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Review Article

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Pseudomonas aeruginosa in Fish and Fish Products: A Review on the Incidence, Public Health Significance, Virulence Factors, Antimicrobial Resistance, and Biofilm Formation

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Abstract

Pseudomonas aeruginosa (*P. aeruginosa*) is a psychotropic pathogenic bacterium that is considered one of the most common spoilage microorganisms related to seafood's consumption. *P. aeruginosa* is widely distributed in nature and isolated from soil, plants, animals, and water. Because of its high resistance to a wide range of antibiotics, *P. aeruginosa* is more dangerous than other spoilage bacteria. It possesses a diverse set of virulence factors capable of causing severe and aggressive infections in humans and animals. Antibiotic resistance genes are easily transmitted to humans via contaminated seafood, resulting in a serious antibiotic resistance. The ability of *P. aeruginosa* to form a biofilm maintains its environmental survival and allows its quick adaptation to harsh environments. Therefore, for the benefit of customers and public health globally, the safety and bacteriological quality of commercially processed fish and its products are crucial.

KEYWORDS
P. aeruginosa, Fish, Antibiotic resistance, Virulence factors, Biofilm

INTRODUCTION

Pseudomonas aeruginosa is a highly pathogenic rod-shaped, Gram-negative bacterium which belongs to family *Pseudomonadaceae*, a member of γ-proteobacteria, that is found abundance in water, plants, soil, and animals (Ali *et al*., 2021). The most frequently isolated bacteria from spoiled seafood are psychrotolerant *Pseudomonas* spp., which produce off flavors and odours as well as slime, which lowers the quality of the product (Benie *et al*., 2017). The prevalence of *P. aeruginosa* infection, which includes infections of the digestive system, is 17% in underdeveloped nations and 11.5% in Europe, contaminated fish with enterotoxigenic *P. aeruginosa* causes diarrhoea, gastrointestinal disorders, and skin infections, especially in patients who are immunocompromised (Losito *et al*., 2022; Ziarati *et al*., 2022).

The pathogenicity of *P. aeruginosa* is associated with the presence of numerous virulence factors, some of which are related to the bacterial cell surface and include lipopolysaccharide, flagella, type IV pili, type III secretion system, exotoxin A, proteases, and alginate, which contribute in the transformation of active proteins as well as the adherence and colonization of bacteria within a host cell (Ali *et al*., 2023).

P. aeruginosa is known for its resistance to an extensive variety of commonly used antibiotics. As a result, it appears to be more hazardous than other food-spoilage bacteria because it is capable of transmitting multi-drug-resistance (MDR) plasmids to individuals after ingesting infected undercooked fish and fish products containing MDR *P. aeruginosa* (Shahrokhi *et al*., 2022).

The majority of Gram-positive and Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Vibrio vulnificus*, *Enterococcus faecalis, Staphylococcus aureus, Streptococcus viridans, Proteus mirabilis*, and *Pseudomonas aeruginosa*, are capable of forming biofilm (MubarakAli *et al*., 2023). *P. aeruginosa* is shielded from exposure to atmospheric oxygen and high antibiotic concentrations by biofilms, which are structured communities of bacterial cells that offer increased resistance to environmental stresses (Vetrivel *et al*., 2021). Since even low concentrations of antibiotics could act as stress signals, biofilm formation is a protective response against the effects of antibiotics. The primary physical obstacle influencing the penetration of antibiotics can be attributed to the biofilm matrix (El Bayomi *et al*., 2020).

As a result, in this review, the characteristics of *P. aeruginosa* food poisoning public health impacts including contamination of fish and fish products by this important pathogen, virulence factors, antimicrobial resistance profile, and biofilm formation were explored.

Fish and fish products as potential sources of *P. aeruginosa*

The microbiological quality of fish and various types of sea food must be managed due to the rising consumption of these products. Fish is rich in omega 6, omega 3, protein, minerals, and vitamins (Morshdy *et al*., 2022a). Fish and seafood are more liable to microbial deterioration than other type of meat due to a higher moisture content and a lower pH. Microbial decomposition of fish may cause off flavor, off-odor, slime formation, and discoloration that makes it undesirable for consumption (Morshdy *et al*., 2019) *Pseudomonadaceae* are aerobic bacteria that are able to develop in the presence of oxygen. However, the total number

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of *Pseudomonas* spp. in a vacuum and CO_2-packed preserved fish is diminished (Lougovois and Kyrana, 2005). *Pseudomonads* are among the most significant specific spoiling organisms (SSOs), as their excessive proliferation accelerates the splitting of nitrogenous materials, which causes product deterioration (Zhang *et al*., 2021). Numerous studies have shown that Gram-negative bacteria from the *Pseudomonadaceae* family are among the most productive populations of microbes to extracellular proteolytic, lipolytic, and saccharolytic enzymes (Abbamondi and Tommonaro, 2022). The most prevalent *Pseudomonas* species isolated from fish are *P. fluorescens*, *P. lundensis, P. fragi, P. anguilliseptica*, and *P. putida* (Abd El Tawab *et al*., 2016). *P. aeruginosa* is the most common *Pseudomonas* species in food products, but it is not widely distributed (Heir *et al*., 2021).

Pseudomonas aeruginosa Characteristics and Public health impact

P. aeruginosa can survive via water, on various surfaces, and on medical devices with the aid of its powerful adhesion components, including flagella, pili, and biofilm. *P. aeruginosa* is therefore prevalent in both natural and artificial settings, such as lakes, hospitals, and household washbasin drains (Remold *et al*., 2011). *P. aeruginosa* is an opportunistic pathogen that infects people with a variety of illnesses (Figure 1). *P. aeruginosa* is the second most common pathogen associated with ventilator-related pneumonia, the seventh major causative pathogen of catheter-linked bloodstream infections, and the sixth most frequent organism associated with nosocomial infections (Hidron *et al*., 2008). In addition, infections at the surgical site, infections of the urinary tract, burn infections of wounds, keratitis, and otitis media (Ito *et al*., 2021). It is now a significant contributor to resistance to antibiotics and nosocomial illnesses (Shariati *et al*., 2018).

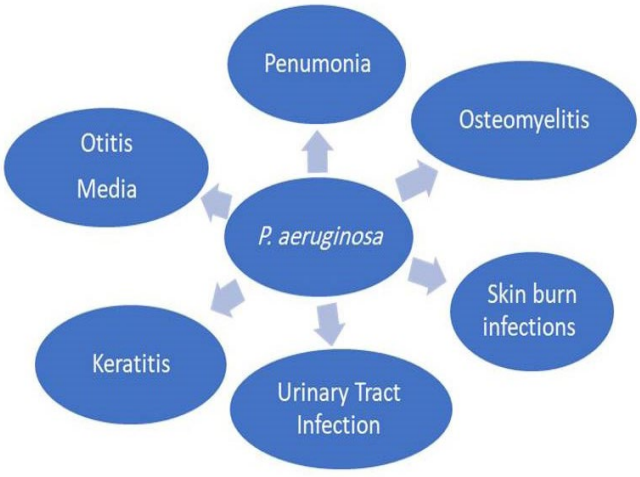

Figure 1. *Pseudomonas aeruginosa* primary infections

P. aeruginosa is an organism that can quickly acquire antibiotic resistance, adapt to environmental changes, and produce a wide range of virulence factors. The fact that this pathogen is capable of bypassing both innate and acquired immune defenses through adhesion, colonization, and biofilm formation, as well as the production of various virulence factors that cause substantial harm to tissues and this makes it a threat to immunocompromised individuals. Additionally, it contributes to illnesses with high mortality rates in people with cystic fibrosis, infections in newborns, tumors, and serious burns (Nathwani *et al*., 2014). When insufficient treatment is used to treat *P. aeruginosa* infections, especially when multidrug-resistant (MDR) strains are involved, infections can be fatal (Bail *et al*., 2022). For the past 30 years, multidrug resistance has posed a threat to both human and animal health (Sarabhai *et al*., 2013). Additionally, *P. aeruginosa* is one of the most common pathogens in hospital settings and is responsible for more than 50% of healthcare-acquired infections (McKay and Bamford, 2015). Although new antimicrobial medications have been created, *P. aeruginosa* mortality rates remain high, which range from 20 to 60% (Kang *et al*., 2003). The primary contributory factors of *P. aeruginosa* infections are structural lung diseases, hematological neoplasms, transplantation, burned skin, current antibiotic use, the presence of implants, extended hospitalization, and mechanical ventilation (Reynolds and Kollef, 2021).

Pseudomonas aeruginosa virulence factors

By producing a wide range of virulence factors, *P. aeruginosa* has the capability to adjust to the unfavorable environment in hosts and enhance the likelihood of illness and infection (Vidaillac and Chotirmall, 2021). First, lipopolysaccharide (LPS) is a crucial surface structural element to safeguard the external host cells toxins. The endotoxicity of the lipid A in LPS facilitates damage to tissues, attachment, and recognition by host receptors (Park *et al*., 2022). The LPS may be involved in the creation of biofilms and antibiotic resistance (Chambers *et al*., 2017). The second is that outer membrane proteins (OMPs) support adhesion, exchange of nutrients, and resistance to antibiotics (Sabnis *et al*., 2021). The third is that the flagellum, pili, and other adhesins are correlated with drug resistance triggered by biofilm formation (Ozer *et al*., 2021). Fourth, there are six different categories of secretion systems. These include flagella (T6SS-associated), pili (T4SS), and multi-toxin components type 3 secretion system (T3SS), which are used for colonizing the host, adhering to it, swimming, and swarming in response to chemotactic signaling. Finally, exopolysaccharides like alginate, Psl, and Pel may hinder bacterial clearance while aiding in the formation of biofilms (Ozer *et al*., 2021).

Concerning toxins produced by *P. aeruginosa*, T3SS is an intricate system that has the potential to seriously impair host defense by injecting cytotoxins such as ExoU, ExoT, ExoS, and ExoY. These toxins have an impact on the intracellular environment, particularly by inhibiting phagocytosis and clearance of bacteria. Exotoxin A (ETA) can prevent the production of host proteins by activating ADP ribosylation (Yang *et al*., 2022). Additionally, pyocyanin is hazardous to hosts, exacerbates disease, harms host tissue, and negatively impacts organ function (Alatraktchi *et al*., 2020). In addition, a significant number of lytic enzymes that control additional virulence factors include the elastases LasA and LasB, alkaline protease (AprA) LipC lipases, phospholipase C, and esterase A (Chadha *et al*., 2022). Furthermore, lung epithelial or tracheal cells can suffer from direct harm from tight junction destruction and lung surfactant degradation caused by rhamnolipids (Zhao *et al*., 2021). Additionally, siderophores (pyoverdine and pyochelin) function as iron uptake systems to aid bacterial survival in environments with low levels of iron, increasing virulence (Perraud *et al*., 2022). Finally, in phagocyte environments, reactive oxygen species (ROS) are neutralized by antioxidant enzymes like catalases (KatA, KatB, and KatE), alkyl hydroperoxide reductases, and superoxide dismutases to prevent bacterial clearance (Dar *et al*., 2021).

Antibiotic resistance in *P. aeruginosa*

Under increasing stress at aquatic systems, numerous studies show that the usage of antimicrobial agents in fish farming has

been increased as a result. Investigators estimate that by 2030, approximately 13,495 tons of antimicrobials will be applied to aquaculture, corresponding to 5.7% of the total amount used globally (including those utilized in humans and all other animals) (Ben Mhenni *et al*., 2023). This also attracts consideration to the reality that most antimicrobial categories are employed to treat infections caused by bacteria in both veterinary and human medicine. This accelerates the generation of drug-resistant bacteria, and antimicrobial-resistant bacteria may diminish treatment efficacy, particularly in infections caused by Gram-negative bacteria (Delannoy *et al*., 2022). Additionally, overusing of antibiotics during therapy hastens the emergence of multidrug-resistant *P. aeruginosa* strains, rendering antibiotic therapy ineffective against this pathogen (Hirsch and Tam, 2010). As a result, improper application of antibiotics in aquaculture contributes to the increasing prevalence of antimicrobial resistance (AMR), potentially resulting in animal, human, and ecosystem consequences (Schar *et al*., 2020). According to Hancock and Speert (2000), *P. aeruginosa* exhibits resistance to a number of antibiotics, including β-lactams aminoglycosides and quinolones. The main defense mechanisms employed by *P. aeruginosa* against antibiotic outbreak can generally be divided into intrinsic, acquired, and adaptive resistance. Numerous *Pseudomonas* strains have been found to have a significant degree of intrinsic resistance to the majority of antibiotics (Kačániová *et al*., 2017). The simultaneously mechanisms of low outer membrane permeability, efflux systems that remove antibiotics from cells, and the synthesis of antibiotic-inactivating enzymes like lactamases are the main contributors to this intrinsic resistance (Breidenstein *et al*., 2011).

Recent investigations confirmed that various strains of *Pseudomonas* spp. are able to be resistant to some antimicrobial agents of different classes, particularly lactams such as penicillins, cephalosporins, carbapenems, and monobactams (Elbehiry *et al*., 2022). According to the World Health Organization, *P. aeruginosa* is carbapenem-resistant (Karampatakis *et al*., 2018). In this regard, Kačániová *et al*. (2019) demonstrated a high percentage of resistant isolates among *Pseudomonas* spp. identified in fish. Furthermore, all *Pseudomonas* spp. were meropenem resistant. As reported by Fazeli and Momtaz (2014), *Pseudomonas* strains displayed the greatest degree of resistance to penicillin (100%), followed by tetracycline (90.19%), streptomycin (64.70%), and erythromycin (43.13%). *P. aeruginosa* develops a biofilm in the lungs of infected patients, acting as a diffusion barrier to prevent the bacterial cells from being exposed to antibiotics (Drenkard, 2003). The biofilm can also develop multidrug-tolerant persisted cells, which can withstand antibiotic treatment (Mulcahy *et al*., 2010).

Biofilm formation ability of *P. aeruginosa*

One of the most important mechanisms for species survival despite unanticipated changes in living conditions, such as temperature and nutrition availability, is the biofilm, which is an extensive collection of bacteria enclosed in a self-generated structure of extracellular polymeric substances (Ahmed *et al*., 2018; Morshdy *et al*., 2022b). Due to an increase in rates of mutations, an increase of efflux pumps, a reduction in metabolic activity, and other physical variables, resistance to antibiotics in attached bacteria is approximately 1000 times greater than in planktonic cells (Høiby *et al*., 2010). *P. aeruginosa* settles a variety of surfaces, such as medical supplies and equipment used in the food industry, and forms biofilms that result in chronic infections because of the organism's increased resistance to antibiotics, different irradiation therapies, environmental factors, disinfecting agents, and immunity (Stewart and Costerton, 2001).

P. aeruginosa biofilms can typically grow on abiotic surfaces like industrial machinery or medical implants. *P. aeruginosa* produces infections with the help of numerous virulence factors based on the cell such as lectins, pili, lipopolysaccharide, alginate, and secreted virulence factors (cytotoxin, pyocyanin, proteases, siderophores, hemolysins, exotoxin A, exoenzyme S, exoenzyme U (Strateva *et al*., 2011). Six separate stages make up the development of the biofilm. Stage 1: Via the assistance of cell appendages such flagella and type IV pili, bacterial cells adhere to a surface (Klausen *et al*., 2003). Flagellar movement restriction has been linked to twitching motility and the formation of exopolysaccharides required for surface association (Guilbaud *et al*., 2017), but this adherence is reversible. Stage 2: The transition of bacterial cells from reversible to irreversible adhesion. Stage 3: Progression of connected bacteria into microcolonies, which have a more organized architecture. Stage 4: As a biofilm matures, these microcolonies grow into substantial three-dimensional mushroom-like structures. Stage 5: To release dispersed cells, the matrix cavity in the center of the microcolony is destroyed by cell autolysis (Ma *et al*., 2009). Stage 6: The biofilm cycle can then repeat after the change from sessile to planktonic growth mode for seeding of uncolonized areas (Rasamiravaka *et al*., 2015).

L-glucuronic acid and D-mannuronic acid make up the unbranched polymer chain known as alginate. For the biofilm structure to be safeguarded and to remain stable, this polymer is crucial. Alginate helps to keep the matrix's nutrients and water from degrading by preserving its contents (Rasamiravaka *et al*., 2015). Another significant component of *P. aeruginosa* biofilm is eDNA, which functions as a nutrient base for embedded bacteria and is involved in cell-to-cell communication (Mulcahy *et al*., 2010). *P. aeruginosa* biofilm structure stability is maintained by many polysaccharides, which comprise pel, alginate, and psl (Ghafoor *et al*., 2011).

CONCLUSION

Pseudomonas aeruginosa is one of the most prevalent emerging bacteria commonly isolated from fish and fish products. Recovery of multi-drug resistant (MDR) *P. aeruginosa* strains serves as a cautionary tale for the appropriate use of antibiotics. Antimicrobial susceptibility screening must be carried out on a regular basis for the purpose of avoiding the development of antibiotic-resistant strains that could pose a public health concern. The majority of *Pseudomonas* species easily form biofilms and persist as the etiological agent of biofilm-mediated illnesses that result in chronic infectious diseases and recurrent infections. Numerous studies and approaches have been used to control the pathogenesis of biofilm formation and understand the underlying mechanism of biofilm development.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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