including *S. aureus*, exhibit changes in gene expression depending on their growth conditions or during infection [89]. Infections commonly arise when *S. aureus* enters an open wound. Unlike biofilm formation observed in vitro, *S. aureus* in vivo can literally “hide” from innate host defences, such as neutrophils, macrophages, and antimicrobial peptides (AMPs) [90,91]. In fact, while the resilience of biofilms against immune responses was initially thought to result from their microenvironment as a physical barrier to immune cells, it is now understood that biofilms also protect bacterial cells by secreting masking pathogen-associated molecular patterns (PAMPs) and evading detection by the immune system [92]. The QS system of *S. aureus* is simpler than in the previous case and relies on the agr (accessory gene regulator) system, which utilises AIPs to regulate the expression of virulence factors, such as toxins, and biofilm formation in response to cell density.

In *S. aureus*, the *agr* system is encoded by the *agrBDCA* operon whose expression is driven by the P2 and P3 promoters. The precursor peptide AgrD is processed and cyclized by AgrB to generate the mature AIP, which accumulates extracellularly and, upon reaching a threshold concentration, binds to the membrane-bound histidine kinase AgrC. This interaction activates the response regulator AgrA, which enhances transcription from both the P2 and P3 promoters through a positive feedback loop. The P3 promoter drives the expression of RNAIII, the main effector molecule of the agr system, which regulates the expression of numerous virulence genes [76].

QQ in *S. aureus* can be achieved through the *first strategy,* inhibiting the response regulator AgrA, thereby preventing the activation of *agr*-dependent virulence genes [93]. Several natural and synthetic compounds, including vismione derivatives, pyocyanin, Azan-7, staquorsin, physalins, and eugenol, have been shown to impair AgrA activity through different mechanisms, such as blocking DNA binding or phosphorylation. These inhibitors reduce toxin production, hemolysis, and biofilm formation without significantly affecting bacterial growth, highlighting AgrA as a promising antivirulence target [94].

Furthermore, synthetic small molecules, including pyrazolopyrimidines and epoxide-containing compounds, inhibit AIP biosynthesis (*second strategy*) and AgrA binding. Repurposed drugs like bumetanide and 5-fluorouracil (5-FU) suppress virulence genes and enhance antibiotic efficacy.

4.4. *Staphylococcus epidermidis*

It is a coagulase-negative staphylococcus that produces minimal amounts of coagulase. Unlike *S. aureus*, a coagulase-positive species, *S. epidermidis* typically exists as a commensal on the skin and mucous membranes, without significant pathogenicity [95]. However, recent studies have highlighted its role as an opportunistic pathogen, capable of causing infections in the skin, soft tissues, endocardium, and other organs, particularly in elderly patients, newborns, or those with compromised immune systems. Notably, *S. epidermidis* has emerged as the leading cause of prosthetic joint and nosocomial infections, primarily due to its ability to colonise surgically implanted medical devices [96].

Because biofilms play a crucial role in the biology of both *S. aureus* and *S. epidermidis*, their formation and disassembly are carefully regulated by multiple systems [97–99]. Among these, the most thoroughly studied regulatory system is the accessory gene regulator (*agr*) QS system. This cell-to-cell communication mechanism regulates bacterial behaviour by using cell density [100].

In *S. epidermidis*, the *agr* QS system shares the same genetic organization (*agrBDCA*) and activation mechanism as in *S. aureus*. The P2 promoter drives the transcription of the *agrBDCA* operon, encoding the components required for AIP synthesis, sensing, and signal transduction: AIP accumulates in the extracellular environment and, upon reaching a threshold concentration, activates the membrane-bound histidine kinase *agrC*, which in turn phosphorylates the response regulator a*grA*. Activated a*grA* enhances transcription from the *agr* promoters through a positive feedback loop and directly upregulates the expression of the *psmα* and *psmβ* operons [101]. The resulting phenol-soluble modulins (PSMs) play key roles in cytotoxicity, induction of inflammatory responses, and biofilm development. PSMβ contributes to biofilm structural integrity, promotes biofilm maturation and dispersal, and facilitates the dissemination of biofilm-associated infections. Therefore, unlike in *S. aureus*, where the *agr* system mainly regulates the expression of toxins and acute virulence factors, in *S. epidermidis* it primarily controls biofilm remodelling and the transition from sessile to planktonic

growth, thereby promoting the persistence and spread of device-associated infections [102].

For this bacterial strain, QQ strategies have primarily focused on disrupting the Agr QS system (*first strategy*), which regulates biofilm development and virulence. Unlike in Gram-negative bacteria, where enzymatic degradation of signalling molecules is widely explored, QQ in *S. epidermidis* mainly relies on interference with AIP signalling. Cross-inhibitory AIPs produced by other staphylococcal species can competitively block Agr activation, while inhibition of the Agr signalling pathway, particularly the response regulator AgrA, has also emerged as a promising antivirulence strategy. However, compared with *S. aureus*, the development of specific QQ agents for *S. epidermidis* remains limited, and further studies are needed to validate their therapeutic potential [103].

Fig. 3 provides a comprehensive summary of the main QS systems and QQ strategies described for the different bacterial strains, highlighting their signalling pathways, molecular targets, and the resulting effects on virulence and biofilm formation.

5. Applications of QQ to mitigate the risk of infections in biomedical devices

Among different biomedical applications, bacterial colonisation is a major concern for medical devices implanted in the body or in contact with biological fluids. Preventing bacterial adhesion in these cases is crucial for reducing infections and severe side effects, improving patient quality of life, and reducing hospitalisation costs. The most critical devices include vascular and urinary catheters, endotracheal tubes, bone implants, and trauma devices. We decided to group biomedical applications prone to biofilm formation into four main categories: implants (e.g., dental, orthopaedic, cardiac), indwelling and medical devices (e.g., catheters, stents, syringes, storage containers, membranes for purification), drug delivery systems (e.g., nanoparticles, composites, capsules), and diagnostic systems (e.g., biosensors, imaging systems). In the following sub-paragraphs, we will report and compare different innovative antibacterial solutions for biomedical applications based on QQ. This approach has the advantage of acting via *in situ* local release of biomolecules, compared with the conventional systemic administration of antibiotics. Even if the latter cannot be completely avoided, coupling with QQ strategies is expected to limit duration, reduce doses, and make it much more effective. In some cases, QQ prevents infections and preserves the microbiome and commensal bacteria, which are necessary to restore physiological conditions.

The different ways to apply a QQ strategy to the different categories of biomedical devices and implants currently under investigation are discussed in the following paragraphs.

5.1. Implants

The main biomaterials for implants considered in this subparagraph are polyurethane (PU), silicone, bioactive glasses, and titanium and its alloys. Polypropylene is also used in 3D-printed prosthetics for its strength-to-weight ratio, but we refer to this biomaterial in the subparagraph devoted to medical devices. PU is found in vascular grafts and heart valves because its biocompatibility, durability, and flexibility make it suitable for long-term implantation. Additionally, its

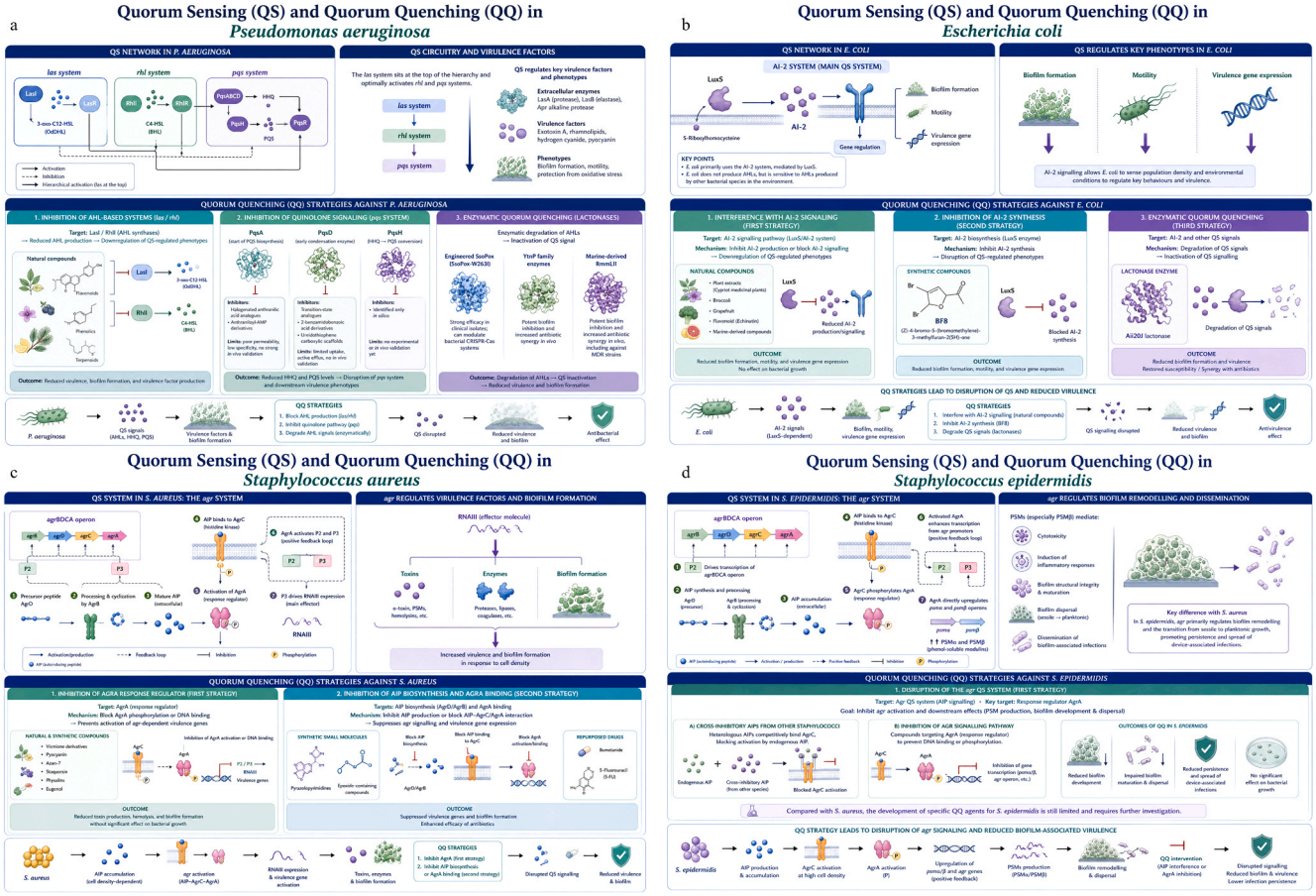


Fig. 3. overview of QS systems and QQ strategies in the four bacterial species. schematic representation of the main QS signalling pathways, key molecular components and virulence-associated phenotypes in a) P. aeruginosa, b) E. coli, c) S. aureus, d) S. epidermidis, together with the principal QQ strategies and their effect on bacterial communication, biofilm formation, and virulence.

hemocompatibility helps to reduce blood clot formation. PU is a non-leaching biocatalytic biomaterial (or coating) that effectively counteracts biofilm formation.

Silicone is used in various implants (orthopaedic and cochlear), heart valves, vascular grafts, pacemaker leads, and dental implants (orthodontic devices) [104]. The advantages of silicone in implants are biocompatibility, minimal immune response, durability, resistance to degradation, flexibility, ability to mimic natural tissue, versatility in shaping, and customisation. Conversely, silicone is generally more prone to bacterial adhesion than other biopolymers due to its hydrophobicity, which promotes biofilm formation. This is why surface modifications are needed to improve its antimicrobial properties [105].

Bioactive glasses are used in bone implants because of their ability to bond with biological tissue and promote bone regeneration. Doped with silver, copper, or zinc, bioactive glasses gain antibacterial properties, reducing infections in medical devices, but synergistic strategies can be coupled to this [106].

Titanium and its alloys are widely used in implants and prosthetics, especially for dental and orthopaedic applications, because they are less stiff and more metal-compatible. Additionally, they can be coated with bioactive materials (e.g., hydroxyapatite) to enhance bone integration, while surface roughening and nanotexturing further improve cell adhesion and healing [107]. On the other hand, these surface modifications increase the risk of biofilm formation and infection, creating niches for bacterial adhesion.

Following the *first strategy* of QQ, furanones can be applied as coatings or physically adsorbed as QSM analogues; research is ongoing to improve stability using covalently bound furanone polymers [48]. Some examples are summarised.

2,5-dihydro-2H-pyrrole (DHP) and furanones can be chemically immobilised onto a bioactive glass surface [53], or it can be attached to glass substrates via a copper-catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) click reaction: the click-DHP coating exhibited excellent activity in reducing bacterial adhesion and biofilm formation of *P. aeruginosa* and *S. aureus* [54].

Furanones, like (Z-)-4- bromo-5-(bromomethylene)-2(5 H)-furanone (BBF), can also be used as QSI grafted to a coating of sulfonated tetrafluoroethylene (Nafion) with anti-biofilm properties against *P. aeruginosa and E. coli.* A BBF-Nafion coating showed excellent activity in reducing bacterial adhesion and biofilm formation by mixed culture and three pure strains [53].

Furthermore, the BBF compound can be loaded into PLLA NPs with high encapsulation efficiency and long-term release behaviour. They were cross-linked on micro-arc-oxidised titanium (MAO-Ti), resulting in an antibacterial coating on Ti implants against *S. aureus*[108].

Studies that refer to the *second strategy* explored a polymer-based coating for silicone, specifically copolymerized with polymethacrylate, which ensures a uniform coating and enables the sustained release of 2-MAMP (2-[(methylamino)methylphenol), a compound known for its anti-biofilm and anti-virulence properties.

Furthermore, a universal anti-biofilm coating composed entirely of natural biomolecules was fabricated: it features a multifunctional phase-transited bovine serum albumin (PTB) matrix providing immediate antifouling properties and acts as a sustained-release reservoir for the QSI Qe, which showed sustained broad-spectrum antibiofilm efficacy against *P. aeruginosa* and *S. aureus* for at least 3 days. The strong interfacial adhesion of the PTB matrix facilitates easy application to various substrates with diverse chemical compositions and structural characteristics [109].

Moreover, a polymeric film can also encapsulate NO, supplementing the naturally produced NO from macrophages. By incorporating NO-releasing coatings, the immune system's physiological antimicrobial properties can be enhanced, helping to prevent the survival of pathogenic bacteria on implant surfaces [110].

Also, a nano-delivery system was created by combining photothermal therapy with controlled QSI release. Mesoporous polydopamine (MPDA) nanoparticles (NPs) offer excellent photothermal properties, while luteolin (LUT - a QSI) can be loaded into MPDA to form the MPDA-LUT nanosystem. A calcium phosphate coating was applied to Ti via biomimetic mineralisation, creating MPDA-LUT@CaP NPs. Finally, these NPs were anchored onto a Ti substrate using an intermediate polydopamine coating. Triggered by the weakly acidic environment of biofilm infection, LUT was released [111].

The *third QQ strategy* is based on the enzymatic degradation of QSMs. Medical-grade PU can react with acylase, enabling enzyme immobilisation for biofilm inhibition. Studies conducted under static culture conditions with *P. aeruginosa* demonstrated that acylase-containing coatings can reduce biofilm formation by approximately 60% [112].

Finally, silicone surfaces can be coated using layer-by-layer (LbL) assembly with negatively charged acylase or amylase [113]. The hybrid coating further enhanced antibiofilm activity against *P. aeruginosa* and multispecies (*P. aeruginosa & E. coli*) biofilms by simultaneously targeting QS signals [114]. By using the same technique, hyaluronic acid (HA), negatively charged, quaternized chitosan, positively charged, and acylase, negatively charged, can be combined to create a multifunctional coating with antibacterial, antibiofilm, and biocompatible properties [115]. In Fig. 4, QQ strategies for implants are summarized.

5.2. Indwelling and medical devices

Indwelling and medical devices (urinary, central venous and endotracheal catheters) are mainly produced by using polystyrene (PS) and polypropylene (PP). PU and titanium (surgical instruments) are also widely used; refer to the previous subsection on implants for these materials.

PS is a key material in medical devices and drug delivery systems, where its optical clarity, ease of fabrication, sterilizability, and chemical resistance are essential. Prevention of bacterial contamination is crucial in PS applications like syringes and blood storage containers. PS is highly hydrophobic and easily colonised by bacteria; it must be functionalised with antimicrobial agents, hydrogels, or enzyme-based coatings to prevent infections of medical tubing and catheters [116].

Polyvinyl chloride (PVC) is a non-toxic and chemically stable material, suitable for direct contact with blood, tissues, and fluids. Plasticized PVC is cost-effective, transparent, soft, and flexible, ideal for single-use medical devices, such as IV bags, catheters, tubing, and blood bags. In all these applications, the risk of bacterial contamination is high; so, even if PVC is less prone to bacterial contamination than other polymers, prevention strategies must be used [117].

Polypropylene (PP) is used in syringe barrels, pill bottles, IV bags, medical packaging, non-woven fabrics for masks, surgical gowns, and drapes due to its chemical resistance, sterilizability, lightweight, breathable and hypoallergenic properties. PP is also used in lab equipment, such as pipette tips, Petri dishes, and test tubes, with heat and chemical resistance. Besides PP, fluorinated ethylene propylene (FEP) has chemical resistance, biocompatibility, high transparency, non-stick properties, and similar biomedical applications [118].

In this context, the *first QQ strategy* depicted in Section 3 was the most widely explored for biomedical devices. A PEG-based low-fouling platform coating was applied to PS to enable targeted incorporation of DHP. This versatile platform coating, formulated with commercially available precursors, supported the incorporation of DHP through either a one- or two-step process. Notably, it maintained both low-fouling and QS-inhibitory properties without compromising individual functionalities while offering precise control over QSI integration [119].

Furanones (like 3-(10-bromohexyl)-5-dibromomethylene-2(5 H)-furanone) were successfully used to coat PVC [48]. Moreover, a FEP surface was incorporated with DHP and a nitric oxide (NO) donor with potent inhibitory activity [120]. Moreover, a furanone compound (3-(10-bromohexyl)-5-dibromomethylene-2(5 H)-furanone) was used to coat PP surface against the adhesion and slime production of *S. epidermidis* and *P. aeruginosa* and showed to prevent implant-related

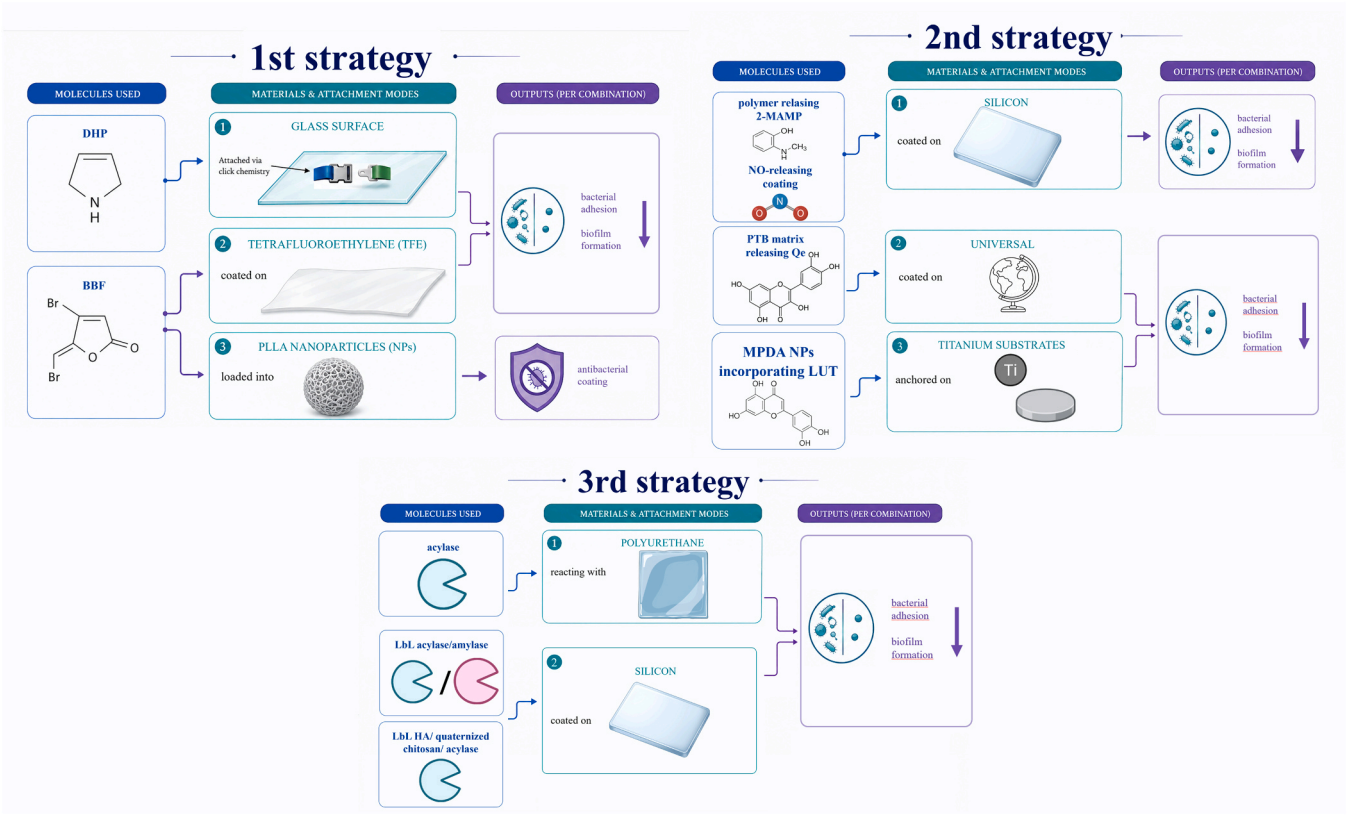


Fig. 4. summary of QQ strategies for implants.

infections in a clinical environment [48].

On the other hand, according to the *second QQ strategy* of delaying or blocking the production of QSMs, a PS coating with PU blended with the coumarin derivative 6-Methylcoumarin (6-MC) exhibited promising anti-virulent and anti-biofilm activity against *P. aeruginosa*. The anti-biofilm effect of PU-blended 6-MC aligns closely with the inhibition of QS-regulated virulence factors [121].

Finally, enzymes, such as lysozyme and acylase, used mainly in the *third QQ strategy*, were immobilised onto PVC catheters using glycidyl methacrylate (GMA) as an intermediate for multipoint covalent binding. Lysozyme significantly prevented *S. aureus* adhesion, while acylase-immobilised PVC-g-GMA catheters degraded a variety of AHL signals responsible for QS, as demonstrated by inhibition of the production of violacein pigment regulated by AHLs in *C. violaceum* [122]. In Fig. 5, QQ strategies for indwelling and medical devices are summarized.

5.2.1. *Membranes*

One of the primary uses of membranes is in hemodialysis, plasmapheresis, blood purification, and the treatment of autoimmune diseases. In addition, membranes play a key role in drug delivery systems, tissue engineering, wound healing, and regenerative medicine as scaffolds for cell growth. Finally, they are used in artificial lungs (oxygenators) for gas exchange in extracorporeal membrane oxygenation and in artificial kidney membranes for ultrafiltration [123].

To mitigate membrane biofouling, the formation of bacterial biofilms on membrane surfaces that reduces filtration efficiency, electrospun polymer coatings were designed by blending hydrophobic and hydrophilic biocompatible polymers in varying ratios to control the

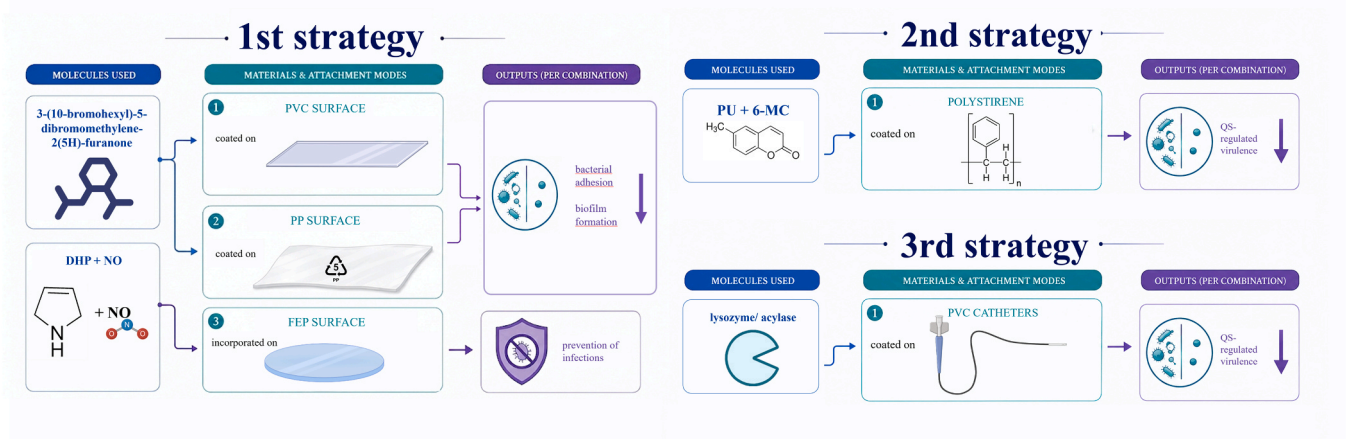


Fig. 5. summary of QQ strategies for indwelling and medical devices.

release dynamics of anti-QSMs, following the *first QQ strategy*. Specifically, a combination of hydrophobic polycaprolactone (PCL) and hydrophilic polyethyleneglycol (PEG) was applied to the surface of mixed cellulose ester membranes, enabling the extended release of Urolithin A [49] or furanone C-30 [50] to effectively inhibit biofouling. Furthermore, polyethersulfone membranes were modified with natural QSI, such as vanillin and furanone, to inhibit membrane biofouling using a biomimetic material (polydopamine), with a self-polymerisation process [51].

A superhydrophobic polyethyleneimine/poly(4,4-vinyldimethy lazlactone) (PEI/PVDMA) layer-by-layer (LbL) coating can be loaded with QSI peptides, without compromising the nonwetting properties of the polymer membrane, in addition to commonly used biomedical materials. The peptide-loaded superhydrophobic materials enabled sustained release of QSIs, effectively modulating QS and QS-regulated *S. aureus* biofilm formation in vitro over prolonged periods, without adversely affecting cell growth [124].

A study from Wang et al [125]. reported a method to endow substrates with a long-term antibiofilm property by simply depositing a hybrid coating of tannic acid (TA)/Cu-PEG (polyethylene glycol). TA/Cu complex acts as a photothermal biocidal agent under irradiation of a near-infrared laser, while PEG has intrinsic antifouling properties.

Moreover, strips of nonwoven mesh were coated with carboxymethylcellulose films containing *S. aureus* QSIs peptides. These coatings withstand basic mechanical challenges associated with handling and physical manipulation. Incubation of film-coated mesh in physiologically relevant media resulted in the rapid release of biologically active peptides [126].

Antibiofouling strategies mediated by QQ can be applied in other fields as well, like membrane bioreactors (MBRs) for high quality and compactness in wastewater treatment [127]: in this regard, a microcapsule product with coupling quenching sterilization and pollutant removal enhancement was successfully prepared, and its anti-membrane biofouling and phosphorus adsorption effects were verified in the continuous MBRs [128]. In Fig. 6, QQ strategies for membranes are summarized.

5.3. Nanosized drug delivery systems

NPs, nanocomposites, and nanocapsules (1–100 nm) are very promising for precise drug delivery, tumour-specific therapy, imaging (MRI, CT), tissue engineering, and gene therapy or vaccines (e.g., mRNA COVID-19 vaccines). NPs have also provided new perspectives on the antibacterial efficacy of antibiotics due to their high surface-to-volume ratio [129]. Micro and nano delivery systems include AgNPs, PU, and PS drug microparticles and hydrogels.

Some NPs showed antibiofilm activity even without a specific functionalization. Biologically synthesised AgNPs using a Piper betle leaf extract showed anti-QS and anti-biofilm activity against *P. aeruginosa*. These phyto-fabricated NPs significantly attenuated QS-regulated virulence factors, including violacein in *C. violaceum* and pyocyanin and elastase in *P. aeruginosa*. Additionally, they exhibited strong anti-biofilm activity, highlighting their potential to reduce bacterial resistance to conventional antibiotics [130].

Furthermore, a nanoplatform was fabricated by coating calcium peroxide nanoparticles (CaO_2 NPs) with a quercetin/copper ion (Qe/Cu^{2+}) complex (CQC NPs). This system eradicates bacterial biofilms by integrating QS inhibition and chemodynamic therapy (CDT), bypassing antibiotic resistance. In the acidic biofilm microenvironment, the CQC NPs undergo triggered disassembly, releasing Cu^{2+} and Qe while exposing a CaO_2 core. By unifying QS inhibition and CDT, this platform overcomes the limitations of monotherapy, offering a scalable strategy for treating biofilm infections [131]. A similar system was developed by Cheng et al. [132], and quercetin/copper (QC) NPs were obtained through a simple process that combines Qe and Cu^{2+} ions via phenolic-metal coordination bonds. The Cu^{2+} ions exhibit potent

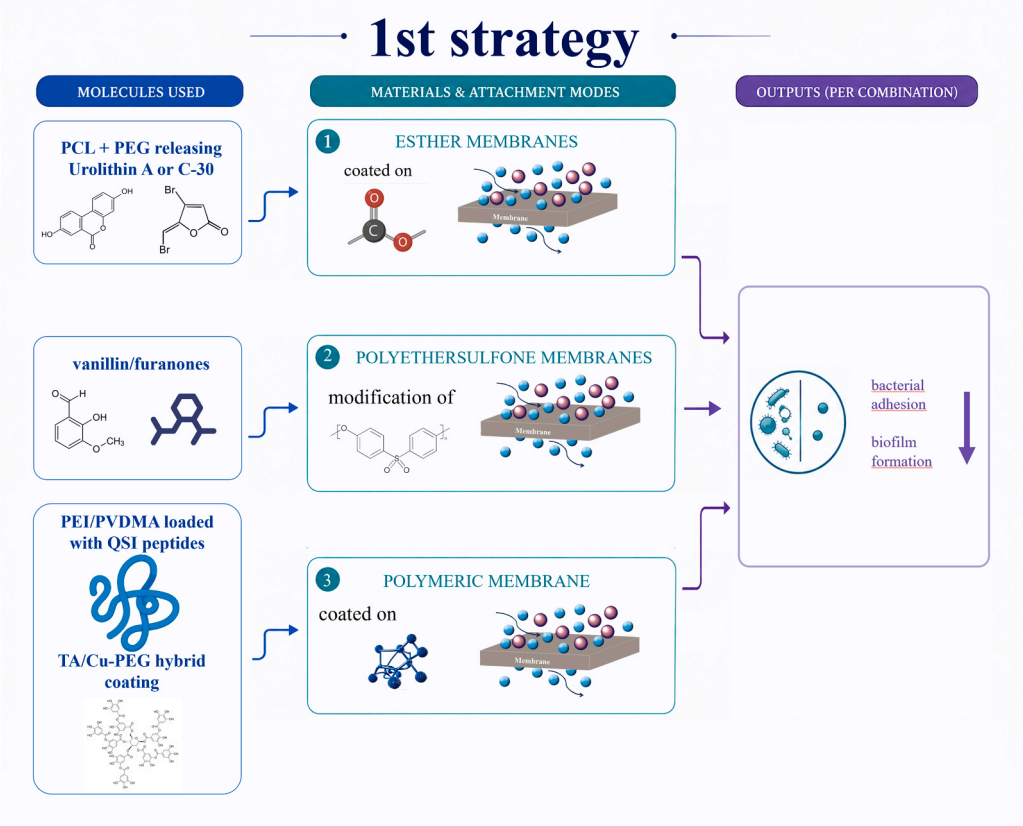


Fig. 6. summary of QQ strategies for membranes.

antimicrobial activity by obstructing bacterial cell-wall synthesis and disrupting cell membranes, and exhibit supplementary biological functionalities, such as promoting of neovascularization [133]. Thus, within the mildly acidic environment of the biofilm, the QC NPs can disintegrate and release both Qe and Cu^{2+} ions simultaneously, potentially leading to enhanced antibiofilm effects. This bi-functional antibiofilm nanoplatform consists of a complex of Qe (a potent QSI) and the Cu^{2+} ion (a bactericide). This nanoplatform effectively overcame the inherent limitations of Qe, specifically its low solubility and absence of antibacterial activity. While both platforms combine the QSI activity of Qe with the antibacterial effects of Cu^{2+}, CQC NPs additionally incorporate a CaO_2 core to enable CDT, whereas QC NPs rely solely on the synergistic Qe–Cu^{2+} coordination complex.

Moreover, chitosan-based AgNPs are gaining recognition for their biocompatibility, biodegradability, and hydrophilicity, making them valuable across various fields. Chitosanase facilitates endo-hydrolysis between D-glucosamine, playing a crucial role in pathogen control. These biomimetically synthesised chitosan AgNPs exhibited outstanding antibacterial, anti-QS, anti-biofilm, and antifungal activity, achieving 100% efficiency against multidrug-resistant pathogens [134].

Metallic NPs have also been investigated in another study [135], modifying 3-amino-1,2,4-triazole-5-thiol (ATT), which contains amine groups and a mercapto group, on GNCs (AGNCs), through the formation of S-Au bond, binding to the extracellular DNA (eDNA) in the EPS by forming hydrogen bonds to achieve targeted therapy. AGNCs can generate ROS to combat bacteria, and the ROS produced by the AGNCs can be enhanced through NIR light irradiation at 808 nm, effectively eradicating the biofilm.

Also, solid lipid nanoparticles (SLNs) loaded with QSI and coated with chitosan (CS) were developed to improve internalisation and immobilised with alginate lyase (AL). The potential of SLNs bearing biofilm-degrading enzyme functionalities to kill *P. aeruginosa*, prohibit biofilm formation, or disassemble the biofilm matrix was assessed. Anionic SLNs were loaded with an early-stage alkylquinolone-based QSI that disrupted bacterial cell-to-cell communication and coated with CS to obtain cationic SLNs. The particles ensured good penetrability across the artificial biofilm model and adequate viability and uptake in human bronchial and alveolar cell lines [136].

Bimetallic NPs, including nanocomposites, have received great attention due to various applications in biomedicine and other industrial fields. Bio-synthesised Ag–TiO_2 and Ag–Cu showed significant anti-planktonic, anti-QS, antibiofilm, and antioxidant activities [137].

Magnetic NPs, such as ternary nickel ferrite (MnF and NF), can be stabilised with polyethyleneimine (PEI), exhibiting strong antibiofilm activity against *S. aureus, E. coli, and C. albicans*. These polyethyleneimine-coated NPs, PEINF, showed excellent antibiofilm activities on pathogenic bacteria *S. aureus, E. coli, and C. albicans*. This could result from a synergistic effect between polyethyleneimine and the magnetic NPs, which exhibited antibiofilm activity. The PEINF NPs showed anti-quorum-sensing activity, attributed to the presence of nickel, an anti-quorum-sensing metal [138].

ZnO nanospikes had an inhibitory effect on QS and biofilm formation, enhancing antibiotic efficacy and decreasing bacterial pathogenicity, which should be exploited in the future for the treatment of drug-resistant infections by *P. aeruginosa* [139].

Moreover, functionalization of NPs following QQ strategies has been reported. Chitosan NPs encapsulated kaempferol, enhancing QS-inhibitory effect against *C. violaceum*, effectively regulated violacein

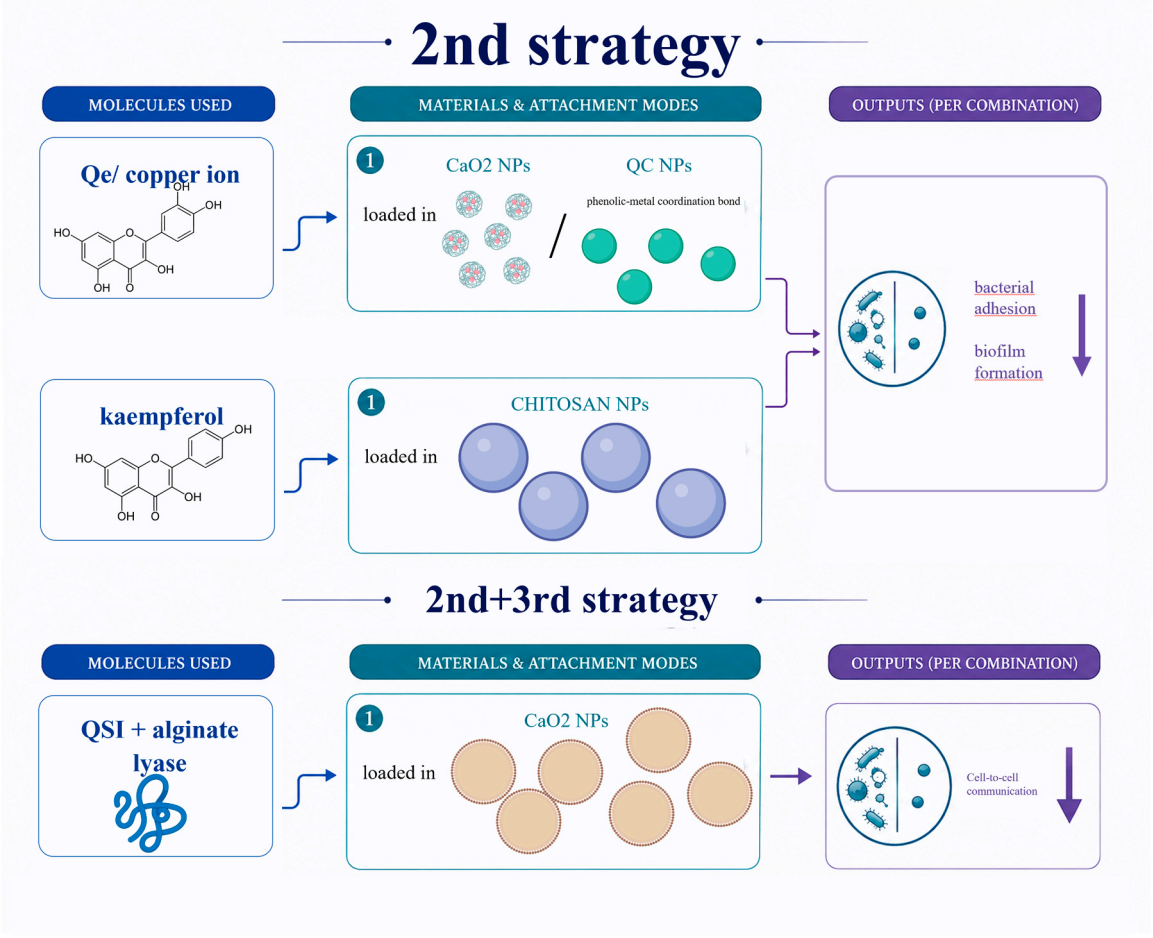


Fig. 7. summary of QQ strategies for nanosized drug delivery systems.

pigmentation and biofilm formation over different storage periods compared to pure kaempferol [140].

Finally, the LbL technique enabled the fabrication of hybrid enzyme/biopolymer/metal AgNPs. A bilayered AgNP template exhibited a four-fold increase in bactericidal activity, driven by the synergy between the metal core, nano-formulated antibacterial aminocellulose, and anti-biofilm acylase [47]. In Fig. 7, QQ strategies for nanosized drug delivery systems are summarized.

5.4. Diagnostic systems

The range of materials used for diagnostics is wide, but we will focus on Molecular Imprinted Polymers (MIPs). Some solutions described for bioactive glasses, in the sub-paragraph focused on implants, can also be considered for diagnostic systems.

MIPs are synthetic materials designed to mimic natural bio-recognition elements by creating selective binding sites for specific molecules. For example, they are used in biosensors to detect biomarkers [141], pathogens, drugs, and in point-of-care diagnostics for rapid and selective detection. Furthermore, MIPs can be tailored for controlled, targeted drug release and used for chemotherapy drugs, antibiotics, and hormones to enhance bioavailability and reduce side effects.

The compound 3-oxo-C12-AHL is a key regulator of extracellular virulence factors and biofilm formation in *P. aeruginosa* and plays a crucial role in infection in animal models. Its racemic form was used for MIP preparation, making MIPs imprinted with QSMs promising for clinical biofilm prevention. These polymers can be easily integrated into medical devices (e.g., catheters, dialysis membranes, contact lenses) via surface grafting, enhancing resistance to biofilm formation and reducing complications from *P. aeruginosa* infections [142,143]. In Fig. 8, QQ strategies for diagnostic systems are summarized:

The strategies employed for the various types of materials and bacterial strains are summarized in Table 2:

6. Advantages and limitations of the QQ approach in biomedical applications

6.1. Overview

The QQ approach in biomedical applications offers several advantages, primarily due to its targeted action against bacterial communication rather than bacterial viability. By disrupting QS, QQ strategies can reduce pathogenicity, enhance antibiotic efficacy, and counteract antimicrobial resistance while preserving beneficial microbiota strains such as pro- and pre-biotics. Unlike systemic approaches, QQ-based treatments can be applied locally, minimising side effects and improving site-specific efficacy, particularly in biofilm-associated infections where traditional antibiotics often fail due to the complexity of reaching the infection site and strains' resistance. However, QQ also presents challenges, including strain-specific limitations, potential bacterial adaptation, and difficulties in sustained delivery. Moreover, its effectiveness in polymicrobial infections remains uncertain, as different bacterial species rely on distinct QS pathways due to strain-specific activity.

Although the specificity of the QQ approach is a potential limit, its efficacy was demonstrated on different strains in an unexpected and very promising manner. Bacterial adhesion assays with *P. aeruginosa* and *S. aureus* confirmed the coating's resistance to colonisation, with the presence of DHP further enhancing its anti-adhesive properties, in the covalent incorporation of the QS inhibitor DHP into a PEG-based multifunctional coating designed to reduce bacterial adhesion. In *S. aureus* biofilm assays, surfaces containing DHP exhibited a greater reduction in bacterial attachment compared to PEG-based surfaces alone. Additionally, in a *P. aeruginosa* QS reporter assay, all DHP-incorporated coatings significantly decreased the number of QS-active bacteria, confirming that DHP retained its QS-inhibitory properties even after covalent integration into the coating.94 From this, we can assess that while *S. aureus* primarily uses the *agr* quorum-sensing system rather than AHL-based QS like *P. aeruginosa*, DHP might still interfere with regulatory pathways that contribute to biofilm formation. Moreover, there could be a synergistic effect with PEG-based coating, which already provides a low-fouling surface, reducing passive bacterial adhesion. In another study, FU compounds and DHPs were immobilised onto a glass surface: the results for *S. aureus* showed significant reductions in overall bacterial coverage of around 80% for FUs and around 85% for DHPs compared to the control surface. *P. aeruginosa*'s attachment to the FU and DHP-coated surfaces was significantly lower than on the control, with reductions of 55% for FUs and around 60% for DHP [53]. The mechanism by which DHPs inhibit QS is speculated to be similar to that of FUs, that is, via displacing the AHL signal from the receptor site without affecting bacterial growth. DHPs and FUs were capable of interfering with the AHL-regulated *las* QS system in *P. aeruginosa*, thereby inhibiting biofilm formation. Therefore, it is likely that the FU and DHP surfaces generated in this study act through the same mechanism of action for Gram-negative bacteria. On the other hand, for Gram-positive bacteria, the mode of action of FUs and DHPs is still not fully understood: it is possible that FUs and DHPs, which are structurally related to AHLs, inhibit QS of Gram-positive bacteria via an indirect approach through a direct interaction with the bacterial membrane [144]. So, while QQ strategies show great promise, further research and clinical validation are needed to integrate them into the conventional medical practice.

As previously discussed, QQ can work synergistically with antibiotics, reducing the required doses and duration of treatment, which in turn may help mitigate antibiotic resistance: the combination of Tobramycin (TOB) and a QSI (coumarin) was carried out to explore

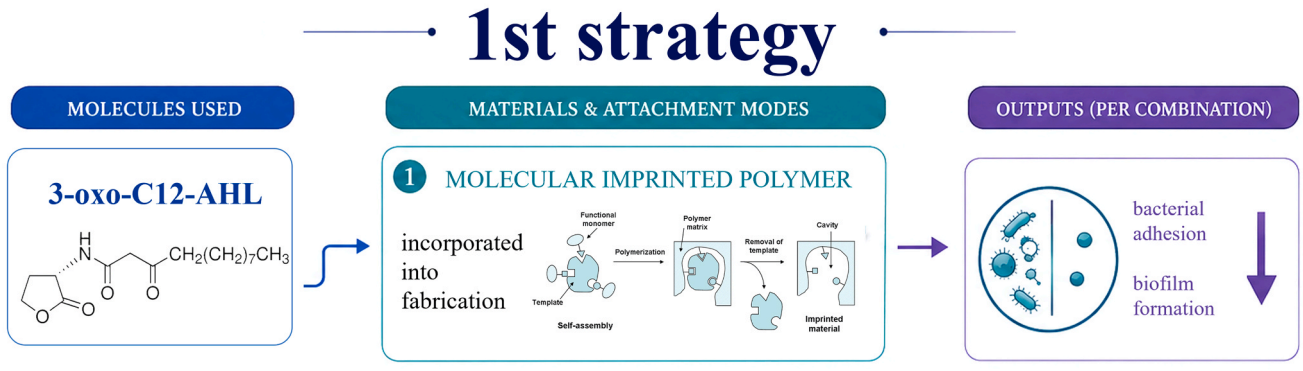


Fig. 8. summary of QQ strategies for diagnostic systems.

Table 2
Summary of the combinations of materials, strategies, performances, and bacterial strains.

STRAIN	BIOMATERIAL	STRATEGY	PERFORMANCE	REFERENCE
Pseudomonas aeruginosa	MIPs	1. 3-oxo-C12-AHL	1. 70% reduction of biofilm formation	[142][143],
	AgNPs	1. QQE acylase 2. Piper betle L.	1. Elimination of 24-hour-grown biofilm 2. QS-regulated virulence factors attenuated: pyocyanin and elastase. Antibiofilm activity	[65,134]
	Silicon	1. HA and acylase 2. Acylase and amylase 3. NO	1. Down-regulation of QS-related gene expression (lasI, lasR, rhlI, rhlR) by 39%, 44%, 30%, and 33%. Inhibition of 100% biofilm formation. 2. Inhibition of biofilm formation by 40% 3. Reduction of 82% of the infection rate	[118,119, 144]
	PS	1. DHP 2. PU + 6MC	1. Reduction of bacterial adhesion of 82% 2. Inhibition of pyocyanin production of 90%, elastase production of 80%, iron chelating agent of 70%, and biofilm production of 70%	[112,119, 121]
	Glass	1. DHP 2. DHP + FU 3. Vanillin/FU	1. Reduced bacterial coverage by 90% and biofilm formation by 61%. 2. Reduction in bacterial coverage of 54.8% 3. Biofilm inhibition capacity of 51%	[54,55,145]
	PU	1. Acylase	1. 60% reduction of CFU and biofilm formation. Secretion of pyocyanin was reduced by 60%.	[112]
	PCL/PEG membrane	1. Urolithin A	1. Biofilm thickness reductions up to 89% and improved flux through the modified membrane at 58.17% over four hours	[49]
	ZnO nanospikes	1. Sol-gel fabrication	1. Decrease in azocasein-degrading protease activity (80%), elastase activity (83%), and pyocyanin production (85%). Decreased swarming motility and exopolysaccharide production by 89 and 85%, respectively.	[139]
	UF membranes	1. Vanillin/FU	1. Biofilm inhibition capacity of 51%	[51]
	Lipid nanocarriers	1. Compound 3 (alkylquinolone-derived)	1. 50% reduction of biofilm formation	[136]
	Alginate-based beads	1. Hydrated zirconium oxide	1. Inhibition of biofilm 13.5% and of swarming motility around 30%	[146]
	Ag-TiO2 and Ag-Cu nanocomposites	1. Extract of Artemisia haussknechtii as green synthesis	1. Inhibition of biofilm formation related to the concentration	[137]
	FEP	1. DHP and NO	1. 3-fold lower bacterial coverage. 65/75% reduction in bacterial coverage	[120]
	Magnetic NPs	1. PEI	1. Antibacterial, antibiofilm and anti-QS activity: lower swarming and swimming motility	[138]
Escherichia coli	Glasses	1. BBF	1. Reduction of biofilm formation of 40%	[147]
	Magnetic NPs	1. PEI	1. Antibacterial, antibiofilm and anti-QS activity.	[138]
	UF membranes	1. Vanillin/FU	1. Biofilm inhibition capacity of 38%	[51]
	AgNPs	1. Chitosanase	1. Swarming motility is completely inhibited	[134]
	CS-based nanocapsules	1. Baicalein and quercetin	1. QS inhibition ability improved	[43]
	Alginate-based NPs	1. Hydrated zirconium oxide	1. 1. Inhibition of biofilm 13.5% and of swarming motility around 30%	[146]
	Ag–TiO2 and Ag-Cu nanocomposites	1. Extract of Artemisia haussknechtii as green synthesis	1. Increased inhibition zone of 36 mm	[137]
Staphylococcus aureus	Titanium	1. BBF-loaded PLLA NPs 2. LUT	1. Inhibition zone throughout the 60-day period, antibacterial rate of −195% during the first 45 days. 2. Antibacterial efficacy up to 59%	[115,148]
	Silicon	1. Eudragit E100, Eudragit RS100 incorporated with 2-MAMP 2. NO	1. Minimal fibrin deposition. Not studied for the long term 2. Reduction of 82% of infection rate	[46,144]
	Glasses	1. DHPs and FUs 2. DHPs	1. Reduction in bacterial coverage of 75.4% 2. Reduced bacterial coverage by 97% and biofilm formation by 68%.	[53,54] [54]
	PVC	1. Lysozyme and acylase	1. Prevention of bacterial attachment	[122]
	PEI/PVDMA	1. Peptidic QSI	1. Biofilm formation inhibition of 70% at day 1, around 40% at day 42	[124]
	PS	1. DHP	1. Reduction of bacterial adhesion by 80%	[119]
	Magnetic NPs	1. PEI	1. Antibacterial, antibiofilm, and anti-QS activity	[138]
	Polymer-based meshes	1. Peptide-based QSI	1. 95% reduction of GFP production relative to suspensions of bacteria	[126]
	AgNPs	1. Chitosanase	1. 100% biofilm inhibition	[134]
	Alginate beads	1. Hydrated zirconium oxide	1. Inhibition of biofilm 13.5% and of swarming motility around 30%	[146]
	Ag–TiO2 and Ag–Cu nanocomposites	1. Extract of Artemisia haussknechtii as green synthesis	1. Increased inhibition zone of12 mm	[137]
	FEP	1. DHP and NO	1. Reduction of adhesion by 70/80%	[120]
Staphylococcus epidermidis	PVC	1. Ag–TiO2, TiO2–Ag, Ag–Cu and Cu–Ag nanocomposites	1. 93% inhibition of biofilm formation	[48]
	Silicon	1. NO	1. Reduction of 82% of infection rate	[110]
Chromobacterium Violaceum	ZnO nanospikes	1. Sol-gel approach	1. Production of violacein decreased by 30 −92%	[139]
	Alginate-based beads	1. Hydrated zirconium oxide	1. Violacein inhibition of 100% and QS inhibition of 13%	[146]
	CS/TPP NPs	1. Kaempferol	1. Anti-QS activity against C. violaceum CV026, indicated by the loss of purple pigmentation (from 76% to 33,92% overtime)	[140]
	AgNPs	1. Piper betle L.	1. QS-regulated virulence factors attenuated: violacein	[130]
Candida albicans	Magnetic NPs	1. PEI	1. Antibacterial, antibiofilm, and anti-QS activity: inhibition of swarming and swimming motilities	[138]
	Alginate-based beads	1. Hydrated zirconium oxide	1. Inhibition of biofilm 13.5% and of swarming motility around 30%	[146]
Bacillus subtilis	Glasses	1. BBF	1. Reduction of biofilm formation of 40%	[147]
Vibrio cholerae	Silicon	1. Acylase/amylase	1. Inhibition of biofilm formation by 40%	[114]

whether naturally active small molecule coumarins and their derivatives can improve the antibacterial activity of TOB. The findings indicated that the proportion of surviving bacteria treated with TOB alone was 86%, and after binding to 5 different coumarin derivatives, the proportion of viable bacteria was 27%, 27%, 34.6%, 66.6%, and 69%, respectively [149].

6.2. Comparison of QQ strategies

Comparing the three main QQ strategies (blocking receptors with QSM analogues, delaying or blocking the production of QSM, and enzymatic degradation of QSM), each has its own strengths and weaknesses. The *first QQ strategy* is highly specific and effective at targeting bacterial strains. This approach minimises off-target effects and preserves beneficial bacteria. However, its very specific target makes it less effective in polymicrobial infections, and bacteria may develop resistance by modifying their QS receptors. Due to their high specificity, QSIs used in this strategy can be combined with other signalling molecules, such as NO, which possess antibiofilm activity, to enhance their effectiveness: novel dual-action biomaterial surfaces have been developed by incorporating both DHP and NO donor onto the FEP surface. Both *P. aeruginosa* and *S. aureus* strains were used to evaluate the combined effect of NO and DHPs on bacterial surface colonisation: results showed extensive bacterial colonisation on control surfaces by both *S. aureus* and *P. aeruginosa*. In contrast to the control samples, the surfaces modified by DHPs showed considerably less bacterial coverage. Further reduction in adherent bacteria was observed on surfaces coated with DHP + NO compared to DHP [93].

The *second QQ strategy,* by interfering at the source, prevents biofilm formation and enhances antibiotic effectiveness. It works against multiple strains but may be circumvented by bacteria with redundant QS pathways, and it could hinder beneficial microbes relying on similar pathways.

Finally, the *third QQ strategy* is broadly effective and less likely to drive resistance: it is ideal for polymicrobial infections and implant coatings; however, enzyme stability and activity remain challenging, as it may disrupt microbiome balance. In one of the studies reported in the previous section, to achieve a unique and efficient antibiofilm strategy, the QQE acylase and α-amylase were used to simultaneously interfere with bacterial QS and biofilm stability of Gram-negative species, respectively. α-Amylase, an enzyme that degrades exopolysaccharide (EPS), the main structural component of extracellular polymeric matrix (EPM), inhibited biofilm formation by several bacteria, including *S. aureus, V. cholerae,* and *P. aeruginosa*. The enzymatic degradation of EPM affects the physical integrity of biofilms, increasing the susceptibility of the encased bacteria to conventional antibacterials [114].

QQ strategies can be combined to enhance their effectiveness in reducing bacterial pathogenicity. For example, the integration of QQE and QSI has been simulated to disrupt both *las* and *rhl* AHL signalling in *P. aeruginosa*[145]. This combinational approach offers multiple points of intervention, broadening the coverage and effectively blocking QS pathways. By targeting both signal production and binding, this strategy significantly lowered *P. aeruginosa*'s ability to survive under stress conditions, making it more vulnerable to conventional treatments [149]. In silico mathematical modelling showed enhanced QS-inhibiting effects on AHL concentration when QQE and QSI were applied together. Future work will aim to evaluate the effectiveness of the combined treatments *in vivo* [145].

6.3. Development of QQ resistance

An open question in the field is whether bacteria can develop resistance to QQ interventions, as they evolve resistance to antibiotics. The evolution of QQ resistance is an emerging area of research, and further investigation is needed to determine whether bacteria can skip QQ-based treatments and how to counteract such adaptations [148]. The very same report also argued that resistance to QSIs might also be conferred by the antibiotic-resistance mechanisms evolved by the pathogen [150]. It is generally believed (although yet not proven) that pathogens are unlikely to develop resistance to QQ strategy because it poses no or little selective pressure. However, several studies investigate QS under conditions that better mimic the host environment, rather than standard laboratory cultures using nutrient-rich synthetic growth media, resulting in conditions more representative of pathogens' experience during infection. They indicate that disruption of QS can pose selective pressure on bacteria. Hence, the risk of resistance to QQ strategies is difficult to estimate at this stage [114]. Overall, while QQ strategies offer a powerful tool for controlling bacterial virulence and biofilm formation, future research should focus on optimising their application in diverse infection models, developing combination therapies, and addressing potential resistance mechanisms.

Overall, despite the encouraging results reported across different biomedical applications, no single QQ strategy currently overcomes all the intrinsic limitations associated with quorum sensing disruption. QSIs, particularly when physically incorporated into coatings or delivery systems, often suffer from uncontrolled burst release, diffusion away from the target site, and progressive depletion, limiting their long-term efficacy. Conversely, enzyme-based approaches provide continuous degradation of signalling molecules; however, they are limited by enzyme instability, loss of catalytic activity under physiological conditions, and potential deactivation during long-term implantation or sterilisation procedures. In addition, although QQ is generally considered to exert lower selective pressure than conventional antibiotics, increasing evidence suggests that prolonged exposure may still promote adaptive bacterial responses, including alterations in QS circuitry, activation of compensatory signalling pathways, or reduced dependence on QS-regulated virulence. These apparently conflicting findings likely reflect differences in bacterial species, infection models, and experimental conditions. Therefore, future research should focus on developing multifunctional and durable QQ platforms combining controlled-release systems, enzyme-stabilisation strategies, and synergistic antimicrobial approaches, while validating their long-term efficacy and adaptive responses in clinically relevant in vivo models.

7. Conclusions

Bacterial colonisation remains a significant challenge in biomedical applications; the emergence of QQ strategies offers a promising alternative to conventional antibacterial agents by disrupting bacterial communication and biofilm formation without promoting antibiotic resistance. Various approaches, including QSM analogues, QSI release systems, and enzymatic degradation, have demonstrated potential in reducing bacterial adhesion on biomaterials such as polyurethane, silicone, bioactive glasses, and titanium. These advancements not only enhance the antimicrobial properties of biomaterials but also improve patient outcomes by reducing infection risks and minimising the need for systemic antibiotics. Ongoing research into optimising QQ-based coatings and delivery systems will further refine their effectiveness, paving the way for safer and more durable biomedical devices. Indwelling medical devices and membranes used in biomedical applications face a significant risk of bacterial colonisation, biofilm formation, and infections. Materials such as PS, PP, PVC, and FEP are widely utilised, but their inherent susceptibility to bacterial adhesion necessitates advanced functionalization strategies to enhance their antimicrobial properties. QQ approaches offer an effective means of mitigating biofilm formation in these medical devices. Various strategies have been explored, including the use of QSIs like FUs and DHP coatings on PS, PVC, and PP, which disrupt bacterial communication pathways. Additionally, enzyme-functionalized surfaces, such as catheters of acylase-immobilised PVC, effectively degrade quorum-sensing molecules, reducing bacterial virulence. The incorporation of NO-releasing systems further enhances antimicrobial activity while preserving

biocompatibility.

Furthermore, NPs and nanocomposites, with a high surface-area-to-volume ratio, enhance drug bioavailability, enable targeted therapies, and provide novel solutions for combating bacterial infections. Many NPs, such as silver (AgNPs), chitosan-based, and bimetallic formulations, have demonstrated inherent antibiofilm and anti-QS inhibition properties, reducing bacterial pathogenicity and antibiotic resistance. QQ-based functionalization of NPs has further improved their efficacy. Moreover, innovative approaches, such as SLNs loaded with QS inhibitors and biofilm-degrading enzymes, have proven effective in disrupting bacterial communication and biofilm integrity. Finally, in diagnostic systems, MIPs provide a promising platform for detecting bacterial QS molecules and preventing biofilm formation on medical devices. These advancements hold great potential to revolutionise antimicrobial strategies, offering innovative solutions for infection control and improving patient outcomes in biomedical applications.

CRediT authorship contribution statement

Anna Rossanese: Writing – original draft, Investigation, Conceptualization. **Silvia Spriano:** Writing – review & editing, Supervision. **Milka Malesevic:** Writing – review & editing. **Andrea Cochis:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not Applicable.

Data Availability

No data was used for the research described in the article.

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