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# *Pseudomonas aeruginosa* and Its Pathogenicity

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ABSTRACT

*Pseudomonas aeruginosa*, belonging to the *Pseudomonadaceae* family, is Gram-negative, rod-shaped, motile, aerobic, endospore negative, oxidase and catalase positive. It is widely found in nature and isolated from soil, plants, water and animals. It can grow rapidly on the surface of the food and form oxidized products and mucous substances. *P. aeruginosa*, one of the leading foodborne pathogens, causes important concerns in food safety due to being a source of contamination, causing food poisoning and antimicrobial resistance in animals, forming biofilms and difficulties in preventing biofilms. In this review, information on history, microbiological, cultural and biochemical characteristics, virulence factors and pathogenicity of *P. aeruginosa* are given. In addition, infections caused by *P. aeruginosa* and its presence in food are described.

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# *Pseudomonas aeruginosa* ve Patojenitesi

MAKALE BİLGİSİ

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ÖZ

*Pseudomonas aeruginosa; Pseudomonadaceae* familyasına ait, Gram-negatif, çubuk şeklinde, aerobik, hareketli, endospor negatif, oksidaz ve katalaz pozitiftir. Doğada yaygın bulunur ve topraktan, bitkilerden, sudan ve hayvanlardan izole edilir. Yiyeceklerin yüzeyinde hızla gelişebilirler ve oksitlenmiş ürünler ve mukus maddeleri oluşturabilirler. Gıda kaynaklı patojenlerin başında gelen *P. aeruginosa*, kontaminasyon kaynağı olması, hayvanlarda gıda zehirlenmesine ve antimikrobiyal dirence neden olması, biyofilm oluşturması ve biyofilmlerinin önlenmesindeki zorluklar nedeniyle gıda güvenliğinde önemli endişelere neden olmaktadır. Bu derlemede, *P. aeruginosa*'nın tarihçesi, mikrobiyolojik, kültürel ve biyokimyasal özellikleri, virülans faktörleri ve patojenitesi hakkında bilgi verilmektedir. Ayrıca *P. aeruginosa* 'nın neden olduğu enfeksiyonlar ve gıdalardaki varlığı anlatılmaktadır.

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## Introduction

*Pseudomonas* belonging to the *Pseudomonadaceae* family are Gram-negative, rod-shaped, mostly motile, aerobic, endospore negative and catalase positive. Some types are oxidase positive, and some negative. There are saprophytic and pathogenic species in the genus *Pseudomonas*. Since the nutritional requirements of *Pseudomonas* species are simple, they can be widely found in many places such as soil, plants, fresh water, and saltwater. Its widespread presence in nature causes *Pseudomonas* to easily enter the food chain. There are types of psychrophiles, psychrotrophs, and mesophiles. The most frequently isolated human pathogen in the genus *Pseudomonas* is *Pseudomonas aeruginosa* (Benie et al., 2017; Rajmohan et al., 2002; Streeter and Katouli, 2016).

*P. aeruginosa* is a bacterium that can easily adapt to various environmental conditions. *P. aeruginosa* subspecies are commonly isolated from plants, water and soil, and colonize some anatomical regions of insects, animals, plants, and humans (Streeter and Katouli, 2016). *P. aeruginosa*, an opportunistic pathogen, mostly causes nosocomial infections and also associated with food and waterborne diseases. It has many virulence factors (Rajmohan et al., 2002; Mitov et al., 2010; Khattab et al., 2015).

*P. aeruginosa* is a dangerous and feared pathogen as it is resistance to antibiotics. It has a natural ability to develop resistance to antibiotics. This limits the use of a defined antibiotic against this bacterium and contributes to increased mortality rates. It has been reported that its resistance to many antibiotics such as tetracycline, gentamicin and penicillin is due to the low permeability provided by the outer membrane lipopolysaccharide (Arumugam et al., 2018).

*P. aeruginosa* causes important concerns in food safety due to being a source of contamination, causing food poisoning and antimicrobial resistance in animals, forming biofilms and difficulties in preventing biofilms. Such sticky bacteria can contaminate food during production. This seriously affects both the quality and safety of processed food and can be a potential hazard to the consumer health (Xu et al., 2019; Azelmad et al., 2018).

## History of *P. aeruginosa*

*P. aeruginosa* has had various names throughout its history due to the characteristic blue-green color produced during its growth. In 1850, Se'dillot observed that discoloration of surgical wound dressings was related with a transferable agent. In 1860, Fordos extracted the pigment causing the blue coloration, and Lucke revealed that this pigment was caused by the rod-shaped organisms in 1862. *P. aeruginosa* was not isolated as pure culture until 1882. Carle Gessard named the rod-shaped organism that caused the infection as *Bacillus pyocyaneus* in 1882. However, in 1894, Migula determined that the bacterial species was different from the *Bacillus* genus in his detailed studies and defined this bacterium as *P. aeruginosa*. A more comprehensive study of the invasion and spread of *P. aeruginosa* causing acute or chronic infection was carried out by Freeman in 1916 (Lister et al., 2009; Pitt, 1998; Villavicencio, 1998; Teixeira et al., 2011).

In 1973, Palleroni classified *Pseudomonas* bacteria into five homologous groups according to their rRNA, and De Vos and De Ley conducted detailed studies on these five homologous groups in 1983. They determined the affinities between species and reclassified the groups according to their phylogenetic affinities. *P. aeruginosa* is in homology group I (Table 1) (Palleroni, 1993; Murray, 2007).

## Microbiological, Cultural and Biochemical Characteristics of *P. aeruginosa*

*Pseudomonas* is Greek and consists of two words: Pseudo and monas. The means of pseudo is 'false', and that of monas is 'single unit'. “Aeruginosa” comes from the Latin “aerūgō” word which means 'greenish-blue' or 'rusty copper' (Diggle and Whiteley, 2020).

*P. aeruginosa* is a strictly aerobic, non-spore forming, Gram-negative rod-shaped (straight or slightly curved) bacterium about 1.5–3.0 μm long and 0.5–0.8 μm wide. It is a motile bacterium with a single polar flagellum, and is methyl red, Voges Proskauer and indole negative, and oxidase, catalase, gelatin and citrate positive.

Table 1. Classification of *Pseudomonas* (Palleroni, 1993)

| rRNA Homology Group and Subgroup | Genus and Species |
|---|---|
| I Fluorescent Group<br><br>Non-Fluorescent Group | Pseudomonas aeruginosa, P. fluorescens, P. putida, P. chlororaphis, P. cichorii, P. syringae,<br>P. viridiflava, P. agarici, P. tolaasii, P. asplenii, P. stutzeri,<br>P. mendocina, P. alcaligenes, P. pseudoalcaligenes, P. fragi |
| II | Burkholderia pseudomallei<br>B. mallei<br>B. cepacia<br>Ralstonia pickettii |
| III | Comamonas spp.<br>Acidovorax spp.<br>Delftia spp.<br>Hydrogenophoga spp. |
| IV | Brevundimonas spp. |
| V | Stenotrophomonas maltophilia<br>Xanthomonas spp. |

They usually appear as single cells but are sometimes found in short chains. Young cultivars usually produce a blue-green pigment, but these colors turn brown as the culture ages. *P. aeruginosa* can oxidize glucose but cannot ferment. They show proteolytic and lipolytic activity. Due to being aerobic, they can grow rapidly on the surface of the food and form oxidized products and mucous substances. *P. aeruginosa* is capable of synthesizing growth factors and vitamins necessary for its own development and is most often associated with human infection (Baltch and Smith, 1994; Rajmohan et al., 2002; Moore et al., 2006; Levinson, 2008; Virupakshaiah and Hemalata, 2016; Crone et al., 2020; Diggle and Whiteley, 2020; Sah et al., 2021).

Although *Pseudomonas* spp. are obligate aerobic bacteria, unlike other species in this genus, *P. aeruginosa* can survive in anaerobic conditions due to its ability to use nitrate ($NO_3$) as a terminal electron acceptor. *P. aeruginosa* can grow in broad temperatures ranging from 4–42°C, and its optimum growth temperature is between 37 and 41°C. Most other pseudomonads cannot grow at 41°C. The ability of *P. aeruginosa* to grow at 41°C distinguishes it from *P. putida* and *P. florescens*. It is resistant to high salt and dye concentrations, weak antiseptics and many antibiotics. *P. aeruginosa* subspecies can grow the pH range of 5.6 and 8.0, but their optimum pH value is pH 6.6-7.0. It grows easily because it does not need organic growth factors. *P. aeruginosa* is one of the rare bacteria that can grow in the presence of a single carbon source. In addition, it is easy to isolate since it can grow in the media frequently used in microbiology laboratories. This bacterium can form 3 types of colonies in solid media in 24 hours at 37°C. The first type of colony is usually isolated from clinical specimens, 2-3 mm in diameter, round, matt surface, raised in the middle, white in color and fluorescent, with blue-green pigments spread all over the medium. The second type of colony is smaller, fluffy, convex and irregular colonies, mostly isolated from natural sources. The third type of colony is R-type colonies, which have a mucoid appearance due to the extracellular alginate secretion of some strains. *P. aeruginosa* growth cultures have a characteristic sweet, fruity, grape or trimethyl amine-like odour (Baltch and Smith, 1994; Teixeira et al., 2011; Rajmohan et al., 2002; Virupakshaiah and Hemalata, 2016).

Although being a pathogenic bacterium, *P. aeruginosa* is one of the most valuable commercial and biotechnological microorganisms. It produces colored, redox-active pigment molecules called phenazines-dibenzo ring pyrazines containing pyoverdin, pyocyanin, pyorubin and pyomelanin. These pigments have wide industrial applications in the food, pharmaceutical, textile, leather and other industries (Anayo et al., 2019). These pigments act as siderophores for the bacteria's iron uptake and therefore, the pigment production increases in iron-limited conditions. Pyoverdine is a pigment that is insoluble in chloroform but soluble in water and gives a greenish color by forming fluorescence with UV rays of 254 nm wavelength. Pyocyanin, on the other hand, is a water- and chloroform-soluble phenazine dye, non-fluorescent, and a blue pigment. This pigment is formed only in an aerobic environment and has high diagnostic value and is also used to control phytopathogens (Laursen and Nielsen, 2004; Ohfuji et al., 2004; Sudhakar et al., 2013). Pyorubin is a red-brown pigment and pyomelanin is a light-brown pigment. The presence of pyorubin and pyomelanin pigments (brown) suppresses the formation of pyocyanin pigment (blue). The formation of pyocyanin and pyoverdin pigments in the medium is a very important feature for the diagnosis of *P. aeruginosa*. Pyocyanin (N-methyl-1-hydroxyphenazine) is a redox active natural compound and has a variety pharmacological effect on prokaryotic and eukaryotic cells and these biological effects are mostly related to the similarity of its chemical structure to isoalloxazine, flavoproteins, flavin mononucleotide and flavin adenine dinucleotide (King and Phillips, 1978; Meyer, 2000; Laursen and Nielsen, 2004; Ohfuji et al., 2004; Jayaseelan et al., 2014). Phenazines have many beneficial physiological functions: cell-signaling, electron shuttling to various oxidants or protection against oxidizing agents, supporting survival in the case of limited electron acceptor, getting nutrients such as iron, ensuring energy production by photosynthesis, promotion of bacterial biofilm development and protection against ultraviolet radiation. Not every phenazine has all the functions mentioned. Each phenazine has different physiological effects (Laursen and Nielsen, 2004; Dietrich et al., 2006; Wang et al., 2010; 2011; Glasser et al., 2014).

In addition to the ability to produce pigment, some strains of *P. aeruginosa* synthesize different antimicrobial proteins known as bacteriocins to compete with other microorganisms (Parret and Mot, 2002). The bacteriocins produced by *P. aeruginosa* are called pyocins. More than 90% of *P. aeruginosa* strains are capable of producing pycins, and each strain can synthesize one or more types of pyocins. Pyocin plays an important role in both invasion of bacterium and defense of its ecological niche (Michel-Briand and Baysse, 2002). Pyocin encoded genes are located in the *P. aeruginosa* chromosome and its synthesis has been reported to be induced by mutagenic agents such as mitomycin C or by ultraviolet (UV) lights. Jacob (1954) was the first to find a protease-resistant pyocin derived from UV-irradiated (wavelength 253.7 nm) *P. aeruginosa*. Further investigations detailed the attachment of pyocin to sensitive bacterial cell surface leading to their eventual killing, similar to colicins. Therefore, this antimicrobial compound was named pyocin (Jacob, 1954; Michel-Briand and Baysse, 2002). Pyocin is synthesized by some *P. aeruginosa* strains and helps destroy other *P. aeruginosa* strains. However, it has been reported that some pyocins have inhibitory effects against other *Pseudomonas* species and other bacteria such as *Neisseria gonorrhoeae,N. meningitidis*, *Haemophilus ducreyi*, *Campylobacter* spp., *Galleria mellonella*, *Escherichia coli*, *Klebsiella pneumoniae*, *Bacillus subtilis, B. cereus, Listeria monocytogenes, Staphylococcus aureus, S. epidermidis, Streptococcus pyogenes, S. pneumonia, Enterococcus faecalis* and *Micrococcus luteus* (Williams et al., 2008; Bakkal et al., 2010; Naz et al., 2015; Atanaskovic et al., 2020). Three types of pyocin have been identified: R-, F- and S-types. They differ from each other by their morphology and mode of action of killing. R-type pyocins tend to show a close resemblance to inflexible and contractile tails of phages like T-even phages due to their morphological and genetic characteristics. However, unlike phages, R-type pyocins are resistant to acids, nuclease and proteases (Kageyama et al., 1964; Scholl and

Martin, 2008). Also, in contrast to the killing mode of bacteriophages, R-type pyocins exert their antibacterial effects without lysing target cells. Eight subtypes of R-type pyocins have been identified: R1, C9, R2, R3, R4, R5, 21 and 430C. They are similar to each other in structural and serological properties, but differ in receptor specificity. The bactericidal effect of R-type pyocins is rapid and specific, with each molecule of pyocin having the ability to kill a sensitive cell. Cell death mechanisms result from depolarization of the cytoplasmic membrane (at least 90 mV) associated with pore formation (Michel-Briand and Baysse, 2002; Williams et al., 2008; Strauch et al., 2001; Scholl et al., 2009; Neves et al., 2014). The adsorption of R-type pyocins to sensitive strains occurs when tail fiber proteins interact with lipoteichoic acids in Gram-positive bacteria and with lipopolysaccharides found in the outer membrane in Gram-negative bacteria (Mohamed et al., 2021). After the tail fiber proteins bind to cell surface receptors, the sheath contracts and the core is inserted into the cell, eventually forming pores in the cell membrane, leading to depolarization of the cell membrane. This causes inhibition of macromolecular syntheses such as protein and DNA synthesis and ultimately cell death (Brackman et al., 2017). F-type pyocins are protease resistant proteins. They also resemble tails of phages with a flexible and non-contractile rod-like structure (Takeya et al., 1967). Three subgroups of F-type pyocins were: F1, F2, and F3. F-type pyocins are similar in structure, morphological and serological properties, but different in receptor specificities (Neves et al., 2014). Phage tail-like bacteriocin R- and F-type pyocins were named tailocins (Ghequire and De Mot, 2014). Unlike R and F types, S type pyocins, colicin-like bacteriocins, are soluble and sensitive to heat treatment and proteases. In addition, S-type pyocins are composed of two protein subunits. The large subunit of S-type pyocin is the effector component and has the killing activity due to its DNase, lipase, tRNase, and channel-forming activity. Its minor subunit is the immune component that protects pyocin-producing strains from their own-produced pyocin. There are six subtypes of S-type pyocin: S1, S2, S3, AP41, S4, S5, and S6 (Duport et al., 1995; Ling et al., 2010; Neves et al., 2014; Ghequire and De Mot, 2014). Pyocin S1, S2, S3 and AP41 show DNase activity, while pyocin S4 and S6 have tRNase and rRNase activity, respectively (Ghequire and De Mot, 2014). While the killing host range of S-type pyocins is limited to *P. aeruginosa*, R- and F-type pyocins have broader lethal spectrum and have inhibitory effects against *P. aeruginosa* and other Gram-negative bacteria (Neves et al., 2014). R- and F-type pyocins are produced by more than 90% of *P. aeruginosa* strains, while the S-type is produced by 70% of these strains (Takeya et al., 1969; Michel-Briand and Baysse, 2002).

One of the important strategies for *P. aeruginosa* to survive during changing environmental conditions is to produce numerous different extracellular polysaccharides. Polysaccharides protect cells against desiccation, oxidizing agents, and host defense processes (Pier et al., 2001; Jackson et al., 2004; Franklin et al., 2011). *P. aeruginosa* mainly produced three major polysaccharides: alginate, Psl and Pel, and they have been reported to play an important role in biofilm formation *in vitro* (Ryder et al., 2007; Diggle and Whiteley, 2020). Alginate is produced mainly by mucoid variants isolated from the lungs of chronically colonized CF patients, while Pel and Psl exopolysaccharides are produced by non-mucoid variants (Hentzer et al., 2001; Wozniak et al., 2003; Colvin et al., 2012). The alginate produced by *P. aeruginosa* is a high molecular weight acidic polysaccharide consisting of non-repeating subunits of selectively O-acetylated D-mannuronic acid and its C5′ epimer L-guluronic acid. Alginate is secreted into the environment or medium and is not covalently bound to the cell surface, resulting in a highly viscous appearance of colonies on agar medium (Franklin and Ohman, 1993; Franklin et al., 2011). The chemical structure of Psl is as repeating units of a branched pentasaccharide composed of D-glucose, L-rhamnose, and D-mannose monosaccharides (Byrd et al., 2009). It is stated that Psl forms a helical distribution surrounding the cell surface of *P. aeruginosa* PAO1 and thus plays a role in cell to cell and cell to surface interactions during biofilm formation (Ma et al., 2009). Pel is a polycationic polymer containing partially acetylated glucosamine and galactosamine (Jennings et al., 2015). It may play an additional protective role by increasing resistance to aminoglycoside antibiotics by binding extracellular DNA (eDNA) via an ionic binding mechanism (Colvin et al., 2011; Jennings et al., 2015; Jennings et al., 2021).

**Virulence factors and pathogenicity of *P. aeruginosa***

Virulence is known as the degree of pathogenicity that microorganisms have to cause damage and disease to the host cell. Pathogenicity is the quality of being pathogenic or the potential disease-causing ability. The microbial factors responsible for this event are called virulence factors. Pathogenic microorganisms have several different virulence factors that help to escape host defenses, enter host cells, and demobilize or lyse host cells (Batt, 2016).

Host and bacterial factors are effective in the pathogenicity of *P. aeruginosa* infections. Bacterial virulence factors can be studied as cell-associated and extracellular factors. The release of virulence factors increases in the logarithmic phase, where growth occurs and cell density increases. The release and regulation of virulence factors are controlled by a complex regulatory system, and the intercellular communication system has an important role in ensuring coordination. Virulence factor production is regulated at the genetic level in bacteria. Much of the regulation at the DNA level include rearrangements in the gene encoding specific virulence factors, changes or rearrangements in genes containing promoters or other regulatory elements (Woods, 2004). Besides, the first step of *Pseudomonas* infection is adhesion and colonization. This is followed by stages of local invasion and widespread systemic infection. *P. aeruginosa* pathogenicity is thought to result from production of several membrane and extracellular virulence factors and its ability to form biofilm. Membrane-associated factors are flagella, lipopolysaccharides, adhesion factor (pili type IV), and alginate. The main extracellular factors are exotoxins, exo-proteases (elastase, staphylolysis, protease IV, alkaline protease), phospholipase C, chromophores and exo-enzymes S, T and U. While cell membrane-associated virulence factors are generally effective in colonization and chronic infection, extremely toxic extracellular factors are related to acute infection (Benie et al., 2017). Virulence factors and mechanism of *P. aeruginosa* were given Figure 1 (Lee and Zhang, 2015; Diggle and Whiteley, 2020)

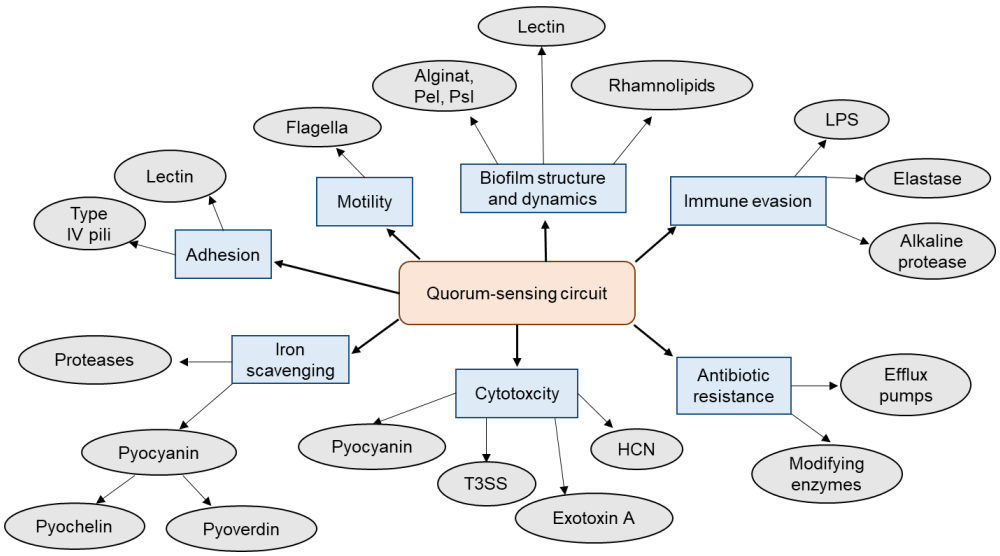


Figure 1. Virulence factors and virulence mechanisms of Pseudomonas aeruginosa (Lee and Zhang, 2015; Diggle and Whiteley, 2020)

***Lipopolysaccharides***

They are the main surface-related virulence factor of *P. aeruginosa*. Lipopolysaccharide (LPS) is an immunogen and plays an important structural role in facilitating the interaction between the bacterial cell surface and the external environment (Le Berre et al., 2011). Bacterial LPS typically comprises a hydrophobic domain known as lipid A (endotoxin), a non-repeating oligosaccharide, and an extrinsic polysaccharide (O-antigen). LPS has a significant effect on the activation of the host's innate and adaptive (or acquired) immune responses. Ultimately, it causes dysregulated inflammatory responses that contribute to morbidity and mortality (Rocha et al., 2019). Also, the LPS O antigen is used for the classification of *P. aeruginosa* isolates or serotypes (Faure et al., 2003).

***Flagella***

Flagella is a complex bacterial organelle, well conserved among various bacterial species. It is thought to be important for the survival of the microorganism due to its chemotaxis and motility. Flagella facilitate the acquisition of essential nutrients. Furthermore, flagella are known to be highly immunogenic (Feldman et al., 1998).

***Adhesion Factor Pili (pili type IV)***

It has an important role in adhesion to many cell types. This feature is important in terms of binding to certain tissues. It mediates biofilm formation, initiation of non-opsonic phagocytosis, and phagocyte receptors that recognize adhesions (Benie et al., 2017; Rocha et al., 2019).

***Alginate***

It is an exopolysaccharide mucoid structure composed of mannuronic and guluronic acid polymer. Mucoid colonies of alginate-forming *P. aeruginosa* protect the bacteria from the host's immune response and antibiotics. Over secretion of alginate protects *P. aeruginosa* from phagocytosis, dehydration, antibiotics, and even acquired host response (Benie et al., 2017; Van Delden, 2004). Although alginate conduces to biofilm structure, it is not required for biofilm formation (Stapper et al., 2004)

***Elastase***

*P. aeruginosa* produces two types elastases: Elastase A (LasA) and B (LasB). LasB (Pseudolysin) and LasA (Staphylolysin) are very important virulence factors since they degrade host tissues and immune components such as collagen, immunoglobulin G (IgG), complementary proteins and surfactant proteins A and D (Mariencheck et al., 2003; Matsumoto, 2004; Mun et al., 2009; Le Berre et al., 2011). LasA, a zinc metalloprotease, enhance elastolytic activity and high staphylolytic activity, causing rapid lysis of *Staphylococcus aureus* but not has proteolytic activity. LasA protease does not cleave elastin, but it increases the elastolytic activity of lasB elastase (Goldberg and Ohman, 1987; Peters et al., 1992; Kessler et al., 1993). LasB, a metalloprotease, cleaves elastin, the components of complement system such as fluid-phase and cell-bound C1 and C3 and fluid-phase C5, C8 and C9, serum α1-proteinase inhibitor, immunoglobulin A (IgA), IgG, mucins, fibrin, collagen, surfactant proteins A and D. In addition, it increases the permeability of the epithelium by breaking the tight junctions in the respiratory tract epithelium and causes an increase in the number of neutrophils in the infection area. Elastase exerts a pro-inflammatory effect by stimulating IL-8 production (Alcorn and Wright, 2004; Matsumoto, 2004; Mun et al., 2009; Kuang et al., 2011; Hoge et al., 2010; Le Berre et al., 2011; Mariencheck et al., 2010).

***Alkaline Protease***

The alkaline protease (AprA) is one of the zinc-dependent metallo-endopeptidase of *P. aeruginosa* and is also known as aeruginolysin. AprA is associated with bacterial virulence and interferes with complement-mediated erythrocytes lysis. It is secreted through type I secretion system and has high proteolytic activity. The enzyme has a molecular weight of 50 kDa and shows the best activity at alkaline pH values (Laarman et al., 2012). AprA inhibits bacterial clearance by cleaving the C2 component of the complement system, thus preventing complement-mediated phagocytosis (Laarman et al., 2012). Also, it degrades flagellin, a known activator of

proinflammatory responses (Bardoel et al., 2012; Pel et al., 2014). AprA degrades laminin which is a biologically active part of the basal lamina, therefore, the alkaline protease may have a function in invasion and hemorrhagic tissue necrosis in *P. aeruginosa* infection (Hoge et al., 2010). In addition, AprA can cleaves interleukin-6 very efficiently (Matheson et al., 2006).

***Protease IV***

It is a serine protease with a molecular mass of 26 kDa and specifically cleaves the carboxyl side substrates of lysine-containing peptides, and therefore, it is lysyl endopeptidase. Protease IV can degrade biologically important host proteins including fibrinogen, plasminogen and IgG, as well as 3 and C1q complement components of the immune defense system. It is an important virulence factor in corneal infections (Van Delden, 2004; Hoge et al., 2010). It has been shown that protease IV degrades surfactant proteins A, D and B and contributes to the pathogenesis of lung infections (Malloy et al., 2005).

***Phospholipase C***

Phospholipase C is secreted from the outer membrane of *P. aeruginosa* by the type II secretion system. *P. aeruginosa* produces II types of phospholipase C (PLC), hemolytic PLC (PlcH) and non-hemolytic PLC (PlcN). Phospholipase C is cytotoxic and has been reported to have a modifying effect on signaling processes in various eukaryotic cells (Barker et al., 2004).

***Pyocyanin***

Pyocyanin is a blue redox active phenazine pigment and produces reactive oxygen species due to the intracellular redox cycle. It modifies the responses of host cells by inhibiting neutrophil superoxide formation and lymphocyte proliferation and increasing IL-8 production by human airway epithelial cells. It is thought that pyocyanin induces apoptosis of human neutrophils, provides rapid production of reactive oxygen intermediates and is associated with lowering intracellular cAMP levels (Van Delden, 2004; Meirelles and Newman, 2018). It has been reported that pyocyanin inhibits cell respiration, damages ciliary function, and promotes oxidative damage to the lung epithelium (Le Berre et al., 2011).

***Pyoverdin***

Pyoverdin is a siderophore (iron-chelating molecule) produced by *P. aeruginosa* consisting of a peptide chain and a chromophore. Pyoverdines are especially a typical feature of fluorescent *Pseudomonas* species including *P. aeruginosa, P. fluorescens, P. syringae, P. putida,* and are produced under low iron conditions. Besides being a siderophore, pyoverdin is a signaling molecule as it triggers the production of the extracellular virulence factor protease PrpL and exotoxin A. Therefore, it is important for bacterial virulence and also biofilm development (Visca et al., 2007; Cornelis and Dingemans, 2013).

***Pyochelin***

Pyochelin is the second siderophore of *P. aeruginosa* and synthesis by all *P. aeruginosa* species. The affinity of pyochelin for iron is much lower than pyoverdine (Brandel et al., 2012). *P. aeruginosa* produces pyochelin first and starts to produce pyoverdine when the iron concentration in the medium becomes too low. Pyochelin-iron was determined to cause oxidative damage and inflammation, especially in the presence of pyocyanin (Dumas et al., 2013; Pierre and Jozef, 2013).

***Ramnolipid***

*P. aeruginosa* produces rhamnose-containing glycolipid biosurfactants called rhamnolipids. Although rhamnolipid production is characteristic of *P. aeruginosa*, some non-pathogenic *P. putida* and *P. chlororaphis* strains were also reported to produce rhamnolipids. Ramnolipid production is regulated by the quorum sensing-QS system. Ramnolipid plays multiple roles in the development of biofilm matrix and is necessary for initial microcolony formation, and also induces necrosis of neutrophils. Due to being a biosurfactant, it is of great interest to manufacturers of food additives, cosmetics, pharmaceuticals and detergents (Soberón-Chávez et al., 2005; Müller et al., 2010; Pamp and Tolker-Nielsen, 2007).

***Exotoxin A (ExoA)***

It is a toxin that is secreted out of the cell by the type II secretion system. ExoA plays an important role in the virulence of *P. aeruginosa*. Similar to diphtheria toxin, it exerts its effect by inhibiting elongation factor 2 (EF-2) and thus inhibits protein synthesis with its ADP-ribosyl transferase property and causes cell death. ExoA has been shown to suppress the host response during the infection. In addition, it has been stated that ExoA has a significant effect on local tissue damage and invasion (Van Delden and Iglewski, 1998; Rocha et al., 2019).

***Type III Secretion System***

This system injects exotoxins or proteins into the cytoplasm of the eukaryotic cell using a translocation needle-like apparatus and porin-forming proteins. It has been stated that 4 types of toxins are secreted by the Type III secretion system of *P. aeruginosa*. These toxins are exoenzyme S (exoS), exoenzyme T (exoT), exoenzyme Y (exoY) and exoenzyme U (exoU) (Le Berre et al., 2011). ExoS, encoded by the *ExoS* gene, is an aggregate of two proteins of 49-kDa size with ADP-ribosyltransferase activity and 53-kDa size with ADP-ribosyltransferase activity. ExoS helps to evade immunity by disrupting the cytoskeletal structure. ExoU, secreted by the type III secretion system, is a cytotoxin that causes host cell rapid death (1 to 2 hours). This death is characterized by loss of cell membrane integrity, typical necrosis. ExoU has phospholipase A2 activity and also disrupts the uptake of phagocytes. ExoU is thought to be 100 times more cytotoxic than ExoS. It is known to activate pro-apoptotic pathways together with ExoT and delay wound healing in other epithelial cell types. ExoT is the only type III secretory system exoenzyme encoded and expressed in all virulent *P. aeruginosa* clinical isolates, and this virulence factor is thought to play a fundamental role in the pathogenesis of *P. aeruginosa*. ExoT damages the cell structural proteins by attacking eukaryotic proteins including collagen and elastin. It has been stated that ExoT inhibits wound healing, alters the actin cytoskeleton, inhibits cell migration and cytokinesis division of the cell. ExoY, a fourth effector protein, is an adenylate cyclase

enzyme that can be displaced in target cells via the type III secretion system. ExoY has also been reported to cause actin cytoskeleton disruption. In addition, proteolytic and elastolytic proteins such as LasA and LasB cause tissue damage and increase the persistence of chronic infections (Van Delden, 2004; Le Berre et al., 2011; Wood et al., 2015; Newman et al., 2017).

***Biofilm***

Biofilms are densely packed communities of microorganisms that grow on a variety of biotic and abiotic surfaces, surround themselves with secreted extracellular polymer or matrix. The extracellular matrix, composed of polysaccharides, proteins, nucleic acids, and lipids, is a hallmark of biofilms and can act as both a structural scaffold and a protective barrier (O'Toole, 2002; Parsek and Singh, 2003). Of these, extracellular polysaccharides (EPS) are the most important component of the matrix, promoting the attachment of bacteria to surfaces and other cells, forming and maintaining the biofilm structure. It also performs a number of functions, such as protecting cells from antimicrobials and host defenses (Stewart and Franklin, 2008; Stoodley et al., 2002). Many bacterial species form biofilms and this is an important bacterial survival strategy. It is thought that biofilm formation begins with the perception of environmental conditions that trigger life change on a surface by bacteria. The structural and physiological complexity of biofilms leads us to think that they work in coordinated and collaborative groups, similar to multicellular organisms (Passerini et al., 1992; Stewart and Costerton, 2001). *P. aeruginosa* biofilms are thought to be the cause of many chronic and recurrent infectious diseases that complicate the treatment of bacterial infections. Antibiotics have been found to be ineffective in bacteria growing in biofilms, due to the inability of drug molecules to penetrate the inner surface of biofilms (Yuan et al., 2019).

***Quorum Sensing***

Quorum sensing (QS) is considered as an important virulence since it is involved in the regulation of many virulence factors. QS is the cell-cell communication mechanism that occurs with signaling molecules called auto-inducers. This mechanism depends on the cell population balance. QS regulates important microbial processes such as virulence factor, sporilization, mortality, toxin production and biofilm formation. The QS mechanism threatens public health because it causes effects such as biofilm, virulence factors and antibiotic resistance (Dong et al., 2007; Jimenez et al., 2012; Duanis-Assaf et al., 2016). In *P. aeruginosa*, the major QS elements are las, rhl, pqs and iqs and their function is to coordinate signal production and virulence expression (Lee and Zhang, 2015). The three main signaling molecules of *P. aeruginosa* are N-3-oxo-dodecanoyl-L-homoserine lactone (C12-HSL), N-butyryl-L-homoserine lactone (C4-HSL) and quad-quinolone. When these signals reach significant levels, they activate their regulatory genes, increasing the transcription of virulence factors (Toder et al., 1994). QS causes *P. aeruginosa* to release virulence factors and perform biofilm synthesis during infection. Las system controls the virulence factors LasB and LasA elastase, alkaline protease, exotoxin A and biofilm formation, while the rhl system controls the production of pyocyanin pigment, rhamnolipids, LasB elastase and hydrogen cyanide (Pesci et al., 1997; Pearson et al., 1997, Williams et al., 2007; Lee and Zhang 2015; Ganesh and Rai, 2018). Therefore, inhibiting QS is an important strategy in controlling microbial pathogenesis (Tang and Zhang, 2014).

***Lectin***

Lectin is a tetrameric protein and *P. aeruginosa* produces lectin A (LecA or PA-IL) and lectin B (LecB or PA-IIL) as intracellular and only a small fraction present on the cell surface. LecA and LecB bind to specifically L-galactose and L-fucose and their derivatives, respectively. These lectins act as virulence factors due to their ability to bind carbohydrates (Gilboa-Garber et al., 2000; Diggle et al., 2006). LecA is adhesive and has a cytotoxic effect. LecA impairs the respiratory of epithelial cells and induces a permeability defect in the intestinal epithelium. Also, it is important for cell-cell interaction, cell attachment, invasion, and biofilm formation (Glick and Garber, 1983; Diggle et al., 2006; Chemani et al., 2009). LecB involves in adhesion, biofilm formation, pilus synthesis and protease IV activity (Sonawane et al., 2006; Chemani et al., 2009).

***Hydrogen Cyanide (HCN)***

*P. aeruginosa* can synthesize HCN as a secondary metabolite by the oxidative decarboxylation of glycine via hydrogen cyanide synthase enzyme. It provides advantages to *P. aeruginosa* in the ecological niches and plays a role in its pathogenicity. HCN is a highly toxic and potent inhibitor of cytochrome c oxidase and other metalloenzymes (Blumer and Haas, 2000; Lenney and Gilchrist, 2011; García-García et al., 2016; Fata et al., 2017).

These virulence factors contributing to the pathogenicity of *P. aeruginosa* are often not studied in strains isolated from some food products. However, it has been reported that these food products and main products of animal origin harbor strains with some risky zoonotic serogroups related to virulence factors. For this reason, virulence factors in strains isolated from animal foods are also important (Benie et al., 2017).

**Infections caused by *P. aeruginosa***

*P. aeruginosa* poses a great risk to humans and animals as it causes frequent secondary infections as well as causing food spoilage. The emergence and spread of multidrug-resistant *P. aeruginosa* strains have recently become a public health concern (Horcajada et al., 2019). *P. aeruginosa* is mostly a nosocomial pathogen (Giamarellou, 2000). Almost all clinical cases of *P. aeruginosa* induced infections can be associated with compromised host defenses. Most cases of *P. aeruginosa* infections are immunocompromised patients undergoing treatment for AIDS and chemotherapy. Such diseases make susceptible the host to a diversity of bacterial and fungal infections. In this context, *P. aeruginosa* causes three main diseases: bacteremia, chronic lung infection and cystic fibrosis in severe burn patients, and acute ulcerative keratitis in long-term soft contact lens wearers (Lyczak et al., 2000).

Recent studies have shown that *P. aeruginosa* is a common source of many social and hospital infections and is very effective, especially in people with compromised immune systems, burns and cystic fibrosis patients. Infections can occur in all anatomical regions, and the most common infections occur in the cornea, skin, respiratory tract and urinary tract. It is the main cause of hospital-acquired diseases such as pneumonia and sepsis syndrome in people who are connected to the ventilator. *P. aeruginosa* is a very important pathogen in medicine due to its multi-antibiotic resistance feature. It causes pneumonia, septic shock, urinary system, gastrointestinal, skin and soft tissue infections (Kumari et al., 2009; Høiby et al., 2010; Lopez et al., 2015). *P. aeruginosa* can also cause endocarditis and ear infections that can result in death (Arumugam et al., 2018).

*P. aeruginosa* is responsible for infections with high mortality due to its ability to acquire antibiotic resistance rapidly and to have multiple antibiotic resistance mechanisms. Beta-lactam resistance in *P. aeruginosa* occurs by enzymatic (penicillinase, wide-spectrum beta-lactamase, imipenemase and cephalosporinases) and non-enzymatic (decreased membrane permeability due to porin loss, active pumping out) mechanisms (Cavallo et al., 1996).

**Availability of *P. aeruginosa* in Foods**

*Pseudomonas* spp. are the primary spoilage factor for red meat, chicken meat, eggs and seafood stored especially in the cold. *Pseudomonas* causes stickiness, rancidity and discoloration on the surface of fresh meats. Although the microbial spoilage caused by *Pseudomonas* affects the appearance, structure and sensory properties of foods, it can also be the cause of serious and fatal diseases (Baltch and Smith, 1994; Arnaut-Rollier et al., 1999; Franzetti and Scarpellini, 2007).

*Achromobacter* and especially *Pseudomonas* are the leading psychrophilic bacteria that cause meat to deteriorate outside of normal cold storage periods. *Pseudomonas* are among the main species that cause problems in the storage and thawing of frozen meat and storage of thawed meat. Some species within the genus *Pseudomonas* are *P. aeruginosa, P. fluorescens, P. putida, P. protegens, P. syringae,* and *P. entomophila*. Among these species, the most important species in the food industry is *P. aeruginosa*. The psychrophilic properties of these bacteria have been known for a long time. Colony and bacterial membranous layer formation in meat facilitate their identification (Yıldırım, 1992; Franzetti and Scarpellini, 2007; Akan, 2009).

Chicken is an important food in human nutrition due to its high nutrient content. *P. aeruginosa* is one of the leading microorganisms that cause problems for the chicken industry. It limits the shelf life of chicken meat stored in the cold by causing slipperiness and unpleasant odors on the surface. In addition to causing food spoilage, *P. aeruginosa* poses a great risk for humans and animals because it frequently causes secondary infections (Arnaut-Rollier et al., 1999; Kumari et al., 2009; Høiby et al., 2010; Lopez et al., 2015).

Early spoilage of food produced from poultry can cause product losses. This affects business names and consumer trust. It creates a negative impact for both companies and consumers. Chicken meat stored in the cold is a highly perishable food due to its high-water activity, relatively neutral pH and abundant nutrient content. This makes it an excellent environment for the proliferation of psychrophilic bacteria (Arnaut-Rollier et al., 1999; Vihavainen and Björkroth, 2010).

The spoilage microbiota of cold-kept poultry is heterogeneous and often the predominant microorganism is *Pseudomonas* spp. This microorganism is not currently included in HACCP plans because its presence is not a primary cause of human disease. However, *Pseudomonas* spp. is the main organism that determines the quality, safety and shelf life of poultry meat that can reach foreign markets, especially by transporting long distances in a globalizing world. Aerobic *Pseudomonas* spp. is recognized as a key factor in establishing the microaerophilic environment that will help the survival of *Campylobacter jejuni*, an important enteric pathogen in chicken (Hilbert et al., 2010; Morales et al., 2016).

*Pseudomonas* spp. play an important role in the spoilage of processed milk, as they reduce the quality and shelf life of milk by producing numerous thermo-tolerant lipolytic and proteolytic enzymes (Raposo et al., 2017).

Dogan and Boor (2003) isolated 338 *Pseudomonas* species from raw milk, processed milk and environmental samples and determined 51% of these isolates as *P. fluorescens*, 14% as *P. putida* and 25% as *P. fluorescens* or *P. putida*. Virupakshaiah and Hemalata (2016) revealed the presence of *P. aeruginosa* in various food products as a result of improper practices during harvest and storage. Among 20 resistance *Pseudomonas* isolates, two *P. aeruginosa* strains HV17 and HV77 were highly resistant to many antibiotics.

Keskin and Ekmekçi (2008) determined the presence of *P. aeruginosa* and its incidence in foods in 100 different water and food (fruit-vegetable, milk, cheese and meat) samples collected from the market. They isolated *P. aeruginosa* only in milk and meat from the examined food samples and identified 8 of the isolates as *P. aeruginosa*.

Morales et al. (2016) isolated *P. fragi* and *P. fluorescens* species from 11 chicken meat samples with different production dates from those whose expiration date was 2 days.

Although *P. aeruginosa* is known as an important opportunistic pathogen, it is an under-recognized microorganism in food safety. *P. aeruginosa* is widely found in the environment due to its high adaptability, rapid reproduction ability, and low growth requirements (such as scarce nutrients and moisture) and usually carried by humans and as a result can cause food safety issues for the following reasons (Xu et al., 2019):

- *P. aeruginosa* is often found in moist environments such as pools, tubs, sinks and water containers and the most dangerous bacterium in drinking water, which can be detected in 3% of drinking water, 9% of tap water, 18.8% of bottled water and 90% of sewage water samples. It is defined as an indicator of contamination in tap water (Xu et al., 2019). The World Health Organization (WHO) accepts *P. aeruginosa* as an indicator of drinking water quality. The European Communities and Codex Alimentarius

Commission stated that *P. aeruginosa* should not be detected in the water. In addition, early diagnosis is critical for the treatment of *P. aeruginosa* infection since it can cause infections at very low concentrations (Tang et al., 2017).

- *Pseudomonas* spp. is one of the most common microorganisms in milk and dairy products, and *P. aeruginosa* can be isolated from milk with rates as high as 45% (Chen et al., 2011).
- In meat products, *P. aeruginosa* was frequently isolated from poultry, beef and fish. It is also thought to be responsible for histamine poisoning (Georgnaras et al., 1999).
- Fruits and vegetables often have a complex microbiota. *P. aeruginosa* has been widely reported in different salads as well as raw and fresh fruits and vegetables, including tomatoes, eggplant, spinach, radishes, celery, chicory, onions, carrots, lettuce, and cucumbers. As a result, it is recommended to exclude salads from the diets of high-risk patients (Remington and Schimpff, 1981; Rodrigues et al., 2014).
- *P. aeruginosa* has been isolated from food in hospitals, canteens, and schools (Xu et al., 2019).

The indiscriminate use of antibiotics in humans or animals has contributed to the proliferation of antimicrobial resistance in bacteria, a growing global threat to public health and food security. Resistant microorganisms can contaminate meat or other animal products during the slaughter and processing of animals. It can spread to fruits, vegetables, or other crops irrigated with contaminated water, or it can be transmitted to humans from meat and other products (Xu et al., 2019).

## Conclusion

*P. aeruginosa* is an opportunistic pathogen, commonly implicated in nosocomial infections and also associated with food and waterborne diseases, and food spoilage. Due to its resistance to many antibiotics, it is a dangerous and feared pathogen. *P. aeruginosa* has many different virulence factors, including lipopolysaccharides, flagella, pili type IV, exotoxin A, exo-proteases (elastase, staphylolysis, alkaline protease, protease IV), phospholipase C, chromophores, siderophores (pyoverdin, pyochelin), ramnolipid, type III secretion system, biofilm and exo-enzymes S, T and U. The synthesis of many virulence factors is regulated through a mechanism called quorum sensing. It causes serious diseases such as pneumonia, septic shock, urinary system, gastrointestinal, skin and soft tissue infections. *P. aeruginosa* can be easily transmitted during food production and can adversely affect both the quality and safety of processed food. Therefore, *P. aeruginosa* causes important concerns in food safety.

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