Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Quorum sensing: its roles in mediating biofilm and viable but non-culturable state formation, and strategies for the prevention and control of foodborne bacteria *via* quorum quenching

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ARTICLE INFO

Article history:
Received 27 March 2024
Received in revised form 19 April 2024
Accepted 8 July 2024

Keywords:
Foodborne bacteria
Quorum sensing
Biofilm formation
Viable but non-culturable state formation
Food quality

ABSTRACT

Foodborne bacteria produce biofilms and their viable but non-culturable (VBNC) formation, can affect food quality and safety. Studies have shown that these characteristics are regulated by the bacterial quorum sensing (QS) system. Quenching the QS system of foodborne bacteria and blocking the expression of the corresponding genes may be an effective way to improve food quality and safety. Therefore, this article reviews the QS systems for foodborne bacteria, the regulatory mechanisms of QS systems in biofilm and VBNC formation and resuscitation, the research progress on quorum sensing inhibitors (QSIs) for Gram-negative and Gram-positive bacteria, and introduces QSIs from various sources. In addition, we have also summarized the current research issues on QS regulation of biofilms and VBNC formation. The systematic study of the QS phenomenon of foodborne bacteria in practical situations, the mechanism of bacterial QS cooperation-cheating, the screening of novel and highly active QSIs, the combination of QSIs and other technologies to improve their bioavailability, and the regulatory network between biofilm and VBNC formation and resuscitation are research directions that need to be paid attention to in the future.

1. Introduction

As societal progression and the augmentation of individuals' living standards continue apace, the significance of food quality and safety has garnered increasing recognition and emphasis among the populace. Animal or plant-based foods are prone to microbial contamination due to improper storage[1-2]. Contaminated food not only reduces eating quality and nutritional value but may also cause foodborne illness and threatens human health[3]. At present, more and more studies have shown that the biofilm formation and viable but non-culturable (VBNC) state of foodborne bacteria are important factors affecting food quality and safety[4-8]. Biofilm can help bacteria avoid adverse factors and develop drug resistance[9-10]. Most of bacterium can form biofilms under specific conditions, and compared to planktonic microorganisms, biofilms have stronger resistance to environmental pressure and are more difficult to remove[11]. Studies have shown that the sensitivity of biofilms to various chemical antibacterial agents is only 1/10−1/1 000 of that of the same type of planktonic bacteria[12]. Therefore, biofilms pose serious hazards to food industries such as brewing, seafood processing, dairy processing, poultry slaughterhouses, and meat processing.

When bacteria are exposed to adverse environmental conditions such as hypoxia, nutrient deficiency, low temperatures, or antibacterial

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Peer review under responsibility of Beijing Academy of Food Sciences.

SciOpen Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2024.9250337

agents, they become smaller or enter a VBNC state, which is an adaptive mechanism for bacteria to cope with harsh environments[13-15]. Planktonic cells, VBNC cells, and biofilm cells of foodborne bacteria can coexist in food or food processing[16]. Most biofilm cells exist in a VBNC state. Moreover, biofilm cells can enter the VBNC state faster than planktonic cells. In addition, VBNC cells have stronger resistance to antibiotics[17-18]. In the VBNC state, bacteria cannot grow into visible colonies and therefore cannot be detected by conventional methods[19]. If the testing method is improper, it can result in false positive or false negative results[20]. VBNC is in a reversible state, and under suitable conditions, VBNC bacteria can return to their normal state, such as by heating, adding nutrients, which can cause some VBNC bacteria to resuscitate[21]. It is worth noting that some pathogenic bacteria with VBNC status can still express virulence genes[22-23]. Jiang et al.[24] developed a propidium monoazide-crossing priming amplification (PMA-CPA) method to rapidly detect the VBNC cells of methicillin-resistant *Staphylococcus aureus*. Results showed PMA-CPA assays could detect different toxins in MRSA in the VBNC state. Truchado et al.[25] found that treatment of process water (PW) with chlorine dioxide (3 mg/L) or chlorine (5 mg/L) for 1 min could induce *Listeria monocytogenes* and *Escherichia coli* O157:H7 to enter the VBNC state. VBNC cells present in PW could cross-contaminate leafy greens during washing, but their ability to resuscitate in the leafy greens during storage was low.

One of the most significant discoveries in microbiology over the past 40 years has been the phenomenon of cell-to-cell communication in microorganisms. The mechanism of communication and exchange between bacteria is called quorum sensing (QS)[26-27]. When microorganisms grow to a certain density, the signaling molecule (also called autoinducer, AI) secreted to the outside of the cell accumulates to a certain threshold in the local environment, binds to the specific receptors in the cells, and activates specific gene transcription, causing the collective response of microbial cells and then regulating the group behavior of bacteria[28]. At present, QS systems that can sense cell density have been found in various microorganisms (mainly bacteria). Several studies have found that the QS system of foodborne bacteria regulates food quality- and safety-related characteristics, such as biofilm, VBNC state, etc.[9-29]. Different kinds of signaling molecules have also been found in different foods[30]. Blocking cell-to-cell communication of foodborne bacteria through specific pathways and cutting off the regulation of the QS system on its related gene expression may be an effective way to slow down the speed of food spoilage and improve food safety. Therefore, the research on quorum sensing inhibitors (QSIs) is of great significance, and preliminary results have been achieved. This paper reviews the research progress of the QS system of foodborne bacteria, the regulation mechanisms of the QS system on biofilm and VBNC states and the research progress of QSIs. It provides a reference for improving food quality and safety by targeting the QS systems.

2. QS system of foodborne bacteria

Microorganisms have always been considered to exist in the environment as single-celled individuals. However, with the continuous deepening of research, it has been discovered that microorganisms actually possess complex and refined "language" for communication and information transmission with their "neighbors"[30]. At the end of the 1960s, researchers found that the genetic competence of *Streptococcus pneumoniae* and the luminescent behavior of the marine luminous bacterium *Vibrio fischeri* were closely related to the secretion of some extracellular molecules and caused widespread concern[31]. Nealson et al.[32] reported for the first time in 1970 that the bioluminescence of *V. fischeri* was regulated by its QS system, thus starting the research on bacterial QS systems. The recognition and identification of *luxI/R*, the gene regulating the bioluminescence of *V. fischeri*, and the extracellular molecule *N*-3-oxohexanoyl-*L*-homoserine lactone ($3OC_6$-HSL) laid the foundation for the theory of intercellular communication[32]. In the 1990s, with the gradual maturity of gene sequencing and sequence comparison analysis technology, a variety of bacteria, including Gram-negative and Gram-positive bacteria, were widely studied. Finally, Fuqua et al.[33] first expounded on the possible intercellular communication mechanism in microorganisms in 1994 and proposed the concept of QS. Specifically, when microorganisms grow to a certain density, the exocrine signaling molecules (also known as AIs) accumulate to a certain threshold in the local environment, bind to specific receptors in cells, activate specific gene transcription, and then regulate group behavior[34-37]. The QS systems of some foodborne bacteria are shown in Table 1. Therefore, in-depth exploration of the QS system of bacteria can better understand the signaling mechanisms of microorganisms, which has great research value in fields such as food, medicine, and microbial fermentation.

2.1 Types of bacterial QS system

Gram-negative and Gram-positive bacteria alike employ QS as a communication mechanism. The QS system in bacteria is facilitated by a diverse array of signaling molecules[38-39]. At present, the primary QS systems encompass the AI-1 type, which is mediated by AHLs in gram-negative bacteria[40-41]; the QS system mediated by AIPs in Gram-positive bacteria[42]; and the AI-2 type QS system, responsible for interspecies and intraspecies information exchange, mediated by furanosyl borate diester[43-44]. In addition, AI-3 serves as a QS signal for the virulence genes of enterohemorrhagic *E. coli* (EHEC) and exhibits cross-talk with the mammalian epinephrine host cell signaling systems. Additional types of signaling molecules exist, including the diffusible signaling factor (DSF)[45], *Pseudomonas* quinolone signal (PQS), and hydroxyl-palmitic acid methyl ester (PAME)[46-47].

2.1.1 AI-1-type QS system of Gram-negative bacteria

N-Acyl homoserine lactones (AHLs) are signaling molecules in the QS system of many Gram-negative bacteria. They are composed of an *N*-acyl homoserine lactone ring as the core and an acyl side chain with a chain length of 4−18 carbons (Fig. 1A). There are many unsaturated bonds in the C-3 position of the acyl side chain. The AI-1 type QS system mediated by AHLs, also known as the LuxI/R type QS system, is the earliest discovered and most extensively studied type of QS system[48]. At present, this system has been found in nearly 100 kinds of Gram-negative bacteria. Research has found that this system is mainly composed of *luxI/R* regulatory genes. *luxI* is the expression gene of signaling molecule synthase, and *luxR* is a transcription activating factor expression gene. In the AI-1 type QS system, the synthesis path of signaling molecules is: under the catalysis of LuxI protein, LuxM protein, AinS, and other proteases, AHLs are synthesized by acylated

Table 1
QS systems in several foodborne bacteria.

Bacteria	Signaling molecule	QS system	Phenotype	References
V. fischeri	AI-2 3-oxo-C_6-HSL C_8-HSL	*luxS-luxP/Q* *luxI/luxR* *ainS/ainR*	Bioluminescence Motility	[63]
Agrobacterium tumefaciens	3-oxo-C_8-HSL	*traI/traR*	Plasmid binding	[64]
Aeromonas hydrophila	C_4-HSL	*ahyI/ahyR*	Protease secretion	[65]
Serratia liquefaciens	C_4-HSL	*swrI/swrR*	Protease secretion migration	[66]
Bacillus subtilis	ComX pheromone, competence, and sporulation factor (CSF)	Com-system	Sporulation Biofilm	[67]
S. aureus	AgrC-AgrA	Agr-system	Toxin formation	[68]
Enterococcus faecalis	FsrA-FsrB	Fsr-system	Virulence factor	[69]
Vibrio cholerae	AI-2	Two-component regulatory system	Virulence factor	[70]
Campylobacter jejuni	AI-2	Two-component regulatory	Motility	[71]
Hafnia alvei	AHL/OHHL	*halI/halR*	Biofilm Extracellular enzymes	[72]
Pseudomonas fluorescens	AHL/OHHL	*pcoI/pcoR*	Biofilm Extracellular enzymes Motility	[73]
Leuconostoc spp.	AI-2	AI-2/LuxS	Biofilm formation	[74]
Yersinia pseudotuberculosis	C_6-HSL 3-oxo-C_6-HSL C_8-HSL	*ypsI/ypsR* *ytbI/ytbR*	Motility Biofilm	[75]
Rhizobium leguminosarum bv. viciae	3OH-$C_{14:1}$-HSL 3OH-C_8-HSL C_6-HSL, C_7-HSL C_8-HSL	*cinI/cinR* *raiI/raiR* *traI/traR* *expR*	Lipopolysaccharide Plasmid transduction	[76]
Burkholderia cenocepacia	C_6-HSL, C_8-HSL	*cepI/cepR* *cciI/cciR*	Flagella, iron ion transport, extracellular enzymes, surface attachment, antioxidants and bacteriophage resistantce	[77]
Sinorhizobium meliloti	3O-C_8-HSL, 3OH-C_8-HSL, 3O-C_{14}-HSL, $C_{16:1}$-HSL, 3O-$C_{16:1}$-HSL, 3O-C_{16}-HSL, JP C_{18}-HSL, C_{12}-HSL	*expR*, *sinI/sinR*	Motility EPSII synthesis	[78]
Serratia plymuthica	3O-C_6-HSL, C_6-HSL, C_4-HSL, C_6-HSL	*splI/splR*, *spsI/spsR*, *sptR*	Antibiotics and extracellular enzymes Biofilm formation	[79]
Chromobacterium violaceum	C_6-HSL	*cvil*	Violacein production	[80]
Bacillus cereus	PlcR AI-2 Rap	*PlcR-PapR*, LuxS, *Rap-Phr*	Expression of virulence factors Biofilm Sporulation	[81–82]
Bacillus thuringiensis	PapR	*PapR*[b]	Extracellular enzyme	[83]
Lactobacillus plantarum	PLNC8IF	AI-2/LuxS	Bacteriocin production	[84]

acyl carrier protein and *S*-adenosyl methionine[49]. Different chain lengths of AHLs have different ways of entering and leaving cells. Short-chain AHLs can freely diffuse into and out of cells, while long-chain AHLs rely on active transport to enter and leave cells. There are 2 main functional domains in the structure of the LuxR family protein, namely the ligand-binding domain (LBD) and the DNA-binding domain (DBD). Generally, signaling molecules bind LBD to form the AI-LuxR complex protein. Due to DBD exposure, it binds to the downstream target gene promoter and activates the gene transcription process. However, some bacteria, such as *E. coli* and *Salmonella*, do not have the *luxI* gene and LuxI protein, so they cannot synthesize their own AHL, but they contain the LuxR protein analog (SdiA), which can sense AHLs produced by other bacteria[50]. This mechanism indicates that AHL is not only related to information exchange within bacterial species but also closely related to inter-bacterial communication.

2.1.2 QS system of Gram-positive bacteria

The QS system of Gram-positive bacteria is mainly composed of histidine kinase receptor protein and response protein, and some autoinducer peptides (AIP) are used as signaling molecules to carry out signal transmission between bacteria (Fig. 1B). Therefore, the QS system mediated by AIP is the main way for Gram-positive bacteria to communicate[50]. AIP is a type of precursor peptide secreted by microorganisms themselves, mainly produced by two-component phosphokinase proteins, usually formed by modified

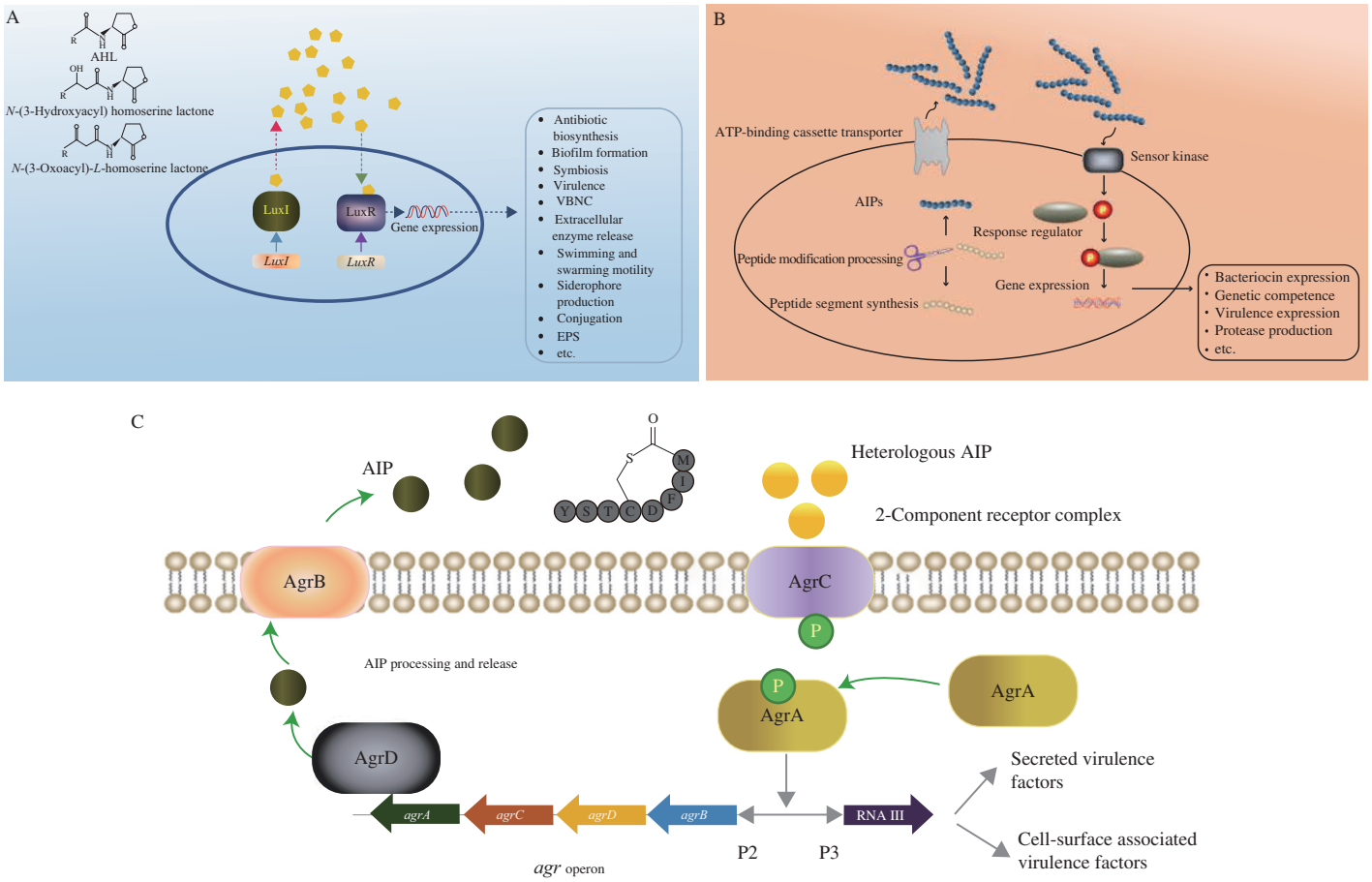

Fig. 1 (A) Action mode of LuxI/LuxR of the Gram-negative bacteria QS system. QS in Gram-negative bacteria LuxI-type proteins produce AHL (yellow pentagons). AHLs specifically bind to the LuxR transcriptional regulator when it reaches threshold concentrations, leading to gene expression. (B) Action mode of the Gram-positive bacteria QS system. (C) *agrBDCA* system of *S. aureus*. QS peptide signaling molecules, and two-component signal transduction in Gram-positive bacteria. Membrane-binding sensor kinase initiates signal transduction by self-phosphorylation. The response regulator controls downstream gene expression. The *agr* operon produces AgrD, which activates the cell membrane-bound AgrB, thereby producing AIPs. AIPs internalize the AgrC channel protein again, bind to AgrA, and stimulate the expression of the RNAIII transcript to secrete virulence factors. The letters inside the balls indicate amino acids in the cyclic peptide QS signal.

cyclic oligopeptides with 5–10 amino acid residues. Although these precursor peptides have different structures, they are mostly small in size, and AIP cannot enter and exit cells freely. Therefore, the assistance of membrane channel proteins or ABC transport systems (ATP-binding cassette) is needed to transport AIP to the extracellular domain for functional purposes, and its signal recognition is achieved by a two-component phosphokinase system[51]. The Agr system in *S. aureus* is a typical QS regulation system of Gram-positive bacteria[52] (Fig. 1C). The AIP signaling molecule is synthesized by the AgrD protein, and then thiolactone cyclization modification is carried out through AgrB and released into the extracellular space. After reaching the threshold concentration, the phosphokinase AgrC is activated, and the signal is transmitted to the downstream AgrA protein through the phosphorylation cascade reaction. Then phosphorylate AgrA, activate the transcription of the *agrBDCA* operon and RNAIII, express virulent factors such as toxin and protease, and inhibit the expression of adhesion proteins[53-55].

2.1.3 AI-2 QS system

The AI-2 type QS system mediated by furanosyl borate diester has been found in more than 500 Gram-negative bacteria and Gram-positive bacteria[56]. As a nonspecific self-inducer, the AI-2 signaling molecule can be recognized by the receptors of different interspecies (intraspecies) microorganisms at the same time and is also vividly called the "universal language" for communication between bacteria. In the AI-2 QS system, the *luxS* gene is the key regulatory gene and participates in the synthesis of the AI-2 signaling molecule[57]. Therefore, the *luxS* gene is often used as evidence for detecting the presence of AI-2. The synthetic pathway of the AI-2 signaling molecule is generally as follows: *S*-adenosyl methionine (SAM) can be used as a methyl donor to produce the toxic intermediate *S*-adenosyl-*L*-homocysteine (SAH), which is hydrolyzed by 5′-methylthioadenosine nucleosidase (MTAN) to produce *S*-ribose homocysteine (SRH) and adenine. LuxS enzyme then converts SRH into the AI-2 precursors 4,5-dihydroxy-2,3-pentanedione (DPD) and homocysteine. Finally, due to the instability of DPD, it spontaneously cyclized to form the AI-2 signaling molecule[58]. AI-2 can participate in regulating the physiological processes of various microorganisms, such as the bioluminescence of *Vibrio harveyi*, the biofilm formation of *Listeria monocytogenes*, the expression of toxic factors in *E. coli*, etc. In *V. harveyi*, AI-2 released by bacteria accumulates in the extracellular environment to reach the threshold concentration, combines with the signaling molecule-

specific protein LuxP to form the AI-2-LuxP complex, and then the complex interacts with the sensor kinase LuxQ to start the phosphate transfer cascade reaction, thus emitting fluorescence. However, the mechanisms by which *E. coli* and *Salmonella typhimurium* respond to AI-2 are different from those of the LuxP/LuxQ system. They transport AI-2 into the cytoplasm through the LuxS-regulated AI-2 uptake system system to induce cellular responses[59-60].

2.1.4 Other QS systems

In addition to the QS regulatory systems mentioned above, research has found that there are other types of QS systems in some microorganisms. For example, epinephrine and norepinephrine are usually regarded as AI-3 signaling molecules[61]. Compared with AI-1 and AI-2 QS regulation systems, the regulation process of the AI-3 QS system is relatively complex, and its synthesis does not depend on LuxS protein but is generated by the symbiosis of gastrointestinal flora or the secretion of the host. In EHEC, researchers found a QseC/B QS system with AI-3/adrenaline/norepinephrine as a signaling molecule. AI-3 is a bacterial aromatic self-inducer secreted by normal flora in the gastrointestinal tract, while adrenaline/norepinephrine is a catecholamine hormone produced by the host. Studies have shown that *luxS* gene deletion mutants could alter cell metabolism, thereby affecting the production of AI-3. The common receptor of AI-3 is QseBC protein, in which QseC protein, as a sensor kinase, can directly bind to AI-3 and adrenaline/norepinephrine, thus playing a role in cross signals, thereby phosphorylating QseB protein as a response regulator and further regulating the expression of QS-related genes such as toxic albumen production, flagella, and motility[62]. This type of QS system has also been verified in *Shigella* spp., *Salmonella* spp., *Enwinia carotovora*, *Klebsiella* spp., *Pasteurella multicida*, *Chromobacterium violaceum*, etc. In addition, there is a kind of hybrid QS system in microorganisms. For example, *V. harveyi* has the characteristics of both Gram-negative bacteria and Gram-positive bacteria QS systems. *V. harveyi* can produce and use AHL as a signaling molecule, but the signal transduction mechanism in its QS system is similar to that of Gram-positive bacteria, which needs the help of histidine kinase in the two-component system. Diketopiperazines (DKPs), PAME and other types of signaling molecules have similar functions with AHLs and can be used for information exchange between Gram-negative bacteria[50]. Their regulation of the QS system is mainly manifested by competing with AHLs for the same LuxR receptor protein binding site, thus enhancing the motility of microorganisms and the ability of biofilm formation.

3. QS system regulates the biofilm formation of foodborne bacteria

Biofilm is an ecological community with a three-dimensional spatial structure formed by the aggregation and adhesion of extracellular polymeric substances (EPS) (such as polysaccharides, DNA, proteins, etc.) secreted by bacteria themselves to adapt to their living environment during the growth process[85]. The biofilm formation of foodborne bacteria generally involves four steps (Fig. 2A). The first step is the initial adhesion of the bacterial cells. The planktonic bacteria attach to the surface of food or food processing equipment, and the initial attachment of cells is carried out through flagella, pili, and some surface proteins. In addition, bacteria can also utilize adhesion proteins anchored on the cell wall for adsorption[86]. In *Shewanella putrefaciens*, adsorption can be achieved through the adhesive protein LapA[87]. Similarly, in *Pseudomonas putida*, LapA and LapF are also used for bacterial adhesion[88]. At this point, the attached cells have not yet formed a complete biofilm. The second step is the proliferation of cells and the formation of microcolonies. Bacteria rapidly proliferate and begin to produce extracellular polysaccharides, proteins, and eDNA, forming small colonies. This process is irreversible and is also a key factor affecting the maturation of biofilms. The third stage is the maturation of the biofilm. Water, proteins, and extracellular polysaccharides are responsible for cell adhesion and the formation of cell scaffolds, thereby maintaining the three-dimensional structure of the biofilm. Cells are tightly wrapped in biofilm, signaling molecules accumulate, and bacteria communicate with each other through QS signaling molecules. The final stage is the dispersal of the biofilm. The polysaccharide and protein decomposing enzymes within the biofilm degrade the biofilm, and then the bacteria dissolve from the biofilm and return to a planktonic state. QS participates in regulating the various stages of biofilm formation, thereby forming a complete "attachment-microbiota formation-maturation-dispersion" biofilm life cycle[89].

Studies have shown that the QS system plays an important role in the biofilm formation of foodborne bacteria[90-91]. For example, *Burkholderia cenocepacia* can use the QS system to regulate the secretion of biofilm matrix components (lectin, lipopolysaccharide, and surface protein)[92]. Studies have found that the deletion or mutation of the signal molecule synthase gene of bacteria would affect the synthesis of the QS system signaling molecule, thus affecting biofilm formation. In *B. cenocepacia*, the *cepI* and *cciI* genes of its QS system encode and synthesize the C_6-HSL and C_8-HSL signaling molecules, respectively. The *cepI* and *cciI* mutants of *B. cenocepacia* could cause defects in biofilm formation[93]. The loss of the *luxR* gene led to down-regulation of *pomA* expression in the flagella motor gene of *Shewanella baltica*, resulting in impaired biofilm formation ability[94]. *luxS* mutants of *S. aureus* regulate biofilm formation by altering the expression of the *rfb* gene[95]. In addition, the QS system could regulate the maturation of biofilms by regulating the secretion of EPS. The homeotic gene *btaR1* mutant of *luxR* in *Burkholderia thalandensis* forms a biofilm that loses dome structure by reducing the fucose content in EPS[96]. At the late stage of biofilm maturation, the LuxR homologous protein SmcR of *Vibrio vulnificus* produced capsular polysaccharide by inducing the transcription of capsular polysaccharide gene clusters, and its hydrophilicity promoted the dispersion of biofilm structure[97]. The Agr QS system of *S. aureus* promoted biofilm dispersion and colonization by controlling the expression of *psm* genes to produce surfactants[98].

The QS system can not only directly mediate the bacterial biofilm formation, but also regulate the level of intracellular second messenger molecules, and indirectly regulate the biofilm formation. The second messenger, cyclic guanosine monophosphate (c-di-GMP), is widely present in bacteria and was discovered as a cellulose synthase isomeric activator in *Acetobacter xylinum* in 1987[99]. c-di-GMP is synthesized by guanylate cyclase (DGCs) and

can be degraded by phosphodiesterase (PDEs). The DGCs and PDEs responsible for c-di-GMP metabolism contain highly conserved GGDEF and EAL domains, respectively. These 2 domains are named after the conserved sequence motifs glycine-glycine-aspartic acid-glutamic acid-phenylalanine (GGDEF) and glutamic acid-alanine-leucine (EAL) in the active center[100]. In recent years, studies have found that c-di-GMP, as a widely used signaling molecule, can regulate bacterial motility, extracellular polysaccharide production, toxic factor expression, and other physiological processes and has an important regulatory role in the formation of Gram-negative bacteria biofilm. There is also cross-action between the QS system and c-di-GMP (Fig. 2B). For example, in the presence of the QS regulator HapR in *V. cholerae*, the regulation of the QS system on biofilm depends on c-di-GMP, while in *Aeromonas veronii* biovar sobria, the increase of c-di-GMP could cause an increase in C_4-HSL[101]. There is a direct interaction between the QS signal and the c-di-GMP signaling pathway. In *Xanthomonas campestris*, its QS signaling molecules directly regulate the HD-GYP enzyme activity, resulting in a decrease in c-di-GMP levels at high cell densities[102]. The Scr system of *Vibrio parahaemolyticus* is very similar to the Rpf system of *X. campestris*, as its QS signaling molecules directly control the activity of c-di-GMP degrading enzymes[103]. There is also an indirect connection between QS and c-di-GMP. The QS system of *V. cholerae* regulates the c-di-GMP signaling pathway through alteration of c-di-GMP synthesis and degradation enzyme expression. The QS signaling molecules of *V. cholerae* do not directly regulate the c-di-GMP synthesis and degradation enzyme activity[104]. In these bacterial systems, c-di-GMP signaling integrates information about local cell density through the QS system. The information about local cell density transmitted by the QS system is one of the numerous environmental signals ultimately integrated into the c-di-GMP signaling network, which is composed of multiple signaling pathways, allowing bacteria to adapt and respond to different environments[105].

At any stage of the food chain, from production to consumption, food products are susceptible to contamination by various microorganisms. Foodborne bacteria firmly adhere to the surface of food processing equipment and raw materials and rapidly proliferate rapidly to produce biofilms. Once a biofilm is formed, it not only pollutes food and increases the difficulty of equipment cleaning but also increases the resistance of bacteria to antibiotics and disinfectants[106-107]. Therefore, the biofilm formed by foodborne bacteria is an important factor affecting food quality and safety. Regulating the production of biofilms and improving food quality through quenching the bacterial QS system may be a potentially effective approach.

4. QS system regulates the formation and resuscitation of VBNC state of foodborne bacteria

Studies have shown that various microorganisms that can be isolated and cultured normally can enter the VBNC state under adverse environmental conditions[108]. After entering the VBNC state, bacteria cannot grow and divide on conventional culture media but maintain cell integrity and low levels of metabolic activity. When the conditions are suitable, the bacteria in the VBNC state can restore their ability to grow and reproduce on the culture medium, and their pathogenicity also recovers accordingly[109]. In the process of food processing, some foodborne bacteria may enter the VBNC state to survive in order to adapt to adverse environments such as low temperatures, high osmotic pressure, and preservatives. Some pathogenic bacteria may even retain their virulence, posing significant challenges and potential hazards to the food industry. Our research group studied the induction, resuscitation, and spoilage ability of microorganisms such as *Lactobacillus lindneri*, *Lactobacillus acetotolerans*, *Lactobacillus brevis*, brewer's yeast, *Lactobacillus plantarum*, and *Lactobacillus casei* in beer and proposed that high attention should be paid to microbiological quality control and particulate VBNC bacteria, providing reference for food quality control in the brewing industry[108,110-115].

Research has found that normal bacteria can enter the VBNC state under the regulation of related genes such as stringent response[116], toxin-antitoxin (TA) system and Lon/Clp protease[117-118]. Furthermore,

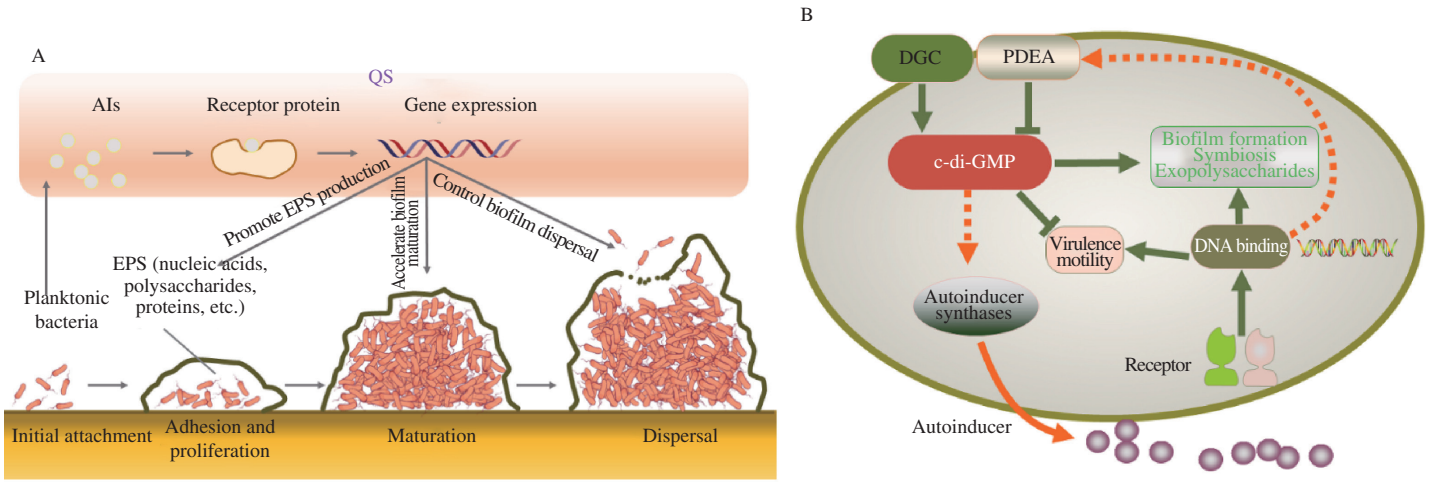

Fig. 2 (A) Direct regulation of the QS system on the process of biofilm formation. The QS system regulates EPS production, biofilm maturation, and biofilm dispersal. (B) Regulation of c-di-GMP levels by the QS system indirectly regulates bacterial biofilm formation. The c-di-GMP signal integrates information about local cell density through QS. The synthesis and degradation of c-di-GMP are controlled by signals such as QS to regulate gene expression. Increased c-di-GMP concentrations induce biofilm matrix formation, and decreased c-di-GMP concentrations promote bacterial motility and shift into planktonic cells.

after removing external pressure factors, increasing nutrients, inoculating hosts, and small molecule substances such as resuscitation promoting factor (Rpf)[119], amino acids, and Sigma factors (σ^S, RpoS)[120-121], OxyR[122], QS[123], etc., bacterial cells in VBNC state can restore pathogenicity and culturability (Fig. 3). Stringent response is a response mechanism in which bacteria increase amino acid synthesis by slowing down growth under amino acid starvation conditions. This mechanism is regulated by signaling molecules (p)ppGpp[124]. When bacteria experience amino acid starvation, the protein (RelA or SpoT) will function to increase the synthesis of (p)ppGpp or reduce the degradation of (p)ppGpp. (p)ppGpp inhibits the degradation of polyphosphates by exopolyphosphatase (PPX), resulting in the accumulation of polyphosphates. Polyphosphates can activate the Lon protease and affect the expression of genes related to the TA system, inhibiting the translation process and bacterial growth and division by increasing the content of free toxins in bacterial cells, thereby regulating the formation of the VBNC state[125]. The TA system is widely present in bacteria and plays a role in adapting to external pressure, toxicity, resisting phage infection, and biofilm formation. Studies have shown that the TA system could affect the VBNC state. The TA systems that regulate the VBNC state of bacteria include *hipAB*, *higBA*, *relEB*, *chpAKAI*, *VapBC*, etc.[126]. RpoS plays a role in transcription, translation, and protein hydrolysis and plays a major regulatory role in the bacterial response to general stress[127]. The involvement of RpoS in regulating VBNC state has been demonstrated in various bacteria such as *Cronobacter sakazakii* and *Salmonella enterica*[92,128]. OxyR is a transcription regulatory factor in the LysR type transcriptional regulators (LTTR) family, which can regulate genes related to oxidative stress and influence the formation and resuscitation of bacterial VBNC states[129]. Rpf was first discovered in *Micrococcus luteus* and is a secreted protein that promotes bacterial growth and plays a role in the resuscitation of VBNC cells. It is widely present in various bacteria[119]. Rpf binds to the surface receptors of VBNC state bacteria, promoting cell growth and resuscitation[130]; Alternatively, Rpf acts on peptidoglycans in the cell wall of VBNC state bacteria to revive and restore normal bacterial growth. YeaZ is also a recovery factor, formed by the product of the *yeaZ* gene to form the conserved structure YjeE/YeaZ/YgjD, which enables Gram-negative bacteria to survive under stress and recover from the VBNC state[131].

Among them, QS plays an important regulatory role in the formation and resuscitation of the VBNC state of foodborne bacteria. The bacterial community is comprised of metabolically active cells and VBNC cells. Under suboptimal environmental conditions, a greater proportion of cells are induced to enter the VBNC state. Due to infrequent and inherently stochastic occurrences, such as alterations in the expression patterns of regulatory genes, solitary bacterial cells intermittently emerge from dormancy. These revived cells are referred to as "scout cells" or "exploration factors", constituting a pivotal aspect in the resuscitation of VBNC bacteria. Intriguingly, exploration factors of certain bacterial species may employ signaling compounds to induce growth, thereby awakening dormant populations[132]. Within the QS system, there exist randomly activated cells that serve as the initial transmitters of phenotypic traits conducive to environmental adaptation among bacterial populations. The stochastic emergence of scout cells is analogous to the random activation of cells within the

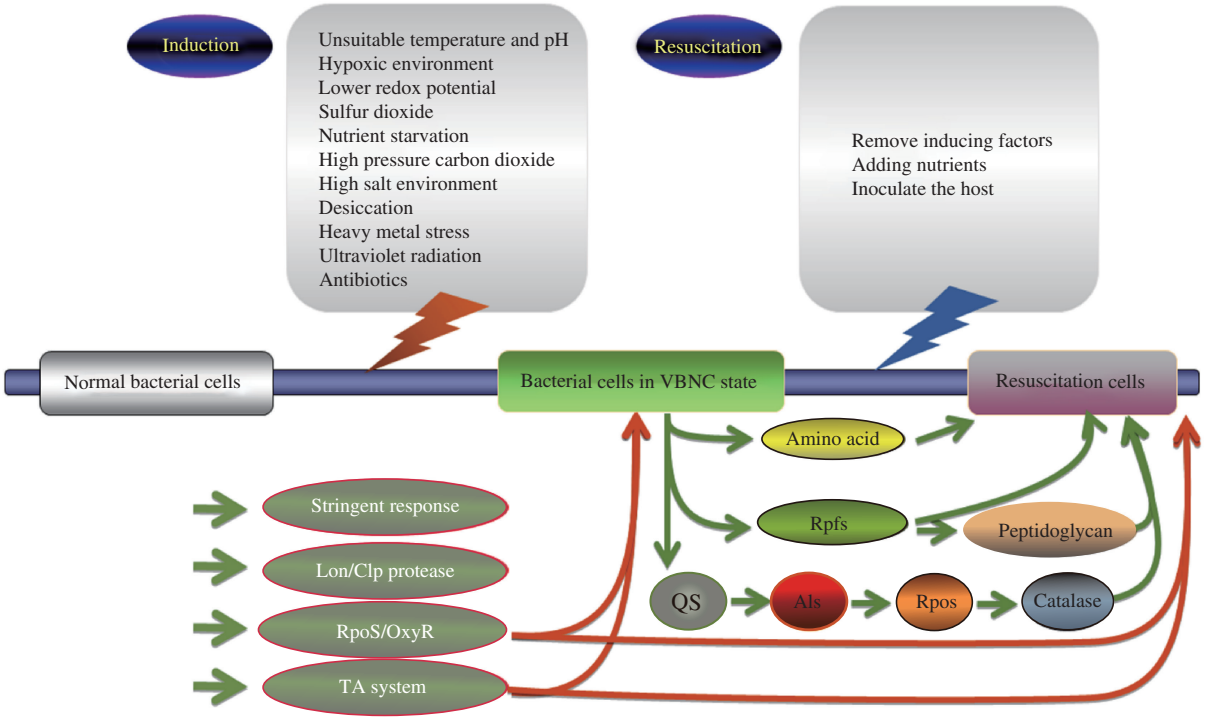

Fig. 3 Induction and resuscitation mechanisms of the bacterial VBNC state. Normal bacterial cells can enter the VBNC state through stringent responses, Lon/Clp protease, Rpos/OxyR, and the TA system. The RpoS/OxyR and TA systems also play a regulatory role in bacterial resuscitation. Bacterial cells in the VBNC state can be revived by adding nutrients such as amino acids. Rpf degrades specific regions of the cell wall of VBNC state bacteria and relieves the inhibition of peptidoglycan on bacterial growth in these regions, thereby promoting the resuscitation of VBNC- state bacteria. Rpf can also degrade peptidoglycans, thereby promoting the resuscitation of VBNC state bacteria. The QS system can enhance the expression of *rpoS* genes, induce excessive expression of catalase, and promote the resuscitation of VBNC-state bacteria.

QS system[133]. Studies have demonstrated the potential presence of the *rpf* gene in activated QS cells[134], suggesting a significant regulatory role of the QS system in the formation and resuscitation of bacterial VBNC states. Bacteria employ QS as a self-regulatory mechanism, relying on feedback from scout cells. Upon sensing adverse environmental changes, scout cells secrete signaling molecules that induce neighboring cells to enter the VBNC state, thereby enhancing survival under unfavorable conditions. Once the stressor is alleviated, scout cells secrete alternative signaling molecules, such as the Rpf protein, that promote the resuscitation of some VBNC cells. However, VBNC cells that remain unresponsive to these signaling molecules ultimately succumb to cell death[135]. Ayrapetyan et al.[136] found that bacterial cell-free supernatants of *C. jejuni* could awaken preexisting dormant *Vibrio* populations within oysters and seawater, while the QS mutant could not revive them. AI-2 could induce the resuscitation of *V. vulnificus in vitro*, and VBNC cells of a mutant unable to produce AI-2 were unable to resuscitate unless the cultures were supplemented with exogenous AI-2. Cinnamaldehyde as a QS inhibitor delayed the resuscitation of wild-type VBNC cells. The above results indicated that QS signals were critical for the natural resuscitation process[136]. Moorhead et al.[137] found that *C. jejuni* responded to QS signaling molecules such as OH-C_4-HSL, C_4-HSL, C_{12}-HSL, and homoserine lactones (HSL) and a novel compound (cjA) isolated from *C. jejuni*. Short-chained HSLs and cjA prolonged the delay to a VBNC state, inhibited biofilm formation, and affected virulence gene expression. The role of QS signaling molecules in the VBNC state may be related to the regulation of *rpoS* genes. In order to identify the key gene responsible for the VBNC state in *Salmonella* spp., Kusumoto et al.[138] constructed the *S. typhimurium* LT2 VBNC mutant. Compared with the wild-type, this mutant had a higher level of expression of the general stress sigma factor RpoS and showed a delay in entering the VBNC state[138]. Wu et al.[139] found that *V. cholerae* could utilize the HapR-mediated QS system to prevent the transition to the VBNC state under low nutrient and temperature conditions. The up-regulation of *hapR* leads to an extension of the cultivable state of *V. cholerae*, while the mutation of *hapR* leads to its rapid entry into the VBNC state[139].

5. QS quenching of foodborne bacteria

The antibacterial mechanism of the widely used antibacterial agents currently targets the metabolic processes of microorganisms, such as the synthesis of bacterial proteins, nucleic acids, and cell walls, to inhibit bacterial growth and metabolism or directly kill them. However, this also leads to bacterial resistance. As mentioned above, multiple physiological activities of foodborne bacteria depend on the regulation and control of their QS system. Therefore, understanding the "language" of communication between microorganisms and using various methods to effectively interfere or block their QS pathway, thereby disrupting the biological functions involved in QS regulation, provides a new way to control food quality and safety. On the premise of not affecting the normal activities of bacteria, substances that can interfere with or inhibit the QS phenomenon of bacteria are called QSIs[140]. Unlike traditional antibacterial agents, QSI acts on the QS system, not only effectively interfering with the production of virulence factors but also does not cause bacterial resistance. Several QSIs for foodborne bacteria from different sources are shown in Table 2. At present, there are many studies on the QS system of Gram-negative bacteria, and QSI mainly plays a role through the following 3 mechanisms (Fig. 4): 1) inhibiting the synthesis of signaling molecules in the QS system. It can be realized by inhibiting the activity of signaling molecule synthetase or eliminating the substrate. Yu et al.[141] found that the combination of hexanal and geraniol significantly inhibited the biofilm formation, motility, and extracellular protease activity, as well as the synthesis of AHLs (C_8-HSL and C_{12}-HSL) of *P. fluorescens*. Hexanal and geraniol significantly down-regulated the expression of *pcoI* and *gacA* genes that regulate AHL synthetase and sensor kinase[141]. 2) Degradation of the synthesized QS signaling molecule, which makes it difficult to reach the threshold concentration of QS regulation outside the cell. Enzymes, as one of the main substances that degrade signaling molecules, can be divided into signaling molecule degrading enzymes and quenching enzymes in terms of mode of action. It has been found that AHL-lactonase, paraoxonase, AHL-acylase, and oxidoreductase could degrade AHLs[142]. AHL-lactonase and AHL-acylase can directly degrade AHLs. AHL-lactonase can hydrolyze the lactone bond of AHL, which greatly reduces the activity of AHLs. Packiavathy et al.[143] found that *Psychrobacter* sp. in the marine sediment of Palk Bay could produce AHL-lactonase. *Psychrobacter* sp. could control the biofilm formation of different bacteria and the production of biofilm-related virulence factors in *Pseudomonas aeruginosa* PAO1[143]. Paraoxonase (PON) and oxidoreductase also have the ability to degrade AHLs, which mainly reduce the carbonyl group in signaling molecules to inactivate signaling molecules for quenching[144]. Wang et al.[145] found that astragaloside IV, eugenol, and baicalin could inhibit the biofilm formation of *P. aeruginosa* PA14 by decreasing the extracellular concentration of the AHL (3-oxo-C_{12}-homoseine lactone) by affecting the function of the efflux pump MexAB-OprM[145]. 3) Interfering with the binding of signaling molecule and receptor proteins to block the QS pathway. If the substances have good affinity with the receptor protein, they can competitively bind to the receptor protein, thus interfering with the binding ability of the signaling molecules to the corresponding receptor protein to block the bacterial QS system. Diketopiperazine (DKP) can competitively bind to receptor proteins, thus blocking the binding ability of signaling molecules and receptor proteins, inhibiting the expression of genes regulated by the QS system, and reducing the infection ability of spoilage bacteria[146]. The structure of quercetin is similar to that of the signaling molecule and could competitively inhibit the binding of the signaling molecule and receptor protein LasR in the QS system of *P. aeruginosa*, thereby inhibiting the production of bacterial EPS, sodium alginate, and violacein[147]. Thakur et al.[148] explored the influence of five traditional Chinese medicines on the QS system of drug-resistant *E. coli* and found that berberis has the effects of anti-biofilm. Xie et al.[149] found that a phosphate ester derivative of chrysin was an effective QSI of *P. aeruginosa*, which could reduce the release of virulence factors of *P. aeruginosa*. It bound to the bacterial QS regulatory factor LasR and abrogated its DNA binding ability[149].

Gram-positive bacteria use AIPs as signaling molecules to communicate among bacteria. Its QSIs mainly include AIP analogues and inhibitor derivatives. *S. aureus* is the most common Gram-positive bacteria, which plays an important role in food spoilage and foodborne illness. Therefore, inhibiting the reproduction of *S. aureus* is of great significance for food preservation and extending food shelf life. At present, there are many studies on QSIs

Table 2
QSIs for foodborne bacteria from different sources.

Classification of QSI	Sources of QSIs	Names of QSIs	Inhibited the types of foodborne bacteria	Impact of QSIs on QS phenotypes	Reference
Animal-derived QSIs	*D. elisea pulchra*	2(5*H*)-Furanone, bromofuranone	*P. aeruginosa*	Inhibited the production of AHLs and reducd extracellular protease activity	[162]
	Pig	Renal acyltransferase	*A. hydrophila*	Inhibited microbial QS signaling	[163]
	Beef	Long-chain fatty acid	*V. harveyi*	Inhibited AI-2 activity	[164-165]
	Bee	Chestnut honey	*E. carotovora*, Y*ersinia enterocolitica*, and *A. hydrophila*	Degraded AHLs, inhibited AHLs production, and reduced biofilm formation	[166]
	D. elisea pulchra	Halogenated furanones	*S. liquefaciens*	Inhibited AHL signal response	[167]
	Soft corals	Soft coral extracts	*E. coli* pSB401, *P. putida*	Inhibited *luxI*/*luxR* QS system	[168]
	Sponges	Manoalide, manoalide monoacetate, and secomanoalide	*P. aeruginosa*	Inhibited a *lasB::gfp* (ASV) fusion	[169]
		Extracts from the sponges *Niphates caycedoi*, *Cliona tenuis*, *P. walpersi*, *Petrosia pellasarca*, *Laurencia catarinensis*, and *Laurencia obtusa*	*C. violaceum* ATCC 31532	Inhibited bacterial QS	[168]
		Extracts from the sponges *Agelas citrina*, *Agelas tubulata*, *Iotrochota arenosa*, and *Topsentia ophiraphidite*	*E. coli* and *P. putida* IsoF	Inhibited bacterial QS	[168]
Plant-derived QSIs	*Sclerocarya birrea*	Methanolic extract	*P. aeruginosa*	Inhibited biofilm formation and swarming motility	[170]
	Tobacco	Cembranoids	*P. putida* IsoF, *E. coli* pSB401, and *C. violaceum*	Inhibited production of violacein pigment	[171]
		Esculetin	*A. hydrophila* SHAe 115	Inhibited the production of protease and hemolysin, the formation of biofilms, and attenuated the swarming motility	[172]
	Grapefruit juice	Furanocoumarin	*S. typhimurium*, *E. coli*, and *P. aeruginosa*	Inhibited biofilm and signaling molecules	[173]
	Psidium guajava	Flavonoids	*P. aeruginosa*	Inhibited AHL signal response	[174]
	Mangifera indica	Polyphenols, flavonoids, and triterpenoids	*P. aeruginosa*, *A. hydrophila*	Reduced AHL-dependent pigment production	[175]
	Arctium lappa	Combination of chlorogenic acid, caffeic acid, *p*-coumaric acid, rutin and quercetin	*P. aeruginosa*	Inhibited the secretion of the QS signaling molecule 3-oxo-C12-HSL	[176]
	Nigella sativa	Alkaloids, steroids, carbohydrates, flavonoids, and fatty acids	*L. monocytogenes*, *E. coli*, *C. violaceum*	Attenuation of AHL-mediated QS	[177]
	Phyllanthus amarus	Phenolic compounds, flavonoids, and flavonols	*E. coli*, *P. aeruginosa*	Inhibited swarming motility, pyocyanin production, and *P. aeruginosa* PA01 *lecA::lux* expression	[178]
	Star anise	Phenolic compounds and flavonoids (*trans*-anethole, caryophyllene, limonene)	*S. aureus*, *S. typhimurium*, and *P. aeruginosa*	Inhibited biofilm formation and swarming motility	[179]
	Citrus limon oils	Lemon essential oil (LEO), lemon terpenes (LT), and lemon essence (LE)	*P. aeruginosa* strains (ATCC 27853 and a multidrug-resistant HT5)	Inhibited bacterial virulence factor production and motility (swarming and swimming)	[180]
	Traditional green tea	Epigallocatechin-3-gallate	*P. aeruginosa*	Inhibited the development of biofilm, protease, elastase activity, swimming, and swarming motility	[181]
	Polyphenols	Epigallocatechin gallate	*E. coli*	Inhibited biofilm formation, swarming motility, and AI-2 concentration	[182]
	Rosa rugosa	Gallic acid, catechin, epicatechin, epigallocatechin gallate, epicatechin gallate, quercetin, and benzoic acid	*P. aeruginosa*, *E. coli*	Inhibited biofilm formation and swarming motility	[183]
	Cuminum cyminum	Methyl eugenol	*C. violaceum*	Inhibited biofilm formation, flagellar motility, and exopolysaccharide production	[184]
		Iinalool	*C. violaceum*	Inhibited the expression of the violacein biosynthetic genes *vioA*, *vioC*, *vioD*, and *vioE*	[185]
	Euodia ruticarpa	Ethanol extract, evodiamine, rutaecarpine, and quinolinone	*C. jejuni*	Inhibited biofilm formation	[186]
	Quercetin	Quercetin	*P. aeruginosa*, *Y. enterocolitica*, and *Klebsiella pneumoniae*	Inhibited biofilm formation	[187]
	Zingiber officinale Roscoe	[6]-Gingerol, [6]-shogaol, zingerone	*C. violaceum*, *P. aeruginosa*	QS inhibitory activity and growth inhibition	[188]
	Horseradish	Iberin	*P. aeruginosa*	Blocked the expression of QS-regulated genes	[189]
		Zingerone	*Aeromonas sobria*	Inhibited biofilm formation and spoilage indicators	[190]

Table 2 (*Continued*)

Classification of QSI	Sources of QSIs	Names of QSIs	Inhibited the types of foodborne bacteria	Impact of QSIs on QS phenotypes	Reference
	Broccoli	Flavonoids (myricetin, kaempferol, and quercetin)	*E. coli*	Inhibited AI-2 synthesis, bacterial motility, and the AI-3 QS system	[191]
	Pomegranate rind	Tannin-rich fraction	*E. coli*	Inhibited biofilm formation, and swarming motility	[192]
	Lemongrass oil	Citral	*C. sakazakii*	Inhibited motility, biofilm formation and endotoxin production	[193]
	Origanum vulgare, *Origanum syriacum*, and *Origanum majorana*	α-Pinene, limonene, linalool, and terpinen-4-ol	*C. violaceum*	Inhibited biofilm formation and the AHL-mediated QS	[194]
	Thymus daenensis, *Satureja hortensis*	Carvacol, α-terpinene, *p*-cymene, γ-terpinene	*S. aureus*	Inhibited biofilm formation	[195]
	Delisea pulchra	Bromofuranone	*S. liquefaciens*	Inhibited biofilm formation	[196]
QSIs of microbial origin	*B. cereus* RC1 extracts		*Lelliottia amnigena*, *P. aeruginosa* MTCC2297	Inhibited pyocyanin production in *P. aeruginosa* and modulated the pathogenicity of *L. amnigena*	[197]
	B. subtilis R-18 extract		*Serratia marcescens*	Inhibited biofilm formation, protease, lipase, and hemolysin production	[198]
	B. subtilis BR4 extracts	Stumletellin Y	*P. aeruginosa*	Inhibited biofilm formation	[199]
	Bacillus pumilus		*P. aeruginosa* PA01, *S. marcescens*	Reduced the accumulation of AHL and showed significant inhibition of LasA protease, LasB elastase, caseinase, pyocyanin, pyoverdin, and biofilm formation.	[200]
	Bacillus 240B1	AiiA enzyme	*E. carotovora*	Inhibited carbapenem antibiotic gene expression, weaken bacterial pathogenic ability	[201].
	Bacillus licheniformis DAHB1	AHL-Lactonase	*V. parahaemolyticus*	Inhibited biofilm formation	[202]
	Bifidobacterium longum ATCC15707 extracts		*E. coli* O157:H7	Inhibited AI-2 and reduces biofilm formation	[203]
	L. acidophilus GP1B extracts		*Clostridium difficile*	Reduced production of AI-2 molecules	[204]
	L. acidophilus La-5		*E. coli* O157:H7	Interfered with QS molecules and reduces adherence and colonization	[205]
	Lactic brevis 3M004 cells/ lysate		*P. aeruginosa*	Inhibited biofilm formation	[206]
	Lactic fermentum Lim*2*		*Clostridium difficile*	Reduced the AI-2 in QS gene *luxS*	[207]
	L. plantarum PA100 cultures and filtrates		*P. aeruginosa*	Inhibited AHLs, elastase and biofilm	[208]
	Metabolites of *Phomopsis liquidambari*	4-Hydroxycinnamic acid	*A. tumefaciens*	Suppressed biofilm formation, motilities, and flagella formation	[209]
	Marine fungal	(*Pestalotiopsis sydowiana* PPR) extract	*P. aeruginosa* PAO1	Inhibited the production of pyocyanin, chitinase, protease, elastase, and staphylolytic activity, reduced the production of exopolysaccharides, rhamnolipids, and alginate, and inhibited the biofilm formation	[210]
QSIs for chemical synthesis		C9-CPA	*S. marcescens*	Inhibition of QS	[211]
		Furanone C-30	*P. aeruginosa*	Inhibition of virulence factor expression	[212]
		Cassialactone	*P. aeruginosa*	Inhibition of biofilm formation and virulence factor production	[213]
		N-(Heptylsulfanylacetyl)-*L*-homoserine lactone (HepS-AHL)	*Aeromonas salmonicida*	Reduced protease production	[214]
		AHL Analogues 20-22	*P. aeruginosa*	Inhibition of LasR activity	[215]

Table 2 (*Continued*)

Classification of QSI	Sources of QSIs	Names of QSIs	Inhibited the types of foodborne bacteria	Impact of QSIs on QS phenotypes	Reference
		2-(4-Bromophenyl)-*N*-(2-oxotetrapyridinefuran-3-yl) butanamide	*P. aeruginosa*	Inhibition of biofilm formation and virulence factor production	[216]
		Hordenine analogs	*P. aeruginosa* and *S. marcescens*	Inhibited biofilm formation	[217]
		Quinazolin-4(3*H*) -one derived PqsRAntagonists	*P. aeruginosa*	Reduced levels of pyocyanin, 2-heptyl-3-hydroxy-4-quinolone, and 4-hydroxy-2-heptylquinoline	[218-221]

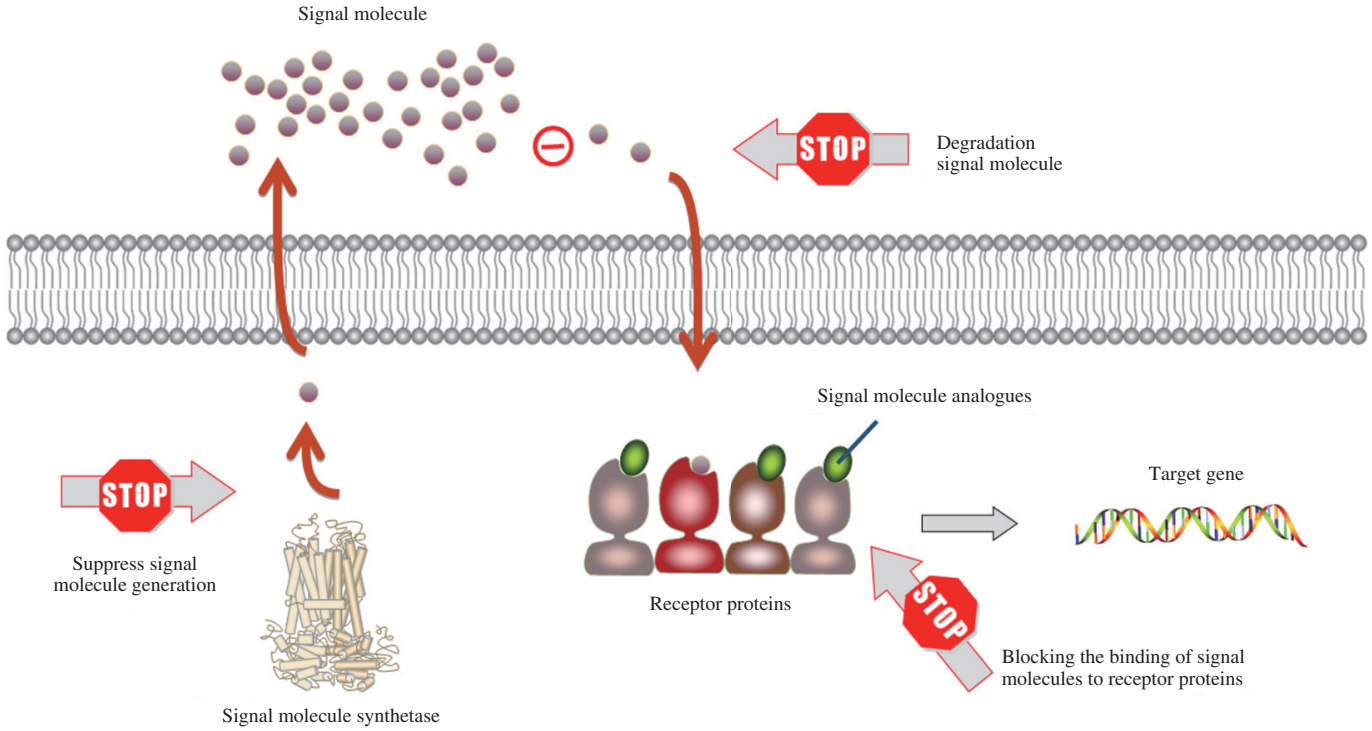

Fig. 4 Schematic diagram of QS and quenching.

of *S. aureus*. AIP analogues could antagonistically bind to receptor proteins, thereby inhibiting the QS process[150]. Tal-Gan et al.[151] developed analogues of a native autoinducing peptide (AIP-III) signal that could inhibit AgrC-type QS receptors and attenuate virulence phenotypes in *S. aureus*. They also developed an amide-linked AIP analogue (AIP-III D4A) to compete with the native ligand for AgrC receptors. They found that AIP-III D4A maintained strong potencies as AgrC receptor inhibitors in *S. aureus*[152]. RNA-III-inhibiting peptide (RIP, YSPWTNF-NH2) was capable of inhibiting toxin production and mitigating wound infections due to *S. aureus*. RIP inhibits the production of *S. aureus* biofilm *in vivo*, interfering with the *agr* QS system. It was suggested that, in addition to the well-known auto-inducer peptide-mediated QS in *S. aureus*, there was an RNA-III activating peptide (RAP) -mediated pathway that targeted a protein called TRAP (target of RNAIII activating protein). RIP could compete with RAP and inhibit the phosphorylation of TRAP, leading to the inhibition of agr QS. Cirioni et al.[153] synthesized a RIP analog (FS3, YAPWTNF-NH_2) and found that FS3 and Daptomycin could prevent the formation of prosthetic biofilm in the rat model of *Staphylococcal vascular* graft infection. As a common signaling molecule between Gram-negative bacteria and Gram-positive bacteria, AI-2 inhibitors include MTAN enzyme inhibitors, LuxS enzyme inhibitors, AI-2 receptor protein inhibitors, DPD analog inhibitors, furanone compounds, *D*-nenenebc galactose, etc. MTAN is encoded by the *pfs* gene and catalyzes 5'-methylthioadenosine (MTA) or SAH depurinization to produce 5'-methylthioribose (MTR) or SRH. If the MTAN enzyme is inhibited, the production of SRH will be blocked, and then the generation of the AI-2 signaling molecule will be interfered with. At the same time, the MTA conversion MTR will be blocked, resulting in the accumulation of MTA, and the AI-1 synthesis pathway will also be inhibited. Therefore, MTAN inhibitors are not only AI-2 QSIs but also AI-1 QSIs. In addition, research has found that MTAN exists in most microbial pathogens but is not found in mammals. MTAN inhibitors selectively inhibit or kill pathogenic microorganisms without affecting the host population[154]. Therefore, developing new inhibitors targeting MTAN is of great significance. Shen et al.[155] designed and synthesized a series of structural analogues of the substrate SRH and a 2-ketone intermediate, and found that the compounds act as reversible, competitive inhibitors against LuxS. Han et al.[156] found that phage-encoded peptides specifically interact with the LuxS enzyme, especially the peptide inhibitor (TNRHNPHHLHHV), which partially inhibits the activity of the enzyme. Brackman et al.[157] found that nucleoside analogues could disturb AI-2. The mechanism most likely interfered with the

signal transduction pathway at the level of LuxPQ in *V. harveyi*. The most active nucleoside analogue (designated LMC-21) was found to reduce the *Vibrio* species starvation response, to affect biofilm formation in *Vibrio anguillarum*, *V. vulnificus*, and *V. cholerae*, to reduce pigment and protease production in *V. anguillarum*, and to protect gnotobiotic Artemia from *V. harveyi*-induced mortality[157]. Ducati et al.[158] determined the inhibition constants for potential transition-state MTAN analogues of *C. jejuni*. The result showed that the most potent *Cj*MTAN transition-state analogue inhibitors inhibited the growth of *C. jejuni* at low micromolar concentrations[158]. DPD analog inhibitors play a crucial role in the AI-2-mediated QS system. Research has found that analogues of DPD have inhibitory effects on the QS system. Roy et al.[159] developed C-1 alkyl analogs of AI-2 that block the QS system in multiple bacterial species simultaneously. The analogs were activated by LsrK, and modulated AI-2 specific gene transcription through the transcriptional regulator, LsrR, and suppressed QS phenomenon[159]. They also found that the C1-alkyl AI-2 analog (isobutyl-DPD) could inhibit the maturation of *E. coli* biofilms grown *in vitro*. Furthermore, another AI-2 analog, phenyl-DPD, used in combination with gentamicin, could clear preformed *P. aeruginosa* biofilms[160]. Stotani et al.[161] designed a library of DPD derivatives. Results showed that 4 compounds were found to be micromolar LsrK inhibitors[161].

6. Conclusion and future perspectives

Mastering and proficiently harnessing mechanisms to regulate biofilm formation and the VBNC state offers a novel paradigm for controlling foodborne bacteria, holding immense potential. Currently, the exploration of QS in foodborne bacteria is nascent, confronting formidable challenges. Existing QS research in food primarily centers on singular, pure-culture microorganisms, thereby limiting the authenticity of insights into QS's role in food spoilage. Future endeavors must address elucidating the QS systems governed by diverse signaling molecules of foodborne bacteria, intricate regulatory networks involving coexisting bacteria, and mechanisms of transboundary signal transduction and molecular interplay between bacteria and eukaryotes. Secondly, recent investigations reveal that bacterial QS-mediated group behavior encompasses not only mutual communication and cooperation but also eavesdropping and deception, where individuals exploit public substances without contributing[222-223]. In the QS process, cooperators expend significant resources to synthesize public substances for group stability. Conversely, cheaters rely solely on environmental public substances, secreting minimal or none, allowing them to redirect resources toward growth and reproduction, thus gaining a competitive advantage. This revelation significantly expands the QS research landscape, offering novel perspectives for the control of harmful microorganisms[224]. The interplay and underlying mechanisms of QS-mediated cooperation and deception constitute a critical focus for future investigations. Thirdly, the traditional approach to screening and validating QSIs is inefficient and lacks specificity, significantly limiting their application in food science. Computer-aided virtual screening technology offers a promising solution. By harnessing computational capabilities such as data processing, storage, visualization, and predictive modeling, this approach can streamline QSI screening and design, reducing experimental costs and accelerating research progress. Future research may focus on leveraging natural product databases, particularly those of marine origin, to identify novel, highly active QSIs, thereby providing novel strategies for targeted control of foodborne bacteria[225]. Fourthly, food packaging materials incorporating QSIs have emerged as promising agents for inhibiting foodborne bacterial growth. The integration of QSIs with technologies such as liposomes and microcapsules can enhance their bioavailability, bolstering their application in food preservation. Finally, given the diverse QS signaling molecules of foodborne bacteria and their complex mechanisms of action, a profound understanding of the QS systems of various bacteria and the underlying mechanisms of signaling molecules is imperative for effective utilization.

To sum up, although there is still insufficient research on the QS system of foodborne bacteria to regulate biofilm formation and VBNC state, it can be determined that quenching the QS pathway of foodborne bacteria, regulating phenotypes related to food quality and safety, and developing safe and pollution-free preservatives for a new generation is of great significance for enhancing the shelf life of food.

Conflict of interest

There is no conflict of interest.

Acknowledgments

This research was financially supported by the National Natural Science Foundation of China (32202191) and (32272279), the Key R&D Project of Shandong Province (2023CXPT007 and 2024CXPT014), and the Key R&D Project of Qingdao Science and Technology Plan (24-2-3-4-zyyd-jch).

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