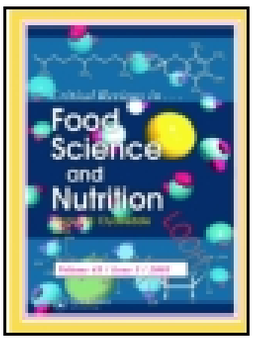

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REVIEW

Current and future perspectives for controlling *Vibrio* biofilms in the seafood industry: a comprehensive review

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ABSTRACT

The contamination of seafood with *Vibrio* species can have severe repercussions in the seafood industry. *Vibrio* species can form mature biofilms and persist on the surface of several seafoods such as crabs, oysters, mussels, and shrimp, for extended duration. Several conventional approaches have been employed to inhibit the growth of planktonic cells and prevent the formation of *Vibrio* biofilms. Since *Vibrio* biofilms are mostly resistant to these control measures, novel alternative methods need to be urgently developed. In this review, we propose environmentally friendly approaches to suppress *Vibrio* biofilm formation using a hypothesized mechanism of action.

KEYWORDS

Vibrio species; contamination; seafood; biofilm formation; biofilm control

Introduction

Vibrio species (spp.) are free-living, gram-negative bacteria found in the gastrointestinal (GI) tracts of marine organisms (Thompson et al. 2004), and are responsible for vibriosis, which causes extensive economic loss in the aquaculture industry (Liu et al. 2013). Various *Vibrio* spp. can contaminate seafoods and are responsible for human gastrointestinal diseases (Iwamoto et al. 2010), which present various symptoms including vomiting, headache, and nausea (Xi et al. 2012). It is, therefore, crucial to develop new environmentally friendly strategies to control *Vibrio* contamination and protect public health.

Seafood safety is considered essential in seafood processing to ensure public welfare. Because the consumption of raw seafood is a possible source of foodborne infection (Jahan 2012), *Vibrio* spp. poses a substantial threat on the safety of seafood consumption, and poses a challenge for the seafood industry (Aagesen et al. 2013).

Aggregations of bacterial cells on biotic or abiotic surfaces are known as biofilms (Mizan, Jahid, and Ha 2015). Approximately 80% of bacterial infections in the body, and diseases associated with bacterial biofilms, include lung infections from cystic fibrosis, as well as colitis, urethritis, conjunctivitis, otitis, endocarditis, and periodontitis (Harro et al. 2010; Worthington et al. 2012). Certain *Vibrio* spp., including *Vibrio harveyi* (Karunasagar, Otta, and Karunasagar 1996), *Vibrio cholerae* (Faruque et al. 2006), *Vibrio vulnificus* (Joseph and Wright 2004), *Vibrio alginolyticus* (Kogure et al. 1998), and *Vibrio parahaemolyticus* (Mizan et al. 2017; Elexson et al. 2013), are capable of forming biofilms on seafood as well as on surfaces that come into contact with food (Mizan et al. 2016). As with other microorganisms, factors such as biofilm formation (Yildiz and Visick 2009; Rodrigues et al. 2015), resistance to antimicrobial drugs (Shaw et al. 2014; Baker-Austin 2015), hydrophobicity, quorum sensing (QS), and motility (Mizan et al. 2016) enable the long-term survival of *Vibrio* spp. and consequently, the incidence of foodborne illnesses (Yildiz and Visick 2009; Rodrigues et al. 2015).

The increasing incidence of antibiotic resistance in *Vibrio* spp. has generated growing interest in identifying new strategies to prevent infections related to *Vibrio* biofilms (Su and Liu 2007). While both chemical and physical methods have been used to control bacterial biofilms, these techniques are also limited by the health risks they pose (Donato and Zani 2010). Additionally, biofilms can adapt to continuous exposure to chemical products, resulting in highly resistant microbes. This situation highlights the need to develop effective antibiofilm agents for the benefit food-processing companies. Biosurfactants, enzymes, proteins, phages, and natural plant extracts have been evaluated as novel antibiofilm products against *Salmonella*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Listeria monocytogenes*, and *V. harveyi* (Donlan 2009; Bajpai et al. 2012; Huang et al. 2014; Hamza et al. 2016). Only a few environmentally friendly antibiofilm agents are able to disrupt cell membranes and are effective against biofilm-related infections from *Vibrio*. spp. (Kiran et al. 2010; Elexson et al. 2013; Manju et al. 2014; Rajalaxmi et al. 2016; Xie et al. 2017).

Surfaces that come into contact with food are generally sanitized with commercial chemical disinfectants (i.e., peroxides, chloramines, and hypochlorites) to mitigate the

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undesirable effects of *Vibrio* biofilms (Meireles et al. 2016). These disinfectants do not always effectively inactivate bacterial cells in a biofilm (Bermúdez-Aguirre and Barbosa-Cánovas 2013). In addition, the risk of product contamination and toxicity can limit the use of these commercial chemical compounds (Akbas 2015). Therefore, there is an urgent need to develop eco-friendly antibiofilm compounds for the seafood industry (Akbas 2015). It has been reported that natural antibiofilm agents are able to disrupt lipid membranes and mitochondria, as well as affect the bacterial biological structure without having adverse effects on human health (Beyth et al. 2015). Nonetheless, several studies have demonstrated the dynamic inactivation effects of antibiofilm agents against *Vibrio* spp. (Radjasa et al. 2005; Packiavathy et al. 2013; Wang et al. 2015; Mizan et al. 2018; Krishna et al. 2019).

The objective of this review is to provide pertinent information on *Vibrio* biofilm formation and environmentally friendly antibiofilm agents for neutralizing *Vibrio* biofilms. In addition, a hypothetical mechanism whereby eugenol inhibits biofilm formation is proposed, suggesting a possible direction for future research.

Adhesion to the surface of seafoods

Bacterial adhesion normally occurs in two stages, namely via reversible and irreversible attachment (An and Friedman 2000). It is typically the first step in the biofilm formation process, which generally comprises several distinct steps. (1) Reversible attachment initially occurs, and is dependent on bacterial motility, diffusion force of the phage's surrounding fluid (Kumar and Anand 1998), and physiochemical properties of the bacterial cell surface (Ferreira et al. 2010). This reversible attachment may occur on biotic or abiotic surfaces via van der Waals forces (Donlan 2002). (2) Irreversible attachment of bacterial cells to the surface occurs next, through hydrophilic or hydrophobic interactions, whereby flagella, fimbriae, lipopolysaccharides, or adhesive proteins play an important role (Sadekuzzaman et al. 2015). (3) Microorganism aggregation follows, and is associated with the production of exopolysaccharides (EPS), a matrix generally composed of polysaccharides, extracellular deoxyribonucleic acid (koraichi Saad et al. 2011), and proteins. (4)) Next in the biofilm architecture is development (Srey, Jahid, and Ha 2013), whereby the mature biofilm develops into an organized structure with water channels that perfectly distribute nutrients and signaling molecules within the biofilm (Dufour, Leung, and Lévesque 2010). (5) Dispersion is the final step in the cycle of biofilm formation, whereby, the cells are allowed to revert individually into their planktonic form (Sauer et al. 2002). An enzymatic degradation increases the release of EPS, which creates the active/passive onset of biofilm dispersion (Nahar et al. 2018). Biofilm formation is dependent on ensuring that microorganisms move closer to the targeted surface and on increasing the structure complexity by promoting intercellular communication. The steps required to complete biofilm formation are illustrated in Figure 1.

Pathogenic *Vibrio* spp. are capable of adhering to the surface of seafood (Abdallah et al. 2009). The capsule of the pathogenic *Vibrio* spp. plays a key role in sustaining a strong interaction between the bacterium and its environment (Paranjpye and Strom 2005; Tercero-Alburo et al. 2014). Several bacterial surface factors and extracellular proteins have been implicated in the pathogenesis of *V. vulnificus*, including an EPS capsule (Strom and Paranjpye 2000). Wright et al. (1990) reported that the polysaccharide capsule was associated with *V. vulnificus* virulence. While cell-

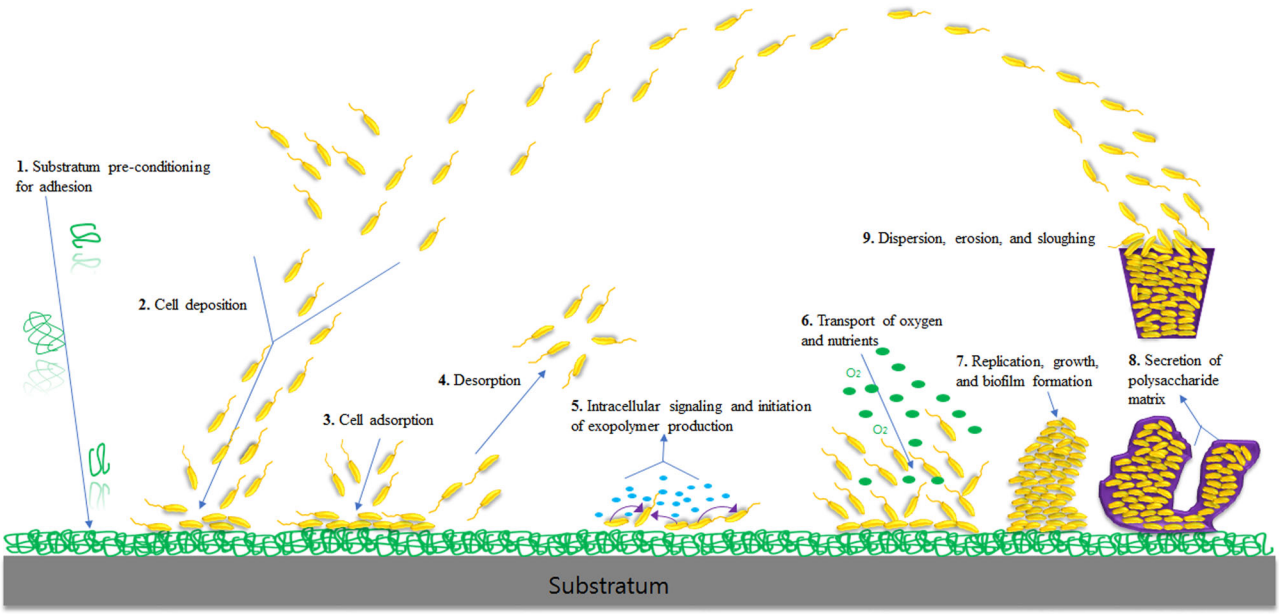

Figure 1. Graphical representation of a hypothetical model of the biofilm-formation process: (1) Substratum preconditioning for surface adhesion of ambient molecules present in the bulk liquid. (2) Transport of planktonic cells to the substratum. (3) Attachment of cells to the surface via either a specific or nonspecific binding reaction. (4) Return of the reversibly adsorbed bacteria into the liquid if the adhesion is weak. (5) Irreversible adsorption to the substratum by intercellular attachment and signaling mechanisms. (6) Production and exchange of signaling molecules between cells. (7) Transport of substrates needed for biofilm assembly. (8) Substrate metabolism with replication, growth, and EPS production. (9) Biofilm dispersion by sloughing (Bryers and Ratner 2004; Simões et al. 2010).

associated bacterial proteins have been implicated in the ability of *V. vulnificus* to cause disease, the presence of the EPS capsule has been positively correlated with virulence (Paranjpye and Strom 2005). The subsequent identification of virulence factors that contribute to the pathogenesis of *Vibrio* species has been especially challenging.

The double flagellar system has been shown to significantly contribute to surface colonization (Stewart and McCarter 2003; Tian et al. 2008). Flagella (complex surface organelles) are a major source of bacteria, which manifest their virulence through adhesion and biofilm formation on host surfaces (Merino, Shaw, and Tomás et al. 2006). Flagellar motility has been recognized as an important virulence factor in *Vibrio* species. In *Vibrio cholerae*, the polar flagellum is important to promote motility, as well as attachment and colonization. Martinez et al. (2010) reported that the novel flagellar protein *FlgT* functions to stabilize the flagellar apparatus at the pole of the cell. *V. cholerae* flagella may affect motility for irreversible attachment and microcolony formation (Utada et al. 2014). The flagellar assembly pathway influenced adhesion ability in *V. alginolyticus* under environmental stress conditions (Wang et al. 2015). Polar flagellar protein from *V. parahaemolyticus*, purified by differential centrifugation, contributed to cell adhesion and colonization (Hongprayoon 1993). Functional flagella systems influence the virulence of pathogenic *V. parahaemolyticus* through adhesion and biofilm formation on host surfaces (Merino, Shaw, and Tomás 2006).

The two type-IV (IVa and IVb) pili are important factors which enable *Vibrio* adhesion and horizontal gene transfer as well as biofilm formation (Paranjpye and Strom 2005; Aagesen and Häse 2012; Shime-Hattori et al. 2006; Pelicic 2008; Hasan et al. 2010). The initial attachment and microcolony formation for biofilm development are influenced by type IV pili during biofilm formation (Klausen et al. 2003). The three main human pathogenic *Vibrio* species, i.e., *V. cholerae, V. parahaemolyticus*, and *V. vulnificus* are major contributors in colonization, as they possess *mshA* and *pilA* genes, as well as their corresponding amino acid sequences (Aagesen and Häse 2012). *pilA, pilD*, and type IV pili play an essential role in the ecology of *V. vulnificus* (Paranjpye and Strom 2005). For example, *pilA* contributed significantly to *V. vulnificus* aggregation and adhesion to human epithelial cells, as well as to biofilm formation on abiotic surfaces (Paranjpye and Strom 2005). Hang et al. (2003) reported that, during human infection with *V. cholerae*, the homologous *pilA* gene may be expressed and involved in colonization of the gastrointestinal tract. The environmental conditions may enhance *pilA* expression and help to colonize on shellfish such as oysters (Paranjpye and Strom 2005). Bacteria display different mechanisms which enable them to specifically interact with target cells. Pili or fimbriae are typically produced from the surface structures, which are often important for survival (Mandlik et al. 2008; Kline et al. 2009). Type IV pili play different roles to assist *Vibrio* species with their survival in various environments, as well as with attachment to a variety of surfaces for biofilm formation (Enos-Berlage et al. 2005; Shime-Hattori et al. 2006). Type IV pili may increase the persistence of *V. vulnificus* in *Crassostrea virginica* oysters (Paranjpye et al. 2007).

In aquatic environments, mannose-sensitive hemagglutinin (MSHA) pilus is used as a survival strategy, to adhere to zooplankton exoskeletons for biofilm formation (Chiavelli, Marsh, and Taylor 2001; Moorthy and Watnick 2004). In *V. cholerae* and *V. parahaemolyticus,* MSHA pilus is used to form biofilms on various surfaces (Moorthy and Watnick 2004; Shime-Hattori et al. 2006), including chitin (Meibom et al. 2004), providing relevant evidence for the role of the MSHA pilus in environmental survival.

The *V. cholerae* outer membrane protein (OmpU) is positively regulated by *toxR*, which may also regulate virulence factors (cholera toxin and toxin-coregulated pilus, which are critical virulence factors of *V. cholerae*) to influence colonization. OmpU exhibits adhesive properties to increase *V. cholerae* pathogenesis. Reports have also described the biochemical, immunological, and functional characterization of OmpU and presented evidence that OmpU may adhere to fibronectin, laminin, collagen, and components of eukaryotic cells, as well as enhance *V. cholerae* adherence to cultured epithelial cells (Sperandio et al. 1995). Bacterial adhesin plays an important role in enhancing the bacterial adhesion to host cells, which in turn initiates bacterial infection of the host (Liu and Chen 2015).

Recently, the novel adhesin gene *vp*1767, referred to as V*pad*F (*V. parahaemolyticus* adhesive factor), was identified and characterized from *V. parahaemolyticus*. It is an essential adhesion factor of *V. parahaemolyticus*, and plays an important role in the attachment, cytotoxicity and pathogenicity against epithelial cells (Liu and Chen 2015). V*pad*F has been distinguished through previously described features of adhesive factors, such as MSHA pilus, enolase, capsular polysaccharides, T6SSs, and outer membrane adhesion factor multivalent adhesion molecule 7 (MAM7) in *V. parahaemolyticus*. *Vpad*F shows multifunctional activity by enhancing interaction activity with both Fn and Fg. This adhesin is able to bind with Fg in *Vibrio* species, and increase the penetration ability of host barriers, and spread in tissues (Rivera et al. 2007). Both the attachment of *V. parahaemolyticus* to epithelial cells and the spread of this pathogen in infected tissues are regulated by the *Vpad*F adhesin factor. The mechanism of action of the interactions between *Vpad*F and host receptors is different from that of other *Vibrio* adhesins (Goo et al. 2006; Krachler and Orth 2011). These structures (i.e., capsules, flagella, and pili) on the membranes of *Vibrio* spp. may contribute to the mechanism of pathogenicity (Thompson, Klose, and Group 2006; Tian et al. 2008; Shime-Hattori et al. 2006). Therefore, the production of these exopolymers is considered to be the first step in biofilm formation (Muller et al. 1993). Nonetheless, pili, flagella, bacterial membrane proteins, MAM7, and other materials influence bacterial attachment to surfaces (Wong et al. 2002; Abdallah et al. 2009; de Souza Santos et al. 2015). Studies have shown that MAM7, MSHA pilus, and capsular polysaccharides also contributed to *V. parahaemolyticus* cell attachment (Krachler et al. 2011; Yu et al. 2012; O'Boyle et al. 2013; Jiang et al. 2014; Liu and Chen 2015). It

was stated that *Vibrio* spp. possess a great ability to adhere to biotic and abiotic surfaces (Abdallah et al. 2009). The major types of bacterial and host factors involved in the attachment of *V. parahaemolyticus* to a surface are presented in Figure 2.

Vibrio biofilm

Biofilm formation based on environmental factors

Vibrio spp. is considered a prominent fish pathogen owing to their common biofilm formation in marine environments and on equipment from the seafood industry (Shikongo-Nambabi, Kachigunda, and Venter 2010; Yang et al. 2014). In fish-processing plants, *Vibrio* can generate mature biofilms in seawater distribution networks during plant operations (Shikongo-Nambabi et al. 2010). The *Vibrio* biofilm is formed by subsequent bacterial settlement in areas with suitable food sources and nutrients (Yang et al. 2014). A *Vibrio* biofilm can easily form on seafoods, thus creating a barrier between the environment and bacteria, which then exhibit lower sensitivity to disinfectants (Kerekes et al. 2015). *V. vulnificus* infected fish (such as eel and tilapia) under aquaculture conditions, resulting in economic losses (Fouz et al. 2006). The ability of *V. harveyi* to form biofilms on various food contact surfaces, such as glass, plastic, and stainless steel, has been evaluated by Karunasagar, Otta, and Karunasagar (1996) and Chari, Viswadeepika, and Kumar (2014). In seafood-processing environments, *V. cholerae* has demonstrated biofilm-formation capabilities on stainless steel (Fernandez-Delgado et al. 2016). In food-processing environments, *V. parahaemolyticus* survives by forming biofilms on shrimp, crabs, oysters, mussels, stainless-steel coupons, and glass surfaces (Wong et al. 2002; Aagesen et al. 2013; Han et al. 2016; Mizan et al. 2018; Ashrafudoulla et al. 2020). Field-emission scanning-electron microscopy (FE-SEM) images of *V. parahaemolyticus* biofilm formation on different surfaces (stainless-steel, shrimp, crabs, and mussels) are shown in Figure 3 (courtesy of the corresponding author's laboratory) to illustrate the versatility of this microorganism when exposed to different material and tissue types.

Factors affecting of biofilm formation

Vibrio biofilm formation is highly dependent on several factors including the medium, substratum, as well as physical and chemical properties of surfaces (Renner and Weibel 2011). The temperature regime, hydrodynamic conditions, and water quality were recognized as the main factors affecting biofilm formation (Krivorot et al. 2011). Hydrodynamic conditions affected biofilm formation by influencing the temperature polarization rates of microbial attachment and nutrient supply (Krivorot et al. 2011). Gryta (2002) reported that bacteria were able to grow in extreme temperature and pH conditions. Cell attachment and biofilm development were increased through a significant relationship among substrate, bacterial species, and fluid present on the targeted surface (Renner and Weibel 2011). Molecular, mechanical, and topographical factors also contribute to bacterial cell attachment. Carbon source, fluid flow, nutrient media composition, and growth factors present around the substrate may significantly contribute to bacterial attachment and biofilm formation (Ista et al. 2009). The substrate's physicochemical properties may influence adsorption, adhesion, and

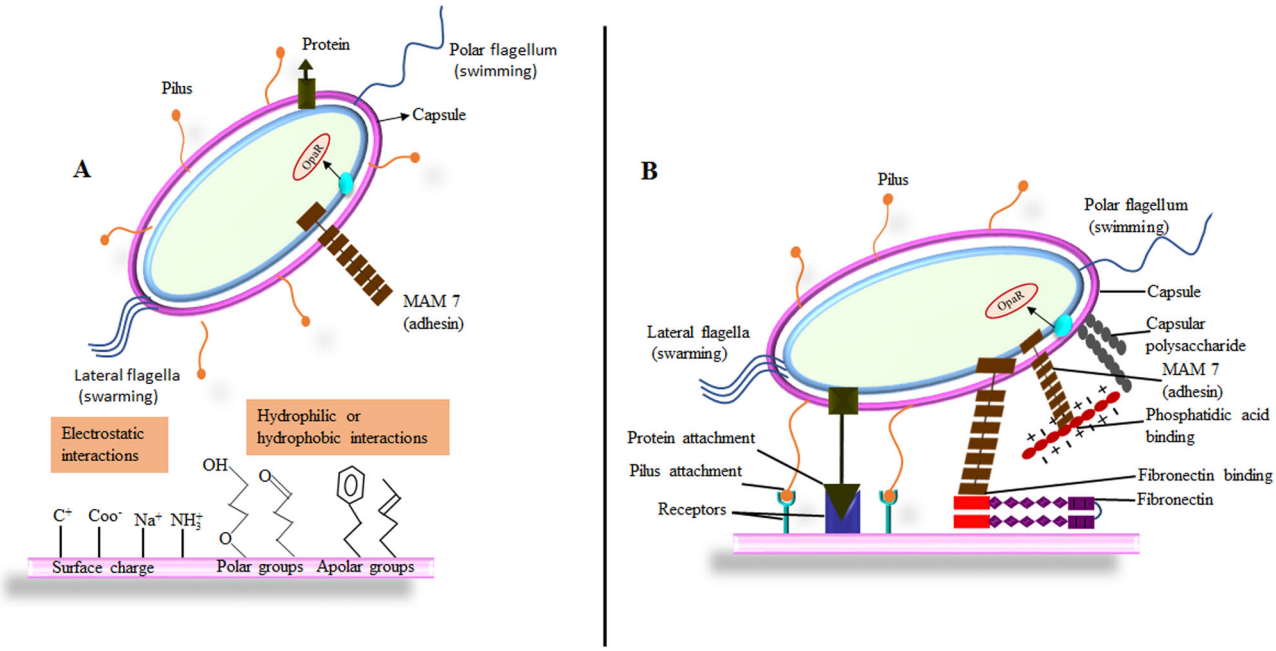

Figure 2. Adhesins as factors mediating *V. parahaemolyticus* adhesion to the surface of host cells. (A) *V. parahaemolyticus* generally possesses two types of flagellar systems. Polar flagella equip bacteria for swimming, whereas lateral flagella equip bacteria for swarming (McCarter 1999; McCarter 2004). The pili, capsule, and MAM 7 aid in bacterial attachment to the host cell. In addition, the electrostatic, hydrophobic, and hydrophilic properties of the medium, and the surface charge are important factors influencing the attachment of bacterial cells. (B) The pili and capsular protein bind to different receptors. The capsular polysaccharide is produced with the activation of OpaR and influences opaque bacterial colonies (Gode-Potratz and McCarter 2011). The multimeric adhesin MAM 7 binds to fibronectin and phosphatidic acids, which is important for initial attachment to the host cell.

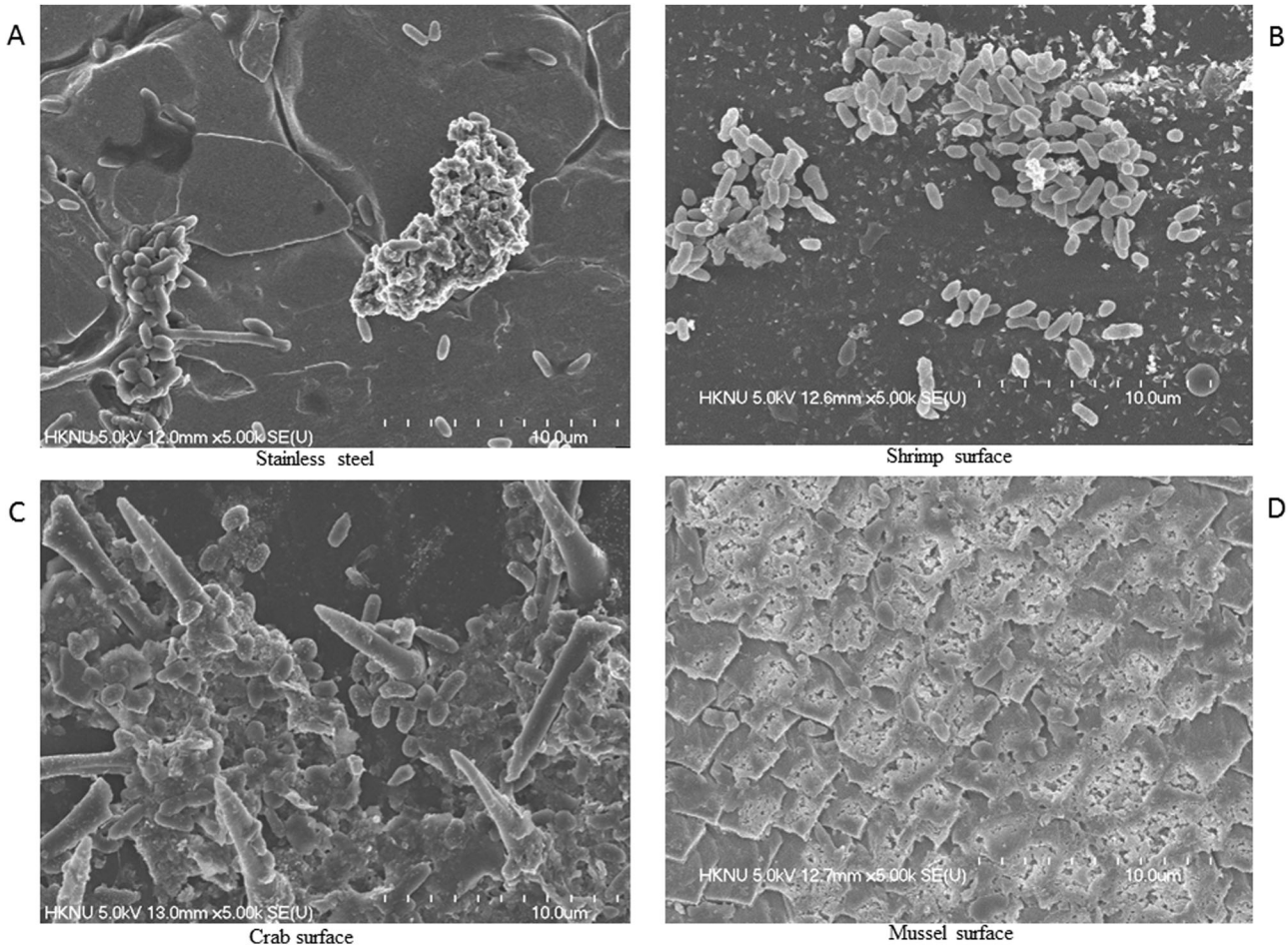

Figure 3. Biofilm formation of *V. parahaemolyticus* (ATCC17802) on different surfaces. (A) A representative SEM image of *V. parahaemolyticus* on stainless steel (food grade 304). (B) Representative SEM image of *V. parahaemolyticus* on the surface of a shrimp (*Penaeus monodon*). (C) Representative SEM image of *V. parahaemolyticus* on the surface of a crab (*Corystes cassivelaunus*). (D) Representative SEM image of *V. parahaemolyticus* on the surface of a mussel (*Mytilus coruscus*).

diffusion, which regulate the physiology of bacteria as well as their biofilm production, by inducing stiffness, mechanical stability, and elasticity, as well as by affecting topography (Flemming and Wingender 2010; Renner and Weibel 2011). Carboxylate, hydroxyl, phosphate, and amine moieties are functional groups of bacterial cells that may interact with substrates and enhance cell attachment (Hong and Brown 2008). Surface roughness, e.g., nano- and micro-scale surface roughness, may increase the adhesion of bacteria to substrates for biofilm formation. Moreover, physicochemical and biological factors such as surface hydrophobicity (Van Loosdrecht et al. 1987), extracellular polymeric materials (Characklis 1990), surface charge, and swimming speed (Marshall, Stout, and Mitchell 1971), are important in biofilm formation. Biofilm formation is also dependent on the organic or inorganic conditions of the surface layer. This conditioning layer helps the bacteria to form a colony on the targeted surface (Bryers and Ratner 2004). Other variables that may affect biofilm formation are listed in Table 1.

Molecular mechanism of Vibrio biofilm formation

The genetic factors of *Vibrio* species play an important role in biofilm development and intestinal colonization. Flagella-mediated motility promotes the initial stage of biofilm formation by enhancing movement toward the surface (O'Toole, Kaplan, and Kolter 2000). Watnick et al. (2001) reported that the *V. cholerae* O139 mutant aggregated in broth culture and attached on the surface with increased biofilm formation. In *V. parahaemolyticus*, the polar flagellum promotes biofilm formation (Enos-Berlage et al. 2005), while *flgE* and *flgD* significantly contribute to the process (Enos-Berlage et al. 2005). *flgE* also contributes to biofilm formation in *V. vulnificus* and *V. fischeri* (Lee Jong-Ho et al. 2004; Hussa et al. 2008). Ashrafudoulla et al. (2019) reported that the biofilm formation-related genes VP950, VP952, and VP962 enhance *V. parahaemolyticus* cell attachment on shrimp and mussel surfaces to form a strong biofilm. The genetic context of *Vibrio* spp. cells, together with surface type, may enhance pili for attachment (Yildiz and Visick 2009). In *V. cholerae*, the MSHA pilus structural gene *mshA* plays an important role in planktonic cell aggregation and 3-D biofilm formation (Moorthy and Watnick 2004). In numerous *Vibrio* spp., EPS production is also involved in biofilm formation. Fong et al. (2010) demonstrated that various *vps* genes contribute to VPS production for *V. cholerae* pathogenesis and biofilm development. In *V. fischeri*, biofilm formation is dependent on a polysaccharide biosynthetic gene cluster (*syp*) consisting of 18 genes, which is absent in *V. cholerae* but conserved in *V. parahaemolyticus* and *V.*

Table 1. Important variables promoting biofilm formation (Donlan 2002; Lipp et al. 2002; Tantillo et al. 2004; Simões et al. 2010).

Surface properties	Aqueous medium properties and factors	Cellular properties
Conditioning film or acquired pellicle	pH, salinity	Production of exopolysaccharides
Solid–liquid-interface chemistry	Presence of nutrients	Presence of fimbriae
High surface area	Temperature	Presence of flagella
Non-polarity	Ionic strength	Production of microbial cells
Roughness or texture	Hydrodynamics	Presence of proteins
Surface charge	Reduced repulsive forces	Extracellular polymeric fibrils
Physicochemical properties	Different aqueous systems	Abilities of signaling molecules
Strength of hydrophobicity	Oxygen content	Cell surface hydrophobicity

vulnificus (Yip et al. 2006; Yildiz and Visick 2009). Global regulators play an important role in biofilm formation in the vibrios, e.g., RR *VpsR* is recognized as a key regulator of biofilm formation in *V. cholerae*. *VpsR* can also promote transcription of the *vps* genes and contribute to form typical 3-D biofilm structures (Yildiz, Dolganov, and Schoolnik 2001; Yildiz et al. 2004). C-di-GMP (a second messenger) significantly contributes to maintain the biofilm lifestyle of bacterial cells (Römling and Amikam 2006), including vibrios (Lim et al. 2006; Ferreira et al. 2008; Nakhamchik et al. 2008; Yildiz and Visick 2009). In *V. cholerae*, c-di-GMP enhances biofilm formation by stimulating *vps, vpsR*, and *vpsT* gene transcription (Beyhan et al. 2006; Lim et al. 2006). Biofilm formation in *V. parahaemolyticus* is increased with increasing c-di-GMP levels, which are controlled by the *scrG* and *scrC* genes (Ferreira et al. 2008; Yildiz and Visick 2009). In *V. vulnificus*, *dcpA* expression may influence biofilm formation without impacting on motility (Nakhamchik, Wilde, and Rowe-Magnus 2008). In *V. fischeri*, overexpression of the putative *MifA* enhances biofilm formation. Therefore, c-di-GMP plays a substantial role in biofilm formation in *V. fischeri* (O'Shea et al. 2006). Despite their similar regulatory proteins and common signaling systems, each *Vibrio* species possesses a unique biofilm regulatory circuitry. Differences in regulation and environmental parameters may reflect the biofilm lifestyle of each *Vibrio* species during their in vivo and in vitro life cycles.

Quorum sensing (QS)

Bacteria use different signaling pathways to develop antibiotic resistance and form biofilms. QS is a widely recognized process through which *Vibrio* can coordinate their behavior (i.e., swarming, bioluminescence, biofilm formation, adhesion, virulence factor production, stress resistance, biofilm antimicrobial tolerance, and toxin production) and molecular signals in a cellular consistency-dependent manner (Zhu and Mekalanos 2003; Waters and Bassler 2005; García-Aljaro et al. 2012). QS is an intercellular communication mechanism that mediates the creation of biofilms by coordinating individual and group behaviors (Liu, Stirling, and Zhu 2007). It is, therefore, an important signaling phenomenon that helps coordinate the bacterial population in terms of the expression of virulence genes (Tay and Yew 2013). QS molecules and associated receptors are important components of an effective QS system. Data from several studies have demonstrated the presence of several QS molecules, such as N-acyl-homoserine lactone (AHL), *harveyi* autoinducer -1 (HAI-1), cholerae autoinducer-1-like (CAI-1), and autoinducer-2 (AI-2), in the family *Vibrionaceae* (Milton 2006; Higgins et al. 2007; Defoirdt et al. 2008; Yang et al. 2011; Mizan et al. 2016). QS molecules participate in the mechanisms of pathogenicity of these bacteria (Garcia-Aljaro et al. 2008) and influence the growth rate and expression of the luminescence genes in *Vibrio* spp. (Bassler et al. 1997; Nackerdien et al. 2008).

Quorum sensing regulates biofilm formation

QS is a chemical communication that occurs in bacteria. It is a central process in biofilm development. Bacterial cells use the QS mechanism to modulate a variety of cellular functions such as nutrient acquisition, motility, and secondary metabolite production (Harmsen et al. 2010). *Vibrio* species use QS to induce luminescence, virulence, as well as biofilm formation (Yildiz and Visick 2009). In *V. harveyi*, the endpoint regulator is termed *LuxR* (Waters and Bassler 2005), and the components of this pathway have been detected in all other vibrios studied to date. The *V. parahaemolyticus LuxR* homolog and *opaR* genes positively regulate opacity and *cps* gene expression, as well as influence biofilm formation (McCarter 1998). The overexpression of *opaR* positively influences *cps* gene expression and colony opacity. A similar phenomenon has been observed in both *V. vulnificus* and *V. fischeri* (Fidopiastis et al. 2002). In the case of *V. cholerae*, the *LuxR* homolog and *HapR* genes increased *vps* expression and indicated that *HapR* is a negative regulator of biofilm formation. *HapR* represses the expression of *vpsT*, through binding with DNA (Waters et al. 2008). Therefore, QS in *V. cholerae* behaves in a contrasting manner relative to the other vibrios, in the control of cell surface properties and biofilm formation (Yildiz and Visick 2009).

Quorum sensing regulates virulence factors

The presence of the QS system in four *Vibrio* pathogens (*V. fischeri*, *V. harveyi*, *V. cholerae*, and *V. vulnificus*) were reviewed by Liu et al. (2013). *Vibrio fischeri* and *V. harveyi* possess three parallel signal-transduction circuits that correlate separately with three different autoinducers. In addition, *V. cholerae* has two parallel QS circuits (CAI-1 and AI-2), whereas *V. vulnificus* has only one (AI-2). According to Liu et al. (2013), it was shown that every described *Vibrio* spp., including *V. parahaemolyticus*, possesses common autoinducer molecules such as AI-2. The type-III and type-VI secretion systems are highly conserved among various *Vibrio* spp. such as *V. harveyi*, *V. cholerae*, and *V. parahaemolyticus*. Both secretion systems form needlelike pores connecting the bacterial and host cell membranes, and immediately

inject effector proteins (generally virulence factors)into the targeted eukaryotic host cells (Waters et al. 2010; Zheng et al. 2010; Ma et al. 2012).

QS in *Vibrio* species occurs through various physiological processes and influence the virulence system (Liu et al. 2013). Exotoxin plays important role in allowing bacteria to invade and spread to different tissues by enabling pore formation in the host cell. In *V. vulnificus*, the expression of major virulence factors such as *vvpE* occurred with increasing cell density. This expression was enhanced by *LuxS* and *SmcR* (Kim et al. 2003; Roh et al. 2006). In *V. alginolyticus*, the extracellular alkaline serine protease *asp* is a major virulence factor and is strongly related to QS. Its production is generally dependent on cell density. The *LuxR* regulator is the core element of QS and regulates *asp* expression by binding with its promoter and activating *asp* gene transcription (Wang et al. 2009). *V. cholerae* contains two main virulence factors, cholera toxin (CT) and toxin-coregulated pilus (TCP), which are encoded by the *ctx* and *tcp* gene clusters, respectively, and indirectly activated by *aphA*. At low cell density, *aphA* expression is increased, while *HapR* inhibits the transcription of *aphA* through expression, causing pathogenicity (Zhu et al. 2002). During infection, the *LuxS* QS system is involved in coordinating the regulation of virulence expression (Kim et al. 2003). The transcriptional activator *toxRS* in *V. vulnificus* regulates hemolysin production in *V. cholerae* (via transmembrane regulator *toxRSvc*), and is suggested as a regulator of virulence in *V. vulnificus* (Miller and Mekalanos 1984; Lee et al. 2000).

Multidrug resistance profile of *Vibrio* and their resistance mechanism

Multidrug resistance of Vibrios

The farming of marine organisms such as shrimp requires a large number of antimicrobials as growth promoters. The inappropriate administration of these antimicrobials is a major cause of bacterial multidrug-resistance (Santos Rocha et al. 2016; Ashrafudoulla et al. 2017; Ashrafudoulla et al. 2019). *Vibrio parahaemolyticus* has been shown to develop resistance against various antibiotics, including ampicillin, streptomycin, ciprofloxacin, clindamycin, cefotaxime, cephazolin, tetracycline, penicillin, vancomycin, and cefuroxime sodium (Al-Othrubi et al. 2014; Sudha et al. 2014; Yano et al. 2014; Ashrafudoulla et al. 2019). The multidrug resistance (MDR) profile of *V. parahaemolyticus* is also gradually expanding due to the excessive use of antibiotics in aquaculture (Kang et al. 2017). This emerging incidence of antibiotic resistance is of major concern and requires new strategies to be developed to prevent *V. parahaemolyticus* biofilm-related infections (Su and Liu 2007). In previous studies, the MDR of *V. vulnificus* strains were identified with resistance to apramycin, streptomycin, ampicillin, lincomycin, carbenicillin, cephalosporins, ceftriaxone, colistin, amoxycillin, penicillin, furazolidone, nalidixic acid, sulfamethoxazole, gentamicin, cefazolin, tobramycin, or cephalothin (Baker-Austin et al. 2009; Okoh and Igbinosa 2010; Raissy et al. 2012; Pan et al. 2013; Shaw et al. 2014; Elmahdi, DaSilva, and Parveen 2016). The MDR properties of *Vibrio* spp. have caused serious public health problems and economic concerns (Elmahdi, DaSilva, and Parveen 2016). For example, *V. cholerae* has developed resistance to various antibiotics, such as kanamycin, tetracycline, streptomycin, trimethoprim, sulfonamides, and trimethoprim-sulfamethoxazole, creating significant problems in developing countries (Vila and Pal 2010). Bacterial resistance to common antibiotics can lead to the failure of available treatment options for general infections (Aarestrup 1999), creating an urgent need for the development of promising natural biocontrol agents without adverse effects.

Specific resistance mechanism

Bacteria typically possess different mechanisms to display resistance against several types of antibiotics. Similar to other *Vibrio* species, *V. cholerae* exhibits its antibiotic resistance mechanisms through efflux pumps, conjugative plasmids, and chromosomal mutation, amongst others. It exports drugs through efflux pumps, while mutations may occur in the chromosome via the exchange of conjugative plasmids, to develop resistance to antibiotics (Kitaoka et al. 2011). *V. cholerae* possesses multidrug efflux pumps, which export a broad range of antibiotics and detergents, thereby allowing the bacteria to become resistant against these antimicrobials (Paulsen, Brown, and Skurray 1996). ATP-driven pumps, which are recognized as multidrug resistance efflux pumps, confer resistance to antibiotics such as tetracycline, norfloxacin, ciprofloxacin and doxorubicin (Kitaoka et al. 2011). The MATE-family efflux systems, such as VcmB, VcmD, VcmH, VcmN, VcmA, and VcrM, enhance the *V. cholerae* resistance profile (Begum et al. 2005). *V.* cholerae also carries a homolog of NorM, which mediates resistance to hydrophilic fluoroquinolones, aminoglycosides, and norfloxacin (Singh et al. 2006). There are six operons, *vexRAB*, *vexCD*, *vexEF*, *vexGH*, *vexIJK*, and *vexLM*, encoded in the *V. cholerae* RND efflux systems (Bina et al. 2008). This RND system plays an important role on the efflux of a variety of compounds (e.g., Triton X-100, erythromycin, and penicillin), as well as in colonization (Bina et al. 2008). These findings suggest that efflux pumps are responsible for both drug resistance and virulence gene expression in *V. cholerae*.

Baranwal et al. (2002) demonstrated that chromosomal mutations in the *V. cholerae gyrA* and *parC* genes in clinical isolates may increase resistance to quinolones. From 2002 to 2008, the quinolone resistance mechanism of *V. cholerae* was investigated in Dhaka hospital in Bangladesh (Baranwal et al. 2002; Kim et al. 2010). The results showed that, over the 6-year period, collected *V. cholerae* strains underwent a mutation in *gyrA* and, later gained an additional mutation in *parC*, thus increasing their resistance to quinolone. Treatment of cholera using quinolones resulted in the bacteria acquiring resistance to the antibiotics (Kim et al. 2010). Large chromosomal integrons in *V. cholerae* rapidly transfer gene cassettes containing the antibiotic resistance gene (Mazel 2006). *V. cholerae* can share its antibiotic resistance genes with other bacteria, consequently spreading the number of antibiotic-resistant *V. cholerae* strains in the

environment (Sedas 2007). *V. cholerae* can also share these resistance traits to other enteric pathogens in the human gut, creating complications during treatment against bacterial infections. To decrease the spread of resistance, the use of antibiotics against cholera patients must therefore be limited.

Resistance mechanism of bacterial biofilm

Common mechanisms of bacterial biofilm resistance to antibiotics

Biofilm formation is the most effective way for bacteria to increase antibiotic resistance and ensure persistent disease. The glycocalyx matrix, an integral part of the biofilm (Costerton 1988), can influence adhesion and cohesion abilities toward a solid surface (Pena, Bargar and Sposito 2011). The glycocalyx composition is flexible and regulated by biofilm growth, which enables pathogenic bacteria to survive in extremely adverse host environments (Anwar, Dasgupta, and Costerton 1990). Bacterial resistance to antibiotics and other antimicrobial agents is supported by the glycocalyx matrix [Figure 4(10)] (Sugano et al. 2016). The transformation of a bactericide to its nontoxic form is mediated by enzymes that provide resistance to the biofilm [Figure 4(5)] (Singh et al. 2017). The metabolic activities of bacterial cells are affected by the available levels of nutrients and oxygen within biofilms [Figure 4(1)]. The level of bacterial growth and activity occurring inside biofilms has been demonstrated using different concentrations of metabolic substrates and products (Singh et al. 2017). Nevertheless, a reduction in oxygen availability enhances antibiotic resistance [Figure 4(1)] (Tresse, Jouenne, and Junter 1995; Walters et al. 2003). Bacterial biofilms contain resistant persister cells that exhibit MDR and tolerance to different bactericidal agents [Figure 4(8)] (Lewis 2005). Late-growing gram-positive or gram-negative bacteria exhibit MDR and antibiotic tolerance (Shockman et al. 1996). Recently, the Kirby–Bauer disk-diffusion test was applied to late-growing bacteria to detect bacterial resistance (Gefen et al. 2017). Most bacteria are fermentative and produce oxidant-degrading and repair enzymes that promote oxidative-stress responses and cellular-stress resistance [Figure 4(9)] (Lee et al. 2009). QS involves the generation and secretion of an AHL (Newton and Fray 2004), as well as biofilm maturation (Abee et al. 2011). In the biofilm matrix, the alteration of gene-expression levels can cause resistance to biocides [Figure 4(7)] (Lee et al. 2009). The efflux system facilitates bacterial survival under extreme conditions, including in the presence of antimicrobial agents [Figure 4(6)]. Efflux pumps exert both intrinsic and acquired resistance to different antibacterial agents that belong to the same or different families (Hogan and Kolter 2002; Liaw, Lee and Hsueh 2010). Overproduction of the efflux pump can lead to MDR [Figure 4(6)] (Davin-Regli et al. 2008).

Common mechanisms of bacterial biofilm resistance to detergents/antimicrobials

Although disinfectants are chemical agents designed to inactivate pathogenic microorganisms, biofilms may induce microbial resistance to these products (Bridier et al. 2011; Toushik et al. 2020). The biofilm contains a multilayer of cells and EPS, which can create difficulties for biocides (chemical substance) to penetrate and reach its internal layer. Thurnheer et al. (2003) reported that chlorine could not penetrate beyond a depth of 100 µm at a biofilm thickness of 150–200 µm, and applied chlorine concentration of 25 mg L^{-1}. This interaction between detergent/antimicrobials and biofilm components may increase the limit of antimicrobial penetration into the biofilm (Lambert and Johnston 2001; Stewart et al. 2001; Bridier et al. 2011). Grobe, Zahller and Stewart (2002) also reported the delayed penetration of chlorine, glutaraldehyde, and 2, 2-dibromo-3-nitrilopropionamide into bacterial biofilm, due to interactions with biofilm constituents. In one study, the bacterial resistance level to benzalkonium was increased due to the C-chain length of the quaternary ammonium compound (QAC from C12 to C18), which increased the hydrophobicity of the molecules and limited their penetration through the hydrophilic matrix, resulting in reduced bactericidal efficacy within the biofilm (Sandt et al. 2007). Another study also proposed that cell wall hydrophobicity in bacteria may alter the diffusion of nanoparticles within a biofilm (Habimana et al. 2011). The cell wall interfacial components (i.e., peptidoglycan, fimbriae, capsules, and

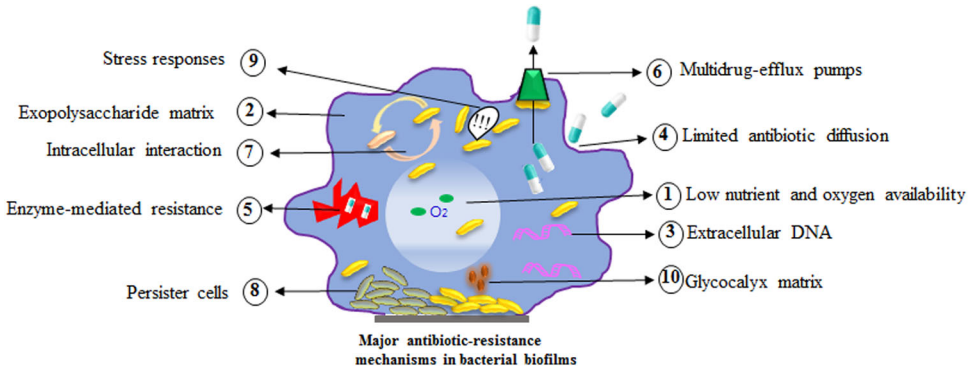

Figure 4. Schematic overview of the antibiotic-resistance mechanisms employed by bacterial biofilms. Biofilm cells (yellow color) are embedded in a mushroom-shaped matrix (shown in blue). The resistance mechanism depends on the following factors (Hall and Mah 2017): (1) Low nutrient and oxygen availabilities in the biofilm center. (2) The EPS matrix. (3) Extracellular DNA. (4) Limited diffusion of an antibiotic through the biofilm matrix. (5) Enzyme-mediated resistance. (6) Multidrug efflux pumps. (7) Intracellular interactions (QS and gene transfer). (8) Persister cells. (9) Stress responses, such as oxidative-stress responses and stringent responses. (10) Regulation of the glycocalyx matrix by biofilm growth, supporting the survival of pathogenic bacteria with antibiotic resistance.

the S-layer) may affect compound diffusion within the biofilm. Stewart et al. (2000) demonstrated that hydrogen peroxide penetrated and killed cells in the biofilm formed by catalase deficient *P. aeruginosa*, while Bridier et al. (2011) determined that H_2O_2 was prevented from penetrating the wild type biofilm. These findings revealed that the limitation in transport was an effective mechanism with applications in biofilm resistance to disinfectants (Bridier et al. 2011). Mangalappalli-Illathu et al. (2008) reported for the first time the adaptation of biofilm cell populations against disinfectant in *Salmonella*. It should be noted that biofilm cells displayed better adaptation to benzalkonium chloride than to planktonic conditions, following continuous exposure to these treatments (Mangalappalli-Illathu and Korber 2006). Moreover, the initial attachment of bacterial cells may enhance biofilm resistance to disinfectants (Dynes et al. 2009). Shemesh, Kolter and Losick (2010) stated that sublethal doses of chlorine dioxide stimulate cell colonization and biofilm formation in *Bacillus subtilis*. Transcription of the major genes enhanced the activation of membrane bound kinase *KinC*, as well as biofilm matrix production, in the presence of chlorine (Bridier et al. 2011). Efflux pumps are a system that enables bacterial cells to eliminate toxic molecules and allow the bacteria to survive in the presence of disinfectants such as triclosan or chlorhexidine (Smith and Hunter 2008; Villagra et al. 2008). However, the mechanism of biocide efflux pumps in biofilm is not clearly understood yet and further research is necessary to determine the importance of its role in biofilm resistance. Lateral gene transfer may contribute to microbial adaptation through the exchange of genetic sequences including plasmid and integrons, which contributes to virulence expression, metabolic activities, and antimicrobial resistance (Kelly, Vespermann and Bolton 2009; Hannan et al. 2010). Using confocal laser scanning microscopy (CLSM), Boles and Singh (2008) found that the wrinkly variant showed a greater ability to form a biofilm with larger cell clusters, and was responsible for the increased biofilm resistance to hydrogen peroxide. Several studies reported that multi-species biofilms have exhibited significant resistance compared to mono-species biofilms (Luppens et al. 2008; Simoes, Simoes, and Vieira 2010; Van der Veen and Abee 2011). Howard and Inglis (2005) demonstrated that *Burkholderia pseudomallei* showed higher resistance to monochloramine, chlorine and ultraviolet (UV) rays. Recently, sodium hypochlorite was used to remove *V. parahaemolyticus* biofilm formed on different surfaces. In this study, the solution contained 20 ppm sodium hypochlorite, a concentration typically used in the fish industry. Interestingly, *V. parahaemolyticus* biofilm showed resistance at this sodium hypochlorite concentration (Rosa et al. 2018). In *V. cholerae*, VPS is associated with matrix production, pellicles, 3-D biofilms, and resistance to chlorine (Yildiz and Visick 2009).

Novel and safe approaches to control *Vibrio* biofilms

Vibrio biofilm formation can be inhibited by using chemical sanitizers such as chlorine, chlorine dioxide (ClO_2), and hydrogen peroxide (H_2O_2). As the residues from these sanitizers are potentially toxic to humans (Sanchez-Vizuete et al. 2015), the development of alternative natural antibiofilm compounds has gained interest recently. In the seafood industry, several methods (Table 2) are currently applied to control *Vibrio* spp. These methods have advantages and disadvantages, according to the demands and processing needs of consumers (Wang et al. 2015). Although chemical treatments (i.e., hypochlorite, ozone, peroxyacetic acid, hydrogen peroxide, and chlorine dioxide) are cost-effective and display strong antimicrobial activities, the residues may constitute a threat to human health (Ölmez and Kretzschmar 2009). The advantages and disadvantages of several physical and chemical methods are summarized in Table 2. At present, it is essential to establish efficient interventions for controlling *Vibrio* spp. in the seafood industry and maintain the fresh color and flavor of seafood products. Therefore, novel anti-*Vibrio* biofilm agents are needed to protect seafood and food-contact surfaces from *Vibrio* biofilm formation.

Natural compounds

Plant extracts

Microbial infections commonly affect humans, with over 100 million microbial infections occurring each year worldwide (Alwan et al. 2011). Certain compounds occurring in nature playsignificant roles in the accomplishment of antimicrobial activity (Juneja, Dwivedi, and Yan 2012; Negi 2012; Savoia 2012). Studies have revealed that grape seed and green tea extracts show promising activity against *V. parahaemolyticus* planktonic cells in Pacific oysters (Xi, Liu, and Su 2012; Shen and Su 2017). The crude extract of Chinese gall (*Galla chinensis*) significantly reduced a *V. parahaemolyticus* population in tuna and shrimp during storage at 12 °C (Wu et al. 2016). *Aloe vera* could potentially be used as a commercial feed with antibiofilm activity in shrimp cultivation (Trejo-Flores et al. 2016). Another study indicated that cloves have a strong ability to control biofilm-producing microorganisms such as *V. parahaemolyticus* in seafood, as compared to lemon leaf, star anise, and curry leaf extracts (Elexson et al. 2013). Silver nanoparticles (Ag-NPs) synthesized from *Calotropis procera* leaf extracts produced the most robust antibiofilm effect against *V. cholerae* by affecting the bacteria present in the biofilm (Salem et al. 2015). Long-term administration of Ag-NPs synthesized from tea leaf extracts has been shown to significantly alleviate *V. harveyi* infections. Thus, Ag-NPs may serve as an alternative to antibiotics for controlling the biofilm-formation ability of *V. harveyi* (Vaseeharan, Ramasamy, and Chen 2010). Citrus limonoids are secondary metabolites secreted by sour oranges and have a significant ability to suppress autoinducer-mediated, intercellular signaling, as well as biofilm formation by *V. harveyi* (Vikram et al. 2011). Recent data revealed that curcumin reduced *V. harveyi* bioluminescence by 88% and increased the survival rate of *Artemia nauplii* by up to 67%, through exopolysaccharide downregulation and motility, biofilm improvement, and production of other virulence factors (Packiavathy et al. 2013). As in the case of plant extracts above, similar approaches can be adopted for antibiofilm testing in other *Vibrio* spp.

Table 2. Advantages and disadvantages of *Vibrio* spp. control methods utilized in the seafood industry (Chae et al. 2009; Ölmez and Kretzschmar 2009; Shikongo-Nambabi et al. 2010; Thantsha et al. 2012; Wang et al. 2015).

Method type	Control methods	Advantages	Disadvantages
Physical	Relaying	Preharvest process without seafood damage	Applications are limited due to the lack of a clean marine environment.
	Depuration	Postharvest process to increase the shelf-life of seafood products	Limited in reducing *Vibrio* spp. counts due to bacterial colonization of the intestinal tracts of seafood species. It is necessary to use depuration in combination with other inactivation methods (refrigeration, ultraviolet light) for a positive effect.
	Thermal process	Requires a short inactivation period Mild heat treatments are preferred	High temperature may lead to protein denaturation and affect the sensory characteristics of seafood.
	Irradiation	Effectively eliminates pathogens from food using ionizing radiation (gamma rays, electron beam, or X-rays) to prevent an outbreak of foodborne diseases.	Directly damages the DNA of living organisms Induces cross-linkages Gamma irradiation could alter several outer-membrane proteins
	High pressure	Prolongs the shelf-life of seafood products	Disruption of the cell membrane changes the morphology of cells and degrades bacterial DNA
Chemical	Electrolyzed oxidizing water	Effective antimicrobial activity at neutral pH Environmentally friendly	Affected by heat Not very effective as a short treatment
	Organic acids	Low cost No toxicity No adverse health effects	Time-consuming Interferes with sensory qualities pH-dependent
	Chlorine dioxide	High antimicrobial activity efficacy at neutral pH	Not approved for seafood processing
	Ozone	High antimicrobial effect with a short contact time No issues with residues	Not allowed for organic products Initial investment cost is high.
	Hydrogen peroxide	Low cost Easy process	Antimicrobial activity is low. Required long incubation period
	Chlorine	Readily available Low cost	Reacts with organic matter Corrosive
	Peroxyacetic acid	Kills pathogenic microorganisms at low concentrations Not corrosive at permitted levels (< 80 ppm)	Not allowed for organic products

Essential oils

Essential oils are natural preservatives that are effective for preserving food products *(*Kerekes et al. 2015). Essential oils are considered non-hazardous and can be used as alternative substances to treat microbial infections (Borges et al. 2013), as they possess antimicrobial properties that inhibit microbial growth and that can keep food products safe (Zengin and Baysal 2014; Niamah and Alali 2016). Plant essential oils and organic extracts have shown good efficacy against biofilm formation by foodborne pathogens (Agarwal, Lal, and Pruthi 2008). In addition to controlling biofilms formed by *Vibrio* spp., the following essential oils may potentially be used to study *Vibrio*-related contamination cases in the seafood industry.

Parsley and basil oils have been employed as ingredients in the food industry for their antibacterial properties during food preservation. These oils can prevent biofilm formation by pathogenic microorganisms (Saggiorato et al. 2012; Gaio et al. 2015). It has been demonstrated that parsley and basil essential oils have strong anti-*Vibrio* activity and antimicrobial efficacy in preventing and eradicating mature biofilms formed on a polystyrene surface (Snoussi et al. 2016). *Mentha spicata* serves as a traditional medicinal remedy owing to its antibacterial, antifungal, antioxidant, and antibiofilm activities (Tetik, Civelek, and Cakilcioglu 2013*;* Snoussi et al. 2015). Owing to its biofilm inhibitory activity, spearmint essential oil possesses great potential as a natural antibiotic and preservative against *Vibrio* contamination in the food and pharmaceutical industries (Snoussi et al. 2015). Spearmint essential oil was reported to inhibit biofilm formation in *V. vulnificus* ATCC27562 by 40% and 28%, at concentrations of 0.046 and 0.092 mg mL^{-1}, respectively (Snoussi et al. 2015). Data from a recent study showed that *Vibrio* species exhibit a distinctive sensitivity to essential peppermint oil, suggesting that this oil can be used as an agent for controlling *Vibrio* biofilms in the future (Al-Sahlany 2016).

Nigella sativa essential oil exhibited significant antibiofilm activity against *V. harveyi* and *V. parahaemolyticus* at 80 µg mL^{-1} after a 24-h incubation, and could be serve as an effective compound against aquatic pathogenic microorganisms (Manju et al. 2014). Dietary oregano essential oils from herbs and spices may also represent an alternative way to control *Vibrio* biofilm formation by inhibiting the growth of microorganisms in foods (Hulankova, Borilova, and Steinhauserova 2013). Future studies may reveal the antibiofilm activities of other essential oils such as garlic, thyme, cumin, cinnamon, and tea tree oils, against *Vibrio* spp. It should be noted that the above-mentioned essential oils have already shown promising effects against biofilm formation of other pathogenic microorganisms (Sadekuzzaman et al. 2015). There is no evidence, however, of the usefulness of these essential oils for controlling *Vibrio* biofilm formation. Collectively, the data suggest that these essential oils could potentially be used in the development of novel and safe approaches for controlling biofilms in the seafood industry.

Antimicrobial mechanisms of essential oils with a focus on eugenol

The antimicrobial activities of essential oils, as well as all-natural extracts, depends on their chemical composition. Several essential oils from natural food sources (i.e., vegetables, spices, and fruits) are quite effective at inhibiting pathogenic organism growth for agricultural and healthcare purposes (Rauha et al. 2000). Therefore, essential oils, as well as natural extracts, may inhibit the growth of bacterial cells with strong protection from bacterial toxin production. Natural compounds can also affect the bacterial cell membrane (Hyldgaard, Mygind, and Meyer 2012).

Eugenol is a major active compound of clove oil (Farag et al. 1989). It reduces the formation of exopolysaccharides and significantly affects the bacterial biofilm of methicillin-resistant *Staphylococcus aureus* (Al-Shabib et al. 2017). The antibiofilm and anti-virulence activity of eugenol against *E. coli* O157:H7 was reported via downregulation of the biofilmforming genes (Kim et al. 2016). Zhang et al. (2017) reported that eugenol promotes the leakage of *P. gingivalis* intracellular nucleic acids and proteins. Eugenol permeabilized the bacterial cell membrane, owing to the loss of cellular macromolecules. It also helps disintegrate the cell membrane, so that propidium iodide can enter the cytoplasm and bind to DNA, leading to cell death (Devi et al. 2010; Zhang et al. 2017). Several reports have shown that eugenol can change the cell morphology by disrupting cell walls and altering membrane permeability, followed by the formation of apertures for ion entry, causing substantial damage to various cellular components (*Streptococcus agalactiae*, *Salmonella* Typhi), and eventually resulting in cell death (Devi et al. 2010; Perugini Biasi-Garbin et al. 2015). Eugenol can disrupt the cytoplasmic membrane and affect ion and ATP transport (Filgueiras and Vanetti 2006; Gill and Holley 2006; Devi et al. 2013), as well as inhibit the growth of pathogenic bacteria (*E. coli*, *Enterobacter aerogenes*, and *L. monocytogenes*) and enzymes such as protease, amylase, and ATPase (Thoroski, Blank, and Biliaderis 1989; Hyldgaard, Mygind, and Meyer 2012). Eugenol has been recognized as a potential synergistic agent against antibiotic-resistant bacteria because its hydroxyl group can bind to the bacterial membrane protein (Zhang et al. 2017). Eugenol also disrupts intercellular connections and alters the normal morphology of bacteria (Gill and Holley 2004; Yadav et al. 2015). These intercellular connections promote bacterial colonization and the formation of organized biofilms. Disruption of these connections induces the detachment of cells within the biofilm, which is then easily washed away (Figure 5) (Mandlik et al. 2008; Yadav et al. 2015). The mechanism by which eugenol acts on *Vibrio* biofilms is still unknown to date, indicating a need for such mechanism-related studies in the future to help obtain a better understanding of *Vibrio* biofilms. Based on the above information, we illustrated the hypothetical mechanism whereby eugenol may inhibit mature *V. parahaemolyticus* biofilm formation, to boost interest in future studies on *Vibrio* biofilms (Figure 6).

Quorum quenching (QQ)

QQ does not interfere with bacterial growth and fitness. Several QQ methods have been developed as novel approaches to understand the communication mechanisms of bacteria and disrupt their virulence. Three common approaches, i.e., inhibiting QS molecule synthesis, inhibiting QS molecule–receptor interactions, and degrading QS molecules, are officially recognized as quorum-disruption strategies (Tay and Yew 2013). Quorum receptor antagonists (S-adenosyl-homocysteine, amidocyclohexenone), quorum-synthesis inhibitors (amidophenol, halogenated furanone), and QQ enzymes (N-acyl-homoserine lactone) are the most effective for disrupting bacterial virulence (Tay and Yew 2013). It was reported that QQ molecules can affect *Vibrio* biofilm structure, composition, and conformation (Jo et al. 2016). Some strategies have been proposed to control quorum signaling for managing certain pathogenic bacteria in aquaculture (Chu and McLean, 2016). Most prokaryotes, some eukaryotes, and certain traditional medicinal

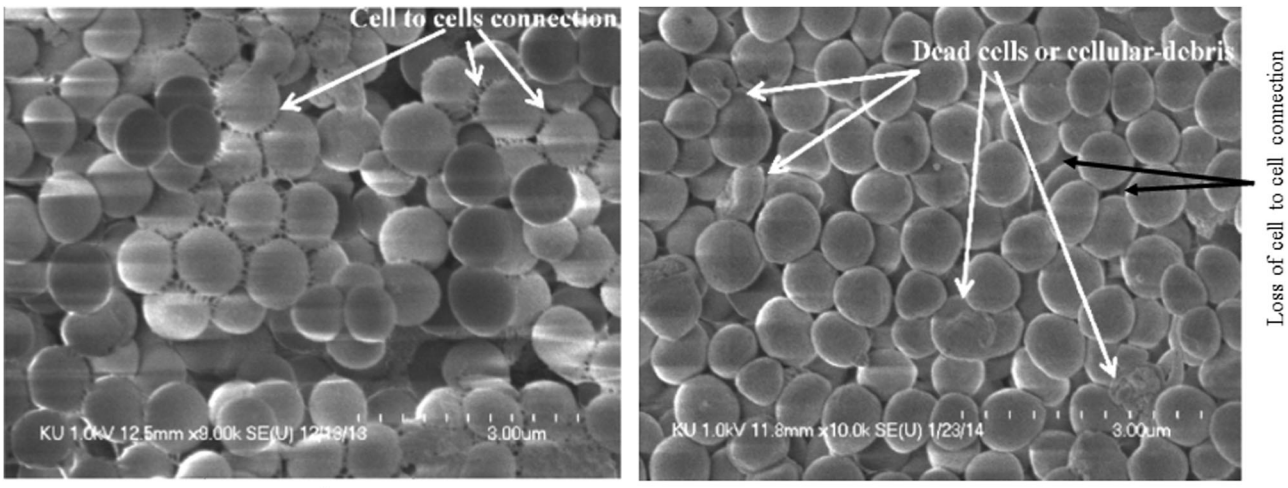

Figure 5. Eradication of established biofilms of *S. aureus* (29213) with eugenol over a range of concentrations (Yadav et al., 2015). (A) Established untreated biofilm of *S. aureus* (29213). The arrows indicate intercellular connections. (B) A representative SEM image of an established biofilm treated with eugenol at the MIC. The white arrows indicate dead cells or cellular debris, and the black arrows indicate the loss of intercellular connections.

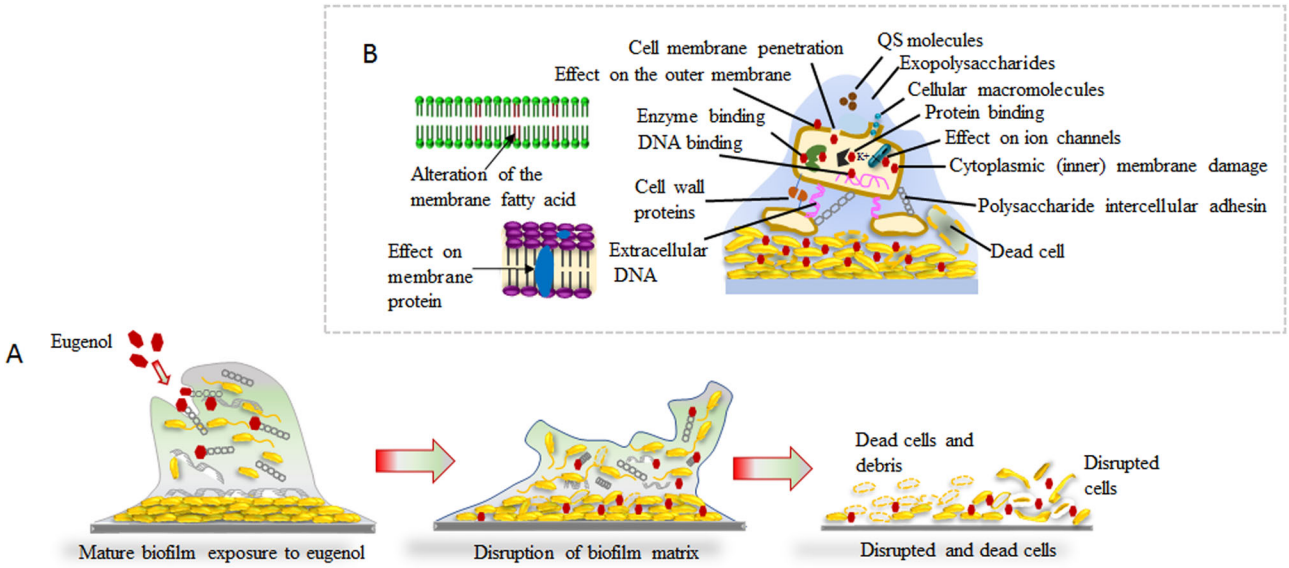

Figure 6. A hypothetical mechanism of action of eugenol against a mature biofilm composed of *V. parahaemolyticus* cells. (A) Schematic representation of the general mechanism of action of eugenol on a mature biofilm, where the biofilm structure become broken down, the bacterial cells become disrupted, and induced cell death. (B) The mechanism of action of eugenol on a bacterial biofilm. Eugenol enters into a bacterial cell by affecting outer-membrane fatty acids and proteins. Eugenol binds with proteins and enzymes leading to their degradation. Eugenol may disrupt intercellular connections to increase the detachment of cells within a biofilm. Eugenol may also have a significant effect on cytoplasmic membrane, intercellular adhesin, nucleic acids, cellular macromolecules, and ion channels, resulting in cell decomposition and death.

plants may produce QS-inhibiting compounds (Sadekuzzaman et al. 2015). Some QS-inhibitory compounds that inhibit *Vibrio* biofilm formation and planktonic cell growth are listed in Tables 3 and 4.

Enzymes

Enzymes significantly contribute to biofilm removal by destroying exopolysaccharides, impairing bacterial signals, and degrading polymers (Zanaroli et al. 2011). Marine-derived lipases can potentially serve as novel inhibitors of *Vibrio* biofilm formation. Recently, a halotolerant thermostable lipase was isolated from *Oceanobacillus species* PUMB02 and characterized. This enzyme has highly stable characteristics over a wide range of pH, salinity, and temperature (50 to 70 °C) conditions. Marine sponge metagenome-derived halotolerant lipase Lpc53E has shown promising antibiofilm activity against the foodborne pathogen *V. parahaemolyticus* (Seghal Kiran et al. 2014a). The extracellular α-amylase enzyme, isolated from marine-originating *Bacillus subtilis* S8-18, can inhibit *V. cholerae* biofilm formation. Spectrophotometric and microscopic assays revealed that a crude enzyme showed 52 to 73% inhibition in *V. cholerae* biofilm formation, whereas a purified enzyme resulted in 44 to 62% inhibition in *V. cholerae* biofilm formation (Kalpana, Aarthy, and Pandian 2012). Acyl-homoserine lactonase (AiiA enzyme), produced by *Bacillus* spp., blocked QS and inhibited *V. cholerae* biofilm formation by 80% (Augustine, Kumar, and Thomas 2010). Several *Bacillus* spp. have been reported to secrete the AiiA enzyme, which cleaves the acyl moieties from lactone rings and renders the compound inactive during signal transduction. This enzyme also exerts QS-inhibitory activity against *V. harveyi* (Bai et al. 2008), indicating its potential to inhibit biofilm formation via QS inhibition. It was demonstrated that the AHL-lactonase isolated from *Bacillus licheniformis* DAHB1 possesses an anti-*Vibrio* biofilm activity (Vinoj et al. 2014). Consequently, further research should focus on developing new approaches for the efficient delivery of the AHL-degrading enzyme in aquatic settings. Nevertheless, enzymes are rarely used against *Vibrio* biofilms, and constitute a promising alternative in the seafood industry as novel agents for protection against *Vibrio* biofilms.

Synthetic compounds

There are some synthetic compounds, such as synthetic analogs of AHLs with either modified lactone rings or side aromatic groups (Rasamiravaka et al. 2015), nitric oxide (Hetrick et al. 2009), 12-methyl-tetradecanoic acid (Inoue, Shingaki, and Fukui 2008), cis-2-dodecenoic acid (Deng et al. 2013), urea, the sulfonamide and thiourea oroidin analogs (Richards et al. 2009), some derivatives of oroidin (Hodnik et al. 2014), and zosteric acid (Polo et al. 2014). As these can inhibit the mature biofilm formation of gram-negative bacteria, they could be used to control biofilm formation by *Vibrio* species in future studies. Indole-3-carboxaldehyde inhibits biofilm formation by *V. parahaemolyticus* and *V. cholerae*, via a reduction in swarming motility (Rajalaxmi, Devi, and Pandian 2016). *Pseudomonas aeruginosa* PsDAHP1 inhibits biofilm-forming exopolysaccharides and QS molecules in *V. parahaemolyticus* (Vinoj et al. 2015). Recently, it was found that chitosan exerts a meaningful preventive effect and can eradicate mature biofilms of *V. parahaemolyticus* (Xie et al. 2017). A minimal inhibitory concentration (MIC; 1.25 mg mL^{-1}) and a 1/2 MIC of chitosan significantly reduced *V. parahaemolyticus* biofilm formation by 71% and 68%, respectively (Xie et al. 2017). The antibiofilm mechanism of chitosan is not well developed, although it was previously reported

Table 3. Natural QS inhibitory compounds with antimicrobial activities against *Vibrio* biofilms and planktonic cell growth.

Compound	Effective against	Target/inhibition method	References
Tumonoic acid	*V. harveyi*	Bioluminescence	(Clark et al. 2008)
Isobutyramide and 3-methyl-N-(2-phenylethyl)-butyramide	*V. harveyi*	Inhibits bioluminescence production	(Teasdale et al. 2011)
Cinnamaldehyde	*V. harveyi*	Inhibits AHL- and AI-2-mediated QS	(Niu et al. 2006)
Cinnamaldehyde	*Vibrio* spp.	AI-2-mediated QS- bioluminescence	(Brackman et al. 2008)
Naringenin	*V. harveyi*	Inhibitor of autoinducer-mediated intercellular signaling	(Vikram et al. 2010)
Citrus limonoids	*V. harveyi*	Inhibit intercellular signaling	(Vikram et al. 2011)

Table 4. Synthetic QS inhibitory compounds that impair *Vibrio* spp.

Compound	Target/inhibition method	References
Synthetic *N*-acyl-homoserine lactone analogs	Inhibit the activity of 3-oxo-hexanoyl-l-homoserine lactone, a natural inducer of bioluminescence	(Reverchon et al. 2002)
3- and 4-substituted analogs of acyl-homoserine lactone	Inhibit the LuxI/LuxR-derived QS reporter system	(Olsen et al. 2002)
N-(heptylsulfanylacetyl)-L-homoserine lactone	Inhibits transcription factors of LuxR	(Persson et al. 2005)
3-Oxohexanoyl HSL	Effective inhibition of LuxR by binding irreversibly	(Schaefer et al. 1996)
N-sulfonyl-HSL	Antagonizes LuxR	(Castang et al. 2004)
Furanone	Blocks QS-regulated gene expression	(Defoirdt et al. 2007)
Cannabinoid HU-210	Inhibits QS molecules	(Soni et al. 2015)
Brominated furanone	Bioluminescence	(Lonn-Stensrud et al. 2007)
Hexadecanoic acid	Antibiofilm and QS inhibitory potential	(Santhakumari et al. 2016)
Cyclic dipeptides	Inhibit LuxR-type proteins in AHL biosensor strains and inhibit luminescence	(Campbell et al. 2009)

that chitosan can promote leaking of bacterial cell components, damaging bacterial cell membranes, and interacting with positively and negatively charged components of bacterial cells (Liu et al. 2004; Jeon et al. 2014; Costa et al. 2015). However, the sensitivity to chitosan could differ with various species. Recently, several studies have demonstrated the potential antimicrobial activities of chitosan microparticles and chitosan-derived nanoparticles (Fang et al. 2015; Garrido-Maestu et al. 2018; Ma et al. 2018).

Batyl alcohol was previously isolated from *Cladiella* species (Radhika 2006), and shown to moderately inhibit the growth of *V. harveyi* (Qi et al. 2008). It was also reported that batyl alcohol inhibits *V. harveyi* biofilm formation by up to 60% (Díaz et al. 2015). Isatin commonlyexerts an antifouling activity against *Vibrio* spp. Thus, isatin and its modified analogs can be used in future research for antifouling and antibiofilm applications in the seafood and aquaculture industries (Majik et al. 2014). One report revealed that poly-β-hydroxybutyric acid maintained poor intracellular adhesion among bacteria, due to the surface accumulation of methyl groups (Lee et al. 2013). Poly-β-hydroxybutyric acid exerts the highest antiadhesive activity (up to 96%) against *V. vulnificus*, 92% activity against *V. parahaemolyticus*, and 88% activity against *V. harveyi* (Kiran et al. 2014b). In a recent study, 2,6-di-tert-butyl-4-methylphenol (DTBMP), isolated from *Chroococcus turgidus* was reported as a potential antibiofilm agent against *Vibrio* spp. (Santhakumari et al. 2018). At 250 μg ml^{-1}, DTBMP effectively inhibited exopolysaccharide (EPS) production, the hydrophobicity index, as well as swimming and swarming motilities when tested against *V. harveyi*, *V. parahaemolyticus*, and *V. vulnificus*. The antibiofilm activity of DTBMP was confirmed through microscopic analyses. In vivo results demonstrated that DTBMP increased the survival rate of *Litopenaeus vannamei* larvae up to 66, 75, and 88% upon infection with *V. vulnificus, V. harveyi,* and *V. parahaemolyticus*, respectively. Therefore, DTBMP could be used as a potential antibiofilm agent, as well as a therapeutic agent, for preventing biofilm-associated *Vibrio* infections in aquaculture (Santhakumari et al. 2018).

Other promising antibiofilm agents for selected *Vibrio* spp

Bacteriophages

Phage therapy can be an effective approach for preventing bacterial infectious diseases in aquaculture (Almeida et al. 2009). Bacteriophages kill bacteria via self-replication within the host cells (Carvalho et al. 2012). Data from a recent study suggested that P4A and P4F bacteriophages significantly decreased the *V. harveyi* biofilm population formed on a polyethylene surface. Therefore, these phages can potentially be used as effective biocontrol agents against *V. harveyi* in the production systems of marine aquaculture (Luo et al. 2016). The application of a virulent *Siphoviridae* phage (pVp-1) reduced the cell count of the antibiotic-resistant foodborne pathogen *V. parahaemolyticus* on the surface of oysters (Jun et al. 2014). Another investigation revealed that the application of lytic phages (A3S and Vpms1) reduced the mortality of seafood species such as shrimp, as well as decreased the growth of *V. parahaemolyticus* (Lomelí-Ortega and Martínez-Díaz 2014). In a study on feed, a mixture containing a freeze-dried phage powder was used to protect sea cucumbers from infection with *Vibrio* spp., indicating that this approach may serve as an alternative to treatment using antibiotics (Li et al. 2016).

Biosurfactants (BSs)

BSs can reduce the interfacial tension between molecules attached to a surface. BSs can be used for some applications, such as dispersing, foaming, and emulsifying, under conditions of high salinity, pH, and temperature (Banat et al. 2010). They can interfere with intercellular contacts and biofilm formation and are widely used as antibiofilm agents

(Rivardo et al. 2009). A glycolipid BS reduced the biofilm formation of pathogenic *Vibrio* spp., such as *V. parahaemolyticus*, *V. harveyi*, *V. alginolyticus*, *V. alcaligenes*, and *V. vulnificus*, and could validated as a novel anti-*Vibrio* biofilm agent in the future (Kiran, Sabarathnam, and Selvin 2010).

Cell-Free supernatant (CFS)

Supernatants are commonly derived from cultured bacteria with antibiofilm properties. In a recent study, bacterial supernatants, as well as the isolates of S8-07 (*Bacillus pumilus*) and S6-01 (*B. indicus*), were found to inhibit mature biofilm formation by *Vibrio* spp. (Nithya and Pandian 2010). It was also demonstrated that the supernatant of *Pseudoalteromonas* 3J6 strongly reduced biofilm formation by *Vibrio* D66. In addition, the cell-free supernatant of *B. licheniformis* inhibited *V. harveyi* biofilm formation by up to ∼80% (Hamza, Kumar, and Zinjarde 2016).

Coating

Coating technologies can be used to mitigate biofilm formation on shipping equipment and on other marine infrastructures within the shellfish industry. Surface biofilm formation by *Vibrio* spp. was successfully inhibited by coating the surface with a biodegradable, wax-based, and nontoxic substance (Fitridge et al. 2012). Silicone-based paints represent a nontoxic coating and can be considered as an alternative method for inhibiting bacterial biofilm formation in the marine transport industry. In addition, it was demonstrated that an air bubble curtain, in conjunction with biofilm-release coatings, was a potentially useful method for controlling biofilm formation in aquaculture infrastructure (Jang et al. 2017). The use of air bubble curtains is generating considerable interest in the aquaculture industry, to control *Vibrio* biofilms via a cost-effective coating of aquaculture nets (Swain and Shinjo 2014). In addition, coating technologies can also be effective at reducing *Vibrio* biofilm formation during mechanical cleaning.

Probiotics

Pathogenic *Vibrio* species are a major factor affecting aquaculture development and seafood safety. The use of probiotic antagonistic activity against pathogens offers a promising alternative in fish and shrimp aquaculture (Hossain, Sadekkuzaman, and Ha 2017). Recent advances in the food industry presented probiotics as alternative and environmentally friendly candidates to inhibit biofilm formation by microbial pathogens, without associated risks to consumers (Hossain et al. 2020). It was demonstrated that *Enterococcus faecium* MC13 may inhibit the pathogenic *V. harveyi* and *V. parahaemolyticus* and control vibriosis by being fed to shrimp (*Penaeus monodon*) (Swain et al. 2009). In another study, *Vagococcus fluvialis* effectively protected the European sea bass (*Dicentrarchus labrax*) from infection by *Vibrio anguillarum* (Sorroza et al. 2012). Grotkjaer et al. (2016) proposed that the tropodithietic acid (TDA)- producing *Phaeobacter* isolated from Mediterranean marine larviculture could be used as an alternative biocontrol agent (probiotic) to protect against pathogenic *Vibrio* spp. in crustacean live-feed cultures of marine fish larvae. In aquaculture, *Litopenaeus plantarum* could be a potential probiotic against *Vibrio spp.* (Tank, Vadher, and Patel 2018). In addition, a seaweed-probiotic blend may constitute an alternative to antibiotics in the control of *V. parahaemolyticus* (Lim, Loo, and Wong 2019). The administration of probiotics improves brine shrimp production in aquaculture, which potentially offers an alternative solution to reduce *Vibrio* species in the production system (Quiroz-Guzmán et al. 2018). Das et al. (2013) demonstrated that the *Bacillus amyloliquefaciens* FPTB16 exhibited antagonistic activity as a potential probiotic strain against fish pathogenic bacteria such as *V. harveyi*, and *V. parahaemolyticus*. It was recently proposed that *Bacillus licheniformis* is a promising probiotic candidate with potential applications for controlling pathogenic *Vibrio* spp. in aquaculture practices (Peng, Zhang, and Song 2019). *Bacillus cereus* could be used as a probiotic, owing to its significant reduction rate of microbial pathogens through the secretion of antimicrobial substances (Vidal et al. 2018). The probiotic *Bacillus pumilus* strain demonstrated notable antagonistic activity against 29 tested *Vibrio* strains, by effecting reduced cell density, as well as the formation of membrane holes, disappearance of cellular contents, and formation of cell cavities, all of which represented the major mechanism against pathogens. This study indicated that *B. pumilus* presents as a strong potential candidate for the prevention of fish vibriosis in the aquaculture industry (Gao et al. 2017). The culture supernatant (CS) of *Lactobacillus* spp. inhibited biofilm formation in *V. cholerae* by more than 90%. In addition, five out of seven isolates inhibited the *V. parahaemolyticus* biofilm by 62–82% (Kaur et al. 2018). Therefore, probiotic strains that have the ability to disperse *Vibrio* biofilms may possess better therapeutic potential against *Vibrio* spp. infections (Kaur et al. 2018). As *Vibrio* spp. are well known for their ability to form strong biofilms in vivo and in vitro (Kaur et al. 2018; Ashrafudoulla et al. 2019), *Lactobacilli* spp. can potentially be used as anti-biofilm biocontrol agents against *Vibrio* species.

Future research directions

Seafood is most commonly contaminated with *Vibrio* spp. in marine environments and in the seafood industry. Coating with the proposed anti-*Vibrio* biofilm agents could be an effective strategy for inhibiting *Vibrio* biofilm formation, while preventing the adhesion of *Vibrio* bacteria to seafood and food-contact surfaces. This review demonstrates the promising contribution of plant extracts (grape seed, green tea, Chinese gall, citrus limonoids, and curcumin) and essential oils (parsley, basil, spearmint, and peppermint) in suppressing biofilm formation and contamination by *Vibrio* spp. The application of natural and synthetic compounds nanoparticles against *Vibrio* spp. could be a promising topic of future studies. However, no commercialized natural anti-biofilm products are currently available in the market. This

might be attributed to their excessive production cost or to a general lack of financial interest (Romero and Kolter 2011). Based on the significant activity of marine-derived lipases, halotolerant thermostable lipase, and Acyl-homoserine lactonase against the virulence properties of *Vibrio* spp., these enzymes could serve as a key resource in future studies to protect seafood from *Vibrio* spp. contamination. Recently, bacteriophages, biosurfactants, and supernatants have been used as novel alternatives to antibiotics against *Vibrio* spp. The hypothetical mechanism of action of eugenol against *V. parahaemolyticus* biofilms could assist in developing novel, natural, and commercially viable antibiofilm agents.

Conclusions

Vibrio species have been under intense scrutiny due to their extensive antimicrobial resistance in aquaculture. They have the ability to transfer their antibiotic resistance genes to surrounding pathogens, posing a threat to human health. Pathogenic *Vibrio* species are also able to form biofilms in different settings in the food industry and are considered a major source of food contamination. The consumption of seafood is steadily increasing across the world. Contamination of seafood with pathogenic *Vibrio* species represents a major public health concern across the globe. Therefore, it is important to protect seafood, the seafood industry, and marine environments, from *Vibrio* contamination. Several innovative approaches have been discussed here as anti-*Vibrio* biofilm strategies. The natural substances, synthetic compounds, enzymes, and other promising agents (bacteriophages, biosurfactants, coatings and probiotics), which have been highlighted may be effective in controlling *Vibrio* biofilms. The combined applications of existing and novel approaches may help in the development of potent anti-*Vibrio* biofilm strategies in the future.

Author contributions

Md. Ashrafudoulla planned, collected, compiled and drafted the manuscript. Md. Furkanur Rahaman Mizan critically reviewed the manuscript. Sang-Do Ha and Si Hong Park evaluated and edited the manuscript.

Disclosure statement

The authors declare no conflicts of interest.

Abbreviations

AHL	N-acyl-homoserine lactone
BSs	biosurfactants
QQ	quorum quenching
QS	quorum sensing

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