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Antibacterial Effect of Plant-based Bioactive Molecule Mixture Against *Pseudomonas aeruginosa*

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ABSTRACT

The aim of this study was to investigate the antibiotic resistance profile of *Pseudomonas aeruginosa* strains collected from the Microbiology Laboratory of Cukurova University Hospital, Adana, Türkiye and to evaluate the antibacterial effect of a plant-based bioactive molecule mixture against these strains. The VITEK-2 system and antibiogram cards were utilized for bacterial identification and antibiotic susceptibility determination. *P. aeruginosa* (N = 37) demonstrated high resistance rates to common antibiotics, including Ampicillin-Sulbactam (100%), Tetracycline (100%), Trimethoprim-Sulfamethoxazole (100%), Tigecycline (97.3%), and Imipenem (64.86%). Resistance was also observed against Levofloxacin, Piperacillin, and Netilmicin (59.46%), Meropenem and Amikacin (56.76%), Ciprofloxacin (40.54%), Cetohexazine-Sulbactam (32.43%), Ceftazidime (25%), Cefepime (24.32%), and Piperacillin-Tazobactam (14.29%). None of the strains were resistant to Colistin. Plant-based bioactive molecule mixture showed significant antibacterial activity, with the highest effect observed in strain P4 (99%). Activity was also notable in strains P2 (98%), P12 (97%), P11 (94%), P37 (81%), P14 (78%), and P1 (35%). In conclusion, the Plant-based bioactive molecule mixture demonstrated high antibacterial efficacy and holds promise as a natural agent for controlling multidrug-resistant (MDR) *P. aeruginosa* strains in the future.

Keywords: Antibiotic resistance profile, Bioactive molecule, *P. aeruginosa*, Nosocomial infection.

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Introduction

Nosocomial infections (NIs) represent a significant global public health concern due to their increasing prevalence and severe consequences. These infections are defined as those not present at the time of hospital admission and typically manifest within 48–72 hours post-admission or following discharge [1,2]. Causative agents may originate from the patient's endogenous flora or from exogenous microorganisms transmitted via environmental sources such as water, air, and food, or through contact with infected individuals [3]. The development of NIs leads to prolonged hospital stays, increased antibiotic consumption, and elevated transmission risks, thereby imposing substantial economic and healthcare burdens on both medical institutions and patients [4]. Studies identify urinary tract infections, respiratory tract infections, bloodstream infections, and surgical site infections as the most common types of NIs. According to the World Health Organization, NIs are responsible for approximately 40,000 deaths annually, with prevalence rates reaching up to 25% in developing countries and 5–15% in developed nations [5].

P. aeruginosa, a non-glucose-fermenting, Gram-negative rod-shaped bacterium, is rarely found in the microbiota of healthy individuals [6]. Although widely distributed in natural environments, it acts as an opportunistic pathogen in hospitalized patients. Various hospital equipment and surfaces, including water outlets, sinks, showerheads, humidifiers, anesthesia machines, hand brushes, and disinfectants -provide ideal habitats for *P. aeruginosa* [7]. This bacterium is responsible for approximately 10–11% of nosocomial infections and is frequently associated with pneumonia, surgical site infections, urinary tract infections, and bacteremia [8]. In recent years, a noticeable increase in the incidence of *P. aeruginosa* infections has been observed. For instance, the mortality rate in ventilator-associated pneumonia caused by *P. aeruginosa* ranges from 32% to 42.8% [9], while 16% of catheter-associated urinary tract infections in intensive care units are attributed to this organism [10]. In pediatric burn in intensive care units (ICUs), 86% of sepsis-related deaths are caused by multidrug-resistant (MDR) pathogens, with P. *aeruginosa* implicated in 64% of these cases [11]. Similarly, mortality rates associated with P. *aeruginosa*-related bloodstream infections have been reported between 43.2% and 58.8% [12].

Currently, antimicrobial resistance in *P. aeruginosa* constitutes a major threat to public health, particularly in ICUs and long-term care facilities. Among *P. aeruginosa* isolates from ICUs patients, resistance rates have been reported as 26.3% to carbapenems, 26.5% to broad-spectrum cephalosporins, and 27.1% to fluoroquinolones. Furthermore, 18.6% of isolates were classified as MDR, demonstrating resistance to three or more antimicrobial agents [13]. This resistance results from the interplay of

intrinsic, acquired, and adaptive mechanisms [14]. Key intrinsic factors include low outer membrane permeability, alterations or loss of the OprD porin, and overexpression of efflux pumps such as MexAB-OprM, which either prevent antibiotic entry or actively expel drugs, thereby reducing their efficacy [15-17]. Acquired resistance typically arises through horizontal gene transfer or spontaneous mutations, enabling the production of β-lactamases (e.g., expended spectrum beta lactamases, metallo-β-lactamases, and AmpC- β-lactamases) that deactivate antibiotics [18]. Resistance to fluoroquinolones and aminoglycosides is similarly linked to genetic mutations or enzymatic inactivation [19]. Adaptive resistance mechanisms involve temporary alterations in gene expression triggered by environmental stimuli. Biofilm formation and the generation of persister cells are hallmark features of such adaptations [20]. Bacteria embedded within biofilms hinder antibiotic penetration, reduce their metabolic activity, and develop heightened tolerance, ultimately contributing to therapeutic failure [21]. This complex and multilayered resistance architecture renders *P. aeruginosa* a particularly challenging pathogen in clinical settings and significantly limits available treatment options.

The growing prevalence of multidrug-resistant *P. aeruginosa* strains raises concerns about overtreatment with broad-spectrum antibiotics. Therefore, antibiotic stewardship, including de-escalation based on culture and susceptibility results, is critical to mitigating further resistance development [8]. These challenges underscore the need to investigate novel therapeutic approaches. In this study, the antibiotic resistance profile of *P. aeruginosa* strains isolated from Çukurova University Hospital was characterized, and the antibacterial efficacy of a plant-derived bioactive mixture (BAM) against multidrug-resistant isolates was evaluated.

Methods

Isolation and Identification of Microorganisms

P. aeruginosa strains were obtained from the Microbiology Laboratory of Balcali Hospital, Adana, Türkiye. Isolates were collected from patients admitted to intensive care units, inpatient wards, and outpatient clinics. Preliminary identification was performed using Glutamate Starch Phenol Red (GSP) Agar, following the procedure described by Kielwein [22]. The composition of GSP Agar per liter was as follows: sodium L-glutamate (10 g), starch (20 g), potassium dihydrogen phosphate (2 g), magnesium sulfate (0.5 g), phenol red (0.36 g), and agar (12 g), dissolved in 1000 mL of distilled water, with the pH adjusted to 7.2 ± 0.2. Plates were incubated at 37°C for 24–48 hours, and characteristic colony morphology was used as a presumptive indicator for *P. aeruginosa.* Final confirmation of the isolates was carried out using the VITEK-2® Compact System (bioMérieux, France), an automated identification system based on biochemical profiling. The standard reference strain P. aeruginosa ATCC 27853 was used as an internal quality control throughout the study.

Sensitivity Testing

Bacterial suspensions were adjusted to a turbidity equivalent to 0.5 McFarland standard using sterile 0.85% saline solution. The identification of isolates was performed using VITEK-2 GN ID cards (Ref. No. 21341), and antibiotic susceptibility profiles were determined using AST-N091 and AST-N092 automated antibiotic susceptibility testing cards (bioMérieux, France). The procedure followed the manufacturer's instructions, and results were interpreted according to the latest CLSI (Clinical and Laboratory Standards Institute) guidelines.

Test Material: Bioactive Molecule (BAM)

Plant materials with known antibacterial properties, including *Hypericum perforatum*, *Thymus vulgaris*, *Satureja thymbra*, *T. serpyllum*, and *T. citriodorus*, were collected from the Tarsus, Türkiye. Bacterial strains (*Bacillus licheniformis* and *Bacillus subtilis*) were isolated from Salt Lake, Türkiye. The plant powders were mixed with the bacterial cultures at a 1:1 (w/v) ratio and fermented for 48 hours at 30 ^{0}C aerobic condition. After fermentation, the mixture was centrifuged at 10,000 rpm for 10 minutes, and the resulting supernatant was filtered sequentially through 0.45 µm and 0.22 µm sterile filters (Sartorius) for further use.

Antibacterial Activity of BAM

MDR *P. aeruginosa* strains were selected for BAM efficacy testing. Strains were inoculated into 2 mL N1 Agar which was used for the routine cultivation, propagation, and stock culture preservation of the bacterial isolates, as described by Anonymous [11]. The composition per liter was as follows meat extract (1.5 g), glucose (1 g), peptone (10 g), yeast extract (3 g), and agar (15 g), dissolved in 1000 mL of distilled water, with the pH adjusted to 7.2.

and incubated at 37°C for 24 hours. Following pre-incubation, culture samples were adjusted to McFarland standard 0.5. Cultures were divided into two groups: one served as the control, while the other was treated with 200 µL BAM. Colony-forming units (cfu/mL) were calculated for both groups after 24 hours of incubation. Experiments were conducted in triplicate, and antibacterial activity was calculated by comparing cfu/mL values [22,23].

Results

A total of 37 *P. aeruginosa* strains were isolated and identified. Antibiotics tested to determine the resistance profile included Amikacin (AN), Gentamicin (GM), Netilmicin (NET), Piperacillin (PIP), Meropenem (MEM), Imipenem (IPM), Ciprofloxacin (CIP), Levofloxacin (LEV), Ceftazidime (CAZ), Cefepime (CFM), Colistin (CS), Tetracycline (TE), Tigecycline (TGC), Piperacillin-Tazobactam (TZP), Ampicillin-Sulbactam (SAM), Cefoperazone-Sulbactam (SFP), and Trimethoprim-Sulfamethoxazole (SXT) (Table 1).

Table 1. Antibiotic resistance profiles of isolated *P.* aeruginosa strains from Cukurova University Hospital

Strain	AN	SAM	FEP	SFP	CAZ	CIP	COL	GM	IPM	LEV	MEM	PIP	TZP	TE	TGC	SXT	NET
P1	R	R	R	R	R	R	R	R	R	R	R	R	ND	R	R	R	R
P2	R	R	M	M	M	R	S	R	R	R	R	R	ND	R	R	R	R
P3	S	R	S	S	S	S	S	S	S	S	S	M	M	R	R	R	S
P4	R	R	R	R	S	R	S	R	R	R	R	R	ND	R	R	R	R
P5	R	R	S	S	S	R	S	R	S	R	S	M	M	R	R	R	R
P6	R	R	M	S	S	S	S	S	R	S	R	M	M	R	R	R	R
P7	R	R	M	M	S	M	S	R	R	R	R	M	M	R	R	R	R
P8	R	R	M	M	M	R	S	R	R	R	R	R	R	R	R	R	R
P9	S	R	R	R	R	R	S	S	R	R	R	R	R	R	M	R	R
P10	S	R	R	R	R	M	S	S	R	R	R	R	ND	R	R	R	S
P11	R	R	R	R	R	R	S	R	R	R	R	R	ND	R	R	R	R
P12	R	R	R	R	S	R	S	R	S	R	S	R	ND	R	R	R	R
P13	R	R	M	M	M	R	S	R	R	R	S	R	ND	R	R	R	R
P14	R	R	M	M	M	R	S	R	R	R	R	R	R	R	R	R	R
P15	S	R	S	S	S	S	S	S	S	S	S	M	M	R	R	R	S
P16	R	R	M	M	M	S	S	R	R	S	R	M	ND	R	R	R	R
P17	R	R	S	S	S	S	S	R	R	S	S	S	S	R	R	R	R
P18	S	R	S	S	S	S	S	S	S	S	S	S	S	R	R	R	S
P19	S	R	S	S	S	S	S	S	S	S	S	S	S	R	R	R	S
P20	R	R	S	S	S	R	S	R	S	R	S	S	S	R	R	R	R
P21	S	R	M	M	M	S	S	S	R	S	R	R	M	R	R	R	S
P22	S	R	R	R	R	S	S	S	R	S	R	R	ND	R	R	R	S
P23	R	R	M	M	M	R	S	R	R	R	S	R	M	R	R	R	R
P24	S	R	R	R	R	S	S	S	S	S	S	R	ND	R	R	R	S
P25	S	R	S	S	S	S	S	S	S	S	S	S	S	R	R	R	S
P26	S	R	S	S	S	S	S	S	S	S	S	S	S	R	R	R	S
P27	R	R	M	R	M	M	S	S	R	R	R	R	ND	R	R	R	R
P28	S	R	M	M	R	S	S	S	S	S	S	R	ND	R	R	R	S
P29	S	R	S	S	S	S	S	S	S	S	S	S	S	R	R	R	S
P30	S	R	M	M	ND	R	S	S	R	R	R	R	M	R	R	R	S
P31	R	R	R	M	R	M	S	S	R	R	R	R	ND	R	R	R	R
P32	S	R	S	M	S	M	S	S	R	R	R	M	M	R	R	R	S
P33	S	R	M	R	M	M	R	R	R	R	R	R	M	R	R	R	S
P34	R	R	M	M	M	R	S	R	R	R	R	R	ND	R	R	R	R
P35	R	R	M	R	M	R	S	R	R	R	R	R	ND	R	R	R	R
P36	R	R	S	S	S	S	S	S	S	S	S	M	M	R	R	R	R
P37	R	R	M	R	R	M	S	R	R	R	R	R	ND	R	R	R	R

Eight strains, specifically P1, P11, P4, P8, P9, P14, P35, and P37, were categorized as multiple antibiotic-resistant (MDR). Among these, P1 and P11 were resistant to 15 antibiotics, P4 to 14 antibiotics, and P8, P9, P14, P35, and P37 to 13 antibiotics each. Strains P1 and P11 showed resistance to all antibiotics except for Colistin. Similarly, strains P2, P8, P14, and P34 demonstrated moderate resistance to Ceftazidime, Cefepime, and Cefoperazone-Sulbactam but were resistant to all other antibiotics except Colistin. The P4 strain exhibited no resistance to Colistin and Ceftazidime, while it was resistant to the other antibiotics. Both P35 and P37 strains demonstrated moderate resistance to Ceftazidime and Cefepime but were resistant to all other antibiotics except for Colistin.

The resistance rates of the isolated *P. aeruginosa* strains were determined as follows: Amikacin (56.76%), Gentamicin (45.95%), Netilmicin (59.46%), Piperacillin (59.46%), Meropenem (56.76%), Imipenem (64.86%), Ciprofloxacin (40.54%), Levofloxacin (59.46%), Ceftazidime (25%), Cefepime (24.32%), Colistin (0%), Tetracycline (100%), Tigecycline (97.30%), Piperacillin-Tazobactam (14.29%), Ampicillin-Sulbactam (100%), Cefoperazone-Sulbactam (32.43%), and Trimethoprim-Sulfamethoxazole (100%) (Table 2).

Table 2. The resistance frequency of the isolated strains against 23 antibiotics

Groups	Antibiotics	Resistance (%)	Group Resistance (%)
Aminoglycoside	Amikacin	56.76%	54.06%
	Gentamicin	45.95%	
	Netilmicin	59.46%	
Penicillins	Piperacillin	59.46%	59.46%
Carbapenem	Meropenem	56.76%	60.81%
	Imipenem	64.86%	
Fluoroquinolones	Ciprofloxacin	40.54%	50%
	Levofloxacin	59.46%	
Cephalosporins	Ceftazidime	25%	24.66%
	Cefepime	24.32%	
Polymyxin	Colistin	0.0%	0.0%
Tetracycline	Tetracycline	100%	100%
Glycylcycline	Tigecycline	97.30%	97.30%
Penicillin + Beta-Lactamase Inhibitor	Piperacillin-Tazobactam	14.29%	57.15%
	Ampicillin-sulbactam	100%	
Cephalosporin + Beta-lactamase Inhibitor	Cefoperazone-sulbactam	32.43%	32.43%
Cephalosporin + Beta-lactamase Inhibitor	Trimethoprim-sulfamethoxazole	100%	100%

The antibacterial activity of BAM was further investigated on seven selected strains (P1, P2, P4, P11, P12, P14, and P37) due to their multidrug resistance profiles. BAM exhibited the highest antibacterial activity against the P4 strain (99%). The antibacterial activity of BAM against P1, P2, P11, P12, P14, and P37 was observed as 35%, 98%, 94%, 97%, 78%, and 81%, respectively (Figure 1).

The mean antibacterial activity of BAM was calculated as 83.14% across all tested *P. aeruginosa* MDR strains (Table 3).

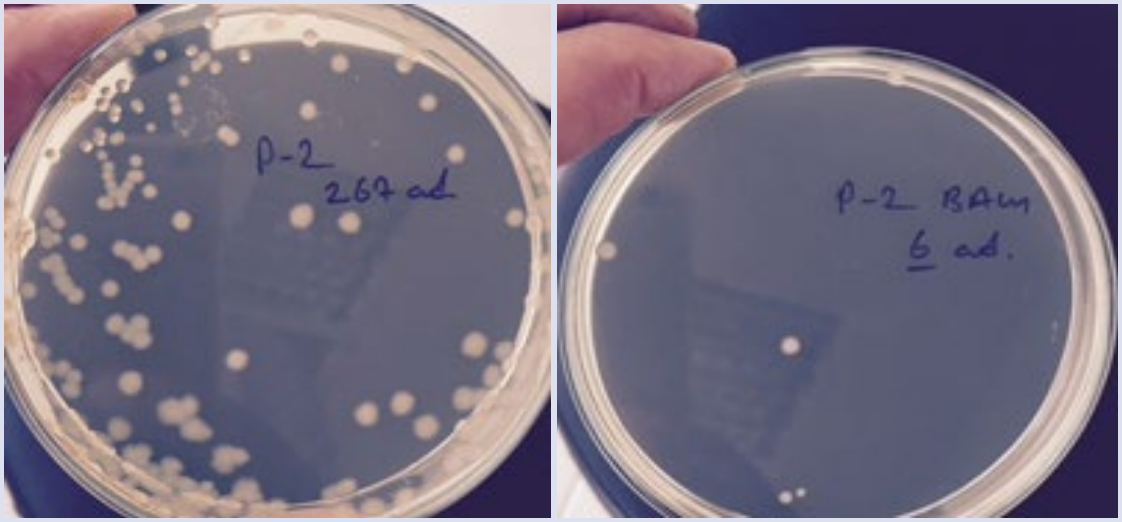


Figure 1. The elimination of *P. aeruginosa*-2 strain (resistant to 11 antibiotics) after BAM treatment

Table 3. The antibacterial effect of BAM on isolated MDR *P. aeruginosa* strains

Strain	Number of Antibiotics	BAM untreated samples cfu/mL	BAM treated samples cfu/mL	Elimination (%)
P. aeruginosa1	15	165	107	35
P. aeruginosa2	12	267	6	98
P. aeruginosa4	14	673	4	99
P. aeruginosa11	15	380	22	94
P. aeruginosa12	12	90	3	97
P. aeruginosa14	13	650	146	78
P. aeruginosa37	13	262	50	81

Discussion

P. aeruginosa is a significant cause of nosocomial infections, ranging from pneumonia to bloodstream infections. As highlighted in the Introduction, *P. aeruginosa* possesses intrinsic and acquired resistance mechanisms, including reduced membrane permeability, active efflux pumps, production of antibiotic-inactivating enzymes, and biofilm formation [24]. In this study, 37 isolated *P. aeruginosa* strains exhibited a high prevalence of antibiotic resistance, with all strains categorized as MDR. The resistance rates observed in this study included 54.06% for aminoglycosides, 59.46% for penicillin, 60.81% for carbapenems, 50% for fluoroquinolones, 24.66% for cephalosporins, 0% for polymyxins (Colistin), 100% for tetracyclines, 97.30% for glycyclines, 57.15% for penicillin + beta-lactamase inhibitors, 32.43% for cephalosporin + beta-lactamase inhibitors, and 100% for sulfonamide + trimethoprim combinations.

It's well known that *P. aeruginosa* strains have innate resistance against to antibiotics such as ampicillin, amoxicillin, amoxicillin-clavulanate, broad spectrum cephalosporins, cefotaxime and ceftriaxone etc. [25]. Previous studies have reported variable resistance rates to aminoglycosides. For instance, Gamero et al. [26] observed resistance rates of 16.7% for Amikacin and 24.2% for Gentamicin, while Tanriverdi Cayci et al. [27] reported rates of 7% for Amikacin and 10% for Gentamicin. A meta-analysis conducted in Türkiye demonstrated resistance rates of 10.8% for Amikacin and 25.2% for Gentamicin between 2002–2012, and 9.9% for Amikacin and 18.7% for Gentamicin between 2013–2017 [28]. The resistance rates observed in this study for Amikacin (56.76%) and Gentamicin (45.95%) are significantly higher than previously reported rates.

Carbapenems, a broad-spectrum beta-lactam antibiotic class, are increasingly encountering resistance due to the production of carbapenem-inactivating enzymes by *Pseudomonas* spp. Teixeira et al. reported resistance rates of 35% for Imipenem and 36.5% for Meropenem [29]. In Türkiye, resistance rates to Imipenem and Meropenem were recorded as 26.2% and 23.5% (2002–2012) and 28.4% and 29.4% (2013–2017), respectively [28]. In comparison, the resistance rates observed in this study for Imipenem (64.86%) and Meropenem (56.76%) are considerably higher.

Fluoroquinolones are another antibiotic class frequently employed to treat *P. aeruginosa* infections. Ciprofloxacin and Levofloxacin resistance rates in this study were observed at 40.54% and 59.46%, respectively. These findings are within the range of previously reported rates for Ciprofloxacin (17–52.5%) and Levofloxacin (27.5–37.6%) [30-32].

The resistance rates to cephalosporins (Ceftazidime and Cefepime) were observed at an average of 24.66%, aligning with previously reported rates ranging from 17.4–45.8% for Ceftazidime and 12.4–48.9% for Cefepime [33, 34]. Additionally, in Türkiye, the resistance rate for Ceftazidime was reported as 35% during 2007–2017 [28].

All the isolated strains in this study demonstrated resistance to Tetracycline and Trimethoprim-Sulfamethoxazole, while remaining uniformly sensitive to Colistin (100%), consistent with findings in the literature[35].

MDR, defined as resistance to at least three antibiotic classes, was observed in 100% of the strains isolated in this study. Among these, resistance to 5, 6, 7, 8, 9, and 10 antibiotics was noted at rates of 81%, 78.4%, 56.76%, 48.65%, 29.73%, and 8%, respectively. Previous studies have documented MDR rates of 2.6% in 1999, 3.5% in 2001, and 3% in 2006 [36]. However, higher MDR rates, such as 82% in Brazil and 68% in Iran, have also been reported [37].

Our findings suggest an increasing prevalence of MDR *P. aeruginosa*, which could significantly complicate the treatment of nosocomial infections in the future. Given this, alternative treatment strategies are urgently required. In this context, we investigated the antibacterial potential of a plant-based BAM mixture. The highest antibacterial activity was observed against the P4 strain (99%), with activities ranging between 35% and 98% across all strains tested. The mean antibacterial efficacy of BAM was calculated as 83.14%.

Conclusion

Nosocomial infections caused by MDR *P. aeruginosa* pose a significant threat to public health due to limited treatment options. This study highlights the potential of plant-based BAM mixtures as an effective alternative for controlling MDR infections. Further research and development are necessary to fully explore its therapeutic potential.

Conflict of Interest

The authors declare no conflicts of interest.

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