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Emergence of extensive drug resistance and high prevalence of multidrug resistance among clinical *Proteus mirabilis* isolates in Egypt

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Abstract

Background *Proteus mirabilis* is an opportunistic pathogen that has been held responsible for numerous nosocomial and community-acquired infections which are difficult to be controlled because of its diverse antimicrobial resistance mechanisms.

Methods Antimicrobial susceptibility patterns of *P. mirabilis* isolates collected from different clinical sources in Mansoura University Hospitals, Egypt was determined. Moreover, the underlying resistance mechanisms and genetic relatedness between isolates were investigated.

Results Antimicrobial susceptibility testing indicated elevated levels of resistance to different classes of antimicrobials among the tested *P. mirabilis* clinical isolates ($n = 66$). ERIC-PCR showed great diversity among the tested isolates. Six isolates (9.1%) were XDR while all the remaining isolates were MDR. ESBLs and AmpCs were detected in 57.6% and 21.2% of the isolates, respectively, where bla_{TEM}, bla_{SHV}, bla_{CTX-M}, bla_{CIT-M} and bla_{AmpC} were detected. Carbapenemases and MBLs were detected in 10.6 and 9.1% of the isolates, respectively, where bla_{OXA-48} and bla_{NDM-1} genes were detected. Quinolone resistant isolates (75.8%) harbored *acc(6')-Ib-cr*, *qnrD, qnrA*, and *qnrS* genes. Resistance to aminoglycosides, trimethoprim-sulfamethoxazole and chloramphenicol exceeded 80%. Fosfomycin was the most active drug against the tested isolates as only 22.7% were resistant. Class I or II integrons were detected in 86.4% of the isolates. Among class I integron positive isolates, four different gene cassette arrays (*dfrA17- aadA5*, *aadB-aadA2*, *aadA2-lnuF*, and *dfrA14-arr-3-*bla_{OXA-10}*-aadA15*) and two gene cassettes (*dfrA7* and *aadA1*) were detected. While class II integron positive isolates carried four different gene cassette arrays (*dfrA1-sat1-aadA1*, *estXVr-sat2-aadA1*, *lnuF- dfrA1-aadA1*, and *dfrA1-sat2*).

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Conclusion *P. Mirabilis* ability to acquire resistance determinants via integrons may be held responsible for the elevated rates of antimicrobial resistance and emergence of XDR or even PDR strains limiting the available therapeutic options for management of infections caused by those strains.

Keywords *Proteus mirabilis*, MDR, XDR, ESBLs, AmpCs, Carbapenemases, PMQR, Integrons, ERIC typing

Background

Proteus mirabilis is Gram-Negative, facultative anaerobe that belongs to family Morganellaceae. It is ubiquitous in nature and a member of the gastrointestinal ora of animals and human. However, it is held responsible for many nosocomial and community acquired outbreaks all over the world including urinary and respiratory tract infections, foot ulcers of the diabetic patients, and wide range of other infections [1].

Misuse or non-speci c use of antibiotics has led to increased levels of drug resistance and wide spread of various resistance genes among clinical *P. mirabilis* isolates. Besides, *P. mirabilis* is characterized by intrinsic resistance to tetracycline, tigecycline, and polymyxins [2]. β-lactam antibiotics, including penicillins and cephalosporins, and carbapenems is considered the rst choice for treatment of infections caused by *P. mirabilis.* One of the most common resistance mechanisms is the enzymatic hydrolysis of β-lactam antibiotics [3]. Structural and functional classi cation of β-lactamases have a critical role in the adequate choice of appropriate antimicrobial agent [4]. Prevalence of carbapenem resistance is relatively low, although it is increasing with time [5].

Recently, elevated levels of resistance to quinolones and aminoglycosides were reported worldwide [6, 7]. In addition, folate pathway inhibitors, nitrofurans, and even fosfomycin resistance are increasingly reported [8–10].

Most of resistance determinants are carried on integron's that can be transferred by plasmids, transposons and other mobile genetic elements. erefore, it is considered a major cause for the transfer of drug resistance traits among di erent bacterial pathogens, especially in family *Enterobacteriaceae.* More than 130 integron's gene cassette arrays of various resistance genes to di erent classes of antibiotics have been identi ed [11].

Clinicians may face very limited therapeutic options, due to spread of multidrug-resistant (MDR), emergence of extensive drug resistant (XDR) and even pandrug resistant (PDR) strains [12]. erefore, the aim of the present study is to assess the prevalence of resistance to di erent classes of antimicrobial agents among *P. mirabilis* isolates collected from di erent clinical sources from Mansoura University Hospitals, Egypt. Moreover, molecular detection of underlying resistance mechanisms and genetic relatedness among collected isolates was unveiled.

Materials and methods

Bacterial isolates

Bacterial isolates were collected from Mansoura University Hospitals from di erent clinical sources between September 2021 and January 2022. Isolates were identi ed as *P. mirabilis* according to standard microbiology and molecular methods [13].

Antimicrobial susceptibility pattern of *P. mirabilis* clinical isolates

Kirby Bauer disk di usion method was used to assess *P. mirabilis* antimicrobial susceptibility pro le using Mueller Hinton agar plates [14]. Interpretation of the results was performed according to the recommendations of Clinical and Laboratory Standard Institute [15]. Antimicrobial discs of various antimicrobial categories (Bioanalyze ® products, Turkey) have been used to assess the resistance pro le of the tested *P. mirabilis* clinical isolates (Table S1).

Bacterial isolates were classi ed into MDR, XDR and PDR. MDR is recognized as being non susceptible to at least one antimicrobial agent in three antimicrobial classes or more. While XDR is being resistant to at least one antimicrobial agent in all antimicrobial classes but susceptible to two or fewer. PDR is recognized as being resistant to all agents in all di erent antimicrobial classes [16].

Phenotypic detection of β-lactamases

Acidimetric method for β-lactamases detection

β-lactamases hydrolyze β-lactam ring resulting in generating a carboxyl group which acidi es un-bu ered systems. e resulting acidity was tested in 96-wells microtiter plates using benzylpenicillin as substrate and phenol red as a pH indicator [17].

Detection of extended spectrum β-lactamases (ESBLs)

Combination disk method (CDM) was used as previously described [15]. e zone of inhibition of cefotaxime (30 µg) and ceftazidime (30 µg) discs alone was measured and compared with that of cefotaxime/clavulanate (30 µg / 10 µg), and ceftazidime/ clavulanate (30 µg / 10 µg) discs, respectively. An increase in the inhibition zone (≥5 mm) of either or both anti-microbial agents when combined with clavulanate indicates ESBLs production.

Detection of plasmid mediated cephalosporinases (AmpCs)

Streaking method on MacConkey agar plates was employed as described previously [18]. In brief, sensitive *E. coli DH5α* strain lawn was inoculated on the surface of MacConkey agar plates. Cefoxitin disc (30 µg) was applied in the center of the plate and the tested isolates were streaked as a line, away from the cefoxitin disc by 5 mm. Isolates that distorted cefoxitin inhibition zone (clover leaf-like shape) was considered AmpC producers.

Detection of carbapenemases

Modi ed Hodge test (MHT) was used according to CLSI recommendations [15]. Sensitive *E. coli DH5α* strain lawn culture was inoculated on MacConkey agar plates [19]. Meropenem disc (10 µg) was applied in the center of the plate. e tested isolates were streaked as a line, 5 mm away from the disc. Distortion of the meropenem inhibition zone (clover leaf-like shape) indicates carbapenemase production [20].

Detection of metallo β-lactamases (MBLs)

Combined disk synergy test (CDST) was used to as described previously. Brie y, two disks of IPM (10 µg) were placed on inoculated Mueller Hinton agar plate and then 2 µL of 0.5 M EDTA was added to one of them [21]. If inhibition zone of IPM/EDTA increased by ≥5 mm compared with that of IPM alone, the isolate was considered MBLs producer [15].

Molecular detection of resistance determinants

Extraction of DNA

DNA was extracted by boiling method as previously described [22]. Ampli cation of *UreC* gene was used for con rming identi cation of *P. mirabilis* isolates (Table 1) [23].

Detection of antimicrobial resistance encoding genes

Prevalence of antimicrobial resistance determinants including β-lactams [

Table 1 Oligonucleotides used in this study

Target Gene		Nucleotide Sequence (5'- 3')	Amplicon size (bp)	Annealing Temp (°C)	Reference
1. β-lactam resistance encoding genes					
1.1. ESBLs encoding genes					
Class A β-lactamases					
bla_{SHV}	Fw	ACTATCGCCAGCAGGATC	356	53.5	59
	Rv	ATCGTCCACCATCCACTG			
bla_{TEM}	Fw	GATCTCAACAGCGGTAAG	786	54	59
	Rv	CAGTGAGGCACCTATCTC			
bla_{CTX-M}	Fw	ATGTGCAGYACCAGTAARGT	593	50	60
	Rv	TGGGTRAARTARGTSACCAGA			
bla_{GES} *(GES-1 to GES-9 and GES-11)*	Fw	AGTCGGCTAGACCGGAAAG	399	60	61
	Rv	TTTGTCCGTGCTCAGGAT			
bla_{PER} *(PER-1 & PER-3)*	Fw	GCTCCGATAATGAAAGCGT	520	60	61
	Rv	TTCGGCTTGACTCGGCTGA			
bla_{VEB} *(VEB-1 to VEB-6)*	Fw	CATTTCCCGATGCAAAGCGT	648	60	61
	Rv	CGAAGTTTCTTTGGACTCTG			
Class D β-lactamases					
$bla_{OXA\text{-}1\text{-}like}$*(OXA-1, OXA-4 & OXA-30)*	Fw	GGCACCAGATTCAACTTTCAAG	564	58	61
	Rv	GACCCCAAGTTTCCTGTAAGTG			
1.2. AmpC encoding genes (Class C A β-lactamases)					
bla_{AmpC}	Fw	ACACGAGTTTGCATCGCCTG	254	68	62
	Rv	CTGAACTTACCGCTAAACAGTGGAAT			
bla_{CIT-M}	Fw	TGGCCAGAACTGACAGGCAAA	462	55	62
	Rv	TTTCTCCTGAACGTGGCTGGC			
bla_{Fox-1}	Fw	GCAAACCAGCAATACCATCCA	642	60	62
	Rv	GCTCACCTTGTCATCCAGCTC			
bla_{ACC-1}	Fw	AGCTGTTATCCGTGATTACCTGTCT	248	60	62
	Rv	AGCGAACCCACTTCAAATAACG			
bla_{ACT-1}	Fw	CATGCTGGATCTGGCAACCT	343	60	62
	Rv	CTTCAGCGTCCAGCATTCCT			
bla_{FOX} *(FOX-1 to FOX-5)*	Fw	CTACAGTGCGGGTGGTTT	162	55	61
	Rv	CTATTTGCGGCCAGGTGA			
bla_{MOX} *(MOX1, MOX2, CMY-CMY-8 to CMY 11 and CMY19)*	Fw	GCAACAACGACAATCCATCCT	895	60	61
	Rv	GGGATAGGCGTAACTCTCCCAA			
1.3. Carbapenemases encoding genes					
Class A (Serine enzymes)					
bla_{KPC} (KPC-1 to KPC-5)	Fw	CATTCAAGGGCTTTCTTGCTGC	538	55	61
	Rv	ACGACGGCATAGTCATTTGC			
Class B (MBLs)					
bla_{IMP}	Fw	CATGGTTTGGTGGTTCTTGT	448	57	55
	Rv	ATAATTTGGCGGACTTTGGC			
bla_{VIM-1}	Fw	TGTTATGGAGCAGCAACGATG	920	56	63
	Rv	AAAGTCCCGCTCCAACGATT			
bla_{NDM-1}	Fw	GGTTTGGCGATCTGGTTTTC	621	52	64
	Rv	CGGAATGGCTCATCACGATC			
Class D (Oxacillinases)					
$bla_{OXA-48-like}$	Fw	GCTTGATCGCCCTCGATT	281	57	61
	Rv	GATTTGCTCCGTGGCCGAAA			
2. Quinolones resistance encoding genes					
qnrA (qnrA1 to qnrA6)	Fw	AGAGGATTTCTCACGCCAGG	580	60	65
	Rv	TGCCAGGCACAGATCTTGAC			
qnrB (qnrB1 to qnrB6)	Fw	GGMATHGAAATTCGCCACTG	264	60	66
	Rv	TTTGCYGYYCGCCAGTCGAA			

Table 1 (continued)

Target Gene		Nucleotide Sequence (5'- 3')	Amplicon size (bp)	Annealing Temp (°C)	Reference
1. β-lactam resistance encoding genes					
1.1. ESBLs encoding genes					
qnrS	Fw	GCAAGTTCATTGAACAGGCT	428	60	65
(qnrS1 to qnrS2)	Rv	TCTAAACCGTCGAGTTCGGCG			
qnr C	Fw	GGGTTGTACATTTATTGAATC	447	55	67
	Rv	TCCACTTTACGAGGTTCT			
qnr D	Fw	CGAGATCAATTTACGGGGAATA	582	55	67
	Rv	AACAAGCTGAAGCGCCTG			
qepA	Fw	CGTGTTGCTGGAGTTCTTC	403	52	68
	Rv	CTGCAGGTACTGCGTCATG			
oqxA	Fw	GACAGCGTCGCACAGAATG	339	57	69
	Rv	GGAGACGAGGTTGGTATGGA			
oqxB	Fw	CGAAGAAAGACCTCCCTACCC	240	57	69
	Rv	CGCCGCCAATGAGATACA			
aac(6')-Ib-cr	Fw	TTGCGATGCTCTATGAGTGGCTA	482	60	70
	Rv	CTCGAATGCCTGGCGTGTTT			
3. Integrons and Variable regions					
Integrons constant regions					
IntI1	Fw	GGTCAAGGATCTGGATTTCG	483	58	71
	Rv	ACATGCGTGTAAATCATCGTC			
IntI2	Fw	CACGGATATGCGACAAAAAGGT	788	58	71
	Rv	GTAGCAAACGAGTGACGAAATG			
Variable region of integron I					
5'CS	Fw	GGCATCCAAGCAGCAAG	Variable	58	71
3'CS	Rv	AAGCAGACTTGACCTGA			
Variable region of integron II					
attI2	Fw	GACGGCATGCACGATTTGTA	Variable	58	71
orfX	Rv	GATGCCATCGCAAGTACGAG			
4. Molecular Identi□cation					
UreC	Fw	GTTATTCGTGATGGTATGGG	317	56.2	58
	Rv	ATAAAGGTGGTTACGCCAGA			
5. Molecular Typing					
ERIC-2 typing	2	AAGTAAGTGACTGGGGTGAGCG	Variable	48	73

bp: base pair, Fw: forward primer, Rv: reverse primer

and molecular procedures (Table S1). Isolates were collected from di erent clinical sources including urine (24 isolates, 36.4%), diabetic foot lesions (12 isolates, 18.2%), sputum (7 isolates, 10.6%), T-Tube drain (6 isolates, 9.1%), bedsores and wound swabs (6 isolates, 9.1%), burn swab (5 isolates, 7.6%), blood (3 isolates, 4.5%), thigh boils swabs (2 isolates, 3%), and aspirate swab (1 isolate, 1.5%).

Clinical isolates of *P. mirabilis* appeared as scattered Gram-negative rods with characteristic shy odor and strong swarming motility on nutrient agar. Identi cation of *P. mirabilis* isolates was performed according to their biochemical pro le including positive phenyl alanine deaminase test, negative indole test, positive citrate utilization test, positive Voges-Proskauer (VP) and methyl red (MR) tests, and non-lactose fermentation on MacConkey's agar media. On triple sugar iron agar slants, isolates showed alkaline red slant with acidic butt (indicative of glucose fermentation only) and heavy black precipitate (indicative of hydrogen sul de production). Moreover, the gene coding for urease enzyme (*UreC*) was successfully ampli ed in all *P. mirabilis* clinical isolates con rming its identi cation.

Antibiotic sensitivity pattern of *P. mirabilis* clinical isolates

Antibiotic sensitivity testing of *P. mirabilis* clinical isolates indicated elevated rates of resistance to ampicillin, amoxicillin-clavulanic acid, cefazolin, cefuroxime, cefepime, trimethoprim-sulfamethoxazole, nitrofurantoin and Chloramphenicol (Fig. 1 and Table S2). Resistance to third generation cephalosporins ranged from 44 to 68%, while resistance to carbapenems was less than 11%. High rates of resistance to uoroquinolones (53 to 76%) and aminoglycosides (45 to 82%) were observed,

Fig. 1 Dendrogram constructed using ERIC-PCR patterns of *P. mirabilis* clinical isolates. Banding patterns were analyzed by using Gel J software version 2.0. Analysis of similarity clustering was performed by using UPGMA and Jaccard's coe□cient. The vertical line is a hypothetical line illustrating 85% similarity. Heatmap representing resistance pro□le of each isolate to di□erent classes of antibiotics (red = resistant, yellow = intermediate, and blue = sensitive), and resistance determinants (red = positive, and yellow = negative) was added for comparison between isolates

while fosfomycin resistance was detected in 23% of the tested isolates. Based on the resistance pro le of *P. mirabilis* clinical isolates against the tested antimicrobials, 60 isolates (90.9%) were MDR, 6 isolates (9.1%) were XDR, and none of the isolates were PDR (Fig. 1 and Table S1).

Phenotypic detection of β-lactamases

Detection of β-lactamases

Acidimetric test was used for general detection of β-lactamases. e results showed that 38 isolates (57.6%), including all the XDR isolates, were β-lactamase producers (Table S1).

Detection of ESBLs

Based on CDM (Fig. S1), 38 isolates (57.6%) were ESBLs producers (Fig. 1 and Table S1).

Detection of AmpC

Fourteen isolates (21.2%) showed distortion of cefoxitin inhibition zone (clover leaf-like shape, Fig. S1) and were considered positive AmpC producers (Fig. 1 and Table S1).

Detection of MBLs

Six isolates (9.1%) showed increase in inhibition zone of Imipenem/EDTA by ≥5 mm compared with that of IPM alone in CDST (Fig. S1) and were considered MBLs producers (Fig. 1 and Table S1).

Detection of carbapenemases

Seven isolates (10.6%) distorted the inhibition zone around meropenem disc (clover leaf like shape, Fig. S1) in MHT indicating carbapenemases production (Fig. 1 and Table S1).

Molecular detection of resistance determinants

Detection of β-lactamases encoding genes

Among the tested *P. mirabilis* clinical isolates, $bla_{\text{OXA-1-like}}$ (class D β-lactamases) was the most predominant as it was detected in 35 isolates (53%) (Fig. 1, Fig. S2 and Table S1). Regarding Class A β-lactamases, bla_{TEM} was detected in 34 isolates (51.5%), bla_{SHV} in 8 isolates (12.1%), $bla_{\text{CTX-M}}$ in 12 isolates (18.2%). While bla_{GES}, bla_{PER}, and bla_{VEB} genes were not detected among the tested isolates.

Detection of AmpC encoding genes

Among the tested genes, bla_{CIT-M} and bla_{AmpC} genes were detected in 5 isolates (7.6%) and 2 isolates (3%), respectively (Fig. 1, Fig. S2 and Table S1). While $bla_{\text{ACC-1}}$, $bla_{\text{ACT-1}}$, bla_{Fox}, and bla_{MOX} genes were not detected among the tested isolates.

Detection of carbapenemases and MBLs encoding genes

$bla_{\text{OXA-48-like}}$ gene (class D β-lactamases) was detected in all carbapenem resistant *P. mirabilis* isolates (7 isolates, 10.6%), while bla_{KPC} gene (class A β-lactamases) was not detected (Fig. 1, Fig. S2 and Table S1). Among MBLs encoding genes, $bla_{\text{NDM-1}}$ was detected in 5 MBLs producing isolates (7.6%). While $bla_{\text{VIM-1}}$ and bla_{IMP} genes were not detected.

Detection of quinolone resistance encoding genes

Analysis of plasmid mediated quinolone resistance (PMQR) genes showed that *acc (6')-Ib-cr* gene was detected in 38 isolates (57.6%). Regarding *qnr* encoding genes, *qnrD* was detected in 26 isolates (39.4%), *qnrA* in 23 isolates (34.8%), and *qnrS* in 6 isolates (9.1%) (Fig. 1, Fig. S2 and Table S1). Other qnr encoding genes (*qnrB* and *qnrC)* and *qepA, oqxA*, and *oqxB* were not detected.

Detection of integrons and their gene cassettes

Integrons Class I and II were screened among all the tested *P. mirabilis* clinical isolates. Fifty-seven isolates (86.4%) harbored either class I or class II integrons. Fifty-one isolates (77.3%) harbored both class I and II integrons, while six isolates (9.1%) lacked both (Fig. S3 and Table S1). e variable regions of class I and class II integrons were successfully ampli ed in 42 isolates (73.7%) and 54 isolates (94.7%), respectively. e size of the variable region ranged from 200 to 3000 bp (Fig. S3 and Table S1). Nucleotide sequences of class I integron's variable region were deposited in GenBank (accessions no. OR567431, and OR573795:OR573799). Four di erent gene cassette arrays, *dfrA17-aadA5* (11 isolates), *aadB-aadA2* (4 isolates), *aadA2-lnuF* (4 isolates), and *dfrA14-arr-3-*$bla_{\text{OXA-10}}$*-aadA15* (3 isolates), and two di erent gene cassettes, *dfrA7* (12 isolates), and *aadA1* (4 isolates), were detected. While four di erent gene cassette arrays, *dfrA1-sat1-aadA1* (34 isolates), *estXVr-sat2-aadA1* (3 isolates), *lnuF-dfrA1-aadA1* (3 isolates), and *dfrA1-sat2* (1 isolate), were detected in class II integron's variable regions (Fig. 2 and Table S1). Nucleotide sequences were deposited in GenBank (accessions no. OR597588, OR597589, OR573800, and OR573801).

Correlation between resistance to aminoglycosides tested and folate pathway inhibitors (trimethoprim/sulfamethoxazole) and their resistance determinants (*aadA*, *sat* and *dfrA* variants) carried by either class I or class II integrons (chi-square test, $P<0.5$). Most isolates lacking integrons (class I and class II) were sensitive to the tested aminoglycosides and folate pathway inhibitors.

Molecular typing

ERIC-PCR typing method demonstrated enormous diversity among the tested *P. mirabilis* clinical isolates. Some isolates were considered genetically related as they showed a similarity coe cient higher than 85% (Fig. 1). Moreover, it showed great diversity among isolates that showed XDR pro le and were considered genetically unrelated.

Discussion

Management of infectious diseases is of great importance for human health, especially with the continuous increase of MDR and the emergence of XDR or even PDR [5, 22, 43–45].

erefore, evaluation of the local antimicrobial resistance patterns and underlying resistance determinants is fundamental for the implementation of e ective stewardship programs in each country/region.

Among *Enterobacterales*, *K. pneumoniae, E. coli* and *P. mirabilis* were held responsible for most of hospital and community-acquired infections. *P. mirabilis* caused several nosocomial and community-acquired outbreaks in di erent regions of the world [46]. It does not produce any chromosomally encoded β-lactamases resulting in full susceptibility to all β-lactams for a wild-type phenotype and it is generally susceptible to uoroquinolones [4]. However, strains resistant to di erent antibiotics are increasingly reported, which complicates the treatment of infections caused by Proteus spp [12].

In this study, 57.6% of the tested isolates were ESBLs producers which coincide with reports in di erent regions of the world [47–49]. In Egypt, low rate ESBLs production (28.3%) has been reported but a recent study recorded a higher rate (51.7%) [9, 10]. bla_{TEM}, $bla_{\mathrm{CTX-M}}$, and bla_{SHV} genes were detected in the tested isolates. Recent studies indicated similar ndings in Egypt [9, 10, 12] and worldwide [3, 50–52].

In Croatia, bla_{TEM} and bla_{PER} genes were detected [53, 54], while $bla_{\mathrm{CTX-M2}}$

acc (6')-Ib-cr, qnrD, and *qnr A* among quinolone resistant proteus isolates [6, 52].

Fosfomycin has attracted a great attention for treating serious systemic infections caused by MDR Enterobacterales. However, resistance to fosfomycin have emerged [65]. Among the tested isolates, (22.7%) were fosfomycin resistant which coincide with recent studies in Brazil and Lebanon [6, 66]. Among the tested isolates, 81.8% were resistant to aminoglycosides. Recent studies in Egypt recorded resistance rate 37.9 to 53.2% [9, 10, 67], while in Ghana, India and Japan, higher rates of resistance (54–100%) were recorded [18, 48, 55, 68]. In addition, 87.9% of the isolates were resistant to trimethoprim/sulfamethoxazole which coincide with recent studies in Egypt [9, 10, 12]. Similarly, elevated rates of resistance were recoded worldwide [3, 18, 52].

Di erent genetic mechanisms are involved in the acquisition of resistance genes to di erent antibiotic classes. Horizontal gene transfer, via plasmids, transposons and integrons, is a major cause of the spread of antimicrobial resistance and turn *P. mirabilis* into MDR, XDR or even PDR resistant [11]. Integrons are not self- transferable elements, however they are frequently located on transposons or plasmids, allowing e cient gene transfer. More than 100 gene cassettes bearing resistance to different classes of antibiotics have been reported [51, 52, 69, 70]. Class I and II integrons were detected in 86.4% of the tested isolates. Sequencing analysis of their variable region revealed that they carried distinctive cassettes encoding aminoglycosides and trimethoprim resistance determinants mainly. Previous reports have also indicated that most integrons-carrying genes are coding for aminoglycosides and trimethoprim resistance [52, 69–71].

MDR phenomenon is frequently linked to integrons as they can be transferred, integrated, expressed, and causes distribution of several antimicrobial resistance genes [72].

e high rate of MDR and emergence of XDR among the tested isolates along with their enormous diversity (ERIC-PCR genotyping) could be explained by horizontal transfer of resistance determinants among bacterial isolates in hospitals. Variable rates of MDR (14.5–100%) were reported worldwide among *P. mirabilis* clinical isolates [3, 52, 69]. Previous studies in Egypt reported MDR (29.3–87.2%) among *P. mirabilis* clinical isolates [9, 10, 67]. A recent study reported 22.8% MDR, 31.4% XDR, and 8.5% PDR, which is considered the rst report of PDR *P. mirabilis* in Egypt [12].

Conclusion

e elevated rate of MDR and emergence of XDR among *P. mirabilis* clinical isolates poses a public threat in Egypt limiting the therapeutic options for management of infections caused by these superbugs. Appropriate use of antimicrobial agents in the health setting along with surveillance of antimicrobial resistance pro les and the underlying resistance determinants are highly requested for controlling the spread of antimicrobial resistance and emergence of PDR stains in the future.

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