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REVIEW

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Genomic and metabolic versatility of *Pseudomonas aeruginosa* contributes to its inter-kingdom transmission and survival

Sakthivel Ambreetha[1,*], Diansy Zincke[2], Dananjeyan Balachandar[3] and Kalai Mathee[4,*]

Abstract

Pseudomonas aeruginosa is one of the most versatile bacteria with renowned pathogenicity and extensive drug resistance. The diverse habitats of this bacterium include fresh, saline and drainage waters, soil, moist surfaces, taps, showerheads, pipelines, medical implants, nematodes, insects, plants, animals, birds and humans. The arsenal of virulence factors produced by *P. aeruginosa* includes pyocyanin, rhamnolipids, siderophores, lytic enzymes, toxins and polysaccharides. All these virulent elements coupled with intrinsic, adaptive and acquired antibiotic resistance facilitate persistent colonization and lethal infections in different hosts. To date, treating pulmonary diseases remains complicated due to the chronic secondary infections triggered by hospital-acquired *P. aeruginosa*. On the contrary, this bacterium can improve plant growth by suppressing phytopathogens and insects. Notably, *P. aeruginosa* is one of the very few bacteria capable of trans-kingdom transmission and infection. Transfer of *P. aeruginosa* strains from plant materials to hospital wards, animals to humans, and humans to their pets occurs relatively often. Recently, we have identified that plant-associated *P. aeruginosa* strains could be pathologically similar to clinical isolates. In this review, we have highlighted the genomic and metabolic factors that facilitate the dominance of *P. aeruginosa* across different biological kingdoms and the varying roles of this bacterium in plant and human health.

INTRODUCTION

Pseudomonas aeruginosa is one of the 'ESKAPE' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa* and *Enterobacter* species) noted for their ability to thwart commonly used antibiotics [1]. The US Centers for Disease Control and Prevention, World Health Organization and UK Public Health England have declared the multi-drug resistant (MDR) *P. aeruginosa* a serious threat [2, 3]. This bacterium is one of the leading causes of hospital-acquired lethal infections [4, 5]. It is one of the most intractable organisms colonizing the lungs of patients with cystic fibrosis (CF), a fatal genetic disease [6]. *P. aeruginosa*-associated lethality usually occurs in critically sick and immunocompromised individuals. However, the healthy population is not exempted from folliculitis, endocarditis, osteomyelitis and keratitis caused by *P. aeruginosa* [7–9]. Although there are antibiotics and other treatment strategies to combat such infections, the organism's inherent and acquired resistance renders many such anti-pseudomonal regimens ineffective [10, 11]. This review provides an overview of *P. aeruginosa* and its (1) habitat, (2) genomic and metabolic versatility, (3) virulence factors, (4) role in healthcare systems and (5) role in agricultural systems.

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Author affiliations: [1]Developmental Biology and Genetics, Division of Biological Sciences, Indian Institute of Science, Bengaluru, Karnataka, 560012, India; [2]Emerging Pathogens Institute, University of Florida, Gainesville, FL 32610, USA; [3]Department of Agricultural Microbiology, Tamil Nadu Agricultural University, Coimbatore, 641003, Tamil Nadu, India; [4]Department of Human and Molecular Genetics, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199, USA.

***Correspondence:** Sakthivel Ambreetha, ambreethas@iisc.ac.in; Kalai Mathee, matheelabfor65roses@gmail.com

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Abbreviations: ABC, ATP-binding cassette; AIDS, acquired immune deficiency syndrome; CAUTI, catheter-associated urinary tract infection; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; EXO, exoenzyme; HAI, Hospital-aquired infection; HGT, horizontal gene transfer; *iqs*, integrated quinolone signal; *las*, acyl-homoserine lactone; MATE, multidrug and toxic compound extrusion; MBL, metallo-β-lactamase; MDR, multi-drug resistant; MFS, major facilitator superfamily; Pel, pellicle polysaccharide; *pqs*, *Pseudomonas* quinolone signal; Psl, polysaccharide synthesis locus; QS, quorum-sensing; RGP, region of genomic plasticity; rhl, *Pseudomonas* quinolone signal; RND, resistance–nodulation–division; ROS, reactive oxygen species; SMR, small multidrug resistance; TCS, two-component system; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

NATURAL HABITATS OF *P. AERUGINOSA*

P. aeruginosa is an aerobic, non-spore-forming, monoflagellated, Gram-negative rod. It is a ubiquitous micro-organism commonly found in water, soil and sewage as well as on the surfaces of plants, animals, insects, fruits and vegetables [12–15]. Natural bodies of water such as oceans, lakes, rivers and sites of urban drainage are major sources of the bacterium [16–18]. A high incidence of *P. aeruginosa* has been recorded in agricultural soil, particularly in the rhizosphere regions with rich root exudation [19–21]. The presence of *P. aeruginosa* on crops has been reported since the 1970s [13, 22]. The occurrence of MDR *P. aeruginosa* in the open ocean was reported for the first time at the University of Tokyo, Japan [16]. MDR *P. aeruginosa* was recently isolated from edible plants such as cucumber, tomato, eggplant and chili [21].

P. aeruginosa's ability to thrive in aqueous environments has made it a problem in the hospital setting, where it is often isolated from soaps, ointments, disinfectants, irrigation fluids and eye drops [23]. The simple nutritional needs allow the organism to grow even on negligible impurities in aqueous solutions found in hospitals. Specifically, a study found that *P. aeruginosa* was able to not only grow but also thrive in the distilled water of mist therapy units [24]. Tap water is also a major source of nosocomial infections when it is inadvertently used to prepare solutions to be used in that setting [25]. The prevalence of *P. aeruginosa* in tap water likely results from the colonization of showerheads, faucets and sinks, from which it has also been detected [26]. Additionally, *P. aeruginosa* has also been isolated from holy water, aerators, baby baths, hot tubs, swimming pools, contact lens solutions, cosmetics and even the insole of sneakers [27–29]. In short, aqueous and moist environments seem to be the natural and preferred reservoirs for *P. aeruginosa* and, when contaminated, can be potential sources of infection.

METABOLIC VERSATILITY

Like other Pseudomonads, renowned for their nutritional versatility, *P. aeruginosa* has simple nutritional needs and can use a multitude of organic compounds for its growth [30]. As a chemo-organotroph, *P. aeruginosa* can metabolize a variety of simple and complex organic substrates as a sole carbon and energy source. If a mixture of diverse carbon sources is offered to this bacterium, carbon catabolite repression is activated to facilitate an orderly use of substrates based on survival needs [31, 32]. *P. aeruginosa* can shunt its tricarboxylic acid (TCA) pathway to gain biochemical protection against aminoglycoside antibiotics [33]. It also harbours multiple metabolite-specific transporters that allow efficient uptake of nutrients, almost sequentially [34, 35]. The well-organized and hierarchical utilization of metabolites is the primary strategy supporting *P. aeruginosa*'s omnipresence [32]. Such metabolic flexibilities help *P. aeruginosa* strains to flourish in multiple hosts and diverse environments. This bacterium can tolerate various physical conditions, including severe drought, salinity, hypoxia, heavy metal pollution and hydrocarbon contamination [36–38]. *P. aeruginosa* is a catalase- and oxidase-positive bacterium. Although it cannot ferment lactose and its metabolism is primarily respiratory, it can also grow under anaerobic conditions by using nitrate as a terminal electron acceptor or fermenting arginine [39]. Additionally, *P. aeruginosa* strains produce a fruity or grape-like odour due to the production of 2-aminoacetophenone [40]. This compound is one of the volatile biomarkers of *P. aeruginosa* infection [41]. Nearly 70 different compounds have been detected in the core volatilome of clinical *P. aeruginosa,* which can be potential diagnostic biomarkers [42]. In particular, a high level of volatile hydrogen cyanide in the nose-exhaled breath of cystic fibrosis (CF) patients helps in the non-invasive detection of *P. aeruginosa* infection in the lower airways [43].

GENOMIC VERSATILITY

P. aeruginosa is one of the few bacterial species with a highly adaptable genome (5.5–7.75 Mbp) [44, 45]. The largest *P. aeruginosa* genome that has been sequenced as of today belongs to an industrial strain, RW109 [45]. *P. aeruginosa* has multiple genes that help to utilize a wide range of carbon and nitrogen sources. The genome encodes numerous regulatory two-component systems (TCSs), which support environmental adaptability [46–48]. CbrA/B is one of the TCSs in the *P. aeruginosa* genome that regulates different catabolic pathways supporting its nutritional versatility [49–51]. The MifS/MifR system allows selective utilization of alpha-ketoglutarate [34]. Nearly 17 respiratory dehydrogenases, including three NADH dehydrogenases and succinate dehydrogenase, have been identified in the *P. aeruginosa* genome [52]. Moreover, *P. aeruginosa* constantly acquires new genes through horizontal gene transfer (HGT) [53–57]. The addition of such new genetic elements accounts for the genomic plasticity of this bacterium. A Liverpool epidemic strain of *P. aeruginosa*, LESB58, acquired 596 new genes indicative of its adaptive evolution [58]. The reference strain of *P. aeruginosa*, PAO1, maintained in different laboratories, showed wide genotypic and phenotypic variations despite being derived from the same parent subline [59]. Similarly, diverse genotypic and phenotypic traits in the *P. aeruginosa* population within a particular host have been documented [60–62].

Comparative genomic analyses have shown that 6.6% of the *P. aeruginosa* genome comprises essential core genes, while the rest of its genome varies from strain to strain [63]. These strain-specific fragments were termed regions of genomic plasticity (RGPs) [54]. Over 100 RGPs have been identified since then [44, 64]. During the past few decades, the *P. aeruginosa* genome has acquired many antibiotic-resistance genes through HGT that are integrated at the RGPs [44, 54, 64, 65]. Several studies have shown that

aminoglycoside and β-lactam resistance genes in *P. aeruginosa* were acquired by HGT through different plasmids and integrons [66–69]. During long-term human infections, *P. aeruginosa* loses its virulence-related genes as an adaptive strategy to evade the host immune system [70]. In a nutshell, the complexity of the *P. aeruginosa* genome reflects its adaptive evolution to sustain in diverse ecosystems [46].

INTER-KINGDOM TRANSMISSION AND SURVIVAL OF *P. AERUGINOSA*

Despite its ubiquitous nature, *P. aeruginosa* been scarce in pristine environments [71–73]. The environmental occurrence of *P. aeruginosa* has shown a strong correlation with human and animal activities [71, 74]. Farmyard manure and composts potentially disseminate *P. aeruginosa* strains into agricultural settings [12, 75]. In addition, contaminated water bodies efficiently distribute *P. aeruginosa* into diverse channels [76]. Nearly 100 different strains of antibiotic-resistant *P. aeruginosa* have been isolated from a freshwater spring contaminated with domestic sewage [77]. Domestic and hospital sewages are major disseminators of pathogenic and drug-resistant *P. aeruginosa*. Specifically, hospital wastewater carries numerous strains of extensively drug-resistant *P. aeruginosa*, which could potentially contaminate other water bodies when managed poorly [78, 79]. Wastewater treatment lagoons also harbour virulent *P. aeruginosa* strains that eventually get dispersed into several rural catchments [75].

Using improperly treated wastewater for irrigation purposes transmits millions of *P. aeruginosa* cells into agricultural ecosystems [80–82]. As a result, *P. aeruginosa* has been isolated in farms from many edible crops, including wheat, chili, pepper, tomato, ginger, sugar cane, chickpea, *Aloe vera* and *Achyranthes* [83–92]. This potentially puts the farm animals and farmworkers at risk of *P. aeruginosa* exposure. Additionally, fresh vegetables, including cabbages, lettuces, tomatoes, carrots and sweet potatoes in more than 50% of the tested supermarkets had *P. aeruginosa* contamination [93]. The constant spread of *P. aeruginosa* in hospitals through contaminated vegetables and flowers was identified and reported decades ago [94, 95]. Similarly, we identified that the *P. aeruginosa* strains present in the endophytic and rhizospheric niches of cucumber, tomato, eggplant and chili harvested directly from agricultural farms carry virulence traits critical for human infection [21].

P. aeruginosa PA14 isolated from the burns ward at Mercy Hospital, Pittsburgh, USA, has virulence genes essential for plant infections [94, 96, 97]. This human-associated strain caused local and systemic disease in *Arabidopsis* and sweet basil [98, 99] and extensive rot of cucumber, lettuce, potato and tomato [14, 100]. Several *P. aeruginosa* strains have been isolated from farm animals and their milk, reflecting the risk of human transmission during milk and meat consumption [101–104]. Zoonotic and zooanthroponotic transmissions of drug-resistant *P. aeruginosa* are predicted to generate severe public health risks [105, 106]. In Brazil, a carbapenem-resistant *P. aeruginosa* sequence type 233 was detected in a hospitalized man, which was also identified in his pet dog and household settings [106]. This report indicates the dissemination of clinical strains of *P. aeruginosa* between the human–animal–environment interfaces [106]. Similarly, there was a case report in the UK on the transmission of a Liverpool epidemic *P. aeruginosa* strain from a CF patient to a pet cat [107]. Inter-kingdom transmission of *P. aeruginosa* strains between plants, animals and humans continues to occur in a vicious cycle (Fig. 1).

P. AERUGINOSA VIRULENCE FACTORS

The success of *P. aeruginosa* across the kingdoms is often driven by the arsenal of virulence factors released by this bacterium irrespective of the niche, including its quorum-sensing (QS) molecules, and major secondary metabolites such as pyocyanin, rhamnolipids and siderophores (pyochelin, and pyoverdine), polysaccharides, toxins and lytic enzymes [108–113]. These virulence factors collectively contribute to the inter-kingdom pathogenicity of *P. aeruginosa*.

Pyocyanin

Pyocyanin, the signature metabolite of *P. aeruginosa*, is a blue–green, water-soluble phenazine pigment [114, 115]. Phenazine compounds are commonly found in nature and are produced by bacteria such as *Streptomyces* and *Pseudomonas*. Pyocyanin (1-hydroxy-5-methyl-phenazine) is derived from chorismate, an intermediate in the biosynthesis of aromatic amino acids in plants and micro-organisms [116, 117]. Pyocyanin and other phenazine compounds appear to contribute to the virulence and competitive fitness of the producing organisms [118–121]. Specifically, pyocyanin disrupts the beating of human cilia and inhibits mammalian cell respiration thereby helping *P. aeruginosa* colonize the host lungs [122]. Pyocyanin is a zwitterion that crosses the host cell membrane and oxidizes NADH and NADPH molecules, generating reactive oxygen species (ROS) [115, 123, 124]. The ROS further contributes to cytotoxicity in the respiratory, vascular and central nervous systems of the eukaryotic hosts [125]. ROS cytotoxicity also inhibits lymphocyte proliferation and epidermal cell growth in eukaryotes. Pyocyanin also plays a major role in the antimicrobial, antibiofilm and anti-QS activities of *P. aeruginosa* [126–129]. Pyocyanin extracted from *P. aeruginosa* can inhibit the growth of several human pathogens, including *Staphylococcus aureus*, *K. pneumonia*, *Enterococcus faecalis*, *Burkholderia cenocepacia* and *Escherichia coli* [130]. *P. aeruginosa* pyocyanin also inhibits the growth of soil-borne pathogens, which protect the plants from several bacterial and fungal plant diseases [131, 132]. Pyocyanin released by endophytic *P. aeruginosa* strains can elicit induced systemic resistance of the host plant against various fungal pathogens [133, 134].

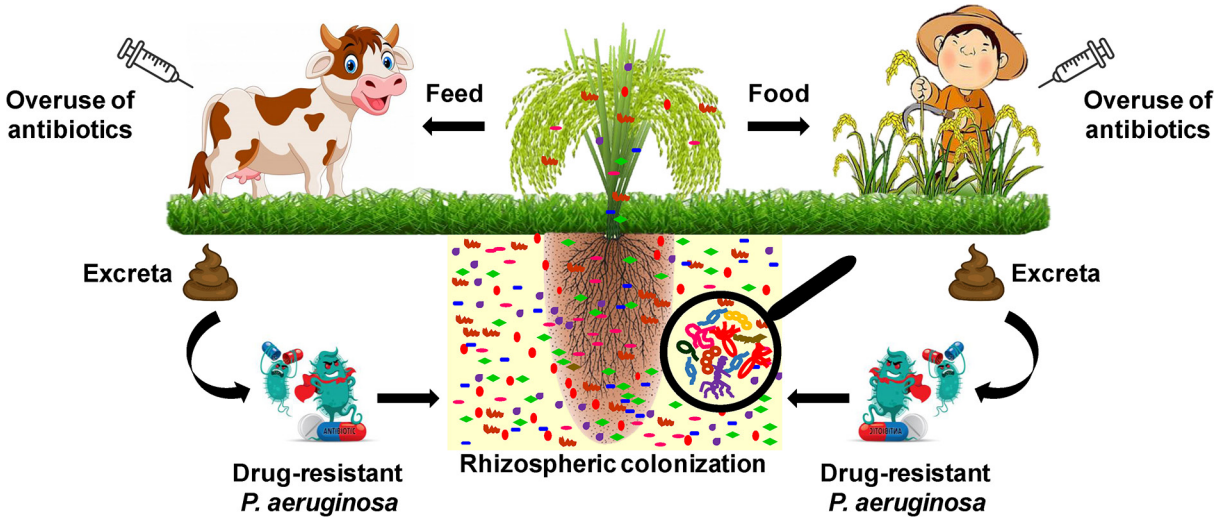

Fig. 1. From Farm to Human: Inter-Kingdom Transmission and Antibiotic Resistance Cycle. This figure portrays the progression of bacteria from animals to humans, highlighting the role of antibiotic use and environmental pathways. The human, animal, and feces symbolize how they serve as reservoirs for bacteria, potentially affecting health through contact or pollution. A syringe suggests antibiotic overuse in livestock and humans. Plants in the center suggest environmental and human transmission via crops. The image underscores human contributions to antibiotic resistance, including medication misuse and agricultural practices. The inset emphasizes soil and root colonization by resistant bacteria, posing challenges for infection control.

Rhamnolipids

Rhamnolipids are amphipathic biosurfactants comprising a hydrophilic rhamnose moiety and a hydrophobic lipid moiety [135]. These are very potent virulence factors capable of destroying polymorphonuclear leukocytes, inhibiting phagocytosis by macrophages, and disrupting the mucociliary clearance and epithelial tight junctions, leading to paracellular infiltration of *P. aeruginosa* [136–139]. *P. aeruginosa* rhamnolipids show antimicrobial activity against several human pathogens including *Staphylococcus aureus*, *E. aerogenes*, *Streptococcus faecalis*, *Serratia marcescens*, *K. pneumoniae* and *Proteus vulgaris* [140]. *P. aeruginosa* can inhibit the growth of phytopathogens, including *Xanthomonas oryzae, Fusarium oxysporum, Pythium aphanidermatum* and *Rhizoctonia solani* [141]. This phytoprotection is in part due to the production of rhamnolipids [142, 143]. In addition, rhamnolipids protect the plants against sucking pests such as green peach aphids [144, 145].

Siderophores

Siderophores, in general, are extracellular compounds that have a high affinity for iron, are produced under iron-deficient conditions, and have been known to stimulate and increase bacterial growth rate [111]. *P. aeruginosa* releases two different siderophores, pyoverdine and pyochelin [110, 111]. Pyoverdine is a water-soluble, fluorescent pigment that gives a yellowish-green appearance to *P. aeruginosa,* while pyochelin is a poorly water-soluble thiazoline derivative [146]. Production of siderophores during infection has been implicated in bacterial virulence as it contributes to an increased growth rate [147]. It has been demonstrated that pyoverdine-deficit mutants lacked virulence in mice models, which suggests the significance of siderophores in *P. aeruginosa* pathogenicity [146]. *P. aeruginosa* also appears to limit the growth of other bacteria by effectively competing for iron [148]. *P. aeruginosa* siderophores can also inhibit the growth of fungal phytopathogens such as *Fusarium*, *Trichoderma*, *Alternaria* and *Macrophomina* [149].

Lytic enzymes

P. aeruginosa uses its lytic enzymes to disrupt cell membrane integrity and cause vascular permeability, resulting in organ damage [108, 150–155]. Haemolysin, in particular, is produced by pathogens to lyse red blood cells and enable tissue invasion [156]. *P. aeruginosa* haemolysins can alter the host lung physiology and induce morbidity and mortality [155, 157]. *P. aeruginosa* LipA and LipC lipases and phospholipases A_2 and C break down the membrane lipids and cause host cell death [158].

P. aeruginosa excretes a myriad of extracellular proteolytic enzymes, including LasA protease and elastase, LasB elastase, alkaline proteinase, staphylolytic endopeptidase, protease IV, PASP, LepA and aminopeptidase [159–161]. *P. aeruginosa* proteases destroy host immunoglobulins and are the major virulence factors during ocular, pulmonary, burn and bacteraemia infections [162–164]. LasA protease, in particular, contributes to the anti-staphylococcal activity of *P. aeruginosa* [165].

Toxins

P. aeruginosa releases Type III secretory effectors such as exoenzymes (Exo) A, S, T, U and Y [166–169]. ExoA, ExoS and ExoT are ADP-ribosyltransferases and the most common toxins involved in the dissemination of *P. aeruginosa* into host organs [170]. Interestingly, *P. aeruginosa* strains mostly harbour either ExoS or ExoU, which indicates the dichotomy between the two toxins [171]. *P. aeruginosa* ExoA causes respiratory failure, metabolic acidosis, hepatocellular necrosis, hypofibrinogenaemia, serosal haemorrhages, haemorrhagic skin necrosis and cytotoxicity in animals and humans [166, 172–174]. ExoU is a phospholipase associated with fatal pneumonia during lung infections and contributes to high mortality [175]. The ExoU and ExoS toxins collectively increase the ability of different *P. aeruginosa* strains to persist in lung tissues [167]. ExoY is a nucleotidyl cyclase that increases endothelial hyperpermeability during chronic lung infections [175]. ExoT protects *P. aeruginosa* cells from host defence mechanisms such as phagocytosis and facilitates host invasion and colonization [176].

Polysaccharides

P. aeruginosa produces three major polysaccharides, namely, alginate, pellicle polysaccharide (Pel) and polysaccharide synthesis locus (Psl) [177–179]. Readers are referred to Franklin *et al.* [180] for the biosynthesis and regulation of these polysaccharides. Polysaccharides. in general, protect bacterial cells from biotic and abiotic stress including the host defence response [181–183]. The mucoid phenotype associated with *P. aeruginosa* in the lungs of CF patients during chronic infection is due to alginate production [184]. Alginate promotes a biofilm mode of growth, which in turn not only protects the bacterium from antimicrobial agents but also helps it to escape phagocytosis by host macrophages [185]. The mucoid conversion of *P. aeruginosa* is due to the constant bombardment of ROS released from activated host neutrophils [186]. The non-mucoid *P. aeruginosa* strains produce Pel, and Psl polysaccharides, which also play a predominant role in biofilm formation [184, 187, 188].

Quorum sensing systems

P. aeruginosa harbours four interconnected quorum sensing (QS) systems such as acyl-homoserine lactone (*las*), rhamnolipid (*rhl*), *Pseudomonas* quinolone signal (*pqs*) and integrated quinolone signal (*iqs*) [109, 189–192]. The *las, rhl* and *pqs* systems concomitantly coordinate the maturation and differentiation of *P. aeruginosa* biofilms [193, 194]. Additionally, the expression of all the virulence factors mentioned above is synchronously regulated by the *P. aeruginosa* QS systems in a population density-dependent manner [195, 196]. Other phenotypic traits controlled by these QS systems include motility (swarming, swimming, and twitching), nutrient metabolism, stress response and antibiotic resistance [197–199]. A significant decline in *P. aeruginosa* virulence and cytotoxicity is noted in QS-deficient mutants [200]. *P. aeruginosa* QS systems are the central regulatory networks that control its virulence, adaptability and versatility [112, 201].

Antibiotic resistance

Unlike other bacteria, *P. aeruginosa* employs multiple strategies to evade antibiotics [202]. For instance, *P. aeruginosa* has a restricted permeability on its outer membrane, preventing the antibiotics from penetrating the bacterial cell membrane and reaching intracellular targets [203]. This bacterium also possesses numerous efflux systems on its cell membrane to pump diverse antibiotics out of its cell. These efflux systems fall under five major families, including resistance–nodulation–division, ATP-binding cassette, small multidrug resistance, major facilitator superfamily, and multidrug and toxic compound extrusion [204, 205]. Concomitant overexpression of multiple efflux systems has been documented in *P. aeruginosa*, making it an extremely drug-resistant (XDR) bacterium [65, 206, 207]. These efflux pumps have also contributed to the pathogenicity of *P. aeruginosa* apart from conferring drug resistance [208, 209]. *P. aeruginosa* can release antibiotic-degrading enzymes targeting specific drugs including penicillin, cephalosporins, streptomycin, aztreonam, kanamycin, neomycin, tobramycin, netilmicin, gentamicin and amikacin [210–212]. All the above-said mechanisms contribute to intrinsic drug resistance in *P. aeruginosa*.

This bacterium also exhibits biofilm- and polysaccharide-mediated adaptive resistance mechanisms [213]. The biofilms and polysaccharides are phenotypic adaptations that protect *P. aeruginosa* cells from antibiotics [214]. The biofilm-forming *P. aeruginosa* being least sensitive to antibiotics causes chronic pulmonary inflammation and is the primary cause of mortality in CF patients [215]. This bacterium also evolves resistance to new antibiotics by acquiring antibiotic resistance genes through HGT from the same or different bacterial species in the environment [216]. The XDR strains of *P. aeruginosa* are considered a severe public health risk and hospitalized patients are frequently predisposed to such strains [2, 217–219].

P. AERUGINOSA IN HUMAN HEALTH

P. aeruginosa is an opportunistic pathogen that could cause devastating infections in immunocompromised individuals and hospitalized patients. This bacterium is one of the common causes of ventilator-associated pneumonia (VAP) and catheter-associated urinary tract infections (CAUTIs) in hospitals. Patients with pulmonary and immunodeficiency diseases and those who have recently undergone organ transplants and invasive surgeries are highly prone to *P. aeruginosa* infection and associated lethality. *P. aeruginosa* can cause meningitis, endocarditis, septicaemia, bacteraemia and other fatal complications

in hospitalized individuals. However, it can also cause folliculitis, otitis, keratitis, osteomyelitis and endocarditis in individuals without pre-existing clinical conditions.

Infections in healthy individuals

P. aeruginosa infections in healthy individuals often result from contact with contaminated water or solutions or after sustaining some form of external trauma such as a puncture wound [24, 220]. Folliculitis, for example, is an infection of the hair follicles caused by bacteria, including *P. aeruginosa,* which can occur after bathing in swimming pools, hot tubs and whirlpools that are not adequately treated with chlorine [8, 221–223]. Individuals involved in aquatic sports as well as those swimming and bathing in contaminated waters can also develop superficial infections of the ear canal known as external otitis [224–226]. *P. aeruginosa* is the causal agent of chronic suppurative otitis media, while acute infection is caused by other pathogens [227]. Chronic suppurative otitis media in the paediatric population could lead to permanent hearing loss if left untreated [228]. Minor injury to the eye or cornea, often related to the use of contact lenses, especially extended-wear lenses, can predispose an individual to eye infections, or keratitis, with *P. aeruginosa* [9, 229–231]. Contact lens solutions that are contaminated or even tap water used to handle contact lenses can all serve as potential sources of infection [232, 233]. Nevertheless, *P. aeruginosa*-related ocular infections could also occur in non-contact lens wearers [7, 234]. Furthermore, *P. aeruginosa* contamination in eye cosmetics has also led to corneal ulceration [235, 236].

Osteomyelitis, or infection of the bone, has also been reported, especially in children after incurring puncture wounds in the feet, with the source of the infection often being the sole or inner pad of the sneaker that was worn at the time of the injury [237, 238]. *P. aeruginosa*-mediated osteomyelitis is predominant mainly in intravenous drug users [239, 240]. Nevertheless, chronic *P. aeruginosa* cervical spine osteomyelitis was documented in a young female with no history of medical illness or intravenous drug usage [241].

One of the most severe *P. aeruginosa* infections that can affect an otherwise healthy person is endocarditis or inflammation of the inner lining of the heart, often requiring replacement of the affected valve [242, 243]. The majority of *P. aeruginosa* endocarditis infections occur in intravenous drug users as the drugs are often mixed with contaminated water leading to bacteraemia and endocarditis [244, 245]. *P. aeruginosa*-related endocarditis, however, can also occur in burns and open-heart surgery patients [246, 247]. Recently, a US deployed military service member in Southwest Asia encountered cardiac arrest induced by an MDR *P. aeruginosa* [248].

Infections in immunocompromised patients

P. aeruginosa is an opportunistic human pathogen that readily exploits any deficiency in the host immune system to mount an infection. Since it is often intractable and resistant to a wide range of antibiotics, it represents a very serious problem not only for critically ill individuals, such as those in the hospital setting and intensive care units but also for immunocompromised patients [249]. *P. aeruginosa* has often been isolated as one of the most common pathogens causing septicaemia in patients with primary immunodeficiency [250, 251]. Several factors predispose the host to *P. aeruginosa* bacteraemia, including taking broad-spectrum antibiotics, receiving chemotherapy, as well as being an acquired immune deficiency syndrome (AIDS), leukaemia, cancer, diabetes, bone marrow or organ transplant patient [252–257].

Although *P. aeruginosa* bacteraemia has been reported in patients with AIDS [258–260], it is not the most common pathogen in such cases [261, 262]. *P. aeruginosa,* however, is one of the leading causes of pneumonia [263, 264] and a prevalent respiratory pathogen in patients with AIDS, where it often leads to chronic and intractable infections [265, 266]. Before 1968, *P. aeruginosa* bacteraemia in cancer patients resulted in ~80–90% fatalities [267–269]. The development potent antipseudomonal drugs has dramatically improved outcomes and survival rates in these patients, with cure rates increasing from 60% in the 1970s to 80% in the 2000s, provided that the infection is quickly and effectively treated [270–273]. Although prognosis has improved, the incidence of *P. aeruginosa* infections in cancer patients in the 1990s is between 5 to 12% [274], and a 2008 report noted a 20% incidence of carbapenem-resistant *P. aeruginosa* infections among these patients [275]. *P. aeruginosa* is assoicated with a 22% incidence of bloodstream infections in patients with haematological malignancies [276]. The recurrence of *P. aeruginosa*-associated bacteraemia is a rare but significantly increases mortality risk [277].

Hospital-acquired infections

P. aeruginosa is one of the leading pathogens accounting for 10–13% of hospital-acquired infections (HAIs), with incidences as high as 23% reported in intensive care units [278–283]. *P. aeruginosa* was the sixth most frequently isolated pathogen, accounting for 7.1% of all healthcare-associated infections in a survey of 183 US hospitals from 10 different states [5]. *P. aeruginosa* outbreaks in hospitals are disastrous due to horizontal transmission from patient to patient [284]. Notably, HAIs caused by metallo-β-lactamase (MBL)-producing *P. aeruginosa* generate higher mortality than its non-MBL counterparts [284]. *P. aeruginosa* pneumonia accounts for the majority of HAIs [5, 285]. This organism can easily colonize endotracheal tubes and mechanical ventilators and as such one of the leading causes of VAP, second

only to *Staphylococcus aureus* [285–287]. VAP has been associated with high mortality rates that exceed those of other types of pneumonia, such as community-acquired, healthcare-associated or hospital-acquired pneumonia [287, 288]. Mortality rates have been reported to be higher than 70% when *P. aeruginosa* or *Acinetobacter* spp. are the causative agents [286–288]. Similarly, patients with lung transplants are highly prone to *P. aeruginosa* infections that might lead to bronchiolitis obliterans syndrome leading to lung failure and death [289]. Catheter-associated urinary tract infection (CAUTI) accounts for 40% of the total HAIs [227]. *P. aeruginosa* is the second most commonly identified pathogen and is responsible for 11% of CAUTIs [5, 285, 290].

P. aeruginosa is also a leading cause of HAIs in burn units primarily colonizing burn wounds but also responsible for pneumonia, bacteraemia and urinary tract infections [291–293]. On admission, generally, *Staphylococcus aureus* and coagulase-negative staphylococci predominate the wounds of burns patients but the incidence of *P. aeruginosa* quickly increases during the first week of admission and continues to rise with time, often surpassing the incidence of other micro-organisms [294–296]. Burn wound infections with *P. aeruginosa* are especially problematic since they are correlated with bacteraemia, a high rate of sepsis and mortality [245, 291, 293]. Other HAIs caused by *P. aeruginosa* include endocarditis, meningitis, bacteraemia, and gastrointestinal and surgical site infections [5, 272, 285]. It causes devastating implant-associated infections which would put the patients at very high risk unless they are regularly administered with antibiotics [297]. *P. aeruginosa* outbreaks have also been reported during clinical diagnostic procedures such as endoscopic bronchoscopy and cholangiopancreatography [298–300].

Secondary infections in pulmonary disorders

P. aeruginosa is the most common and clinically relevant pathogen found in CF patients [301–304]. It is estimated that over 80% of CF patients will be infected with this bacterium by the time they reach adulthood [304]. Chronic infection of the airways with *P. aeruginosa* and the inflammation that follows represent a major problem for CF patients as the lungs steadily deteriorate auguring very poor overall prognosis and high mortality rates [305, 306]. CF is an autosomal, recessive genetic disease affecting about 30000 people in the USA and about 70000 worldwide [304]. This disease mainly affects Caucasian populations of European descent and is caused by mutations in the CF transmembrane conductance regulator gene located in the long arm of chromosome VII [307–309]. It leads to impairment of the mucociliary clearance apparatus setting the stage for persistent and chronic bacterial infections that are a hallmark of airway disease in CF patients. The conditions present in CF airways, namely, dehydrated, thick mucus coupled with impaired mucociliary clearance, provide an ideal environment that is conducive to colonization by several pathogens [301, 310]. *Staphylococcus aureus*, for example, often the first to colonize the respiratory tract of CF patients, is common in children less than 10 years old and is responsible for infant morbidity and mortality in the pre-antibiotic era [301, 304]. Few studies have shown the coexistence of *Staphylococcus aureus* and *P. aeruginosa* during CF, which worsens the patient's health much faster than usual [311–313]. *Haemophilus influenzae* is another common pathogen and is predominantly found in young children [301, 310]. Other less common pathogens, such as *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans* and *B. cenocepacia* complex, have also been isolated from the respiratory tract of CF patients [304]. Though found in in less than 10% of the CF patients, *B. cenocepacia* has the worst prognosis [304].

Examining the microbiome in the sputum of CF patients has shown that many (18/19) carry pathogenic fungal species of *Aspergillus*, *Candida*, *Cryptococcus* and *Exophiala*, among others [314]. Fungal infections are not uncommon in CF patients and can occur in association with other microorganisms [314, 315]. *P. aeruginosa*, however, remains the primary pathogen associated with morbidity and mortality in CF patients and is more frequently found in adults [305, 306]. An essential feature of *P. aeruginosa* infections is the tendency of the bacteria to convert into a mucoid phenotype in the lungs of CF patients [316]. This seminal study highlighted the importance of mucoid strains of *P. aeruginosa*, which produce a thick, protective alginate biofilm, in the decline of lung function in CF patients. The presence of mucoid *P. aeruginosa* was linked to more severe lung disease, increased morbidity, and a higher risk of mortality, marking a significant shift in understanding the pathophysiology of CF lung infections and the management of these infections in CF patients. This mucoid phenotype plays a very important role in helping the bacterium evade the host immune system [186, 301]. Alginate overproduction exacerbates the already detrimental conditions of the CF lungs leading to further blocking of the airways and inexorable death.

P. aeruginosa is increasingly recognized as an important pathogen colonizing the lungs of individuals afflicted with chronic respiratory diseases such as diffuse panbronchiolitis and chronic obstructive pulmonary disease (COPD). COPD, the third leading cause of death in the USA [317], is a progressive lung disease that makes it increasingly difficult to breathe and is primarily caused by cigarette smoking or exposure to smoke [318]. Bacterial and viral exacerbations are the main cause of hospitalizations and mortality in patients with COPD [319, 320]. In particular, *P. aeruginosa* is responsible for 5–10% of COPD exacerbations [321–323], with such infections being associated with hyper-mutability, antibiotic resistance, a poor prognosis and an increase in morbidity and mortality [324, 325].

P. AERUGINOSA IN PLANT HEALTH

P. aeruginosa has both beneficial and pathogenic interactions with field crops. This organism plays a significant role in growth promotion in healthy plants and protects the host from pests and diseases [326–333]. Despite these reports, this bacterium has been identified as the causal agent of rot and wilt in a wide range of plants, including melon, ginseng, chickpea and maize [14, 22, 334–340].

Plant growth promotion

P. aeruginosa can solubilize the complex minerals in the soil, which supplies simple nutrients such as zinc, phosphorous and potassium to the associated plants [341–345]. Mineral-solubilizing *P. aeruginosa* strains have been identified to increase the growth of green gram, tomato, okra and spinach [346, 347]. An endophytic strain of *P. aeruginosa*, AL2-14B, isolated from a medicinal plant, *Achyranthes aspera,* was able to increase the nitrogen, phosphorous and potassium contents of its host by 3.8, 12.59 and 19.15%, respectively, apart from increasing growth and antioxidant activity [86]. Plants generally cannot uptake organic forms of nitrogen or convert them into inorganic forms. Bacteria like *P. aeruginosa* convert the organic form of nitrogen into ammonia [86]. For instance, a *P. aeruginosa* strain, RRALC3, was identified to enhance the carbon and nitrogen contents of *Pongamia* in a degraded forest ecosystem [329]. Yet another strain, *P. aeruginosa* PGP, isolated from garbage soil, was capable of increasing the nitrogen and phosphorous contents of Indian mustard by 40 and 100%, respectively [348]. Also, seed treatment with *P. aeruginosa* can significantly increase the dry biomass of *Abelmoschus esculentus* (okra), *Lycopersicon esculentum* (tomato), and *Amaranthus* sp. (African spinach) [327]. A substantial increase in the germination percentage, shoot, root length, leaf area and number of pods has been noted in mung beans treated with *P. aeruginosa* [349]. Additionally, a salinity-tolerant *P. aeruginosa* FP6 improved seed germination, seedling vigour and plant height in cowpeas [350], and a multi-metal-resistant strain of *P. aeruginosa* KUJM isolated from a sewage treatment plant promoted seed germination in lentils [351].

Plant protection against abiotic stress

P. aeruginosa can protect the host plants from drought, salinity, heavy metal contamination and insecticide-mediated cytotoxicity. *P. aeruginosa* strains have alleviated salinity, heat and drought stresses in soybean, mung bean, sorghum and tomato [352–355]. In particular, *P. aeruginosa* GGRJ21 inoculation alleviated drought stress in mung bean plants by upregulating the stress-responsive genes and inducing the production of cellular osmolytes and antioxidant enzymes [354]. Despite drought stress, maize seed treatment with *P. aeruginosa* Pa2 increased plant biomass, leaf area, and shoot and root length [356]. Moreover, the inoculated maize plants had relatively high levels of water content, proline and sugars compared with the uninoculated controls [356]. *P. aeruginosa* PF_{23} treatment protected sunflower crops from high-concentration salt stress [357]. Using an insecticide-tolerant *P. aeruginosa* PS1 as a biofertilizer augmented the growth of green gram plants cultivated in insecticide-contaminated soil [347]. Additionally, *P. aeruginosa* can also reduce the toxic hexavalent chromium, Cr(VI), in the soil into a non-toxic form, Cr(III), thereby protecting the plants from phytotoxic effects [358]. *P. aeruginosa* OSG41 has been recommended as a bio-inoculant to increase nodulation efficiency, grain yield and protein content of chickpeas grown in chromium-contaminated soil [359]. Also, a cadmium-resistant strain of *P. aeruginosa* has helped in rhizoremediation of cadmium contamination in black gram-cultivated fields [360]. Yet another study has recommended a multi-metal-resistant *P. aeruginosa* KUJM for bioremediation of heavy metal-contaminated agricultural soil due to its xenobiotic resistance and plant-growth-promoting abilities [351].

Plant protection against biotic stress

P. aeruginosa can protect plants from biotic stress (pests and pathogens) through its volatile and non-volatile metabolites including phenazines, rhamnolipid, siderophores, salicylic acid and hydrogen cyanide [134, 142, 361–363]. A phenazine-producing *P. aeruginosa* strain, CMR12a, effectively controlled *Rhizoctonia* root rot in beans compared to a phenazine-deficit mutant [364]. Pyocyanin, the most-studied phenazine of *P. aeruginosa*, is a redox-active secondary metabolite that can inhibit the growth of soil pathogens [126, 131, 132]. This compound also elicits the plant immune system against diverse fungal pathogens [133, 134].

Rhamnolipids released by *P. aeruginosa* help in the killing of several insects and pathogens [142–145]. *P. aeruginosa* rhamnolipid causes 80% mortality in aphids within a day and has been recommended as a bio-insecticide [144]. Rhamnolipids can also lyse fungal zoospores and prevent the mycelial growth of pathogenic fungi [365]. Several studies have shown that 0.005–1 mg ml^{-1} of rhamnolipid from *P. aeruginosa* effectively triggers plant immunity against many phytopathogens, including *Leptosphaeria maculans*, *Botrytis cinerea*, *Brassica napus, Colletotrichum orbiculare*, *Pseudomonas syringae* and *Alternaria alternata* [142, 143, 366–369]. Also, 10–20 mg ml^{-1} of this metabolite has been recommended for direct inhibition of *Xanthomonas campestris, Fusarium solani* and *Corticium invisum* [369]. A drastic decline in biocontrol ability has been observed in pyocyanin- and rhamnolipid-deficit mutants of *P. aeruginosa* [370].

The *P. aeruginosa* siderophores, pyoverdine and pyochelin, impede the growth of fungal pathogens such as *Fusarium, Trichoderma, Alternaria* and *Macrophomina* [149]. In addition, *P. aeruginosa* can also inhibit the plant cell wall degrading enzyme produced by a fungal pathogen, *Agroathelia rolfsii* (*Sclerotium rolfsii)*, thereby reducing the severity of stem rot in groundnut plants [371].

Plant pathogenicity

The plant pathogenicity of *P. aeruginosa* has yet to be studied as extensively as its human pathogenicity. However, this bacterium has been identified as an opportunistic pathogen causing diseases in a wide range of plants, including ginseng, wheat, maize, melon, calla lily, chickpea and tobacco [14, 22, 334–340]. *P. aeruginosa*-mediated fruit rot disease has occurred in India during round melon cultivation [337]. Similarly, *P. aeruginosa* was identified as the causal agent of bacterial leaf spots in tobacco seedlings in China [372]. Furthermore, this organism has caused collar rot in lily and root rot in ginseng and inhibited maize seed germination [338–340]. A QS-regulated compound, L-2-amino-4-methoxy-*trans*-3-butenoic acid, released by rhizospheric *P. aeruginosa* was identified as the inhibitor of seed germination [373]. *P. aeruginosa* PA14 *mucD* mutants had a significantly lower ability to infect *Arabidopsis* than the wild strain, indicating the role of serine protease in plant pathogenicity [374]. Nevertheless, most of the *P. aeruginosa* isolates from agricultural ecosystems have so far been plant-beneficial rather than plant-pathogenic.

CONCLUDING REMARKS

P. aeruginosa uses its metabolic and genomic versatility to survive in multiple ecosystems and establish host infections. It is quite interesting to find controversial reports on the association of *P. aeruginosa* with the plant kingdom. Since it is an opportunistic bacterium, it might support plant growth or cause an infection based on the circumstances. The anti-microbial and anti-insecticidal compounds released by *P. aeruginosa* for their own defence might unintentionally protect the plants from pests and diseases. However, the ability of this bacterium to cause numerous infections and lethality in the animal kingdom is indisputable. Understanding the key factors that facilitate the rapid transmission and survival of *P. aeruginosa* in diverse habitats is essential for regulating the environment-to-host, host-to-environment and host-to-host dissemination of this bacterium.

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Conflicts of interest
The authors declare no conflicts of interest.

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