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ESKAPE pathogens and associated quorum sensing systems: New targets for novel antimicrobials development

Christiana E. Aruwa, Theolyn Chellan, Nosipho W. S'thebe, Yamkela Dweba, Saheed Sabiu [*]

Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, Durban 4000, South Africa

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ABSTRACT

Globally, antimicrobial (AMR) or multi-drug resistance (MDR) constitutes a current health challenge that is predicted to cause increased infections rates with adverse socioeconomic impacts through increase in healthcare costs. In addition, the group of *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp. (ESKAPE) pathogens cause debilitating infections (community and nosocomial) and are classed as priority 1 AMR pathogens. This systematic report therefore aimed at providing detailed coverage of new targets for novel antimicrobials development against MDR ESKAPE pathogens to mitigate future AMR spread and improve current public health indices. The prevalent ESKAPE bacterial group show high resistance to quinolones, lactams, cephalosporins, carbapenems and other antibiotic groups, and ability to form biofilms linked to various quorum sensing systems (QSSs) that boost their virulence. These QS pathways have become viable targets in drug design efforts for new antimicrobials development. Also, since antibiotics discovery and development has waned in the past decade, the emergence of advanced computational modelling technologies in drug design, repurposing and development efforts may yet bridge the gap. As such, in this work we provided a comprehensive and systematic overview using relevant, included data and findings on ESKAPE pathogens, their QSSs to target for novel antimicrobial agents' development, the contributions of computational tools at the heart of novel antimicrobial advancements and their roles in bioprospecting and developing novel 'druggable' candidates and therapies with anti-biofilm, and anti-quorum sensing activities to mitigate AMR, biofilm and QS-related pathogenicity factors.

1. Introduction

Currently available antibiotics have either been misused or abused, culminating in an upsurge in multidrug resistance (MDR) or antimicrobial resistance (AMR) in microbes [1]. As such, there has been a record increase in AMR-related infections, as well as in pan-drug-resistant infections in patients, and this calls for a drastic evolution of therapeutic and control measures. Predictions show that by 2050, annual deaths from AMR infections would be approximately 10 million, with over 80 % of cases emanating from the Asian and African continents [2]. AMR remains a faceless, and evolving risk to public health, with high probability of reaching pandemic proportions. The global AMR problem is exacerbated by the ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species) pathogens which have been identified as key AMR microbes. Within the group the highest mortality rates of 43 % and 30 % have been reported for *P. aeruginosa* and *K. pneumoniae*, respectively [3]. The causation of comorbidities among ESKAPE pathogens have also been reported (34 % mortality rate), while with other bacteria a 22 % mortality rate has been recorded [4].

Again, of the global 1.3 million AMR-associated deaths reported annually, about 80 % of deaths are ESKAPE (with inclusion of *Escherichia coli*) pathogens related [5]. These pathogens thrive due to their possession of peculiar resistant capabilities strengthened by their quorum sensing (QS) or 'communication' mechanisms within formed biofilms. The same sensing systems control virulence factors such as swimming and swarming motilities, and adhesins expressions. In line with these, the need for new antimicrobials cannot be overemphasised as current antibiotic interventions like fluoroquinolones, polymyxins, carbapenems, macrolides, β-lactams have adverse side effects and/or are ineffective. As such, new antimicrobials development is targeted to reduce current threating ESKAPE pathogens-related AMR trends, and the search for metabolites with 'drug-like' features which target QS proteins and/or inducer molecules associated with ESKAPE pathogens

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* Corresponding author.
E-mail addresses: christianaa@dut.ac.za (C.E. Aruwa), sabius@dut.ac.za (S. Sabiu).

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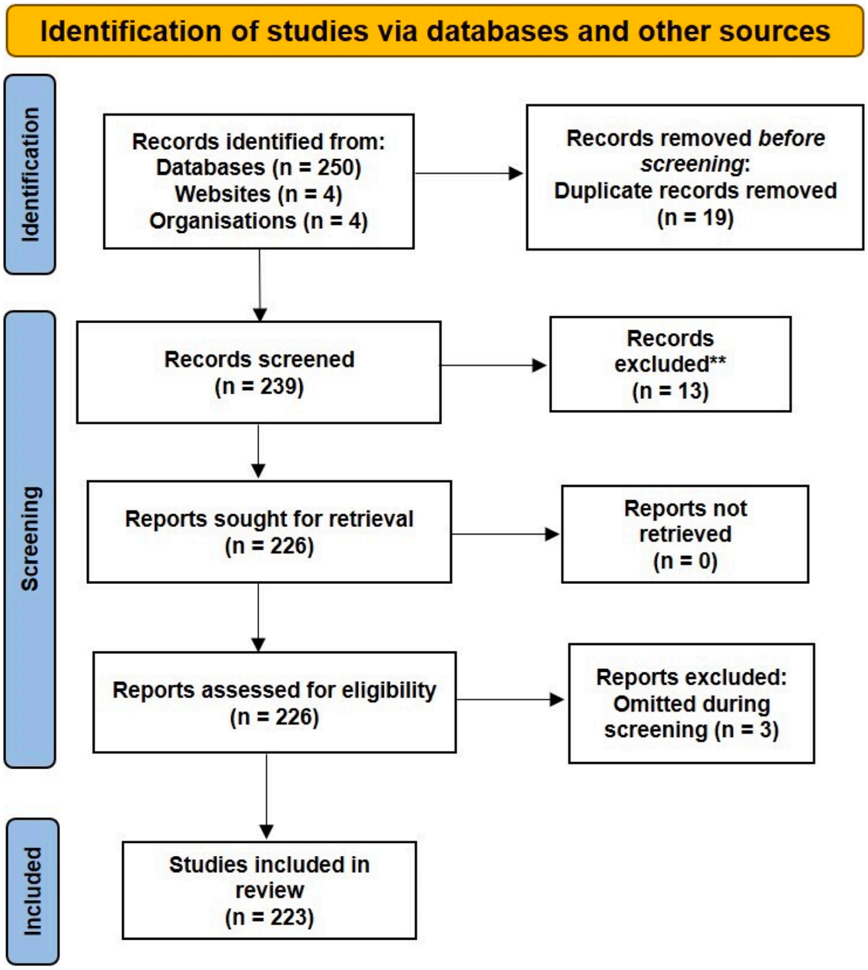

Fig. 1. The PRISMA flow chart showing articles identification, selection, inclusion and exclusion criteria used in this review strategy.

QS systems (QSSs) have formed the basis of current research efforts [6–8].

The first case of an untreatable pan resistant *K. pneumoniae* from a cardiac surgery patient's urine, and colistin resistance in humans and animals (poultry) constituted extreme cases of increasing AMR in bacterial infections in Africa [9]. Such scenarios informed several national and international public health frameworks to recognize that development of new drug design and discovery (DDD) or repurposing drives could be viable options for production of alternative medicines to tackle resistant infections linked to ESKAPE pathogens [10]. So, research into the identification of new antibacterial agents against the ESKAPE strains remain imperative, given that new microbe-sourced antibiotic moieties have not been discovered in over a decade. This scenario has fuelled research interests into DDD approaches to facilitate the derivation of novel antimicrobial agents targeting ESKAPE pathogens and their range of QS-related AMR mechanisms. Targeting QSSs could aid in disrupting bacterial growth, survival, communication, their ability to form biofilms or express other virulence factors, as well as increasing susceptibility to antimicrobial interventions and mitigating further evolution of resistance in microbes [11,12]. Hence the current investigation and elaboration on ESKAPE pathogens sensing systems as novel druggable targets to advance antimicrobials development.

Overall, QS-based therapies target the interference of gene regulation in bacterial populations. Quorum sensing involves bacterial regulation of genes in response to cellular density changes. Communication within biofilms formed by QS bacteria is an interplay of inducer molecules (autoinducers-AIs) synthesis, release, and build up in the external environment following bacterial cell population growth. Thus, QS-based therapeutics could curb bacterial virulence factors, inhibit cell fitness and population survival (QS inhibition and modulation). Also, anti-QS therapies could lead to the reduced potential for AMR transfer [13]. In bacterial QS, signalling pathways and molecules help pathogenic bacteria to acclimatize to stressors such as antibiotics. Gram-positive and Gram-negative autoinducer-2 (AI-2), Gram-negative acyl-homoserine lactone (AHLs) and Gram-positive autoinducing peptide (AIPs) make up the coordinate signalling molecules for varied bacterial groups. These systems play major roles in regulating microbial infection progression, survival and growth. Quorum sensing signalling activation and biofilm formation contribute to AMR development in pathogens, and thus increase the challenges with treating bacterial infections [13]. Anti-QS (AQS) compounds or QS inhibitors (QSIs) could thus mitigate this resistance enabling pathways, making them potential interventions in place of antibiotics [13].

Research has shown that plants are a rich and readily available bioresource of natural bioactive antimicrobial metabolites and QSIs [14]. Also, the modification of natural products like phenols have been shown to produce more potent molecules with enhanced antibacterial activities against human infections [15]. Although, the antibacterial properties of plant extracts have been linked to the synergistic action of the diverse bioactive constituents, the bioprospection of key bioactive compound(s) and associated mechanism of action responsible for reported pharmacological effects are not clearly elaborated and remain elusive [16]. This research/knowledge gap could be bridged using computational strategies such as molecular docking and molecular dynamics (MD) simulation to improve specificity of drug candidate 'hits', while also guiding the derivation of new pharmacologically active antibacterial compounds [17]. For example, the QSS signals like the *lasR* (*P. aeruginosa*) [18], AI-2/*luxS* (*E. faecium*) and Agr (*S. aureus*) [19] participate in virulence factors synthesis, and the presence of their biofilms on pathological tissues and hospital medical devices have been reported [20]. To mitigate adverse health outcomes, the development of certain QS signal blockers could be effective in preventing biofilm formation and increasing pathogen susceptibility to antibacterial agents [21]. The identification of such QSIs could be facilitated through *in silico* natural products bioprospection which also enable further insight into associated mechanisms of action of 'lead' or 'hit' antimicrobial agents [22]. The computational exploration of important bioactive plant metabolites could aid the identification of potent, less toxic drug candidates which may be developed as novel anti-bacterial and anti-QS therapeutics [23].

Furthermore, the *in silico* derivation of binding affinities of metabolites or ligands to QS receptors has been reported to evince a major decrease in *P. aeruginosa* virulence [24], and likewise for azithromycin with broad spectrum QS inhibiting properties [25,26]. Still, the inhibition of key receptor targets has not been fully applicable in bacterial diseases therapy and remains to be seen due to the degradability and poor stability properties. As such, research focusing on the enhancement of AQS molecules stability are needed. Likewise, while the strategy of breakdown of QS signalling pathways has been useful in plant infection prevention [27], its application in human infections less explored. As such, QS inhibition or quenching exploration in the ESKAPE pathogens may be possible to cure associated resistant infections.

Overall, although there have been attempts to collate information on ESKAPE pathogens [28], more focus has been given to either only one pathogen (*P. aeruginosa*) [29], the Gram-positive ESKAPEs [30] or plants with AQS activity [31]. As such, our systematic report aimed at the detailed coverage of novel targets for new antimicrobials (QSIs) development against the highly resistant group of ESKAPE pathogens to mitigate AMR spread and safeguard public health. Also, considering the lack of synergised reports on the contribution of computational studies (fast-tracking process of 'hits' identification to trial and market) to AQS antimicrobials discovery and development, this work stands out by providing a comprehensive and systematic report on all the ESKAPE pathogens, while highlighting the significance of *in silico* studies in the identification of lead molecules for novel antimicrobials development to guide future *in silico* and wet laboratory research targeting new antimicrobials derivation. The article further highlights relevant study gaps, and showcases the array of computational tools at the centre of new AQS antimicrobials bioprospection, discovery and development.

1.1. *Systematic review strategy*

All information and data synthesized into sections in this article were sought out by four independent records' reviewers from a range of online literature, database and library (Google scholar, Wiley online, The Lancet, ScienceDirect, Scopus, PubMed, Cell press resources) sources, standard organization (World Health Organization, WHO) reports, scientific and institutional databases or websites. Search keywords and phrases were carefully chosen and combined to ensure optimal outputs that were relevant to the topic under investigations and study aim. Search words scope covered ESKAPE pathogens, ESKAPE impact on global health indices, AMR spread, quorum sensing systems, mechanisms of QS and biofilm formation, QSSs in ESKAPE pathogens, *in silico* research advancements in QSSs and AMR, anti-biofilm and QS modulating drugs, molecular docking, simulation and pharmacokinetic-based QS inhibition (QSI) studies, QSI antimicrobials, among others. Records depicted in the article spanned 1997 to 2024 to ensure significant coverage of past and current perspectives that could efficiently guide future research interests on the topic. We reviewed 258 articles, and found 220 relevant reports relevant in article drafting (over 100 articles were from 2013 to 2024), and also targeted the provision of first hand, updated and objective synthesis on computational and systems biology-based studies looking into QSSs of ESKAPE pathogens as viable new antimicrobials' targets with identification of potential QS modulating biomolecules. The data were used in generating a PRISMA flow diagram (Fig. 1) showing the records screening, inclusion and exclusion criteria.

2. The ESKAPE pathogens and their quorum sensing systems

2.1. *Enterococcus faecium and Staphylococcus aureus as ESKAPE pathogens*

2.1.1. *Enterococcus faecium*

Enterococcus faecium is a Gram-positive, facultatively anaerobic, non-motile coccus bacteria which is naturally found in the gut of animals and humans [32]. It is also found in the environment, including soil, water, and food sources [33]. In the past 10 years, *E. faecium* evolved to become as prominent nosocomial disease-causing microbes responsible for various surgical, wound and urinary tract infections [34]. More than 50 different *Enterococcus* species are known, though *E. faecium* and *E. faecalis* are the most clinically significant [35]. Cross-infections could also occur in hospitalized patients, with endogenous contraction accounting for the majority of enterococcal infections [36]. Its clinical significance is compounded by its remarkable acquisition of multi-drug/antibiotic resistance [37], with resistant *E. faecium* infections increasing in prevalence [38]. This microbe's intrinsic antibiotic resistance profile covers penicillin, cephalosporins and ampicillins [39]. The notable emergence of vancomycin-resistant enterococci (VRE) is most concerning [40], and has gradually spread from northern America to various regions around the world [41]. The VRE are of 6 types, Van A to E and Van-G, however, Van-A has the widest resistance spectrum to glycopeptide class of antibiotics [42].

Resistance to glycopeptide (vancomycin) antibiotics arises from changes in the biosynthetic pathway for peptidoglycan, particularly amino acids substitution during gene expression where D-Alanine (D-Ala) is substituted for D-Serine (D-Ser) or D-Lactate (D-Lac) [43]. Glycopeptide resistance can take different forms because of these alterations. For example, compared to the typical precursor, the changed forms display decreased binding affinity for the glycopeptide antimicrobial agent, with roughly a 1000-fold and 7-fold drop in binding affinity, respectively [44]. Numerous mobile genetic elements (MGEs) or chromosomal regions in several *Enterococcus* species have been linked to the ability to cause such alterations [37]. Most vancomycin-resistant characteristics and the wide spectrum of resistance linked to Van-related forms appear to be mediated by these later mechanisms [45]. In addition to vancomycin resistance, *E. faecium* employs various virulence factors, including adhesins, invasins, and biofilm formation, to establish infections [46]. One feature of *E. faecium* lies in ability of this bacterium to produce enzymes known as beta-lactamases which have the capability to break down beta-lactam antibiotics commonly used in clinical settings [47]. This enzymatic activity possesses a significant challenge in treating infections caused by *E. faecium*, as it limits the effectiveness of these antibiotics [48].

As with most ESKAPE pathogens, biofilm formation in *E. faecium* is a notable characteristic challenging effective treatment against the microbe [49]. These biofilms serve as protective environments, offering a shield against the host's immune defences and antimicrobial agents [50]. This resilience complicates the therapy process, leading to persistence of *E. faecium* in hospital environments [51]. Moreover, *E. faecium* possesses plasmids that facilitate the horizontal transfer of resistance genes, allowing the spread of AMR traits within bacterial communities. This mechanism has played a significant role in the rapid spread of AMR among Enterococci. For instance, the *Esp* (Enterococcal surface protein) family of proteins facilitates adhesion to host tissues and the formation of biofilms, contributing to the persistence of infections and making treatment more challenging [52]. Furthermore, the acquisition of vancomycin resistance genes often occurs through plasmids, which can also carry genes encoding virulence factors [53]. This

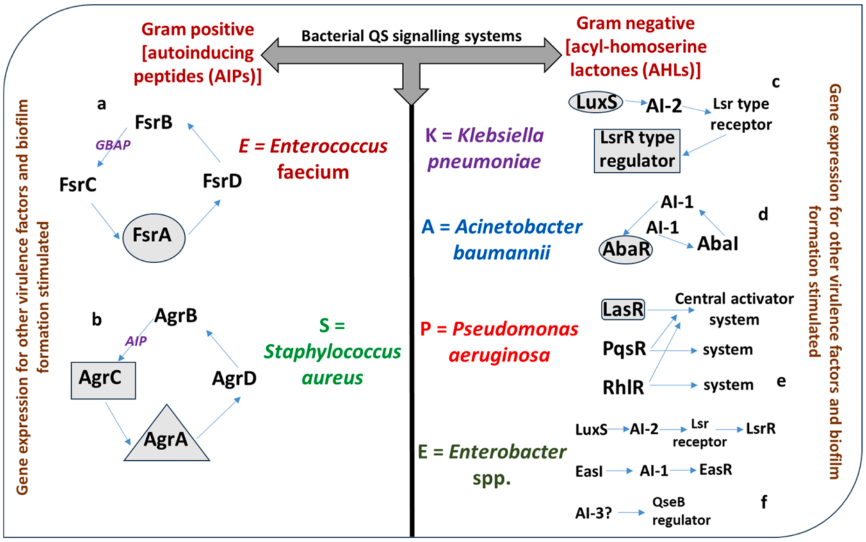

Fig. 2. The key and/or hierarchical quorum sensing systems (QSSs) in ESKAPE pathogens. (a) *Enterococcus* spp.: The FsrB transports and processes gelatinase biosynthesis-activating pheromone (GBAP) toward FsrD propeptide. FsrA (intracellular response regulator) undergoes phosphorylation in the presence of GBAP (extracellular) by FsrC (2-component regulation system. FsrA activates the expression of virulence/pathogenicity genes which contribute to formation of biofilm. (b) *Staphylococcus aureus*: Utilizes a 2-component signal pathway where AIP mediate QS (AgrC and AgrA). (c) *Klebsiella pneumonia*: The LuxS homolog releases AI-2, and other native ligands/molecules (C8 and C12 homoserine lactones (HSLs). This system is also involved in biofilm, capsule, lipopolysaccharide (LPS), fimbria, etc., synthesis genes expression. (d) *Acinetobacter baumanni*: In this bacterium, the LuxR receptor (AbaR) and LuxI synthase (AbaI) systems are mediated by AI-1 to initiate QS. (e) *Pseudomonas aeruginosa*: The recognized QSSs in this Gram-negative bacterium are the Las, Rhl, and PQS (Pseudomonas quinolone signal). (f) *Enterobacter* spp.: Insights on this group's QSSs are still unfolding. For now, Quorum sensing signalling is mediated *via* AI-1, AI-2 & AI-3 cascades to stimulate biofilm and other virulence factor expression.

linkage between AMR and virulence highlights the complexity of combating *E. faecium* infections.

2.1.2. *Staphylococcus aureus*

Staphylococcus aureus, a Gram-positive bacterium, is associated with soft tissue, skin and bloodstream infections, and pneumonia, with methicillin-resistant *S. aureus* (MRSA) emergence drastically limiting treatment options [54]. Its resistance primarily stemmed from the activation of the mecA gene, responsible for producing a penicillin-binding protein 2a that reduces the binding affinity of β-lactam antibiotic agents [55]. This genetic element spreads through horizontal gene transfer [56]. Additionally, auxiliary genes like *fem* factors are key in the expression of methicillin resistance in *S. aureus* [57]. Vancomycin was used as the choice drug to treat MRSA but its recurrent usage created the antibiotic pressure necessary for the formation of VRE and vancomycin-intermediate-resistant (VIR) staphylococci [58].

The MRSA is now considered an endemic pathogen in healthcare settings and poses a considerable threat to public health [59]. According to the World Health Organization (WHO), MRSA is associated with a mean median resistance rate of 24.9 % in bloodstream infections as of 2019 [60]. It was estimated that *S. aureus* ranked second in regard to global AMR burden, with thousands of deaths attributed to the bacterium [61]. In the context of Africa, the WHO reported that up to 80 % of *S. aureus* infections are methicillin-resistant [62]. *S. aureus* deploys an array of virulence factors, including toxins, adhesins, and exoenzymes, which enable it to evade host defences and cause disease [63]. Importantly, these virulence factors also play a role in the development of AMR. For example, biofilm formation by *S. aureus* not only contributes to chronic infections but also protects the bacterium from the host immune response and antibiotics [64]. Moreover, genes encoding virulence factors are often located on MGEs that can be transferred horizontally, thus facilitating the spread of both virulence and resistance determinants [65]. In addition, *S. aureus* can adapt to various environmental stressors, allowing it to persist on surfaces and in medical equipment for extended periods [66].

One example of virulence factors produced by certain strains of *S. aureus* is Panton-Valentine Leukocidin (PVL). The PVL plays a significant role in causing severe skin and soft tissue infections, as well as necrotizing pneumonia [67]. Strains carrying the genes encoding PVL tend to be more challenging to treat. Additionally, PVL has been implicated in the pathogenesis of MRSA infections, contributing to their increased virulence and resistance. Another facet of virulence displayed by the microbe is in the development of a biofilm. *S. aureus* possesses a variety of adhesins and biofilm-associated proteins (Baps) that augment its ability to attach to host tissues and medical devices [68]. This adherence capability contributes to the establishment of chronic infections, posing significant challenges for effective treatment [69]. Biofilm development is also known to interfere with macrophage function, hindering the immune system's ability to clear infections [70].

2.2. *E. faecium* and *S. aureus* quorum sensing systems- Mechanisms, regulation, targets

Quorum sensing is a sophisticated communication system for coordination of microbial gene expression and behaviours [71]. In pathogens like *E. faecium* and *S. aureus*, QS systems regulate virulence factors, resistance and biofilm formation [72]. In order to reduce AMR and promote sensitivity of microbes to host defences with exclusion of evolutionary pressure exertion, it is necessary to understand the complex mechanisms behind these QSSs and ways to disrupt them in ESKAPE bacteria [28]. Strategies that target QSSs represent an attractive solution to combat these clinically significant MDR microbes [73]. Various strategies have been suggested as AQS targets including inhibiting autoinducer synthesis, degrading or inactivating autoinducer molecules, deactivating transcriptional regulators to disrupt signalling cascade (Fig. 2a–f), interfering with ligand-receptor interactions, decreasing extracellular autoinducer levels by inhibiting autoinducer efflux, and employing combined therapy [74,75].

2.2.1. *The fsr quorum sensing system in E. faecium*

Enterococcal pathogens possess virulence genes that code for AMR and aggregation factor determinants. *E. faecium* primarily makes use of the *fsr* QS pathway (Fig. 2a). The *fsr* (gelatinase biosynthesis-activating pheromone) system is a crucial regulatory mechanism in *E. faecium* [76], and involves a set of genes responsible for orchestrating the production of gelatinase biosynthesis-activating pheromone (GBAP). Notably, the FsrD enzyme is instrumental in processing a precursor peptide, pro-GBAP, into its active form. The GBAP serves as the autoinducer molecule that is pivotal role in intercellular communication within *E. faecium* populations. Given its role as an autoinducer in the fsr QS system, the degradation or inactivation of GBAP represents one possible target for AQS purposes [77].

When GBAP reaches a critical concentration, it engages with a membrane-bound histidine kinase receptor called FsrC. This interaction initiates a conformational change in FsrC, as well as a complex signalling cascade which further influences various cellular processes [78]. Activated FsrC undergoes autophosphorylation and subsequently transfers the phosphate group to the cytoplasmic response regulator FsrA [79]. Phosphorylated FsrA assumes the role of a transcription factor, influencing the expression of genes, the fsr locus, gelE (gelatinase) and sprE (serine protease), ultimately leading to the formation of biofilms and increased virulence [80]. FsrA in itself is another target for potentiating AQS activity in *E. faecium* because it allows expression of biofilm-related genes and pathogenicity [81].

2.2.2. Staphylococcus aureus Agr quorum sensing system

The Agr system in many Gram-positive bacteria such as *S. aureus* has a bilateral QS mechanism regulated from the agr locus [82]. This system induces *S. aureus* associated infections by influencing toxins, adhesins production, as well as compounds that disrupt host immunological responses [83,84]. This agr QS system (Fig. 2b) includes RNA transcripts, and within the RNAII operon are agr A-D genes which are necessary for QS and virulence factor regulation [85]. The signalling process is initiated by the creation of a peptide encoded by agrD, that is then changed/modified by AgrB [86]. This modified peptide functions as the autoinducing peptide (AIP) (Fig. 2b) [87]. Activation of the dual system initiates the RNAII operon that modulates RNAIII transcription [88].

When a bacterial population reaches a critical density, AI-2 accumulates extracellularly and then binds to and activates its cognate receptor AgrC (a histidine kinase located in the bacterial membrane) *via* autophosphorylation [86]. Given that AIP is required to reach a particular concentration for the agr QS system to initiate activity, prevention of AI-2 synthesis by inhibition of agrD and/or degradation of AIP itself may be utilized as targets to accomplish AQS in the microbe [89]. The activated AgrC transfers the phosphate group to its cognate response regulator, AgrA [90]. Phosphorylated AgrA acts as a transcription factor that can bind to specific promoter regions of target genes, modulating their expression [91]. This phosphorylation event initiates a cascade of gene regulation. Therefore, inactivation of AgrA would prevent virulent genes expression which in turn warrants its usage as a target for AQS purposes [92]. The *S. aureus* agr system is a critical QSS regulating the expression of virulence factors. It allows *S. aureus* to transition between colonization and invasive infection states, making it a key player in the bacterium's pathogenicity. Understanding this system's intricacies and exploring therapeutic strategies targeting it are essential steps in combating *S. aureus* infections.

2.3. Klebsiella pneumoniae and Acinetobacter baumannii quorum sensing systems

The World Health Organization has recognized the ESKAPE pathogens as the most notorious group of bacteria due to the increased prevalence of AMR related infections associated with them and their ability to cause nosocomial infections and limit treatment options [76,93]. The list of WHO pathogens needing new antibiotic interventions is divided into three categories namely critical, high, and medium priority, in order of urgency. *A. baumannii* (carbapenem-resistant) and *K. pnuemoniae* [extended spectrum β-lactamase (ESBL)/carbapenem resistant] alongside other ESKAPE pathogens are assigned to the critical priority group, thus highlighting the scale of their detrimental impacts [93]. These pathogens commonly cause life-threatening diseases in immunocompromised individuals, especially in intensive care units (ICUs) where high mortality rates between 40 and 80 % have been observed [94,95]. Both pathogens evolve using a plethora of drug resistance strategies such as drug inactivation, alteration of target site, reduced permeability, increased efflux pumping and biofilm formation [76].

2.3.1. Klebsiella pneumoniae pathogen

As an opportunistic Gram-negative pathogen of clinical relevance belonging to the Enterobacteriaceae family, this pathogen has gained much relevance due to its ability to evolve resistance mechanisms against multiple drugs. It is also a common culprit in nosocomial infections associated with high rates of death and illness. As part of the healthy human and animal microbiota and opportunistic pathogen, it is responsible for more than 30 % of all Gram-negative infections such as pneumonia, diarrhoea, septicaemia, wound infection, urinary tract infections (UTIs), meningitis, and respiratory diseases, particularly in immunocompromised individuals and those implanted with catheters [3]. Over the years, *K. pneumoniae* has gradually developed resistance to aminoglycosides, penicillins, β-lactams and fluoroquinolones, with multidrug resistant *K. pneumoniae* emerging as a major global public health concern. This pathogen mainly uses carbapenemase, β-lactamase [96] and biofilm formation [97] as its resistance and virulence factors.

Certain virulence factors must be expressed for successful establishment of infection and survival within the host environment. The severity of *K. pneumoniae* in causing infections and evading host defences is associated with iron uptake systems and presence of adhesins, lipopolysaccharides (LPSs), biofilms and capsule polysaccharides [98]. The capsule protects the microorganism from phagocytosis and directly disrupts the vulnerable host response system. Bacterial capsules are constantly found to be involved in severe human infections [99]. Again, enterobactin, yersiniabactin, salmochelin and aerobactin are some of the siderophores (iron chelating composites that remove iron from host iron-chelating protein) that have been expressed by *K. pneumoniae* [100]. Adhesions enable attachment to other cells or surfaces on the host where they will reside or cause infection and are crucial in pathogenesis of bacteria. *K. pneumoniae* produces three types of fimbriae or pili [type 1, 3 and *K. pneumoniae* carbapenemase (KPC)] which are important proteins that help attach the cells to surfaces or aid in targeting specific places within the host. These factors are responsible for colonization and pathogenicity [101]. One of the most noteworthy virulence factors used by *K. pneumoniae* is biofilm formation, which provides a protective barrier that limits the contact of the cells with antibodies, thus reducing antibiotics effectiveness. Biofilms have been described as a hub for increased infection virulence and significant aggravation of resistance to antimicrobials [102].

2.3.1.1. Quorum sensing systems in Klebsiella pneumoniae. *Klebsiella pnuemoniae* predominantly uses the type 2 interspecies communication system (Fig. 2c) that responds to AI-2, unlike other Gram-negative bacteria which use intraspecies communication (type 1 QS) that involves the *LuxI*/*LuxR* system and response to autoinducer 1 (AI-1) [103]. The type 2 QSS usually allows *K. pneumoniae* to respond to AI-2 that is synthesized and released by other bacterial species. One study confirmed that the presences of *luxS* gene is crucial in the production of AI-2. The *LuxS* synthase produces AI-2 through a series of reactions by converting S-ribosylhomocysteine (SRH) to 4,5-dihydroxy2-2,3-pentanedione (DPD), which subsequently undergoes cyclization to form a furanosyl borate diester (AI-2 molecule) [104]. In other bacteria like *E. coli,* the movement of AI-2, in and out of the cells is facilitated by transmembrane protein TqsA and ABC transporter *Lsr*ACDB, respectively [105]. Once the AI-2 threshold concentration is attained, it is detected by associated protein receptors which initiate a series of reactions to bring about the expression of several genes that regulate certain bacterial behaviours such as virulence, generation of biofilm and extracellular polysaccharides, iron acquisition, motility and endotoxin production [103].

K. pneumoniae has also been reported to possess an SdiA (suppressor of cell division inhibitor) orphan receptor which is LuxR homolog and believed to not produce AHLs since it lacks a LuxI synthase [106]. The SdiA has been suggested as a regulator of the expression of various proteins that are crucial for cell division through ftzQAZ operon activation. It has been shown to not only sense exogenous AHLs from different bacteria, but to also control genetic expression even when AHLs are not present [107].

2.3.2. *Acinetobacter baumannii pathogen*

Acinetobacter baumannii is a clinically significant opportunistic pathogen known to cause nosocomial infections like septicaemia, pneumonia, meningitis, wound and UTIs [108]. It is mainly known for its prevalent MDR strains, which limit the effectiveness of many antibiotics and accounts for 2 % of all nosocomial infections. The mortality rate associated with *A. baumannii* infections in ICUs is 45–60 %, sometimes reaching close to 80 % when individuals are infected with extensive drug resistant (XDR) strains [95]. The infections caused by *A. baumannii* have been linked to many risk factors like catheter and feeding tube devices, prolonged stay in hospital, burns, and high exposure to antibiotic therapy [109]. The WHO recognizes the MDR *A. baumannii* strain, especially for its resistance to third generation cephalosporin and carbapenem antibiotics [110]. It has also been reported to exhibit resistance against the last resort antibiotic, tigecycline, which has been used to treat infections caused by XDR *A. baumannii* strains, thus leading to treatment failure [111].

Acinetobacter baumannii virulence is linked to presence of biofilms, outer membrane proteins (Omps), LPSs, capsule, phospholipase, nutrient-acquisition systems and efflux pumps [112,113]. It also exhibits two types of motilities, twitching and surface associated motility which aid in increased virulence [114]. The capsule acts as a defence barrier that protects the cell from host immune defences and antibiotics and is vital for pathogenicity and overall survival [115]. *A. baumannii* codes for phospholipase C and D which exhibit a lipolytic activity and are capable of breaking down human erythrocytes and can chelate iron [116]. Biofilm formation is the most well-established virulence factor in this microorganism. The biofilm acts as a barrier protecting the cells from harsh environmental conditions. It is a hub for MDR and key in microbial colonization [117].

2.3.2.1. Acinetobacter baumannii quorum sensing systems. *Acinetobacter* spp. possess a QS system that is similar to the typical LuxI/LuxR sensing pathway, that is, the AbaI/AbaR QSS which is made up of the three component AbaI (autoinducer synthase), signalling AHL and the AbaR (transcriptional activator), all regulated by the abaR/abaI locus (Fig. 2d) [118]. The generated AHL binds to the cognate receptor, AbaR, forming a complex that will trigger a series of reactions *via* the putative lux-box sequence (CTGTAAATTCTTACAG) [119]. The outcome of these reactions is linked to exopolysaccharide poly-β-1,6-N-acetylglucosamine (PNAG) generation, surface motility and AMR mechanisms, which are important components required in the formation of biofilms and cell to cell aggregation [120]. *A. baumannii* produces AHLs of differing chain lengths, with the most produced being 3-hydroxy-C12-HSL [121]. A third gene *aba*M, has been located in a locus between *aba*R and *aba*I, and assumes the role of regulating an unspecified RsaM family of receptors. However, the product of *aba*M has been shown to limits *A. baumannii* ability to produce AHLs and enhance formation of biofilm and swarming potential [122]. A link between the efflux pump systems such as AdeABC, AdeIJK and AdeFGH and resistance have also been shown. These systems are responsible for the movement of QS moieties, virulence and expulsion of antimicrobial agents by *A. baumannii*. Also, the presence of iron as an essential mineral is needed for energy generation and replication, and limited levels have been shown to complement the production of AHLs, thus resulting in elevated population levels and virulence factor production in microorganisms [108].

2.4. *Potential K. pneumoniae and A. baumannii targets for new drugs discovery*

Quorum sensing provides the most viable broad-spectrum alternative toward addressing the issue of AMR in ESKAPE pathogens as it aids in reducing bacterial virulence and pathogenicity whilst exposing the pathogens to host defences without the possibility of exerting a selective pressure on the pathogens [21]. Several AQS strategies have been suggested such as blocking the synthesis of AIs (synthases) by using QSIs or AQS agents such as sinefungin and butyryl-S-adenosyl methionine (butyryl-SAM) which have similar structures with an acyl-carrier protein (ACP) and SAM (AHL synthase substrates) [123]. The degradation of the AIs using lactonases (SsoPox, Aii810, AHL-1) is one of the strategies that show great potential. These molecules degrade the inducer to reveal only acyl homoserine (AH) following the lactone ring breakdown [28]. Another viable option is the blockage of the transcriptional regulators (cognate receptors) using flavonoids, meta-bromo-thiolactone, *N*-decanoyl-L-homoserine ester, and particularly with virstatin to inhibit anoR which is a gene similar to the AbaI/AbaR pathway, and type of LuxR regulator [124]. The use of plant extracts and natural products with anti-biofilm properties such as terpenoids (linalool) have been shown to hinder production of *A. baumannii* biofilm and alter surface adhesion [125,126]. These strategies bring about different reactions, reduce biofilm formation, QS precursors, suppress flagella mobilization and limit production of virulence factors (swarming motility, extracellular proteases) [28].

2.5. *Enterobacter spp. and P. aeruginosa pathogens*

Both pathogens are designated as priority 1 critical pathogens, that is, MDR, carbapenem-resistant *P. aeruginosa* and cephalosporin resistant *Enterobacter* spp. [127]. In both developed and developing countries, these pathogens have a significant impact on disease burden. These pathogens are often detected in hospital environments and linked to a number of potentially fatal hospital-acquired (HA) infections, particularly in ICUs [128]. These microbes use a variety of strategies which are classified into four categories; bacterial target site changes, reduced antibiotic penetration/accumulation, creation of bacterial biofilms and deactivation or modification of the antimicrobial molecule [129,130].

2.5.1. *P. aeruginosa quorum sensing systems*

The *P. aeruginosa* pathogen has been linked to various illnesses that can be fatal, including septicaemia, endocarditis, pneumonia, cystitis, UTIs, and infections in surgical wounds [131]. Treatment is becoming more challenging due to the MDR status of the organism [132]. Many regulatory genes (>8 % of the 6-Mb genome) give the *P. aeruginosa* genome its plasticity and adaptability, and are crucial for the pathogen's capacity to survive host defences over time without succumbing to antibiotics [133]. To counteract the effects of antipseudomonal antibiotics, *P. aeruginosa* employs several strategies that include formation of biofilms, efflux systems, porins expression, antigenic shift and drift, aminoglycoside-modifying and β-lactamases activation. *P. aeruginosa* also shows resistance to colistin [132].

The QSSs in *Pseudomonas aeruginosa* are the integrated quorum (IQS) and *Pseudomonas* quinolone (PQS) signalling, and *Rhl* and *Las* systems (Fig. 2e), all having different AI molecules. The *Las* system activator/regulator (LasR) triggers LasI synthase to produce 3-oxo-C12-homoserine lactone (3-oxo-C12-HSL). The Rhl pathway comprises the activator RhlR and RhlI synthase which produce C4-HSL. On the other hand, the distinct PQS pathway generates 2-heptyl-3-hydroxy-4-quinolone as the

Table 1
Anti-QS tactics that could decrease bacterial virulence and counteract antibiotic resistance

Strategies	Anti-QS agents	Modes of action	Effect on the pathogens	References
Inhibition of AI synthases	Sinefungin Butyryl-SAM 4,5-dihydroxy-2,3-pentanedione (DPD)	Structural analogs of the substrates for AHL synthases, acyl-carrier protein (ACP) and S-adenosyl methionine (SAM)	Block AHL synthesis to stop bacterial infection and reduce QS-mediated virulence factors	[123]
Targeting of QS Ligands	AHL lactonases (such as SsoPox, lactonase Aii810, Quorum quenching lactonase enzyme AHL-1, a novel lactonase cloned by bpiB01 and bpiB04 and lactonase AiiK)	Production of N-acyl homoserine by hydrolysis of the AHL lactone ring	Reduce the development of rhamnolipids, swarming motility, biofilms, extracellular proteases, pyocyanin, and extracellular proteases to stop the spread of bacteria	[166]
Blockade of QS Transcriptional Regulators	Flavonoids	Blocking AI-binding receptors LasR and RhlR allosterically	Control the transcription of QS-controlled target promoters and prevent the production of virulence factors	[167]
Plant extracts	Eugenol	Minimize the expression of the QS systems	Prevent the growth of biofilms	[168,169]
		Reduction in the expression of the QS synthase genes	impede the development of biofilms and regressed pathogenicity	[170]

AI signalling chemical [28]. Finally, the IQS determined the structure of the 2-(2-hydroxyphenyl)-thiazole-4-carbaldehydemolecule. However, these chemical signalling systems are hierarchically regulated and connected (*LasR* signalling controlling Rhl, Pqs, and Iqs pathways expression), resulting in the activation of AMR and other virulence parameters though biofilm formation, thus necessitating novel approaches to combating *P. aeruginosa* infections [132].

2.5.2. *Enterobacter spp. quorum sensing systems*

The lack of research in this field has led to a lack of knowledge regarding the pathogenicity and virulence traits of *Enterobacter* spp. However, according to Davin-Regli et al. [134], infections with *Enterobacter* spp. could cause meningitis, UTIs, gut and stomach cavity infections. Again, the manifestation of ESBLs (including metallo-β-lactamase-1) and carbapenemases suggest that *Enterobacter* spp. show intrinsic resistance to first-generation cephalosporins, cefoxitin, β-lactams and other antibiotic groups [135]. They have a flagellum, just like other enterobacteria. Flagella also serve the purposes of adhesion, exporting proteins, and forming biofilms in addition to enabling mobility [136]. Various endotoxins are also produced by *Enterobacter* spp. [137]. The development of antimicrobial resistance mostly affects *Enterobacter cloacae* and *E. aerogenes* [138].

The functional signalling ligands for *Enterobacter* species QS signalling may include the autoinducers 1 to 3 (Fig. 2f) [139]. Although little is known about the pathogenesis and QS controlled drug resistance of this particular bacterial group, numerous research initiatives are being designed to provide more insight on the mechanistic intricacies that govern AMR and virulence in *Enterobacter* species [28]. According to certain data, C6-HSLs and C4-HSLs are used as signalling molecules by *Enterobacter* spp. [140]. The molecules are produced through a LuxR homolog that has the established ability to inhibit microbial adhesion with resultant suppression of biofilm growth [141]. In *E. asburiae*, the EasR (transcriptional regulator LuxR homolog) binds to the homologous C4-HSL and C6-HSL molecules, activating the sensing system and inducing its associated phenotypes and biofilm formation [140].

Given that strains of *E. cloacae, E. cancerogenus*, and *E. mori* have been shown to contain cognate Lsr-type receptors, intercellular negotiation between *Enterobacter* spp. also takes place *via* the AI-2-mediated QS system with LsrB and its synthase LuxS [142]. Likewise, the use of norepinephrine, AI-3 and epinephrine is reported to have potential anti-biofilm and AQS effects *via* the enhanced QseC/QseB induction pathway in *E. cloacae* and other Enterobacteriaceae [143]. Hence, AI-2 and AI-3 mediated QS systems may be regarded as the most crucial systems as they manifest biofilm development and virulence phenotypes.

2.6. *Targeting quorum sensing versus conventional antibiotics: a shift in antimicrobial discovery and development strategies*

The escalating global crisis of antibiotic resistance has necessitated a paradigm shift in antimicrobial strategies [144]. Annual deaths from antibiotic resistance are estimated to surpass those associated with cancer by the year 2050 [145]. Members of the ESKAPE group such as *Enterococcus faecium* and *S. aureus* have developed resistance to multiple antibiotics, including vancomycin and methicillin, respectively [146]. However, traditional antibiotics indiscriminately target bacterial growth, often leading to selection pressure and subsequent development of resistance [147]. In contrast, QS inhibition offers a promising alternative by disrupting intercellular communication systems crucial for bacterial virulence and pathogenesis [148], rendering bacteria unable to form cohesive biofilms [149].

Some of the advantages that QS inhibition provides over conventional antibiotics include reduced selection pressure and resistance development. Unlike traditional antibiotics that target essential cellular processes, QS inhibitors disrupt the communication mechanisms between bacteria and virulence, rendering QS-regulated genes non-essential for viability [150]. This significantly reduces the likelihood of mutations conferring resistance, as these genes are not vital for bacterial survival directly [151]. This has been demonstrated in various studies, highlighting the potential of QS inhibitors as a promising avenue in the fight against antimicrobial resistance [152]. A second advantage is the synergistic potential with conventional antibiotics that has been demonstrated in combatting bacterial infections [153]. This is because by inhibiting the communication mechanisms that bacteria use to coordinate virulent activities, the bacteria become more vulnerable to the action of antibiotics [154]. This synergistic potential further allows for the use of lower antibiotic doses, reducing the risk of side effects and AMR re-emergence [155].

A third benefit lies in QSI stalling horizontal gene transfer. The QSI is a potential mechanism to impede the horizontal transfer of resistance genes [156]. This is supported by the fact that QS-regulated factors possess essential functions in the mobilization of plasmids and horizontal gene transfer mechanisms [157]. By targeting QS-regulated processes, it could be possible to hinder the dissemination of resistance determinants [158]. Fourth is the potential for reduced environmental impact compared to traditional antibiotics. Antibiotics in the environment contribute to AMR acquisition, development and transfer by microbial strains [159], and constitute pharmacologically active environmental micropollutants [160]. This phenomenon constitutes a significant menace to both human and environmental health since antibiotic-resistant bacteria may potentially be spread through various pathways (food, fomites) [161]. Due to QSIs targeting virulence rather than bacterial viability, there is a lack of selective pressure required for AMR development, potentially resulting in a lower environmental risk if

Table 2
Computational efforts targeting anti-QS druggable candidates' discovery

Pathogen	Protein targets (PBD ID)	Metabolites (Proposed mechanism)	Data towards new drug discovery	*In silico* method	Reference (s)
Pseudomonas aeruginosa	LasR (2UV0)	Guanosine	*Melianthus comosus* extracts and guanosine as ideal candidates to disrupt biofilm formation	Docking	[174]
	QS receptor (PqsR, MvfR)	Over 1200 repurposed FDA approved drugs - pimozide best antagonist (reduction of PqsR activity and QS inhibition)	Active site amino-acid residue interactions, Low toxicity, good pharmacological attributes	Docking	[172]
	LasR, PqsE	19 natural compounds screened - catechin and nakinadine B best antagonists (QS modulation)	Non cytotoxic, immunotoxic, carcinogenic, mutagenic, hepatotoxic nature of best drug leads.	Docking, MDS	[175]
	LasR (2UV0, 3IX3)	12 bio-actives profiled - limonene with best anti-biofilm attributes	*Anethum graveolens* oil extract and limonene as anti-QS drug candidates. Good pharmacokinetic properties	Docking, ADME	[176]
	-	*Thymus musilii* methanol extract compounds	*Thymus musilii* methanol extract with antibiofilm activity	Docking, ADME	[177]
	PqsR (4JVD)	NSAIDs, ketoprofen best of its derivatives (PqsR inhibition enhanced in combination with antibiotics) 4-farnesyloxy-coumarin and farnesifrol B (Inhibition of biofilm, virulence and Qs genes regulation)	NSAIDs as candidates with good pharmacokinetic, druggable properties. 4-farnesyloxycoumarin and farnesifrol B as potent biofilm and QS inhibitors	Docking Docking, MDS	[178], [179]
	LasR (2UV0), PqsR (4JVI), LasA (3IT7), RhlR	Coumarin (inhibition of pyocyanin, lasB elastase activity, swimming motility)	Form stable complexes, causes inhibition of AHL synthesis and QS regulatory proteins, blocks receptor proteins transcription.	Docking, MDS	[173]
	-	1,3-benzoxazol-2(3H)-one and derivatives (reduction of elastase, biofilm formation & swarming motility)	1,3-benzoxazol-2(3H)-one and derivatives as lead molecules for possible anti-QS drugs development	-	[180]
	LasR (2UV0)	Cranberry fraction proanthocyanidins (antagonism and inhibition of AHL synthetase and QS transcription genes regulation)	Cranberry extract and proanthocyanidins have good anti-QS potential	Docking	[181]
	LasR (2UV0), LasA (3IX7), LasB (3DBK), LasI (1RO5)	*Helianthus annuus* compounds -phylloquinone as best relative to linoleic acid, oleic acid (modulation of LasR system)	Sunflower seed oil and compounds as explorable anti-QS candidates	Docking, MDS, ADME	[6]
	LasI/R, RhlI/R, PQS/MvfR (1RO5, 2UV0, 4JVC)	Selenium nanoparticles (SeNPs) (inhibition of AHL synthetase and QS transcription)	Key interactive residues between selenium nanoparticles (SeNPs) and the QS proteins shown for the 1st time. SeNPs as potent alternative solution to tackle AMR.	Docking	[182]
	LasR, Rh1R, PqsR	Vanillin-based hybrids derived from zingerone, eugenol, Guaiacol, cinnamaldehyde, ferulic acid (attenuation of virulence factors)	Key interactive residues identified	Docking	[183]
	LasR	1, 3, 4-oxadiazole derivatives	2 compounds containing naphthalene and fluorophenyl functional groups showed anti-QS activity	Docking	[184]
	RhlI, RhlR, PqsE	16 top-hit AHL analogues	Cassialactone showed highest binding affinity and anti-QS activity	Docking, MDS, Network analysis	[185]
	LasI/R (1RO5/ 3IX3), RhlI/R (P54291/ P54292)	Naproxen (down-regulation of lasI, rhlI genes expression, bacterial protease, hemolysin, pyocyanin, biofilm, and motility)	Naproxen as inhibitor QS	Docking	[186]
	1JIJ, 2VAM, 6B8A, 6F86, 2CDU, 1OG5	Saudi Sidr honey and compounds [1-cyclohexylimidazolidin-2-one, 3-Butyl-3-methylcyclohexanone, 4-butyl-3-methoxy-2-cyclo penten-1-one, 2,2,3,3-Tetramethyl cyclopropane carboxylic acid, and 3,5-dihydroxy-2-(3-methylbut-2-en-1-yl]	Identification of Saudi Sidr honey and associated compounds as QS regulators	Docking, ADMET	[187]
	LasR, FabI; MvfR, Sialidase	Patchouli essential oil and metabolites (regulate violacein synthesis, virulence and biofilm formation)	Essential oil and metabolite as potent QS inhibitors	Docking	[188]
	LasR (2UV0, 3IX3)	Caraway essential oil and 12 compounds (inhibit QS-related virulence factors)	Oil, compounds (trans-dihydrocarvone, eugenol, and trans-carveol) for QS inhibition	Docking	[189]
	LasR (2UV0), RhlR	Cinnamic acid and 5-hydroxymethylfurfural (reduced expression of QS-related genes)	Compounds with anti-QS action	Docking	[190,191]
	LasR (2UV0), PqsR (4JVI)	Methyl eugenol (ME)- and β-phellandrene (β-PH)-rich tarragon essential oil (downward regulation of protease and QS autoinducer synthesis)	Methyl eugenol (ME)- and β-phellandrene (β-PH)-rich tarragon essential oil as anti-QS agents	Docking	[192]
	-	Boronic, quercetin, plus novel ligands B1(2,2′-(1,4-phenylenebis (benzo [1,3,2] dioxaborole-2,5-diyl)) bis (3,5, 7-trihydroxy-4H- chromen-4-one) and B2(3.3.6. 3,5,7-tri-hydroxy-2-(2-(6-methoxypyridin-3-yl) benzo [d][1,3,2] dioxaborol-5-yl)– 4 H-chromene-4)	These compounds as potential anti-QS and biofilm agents	Docking	[193]
	LasR	Metformin and sitaglitin (reduced expression of QS genes - lasI, lasR, rhlI, rhlR, pqsA, pqsR)	Metformin and sitagliptin identification as a novel potent QS inhibitor	Docking	[194,195]

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Table 2 (*continued*)

Pathogen	Protein targets (PBD ID)	Metabolites (Proposed mechanism)	Data towards new drug discovery	*In silico* method	Reference (s)
	LasR (2UV0), RhlR (UniProtKB-P54292)	Sesamin and sesamolin (biofilm and QS genes down regulation)	Compounds with antibiofilm and QS activity identified	Docking, MDS, ADME	[196]
	QscR (3SZT, 6Y4F)	Atenolol (β-adrenoreceptor blocker)	Compound with anti-QS activity against a range of Gram-negative microbes	Docking, ADME	[197]
	LasR (6MVN), QscR (6CC0), LasI (1RO5)	Linagliptin (downregulation QS associated genes)	Identified an hypoglaemic agent with promising anti-virulence and QS activities	Docking	[198]
	LasR (2UV0), RhlR (UniProtKB-(P54292.1)	*Diaporthe phaseolorum* SSP12 extract	Extract with antibiofilm and anti-QS attributes	Docking	[199]
	CviR, LasI, LasR	*Centella asiatica* extracts	Extract with antibiofilm and anti-QS attributes identified	Docking	[200]
	LasR	*Stevia* extract, stevioside, rebaudioside A, steviol (non-competitive inhibition of LasR-mediated QS)	Extract and related compounds with antibiofilm and anti-QS activities	Docking	[201]
	LasR	Selenium nanoparticles (SeNPs imbued with honey polyphenols)	Nanoparticle delivery systems enhance anti-QS, anti-biofilm and anti-virulence effects	Docking	[202]
	LasR, CviR, rhlR (PilY1, PilT)	*Artemisia annua* leaf extract and 1,8- cineole	Extract and metabolite with anti-QS activity	Docking, MDS	[203]
	Response regulator protein (PmrA) (Q9HV32), 3SZT)	Doxazosin (interference with QS protein)	Potential anti-QS candidate against Gram-negative microbes	Docking, ADME	[204]
P. aeruginosa, S. aureus	Pqs (1ROS)	Novel series of 5(4H)-oxazolone-based-sulfonamides (OBS)	Novel metabolites with anti-biofilm activity.	Docking	[205]
K. pneumoniae	-	Selenocystine [degrading eDNA component of the Extracellular Polymeric Substance (EPX) matrix]	Selenocystine with good anti-biofilm/ QS action	Docking	[206]
A. baumanni	CsuE, OmpA (6FJY, 3TD3)	Cinnamic and gallic acids (downward regulation of biofilm-associated genes – bap, csuE, ompA)	Interacting residues identified at active site. In combination with antibiotics significantly reduced AMR	Docking	[207]
	Potassium channel protein	ZINC12496555	Anti-biofilm activity, non-cytotoxic, good binding affinity, stability of complex formed.	Docking, MDS	[208]
	BfmR (6BR7)	Rutin, catechin, quercetin, syringic acid, vanillic and caffeic acid	Polyphenols with antibiofilm activity identified	Docking	[209]
	-	Linalool from *Coriandrum sativum*	Compound with antibiofilm potential	-	[125]
	-	Engineered quorum quenching lactonase	Engineered lactonase antibiofilm and anti-virulence activity	-	[210]
	-	Caffeic acid, cinnamic acid, myricetin (reduced expression of virulence genes-abaI, abaR, csuE, pgaA, and bap)	Compounds identified as QS inhibitors	-	[211]
S. aureus	SarA	2-[(Methylamino) methyl] phenol (downward regulation of virulence QS genes - fnbA, hla and hld; biofilm inhibition)	Compound action enhanced in combination with antibiotics	-	[212]
	SarA, CrtM (2FNP, 2ZCO)	Hesperidin (inhibition of biofilm or QS genes)	Key residues at the ligand binding domain identified. Hesperidin as potential antibiofilm and anti-virulence agent	Docking	[213]
	AgrC and AgrA	3-[(4-Methylphenyl) sulfonyl] [1,2,3] triazolo[1,5-a] quinazolin-5(4H)-one (inhibition of AgrA system & QS associated enzymes)	Potential anti-QS compounds requiring further *in vivo* and *in vitro* validations	Docking, ADMET	[214]
	AgrA (3BS1)	Pyocyanin [QS-dependent virulence factors (hemolysin, protease, and motility), agrA gene expression decrease]	Pyocyanin as a potent QSI	Docking	[215]
	SarA (2FNP)	Morin	Morin as a potential anti-QS drug candidate	Docking, MDS	[216]
	Agr	Staquorsin	Staquorsin as a novel *in vivo* QSI and drug candidate		[217]
	AgrA (4G4K)	Azan-7 and clindamycin	Azan-7 combined with clindamycin show enhanced anti-biofilm activity	Docking	[218]
S. aureus and *Enterococcus faecalis*	AgrA (3BS1), Fsr	Synerazol, phenalinolactones A-D, BU-4664LMe, 4,5-dehydrogeldamycin, questinomycin A, decatromicin A and B, okilactomycin, rishirilide A, abyssomicin I, rebeccamycin	Compounds identified as potential anti-QS candidates	Docking	[219]
S. aureus and *E. faecalis*	SrtA (1T2W)	Acetylsalicylic acid, trifluoperazine	Interacting amino acid residues and bonds at active site identified. Compounds as potential QSIs	Docking	[171]
S. aureus and *Enterococcus faecium*	Agr	*Zanthoxylum chalybeum, Harungana madagascariensis, Solanum aculeastrum, Sesamum calycinum angustifolium*	Plant extracts as QSIs	-	[220]
Chromobacterium violaceum (a QS inhibition indicator)	CviR (3QP6) CviR (3QP1)-	123 metabolites [Coniochaetone A, B, K, Viriditoxin SC-30532, Citrinin H1, (3S)-3,8-Dihydroxy-6,7-dimethyl-alpha-tetralone)] 50 compounds tested (7-methoxycoumarin, flavone, batatasin III, resveratrol,	*Cladosporium* spp. anti-QS compounds interact with key bond amino acid residues Batatasin III best; top 5 showed QS inhibitory effect 14 lead druggable	Docking, MDS Docking ADMET	[7],[221], [222]

(*continued on next page*)

Table 2 (*continued*)

Pathogen	Protein targets (PBD ID)	Metabolites (Proposed mechanism)	Data towards new drug discovery	*In silico* method	Reference (s)
		psoralen, isopsoralen) 15 *Allium subhirsutum* extract compounds (inhibit violacein production)	compounds identified with antibiofilm and anti-QS action		
C. violaceum	-	Patchouli essential oil and metabolites (regulates violacein synthesis, virulence, biofilm formation)	Essential oil and metabolite as potent QS inhibitors	Docking	[188]
	CviR (3QP1)	Caraway essential oil and 12 compounds (inhibits QS-related virulence factors)	Oil, compounds (trans-dihydrocarvone, eugenol, and trans-carveol) for QS inhibition	Docking	[189]

- =Not available; PDB ID = protein databank identification code; QS = quorum sensing; NSAIDs = non-steroidal anti-inflammatory drugs; AHL = N-acyl homoserine lactone; ADMET = absorption, distribution, metabolism, excretion, toxicity; MDS = molecular dynamics simulations; QSI = quorum sensing inhibitor/inhibition.

they are introduced to natural settings [162]. This eco-friendly impact is crucial in combating the growing concern of environmental dissemination of antibiotic resistance [163].

With no evolutionary pressure, QS-based therapeutic approaches (Table 1) could be a promising comprehensive approach for decreasing current AMR trends, suppressing bacterial pathogenicity, and boosting sensitivity to host immune responses. In the hunt for QS inhibitors, several molecules like propranolol and levamisole which were chemosynthesized, and also organic plant fractions derived from *Syzygium aromaticum, Citrus reticulata, Pisum sativum* and others have demonstrated anti-biofilm/QS properties [164]. Unfortunately, the use of some synthetic US Food and Drug Administration (FDA)-approved QSI antibiotics (azithromycin) has now been prohibited given the increased pathogenicity observed for some *P. aeruginosa* strains following antibiotic treatment [165]. Several methods (Table 1) have been put out as potential anti-QS strategies to date, including inhibiting AI synthases, obstructing complexation parameters between receptors and ligands, destroying AIs, disrupting transcriptional regulator function, and combining standard medications and/or medications with extracts [21].

2.7. *In silico anti-QS targeting for novel antimicrobials discovery and development*

Studies incorporating *in silico* bioprospection of existing (re-purposing drives) or new synthetic and natural products or drugs to derive useful data and information on potential 'drugs' at the molecular level and fast track antimicrobials development against ESKAPE pathogens have increased steadily over the past decade [171,172]. Of the QSSs, the *P. aeruginosa* lasR system and its associated proteins are the most commonly targeted since they have been well elucidated [173]. Likewise, this may be linked to the central role played by LasR in the QSS cascade, as well as the microbe having the highest mortality rate of all the ESKAPE pathogens [3]. Still, studies targeting *K. pneumoniae, S. aureus* and other ESKAPE pathogens QS systems fall short, and the impact of other pathogens are also undermined, either alone or under co-infection conditions. Nonetheless, research efforts in the areas of QSSs protein targets elucidation, variation of study pathogen-QS targets and discovery of potentially novel druggable metabolites and natural products are still required to facilitate efforts. A cross-section of studies incorporating computational screening of compounds against QS targets are depicted in Table 2. The table further shows the contribution of *in silico* studies to lead metabolites identification, elucidation of their mechanisms of action, drug discovery and re-purposing, and research gap highlights. Some identified study gaps requiring scientific focus include the nanoparticulated delivery systems interaction with QS targets, enhanced drug repurposing drives, identification of extracts and essential oils (and their key bioactive metabolites) with AQS activities, combination therapy exploitation, and lead compounds derivatization and engineering of QS inhibiting molecules, among others.

Interestingly, between 2014 and 2021, 18 new antibiotics (nitroimidazoles, triazoles, aminoglycosides, glycopeptides, siderophore β-lactams and β-lactamase inhibitors, tetracyclines, fluoroquinolones, oxazolidinones, and those with new action mechanisms) were approved. Approval across agencies include the US Food and Drug Administration (FDA) (16), Central Drugs Standard Control Organization of the Government of India (1), Pharmaceuticals and Medical Devices Agency, Japan (1), Chinese National Medical Products Administration (1, contezolid), and European Medicines Agency (1). Of these antibiotics, action against carbapenem-resistant Enterobacteriaceae (plazomicin, eravacycline, cefiderocol, cefazidime, omadacycline, meropenem), *P. aeruginosa* (cefiderocol) and *A. baumanni* (cefiderocol), as well as MRSA (omadacycline, contezolid) were recorded [223,224].

Likewise, 217 antibacterial agents (33 peptides, 90 direct-acting small molecules, 92 unconventional chemicals, and 2 agents placed in the 'other' group) were identified from *in silico* and artificial intelligence (AI)-based tools for development into new antimicrobials, and are in the preclinical trial stages. Of these new agents, SPR206, QPX 9003, MRX-8, and murepavadin target carbapenem-resistant *K. pneumoniae, P. aeruginosa*, and *A. baumannii* pathogens. The development of these new agents is associated with AI-centred *in silico* workflows [structure-activity (SAR), -toxicity (STR) and -pharmacokinetic relationship (SPR) based designs, and molecular dynamics (MD) simulation] which accelerate and enhance prediction of resistance mechanisms, antimicrobial molecules design and dynamic modelling of their interactions [223–225]. Hence, without a doubt the continued advancements in computational and systems biology-based approaches, as well as *in silico* analytical open-source platforms, databases, and front and back-end programming algorithms in the past decade, have given human's a fighting chance against AMR.

3. Future perspectives and concluding remarks

The rate of antibiotics discovery has waned and falls short of current emerging global demands, especially in the face of growing AMR/MDR trends and pathogens evolution which circumvent conventional therapeutic approaches. This work highlighted the need to steer research towards targeting the non-pressured evolutionary approach that could nip the AMR in the bud. This approach is based on QS treatment targets that could interfere with core gene regulation and expression pathways in bacterial biofilm populations. The QS signalling cascade and biofilm formation contribute to AMR development in pathogens and make infections treatment more difficult. The QS approach targets the inhibition or quenching of the effect of autoinducer molecules, enzyme and other QS related metabolites that are central to QS bacterial communication in biofilms. Thus, QS-based therapeutics may curb bacterial virulence factors by inhibiting fitness and ability of entire bacterial populations to survive. Anti-QS therapies could further indirectly lead to a reduced ability of the pathogen to transmit itself within and across populations, and hence, reduce adverse health outcomes. Anti-QS compounds or QS signal blockers could mitigate MDR enabling pathways, enhance bactericidal effect of available conventional antibiotics, prevent pathogen biofilm formation and increase pathogen susceptibility to antimicrobials, making them potential interventions in place of antibiotics. In the bioprospection drive for the design and discovery of novel, safer and natural plant-based products as QSIs or quenchers (either singly or in combination with known antibiotics), the wide assortment of underutilized species could be explored alongside *in silico* tools for new antimicrobials development and mitigation of current global MDR trends.

CRediT authorship contribution statement

Christiana E. Aruwa: Supervision, Writing – original draft, Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition. **Theolyn Chellan:** Writing – original draft, Resources, Investigation. **Nosipho W. S'thebe:** Writing – original draft, Resources, Investigation. **Yamkela Dweba:** Writing – original draft, Resources, Investigation. **Saheed Sabiu:** Conceptualization, Funding acquisition, Supervision, 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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Supplementary materials

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