Medical Science Journal for Advance Research

Vol.7, No. 1, March 2026
e-ISSN: 2774-4892

Quantitative Analysis of Luxs Gene Expression and Its Role in Pathogenesis of Proteus mirabilis

Fatima Hamza Alzubaidy[1]*

[1]*Al-Furat Al-Awsat Technical University, Kufa Technical Institute, Iraq.*

Corresponding Author Email:* Fatima.alzubaidy@atu.edu.iq

ABSTRACT

Background*: Proteus mirabilis was the most important pathogens that cause infection, these bacteria have many different characteristic lead to become more virulence and pathogenesis such as swarming motility, Biofilm formation lead to antibiotic resistance. The inflammation and tissue necrosis result from ability of bacteria to urease production. Many different type of virulence gene found in P. mirabilis, such as (Rsb A, Lux S and Ure R).In the current study the identification of P.mirabilis by VITEK-2 Compact system,then detect the correlation between some virulence gene with different type of antibiotic and detect the 16SRNA and Lux S gene by Real time PCR. The conclusion of study displays the ability of Proteus infection result from have many different virulence factors, and the correlation with antibiotic was significant as result showed (nitrofurantoin and trimethoprim) highly significant against (lux s, rsb, ure r), but (ampicillin) gave significant only against (lux s, rsb, ure r).*

Keywords: *Proteus mirabilis*, Antibiotic resistance, Virulence gene, Real time PCR.

Article Information

Received: Februry1, 2026; Revised: February 28, 2026; Online: March 2026

INTRODUCTION

P. mirabilis is opportunistic pathogen that effects on immune-compromised persons with different illnesses lead to nosocomial infections and urinary system infection (1).Swarming motility of Proteus mirabilis increase the pathogenicity (2). Rapid surface-based swarm motility of P. mirabilis increase pathogenesis through catheter-associated urinary tract infections (3). On solid agar (1.5% to 2%) ,cells confirm to hyper flagellated from ∼2-μm rods, snake-like "swarmer" cells have numerous chromosomes length ranging from 10 to 80 μm(2). The swarming motility is vital because it is joined to the expression of virulence-associated genes (VAGs) and invade cells ability (4). Biofilm is a structural coating of bacteriological colony adheres to abiotic or biotic surface surrounded inside a exopolysaccharide matrix. Lead to increase bacterial ability to fight host self-protective tools (5). So it renders bacterial colonies antibiotic-resistant, improves resistance gene transfer, improvements efflux pump expression and rise antibiotic metabolism (6).The last cause of destructive and persistent infections and inflammatory procedures is the biofilm (7) . Urease production in p.mirabilis simplify urea hydrolysis and cause infection ,which lead to inflammation and tissue necrosis and finally avoids antibiotics from reaching the bacteria, Proteus mirabilis infection is a long time, problematic to treat, with mortality and morbidity over assessed (8).

Virulence genes

1-Rsb A gene

The rsb A gene control on the swarming motility that codes a sensory, rsb A possibly will function as a protein sensor of ecological conditions (9).RsbA gene stimulated biofilm production as an autoinducer-2 (AI-2), which is believed to be complicated in interspecies communication (10).Through the creation of swarm cells, DNA replicat without septation, lead to development of elongated, polyploidy

https://doi.org/10.46966/msjar.v7i1.382

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cells. The swarming behavior of P. mirabilis activates key virulence factors, making it more virulent relative to aged bacteria within a swarm colony. Most conspicuously, during swarming, virulence factors like urease, ZapA protease, and hemolysin demonstrate increased expression, underscoring the actively changing nature of this phenomenon (11).

2- Lux S

Studies have shown that luxS genes produce autoinducer 2, which is significant for various forms of intercellular communication in bacteria. When luxR coupled to auto inducer the transcription of the luxS structural operon lux CDABF was improved. Next luxS gene formed auto inducer 2 signal, which used to sense intra- and inter-species connections as well as its own cell concentration in a polymicrobial public and plays a vital role in virulence factor regulator (12).

3 -Ure R

Ure R is the molecule that triggers activation of the urease operon. Ure R is a positive transcriptional activator of the ure gene cluster in the presence of urea and is a member of the AraC/XylS class of transcriptional regulators. (13). The ureR controlling gene of P.mirabilis, E. coli and P. stuartii don't have a homolog in urease gene groups of Klebsiella aerogenes, Helicobacter pylori and Bacillus spp.(14) , by scheming an original pair of exact primers according to ure R nucleotide sequence, a ureR-based PCR technique was presented to detect P. mirabilis for the first time.

Certain bacterial urease clusters have extra genes, such as ure R, which regulate urease expression in Enterobacteriaceae family (15).The actual urease of Proteus strains consequences in the urinary tract having an abundance of ammonia that would not be current through a single-species infection by a urease-negative organism such as uropathogenic E. coli (UPEC), so additional species might advantage from the generation of this favorite nitrogen source through a polymicrobial infection (16).Co-infection with Proteus might improve the nitrogen-limited circumstances for UPEC, thereby improving the growth or persistence of this urease-negative organism (17).

Antibiotics Resistance

Antibiotic resistant was a greater global health defect, according to the WHO. Multiple risk factors lead to antibiotic resistance, such as catheter use, co illnesses, and increasing transmission chances. The antibiotic misuses consider a possible source of MDR bacteria (18). Antimicrobial resistance (AMR) is the greatest global public health threats during 21st century (19). AMR demonstrates once microorganisms, including bacteria, fungi, parasites and viruses, suffer evolutionary developments leading to their resistance against antimicrobial medication (20). P. mirabilis is recognized for extensive resistance to kill by antimicrobial, specially polymyxins. The lipopolysaccharide (LPS) modifications, which modify surface charge, and protease, which degrades antimicrobial peptides was the two components of this resistance (21). The antibiotic resistance can be inherited or acquired. Intrinsic resistance is the ability of microorganism to become resistance to antibiotic . The other kind of resistance, which can be either genotypic or phenotypic, was result in a decrease in the quantity of previously effective antibiotics (22). Plasmid mediated resistance found in Proteus mirabilis. Lead to confuse clinical circumstances through therapy and increase community health illness (23). To identify the developing projects of antibiotic resistance, it is essential to recognize the greatest common ESBL enzymes . These results offer beneficial data on ESBL epidemiology and may help medicinal specialists (24).Proteus mirabilis isolates from indwelling catheters displayed high resistance to cefuroxime, ampicillin , amoxicillin-clavulanic acid and ceftazidime with lower

resistance to gentamicin, fluoroquinolones, and nitrofurantoin (25).

MATERIAL AND METHODS

Specimen collection and processing

During study , 300 medical samples of mid-stream urine was collect in sterilized screw-cap container from patients be present at diverse hospitals, laboratories in Al –Najaf Al –Ashraf province /Iraq (Al –Najaf Al –Ashraf Teaching hospital ,Al-Sader teaching hospital and Al-Hakeem hospital). Which were isolated during August 2025 to December 2025, then identified by routine biochemical tests and culturing .

Bacterial isolation

The bacterial isolates directly streaked on MacConkey agar and blood agar plates after existence in sterilized screw-capped test tubes (26), any growing other than proteus mirabilis bacteria are exclusion from study .

Identification of the bacteria

The identification based on morphological, biochemical tests and Vitek2 Compact system for isolate.

Cultivation on Different Culture Media

A loop full of urine samples plated onto the culture media (MacConkey agar,blood agar media) then incubated at 37ºC aerobically for 24 h, additional analytical processing used for plates with positive bacterial culture (27).

Real Time PCR Technique

(RT-PCR) technique was used to intensify lux genes and 16s RNA for finding of Proteus mirabilis in all tested urine samples .The mix was organized to a final volume 20 µl by added all contents stated in table (1).(28).

Then, the combination centrifuged at 10000 rpm/ min, after that PCR tubes transported to thermo cycler. The Real Time -PCR thermo cycler was attuned on SYBR Green PCR.

Table 1: Contents of Real time (RT-PCR)mixture.

Items	Volume (µl)
Real MODTM cyber green SF 2X RT-PCR mix (1x)	10
Forward Primer	1.0
Reverse Primer	1.0
Template DNA	4
DNase/RNase free Water	4
Total Volume	20

Procedure of Gene expression

Initially, the GoTaq 1-Step RT-qPCR system components, primer pairs and RNA templates, were warm up under appropriate conditions (on ice, at room temperature, or at 37°C) and mixed well. A 16.3 µl aliquot of the master mix,which included the primers, $MgCl_2$, RT, and XR-was added to each PCR tube. Then, 3.7 µl of the RNA sample was added into the mix, with gentle vortex useful after each step to ensure good mixing. The prepared plate was then directly transported to the device for the preprogrammed run. After the cycle finished, the resulting data were collected and analyzed.

Ethical Approval

The essential ethical approval gained by spoken agreement from patients. The study was accepted by the commission of publication ethics at College of Science /Alnajaf Province, Iraq. Furthermore, effective agreement was attained from each topics patient before inclusion in the research. For every member, the topics were sentient they able to reject to be involved in the study research without any harmful effects.

Statistical analysis

Collected data, summarized, examined and existing using statistical package for social

sciences (SPSS) version 26 and Microsoft Office, Excel 2010 statistical analysis continued in all groups of study, expressive statistics analyzed by using Chi-square and T test , P. value ≤ 0.01 was considered to be all analyses. Independent sample t-test was used to study alteration in mean between any two groups providing the variable is typically spread. While chi-square test apply to detect the association between any two categorical variables.

RESULT AND DISCUSSION

Identification of *Proteus Mirabilis* from Patients with UTI

The *Proteus mirabilis* was identified by phenotypically , biochemically, obtain pure culture by subculture on media and finally, identification by VITEK-2-Compact system . The culturing on blood agar and MacConkey agar, The swarming phenomenon appeared on blood agar, characteristic odor, and light appearance of bacteria (non-lactose fermenting) with a distinct fishy smell on MacConkey agar showed in figure (2,3).

Figure (2): Growth of *P.mirabilis* on blood agar

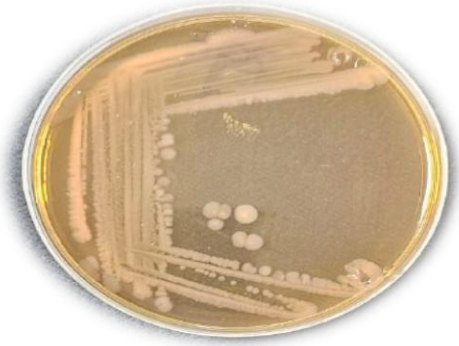

Figure (3): Growth of *Proteus spp*. on MacConkey agar

Widely recognized for its involvement in complicated UTIs, Proteus mirabilis is aprevalent *uropathogen , often secondary only to E.coli , K. pneumoniae* and *E. faecalis* (29). The prevalence rates observed in the current work consistent with previous Iraqi literature. Exactly the isolation rates of 10%were reported by(30) . While 7% to 19% in Duhok and Baghdad study (31, 32 ,33) Also, isolation rate in Baghdad (34) and in Thiqar (35 was at rate (8%) and (6%) respectively. In Indonesia (36) had prospered to isolate *Proteus mirabilis* at rate attainment (7.4%). But in evaluation to all those other research including (37) from Maysan, and (38) from AL Diwanyah city and (39) revealed that the isolation rate was (37%), (32%) and (35.3%) respectively.

Correlation between antibiotic and virulence genes in *P.mirabilis (lux S , Rsb , ure R*

The result of data shown in tables (2,3,4) have a statistical significant correlation between presence of virulence genes and antibiotic resistance .In this study, the antibiotic (nitrofurantoin and trimethoprim) gave highly significant against (*lux s , rsb , ure r*) but (ampicillin) gave significant only against (*lux s , rsb , ure r*).Multidrug resistance in *P. mirabilis* is progressively observed. Public health result from basic resistance with high virulence of bacteria *(*40).

Multidrug resistance in *P. mirabilis* has enlarged by horizontal gene transfer from other bacterial species such as *K. pneumoniae*, with the final formation of a hybrid (mosaic) plasmid that transmits resistance and virulence genes between species (41). (42) Agree with my research, By which the correlation between virulence agents existing in clinical samples of *P. mirabilis*. Also (43) approve my study by noticed *ure*C gene in only (85.7%) of their urease-producing isolates. But , the negative correlation between multidrug resistance and virulence reported by (44). Who found the

non-MDR *P.mirabilis* influenced a greater number of virulence agents associated to MDR. An additional new study in India also exposed an abundant greater prevalence of MDR (85%) amongst UTI isolates of *P. mirabilis* (45). Lower occurrence was described in Europe and Taiwan (46).

Table 2. Association between luxS gene carriage and antibiotic susceptibility profile among Proteus mirabilis isolates.

Antibiotic	luxS-positive isolates				luxS-negative isolates	
	Resistance %,n	Sensitive %, n	Chi-square	P-value	Resistance %, n	Sensitive %, n
Ampicillin	75 (15)	20 (4)	38.32	<0.0001**	5 (1)	0 (0)
Amoxicillin	30 (6)	65 (13)	11.94	0.0006*	0 (0)	5 (1)
Piperacillin	0 (0)	95 (19)	783.9	<0.0001***	0 (0)	5 (1)
Cefuroxime	25 (5)	70 (14)	21.99	<0.0001**	5 (1)	0 (0)
cefuroxime axetil	25 (5)	70 (14)	21.99	<0.0001**	5 (1)	0 (0)
Cefoxitin	20 (4)	75 (15)	38.32	<0.0001**	0 (0)	5 (1)
Cefixim	25 (5)	70 (14)	21.99	<0.0001**	5 (1)	0 (0)
Ceftazidime	30 (6)	65 (13)	11.94	0.0006*	5 (1)	0 (0)
Ceftriaxone	20 (4)	75 (15)	38.32	<0.0001**	5 (1)	0 (0)
Cefepim	20 (4)	75 (15)	38.32	<0.0001**	5 (1)	0 (0)
Cefazolin	40 (8)	55 (11)	1.943	0.1633 NS	0 (0)	5 (1)
Ertapenem	0 (0)	95 (19)	783.9	<0.0001***	0 (0)	5 (1)
Meropenem	0 (0)	95 (19)	783.9	<0.0001***	0 (0)	5 (1)
Amikacin	5 (1)	90 (18)	305.1	<0.0001***	5 (1)	0 (0)
Gentamycin	30 (6)	65 (13)	11.94	0.0006*	0 (0)	5 (1)
ciprofloxacin	20 (4)	75 (15)	38.32	<0.0001**	5 (1)	0 (0)
nitrofurantoin	90 (18)	5 (1)	305.1	<0.0001***	5 (1)	0 (0)
Trimethoprim	85 (17)	10 (2)	125.7	<0.0001***	5 (1)	0 (0)

Note: Values are reproduced exactly from the source file; only layout and presentation were redesigned.

Table 3. Association between rsbA gene carriage and antibiotic susceptibility profile among Proteus mirabilis isolates.

Antibiotic	rsbA-positive isolates				rsbA-negative isolates	
	Resistance %, n	Sensitive %, n	Chi-square	P-value	Resistance %, n	Sensitive %, n
Ampicillin	75 (15)	20 (4)	38.32	<0.0001**	5 (1)	0 (0)
Amoxicillin	35 (7)	60 (12)	5.655	0.0174*	0 (0)	5 (1)
Piperacillin	0 (0)	95 (19)	783.9	<0.0001***	0 (0)	5 (1)
Cefuroxime	25 (5)	70 (14)	21.99	<0.0001**	5 (1)	0 (0)
cefuroxime axetil	25 (5)	70 (14)	21.99	<0.0001**	5 (1)	0 (0)
Cefoxitin	20 (4)	75 (15)	38.32	<0.0001**	0 (0)	5 (1)
Cefixim	20 (4)	75 (15)	38.32	<0.0001**	5 (1)	0 (0)
Ceftazidime	30 (6)	65 (13)	11.94	0.0006*	5 (1)	0 (0)
Ceftriaxone	20 (4)	75 (15)	38.32	<0.0001**	5 (1)	0 (0)
Cefepim	20 (4)	75 (15)	38.32	<0.0001**	5 (1)	0 (0)
Cefazolin	40 (8)	55 (11)	1.943	0.1633 NS	0 (0)	5 (1)
Ertapenem	0 (0)	95 (19)	783.9	<0.0001***	0 (0)	5 (1)
Meropenem	0 (0)	95 (19)	783.9	<0.0001***	0 (0)	5 (1)
Amikacin	5 (1)	90 (18)	305.1	<0.0001***	5 (1)	0 (0)
Gentamycin	30 (6)	65 (13)	11.94	0.0006*	0 (0)	5 (1)
ciprofloxacin	20 (4)	75 (15)	38.32	<0.0001**	5 (1)	0 (0)
nitrofurantoin	90 (18)	5 (1)	305.1	<0.0001***	5 (1)	0 (0)
Trimethoprim	85 (17)	10 (2)	125.7	<0.0001***	5 (1)	0 (0)

Note: Statistical significance symbols were retained exactly as they appear in the manuscript.

Table 4. Association between ureR gene carriage and antibiotic susceptibility profile among Proteus mirabilis isolates.

Antibiotic	ureR-positive isolates				ureR-negative isolates			
	Resistance %, n	Sensitive %, n	Chi-square	P-value	Resistance %, n	Sensitive %, n	Chi-square	P-value
Ampicillin	75 (15)	15 (3)	57.60	<0.0001**	5 (1)	5 (1)	0.0002	0.99 NS
Amoxicillin	35 (7)	55 (11)	3.740	0.0531 NS	0 (0)	10 (2)	67.05	<0.0001**
Piperacillin	0 (0)	90 (18)	630.5	<0.0001***	0 (0)	10 (2)	67.05	<0.0001**
Cefuroxime	25 (5)	65 (13)	17.72	<0.0001**	5 (1)	5 (1)	0.0002	0.99 NS
cefuroxime axetil	25 (5)	65 (13)	17.72	<0.0001**	5 (1)	5 (1)	0.0002	0.99 NS
Cefoxitin	20 (4)	70 (14)	32.14	<0.0001**	0 (0)	10 (2)	67.05	<0.0001**
Cefixim	25 (5)	65 (13)	17.72	<0.0001**	5 (1)	5 (1)	0.0002	0.99 NS
Ceftazidime	30 (6)	60 (12)	9.000	<0.0001**	5 (1)	5 (1)	0.0002	0.99 NS
Ceftriaxone	30 (6)	60 (12)	9.000	<0.0001**	5 (1)	5 (1)	0.0002	0.99 NS
Cefepim	30 (6)	60 (12)	9.000	<0.0001**	5 (1)	5 (1)	0.0002	0.99 NS
Cefazolin	40 (8)	50 (10)	0.9	0.343 NS	0 (0)	10 (2)	67.05	<0.0001**
Ertapenem	0 (0)	90 (18)	630.5	<0.0001***	0 (0)	10 (2)	67.05	<0.0001**
Meropenem	0 (0)	90 (18)	630.5	<0.0001***	0 (0)	10 (2)	67.05	<0.0001**
Amikacin	5 (1)	85 (17)	271.1	<0.0001***	5 (1)	5 (1)	0.0002	0.99 NS
Gentamycin	30 (6)	60 (12)	9.000	<0.0001**	0 (0)	10 (2)	67.05	<0.0001**
Ciprofloxacin	15 (3)	75 (15)	57.60	<0.0001**	10 (2)	0 (0)	67.05	<0.0001**
Nitrofurantoin	85 (17)	5 (1)	271.1	<0.0001***	10 (2)	0 (0)	67.05	<0.0001**
Trimethoprim	80 (16)	10 (2)	110.3	<0.0001***	10 (2)	0 (0)	67.05	<0.0001**

Note: Positive and negative ureR groups both retain the original chi-square and P-value fields reported in the source file.

RT-PCR quantitation of *Lux s* gene

Three samples that gave positive results by RT –PCR detected as in table (5) . three for patient samples and 3 control samples, Extracted RNA was used to detect the gene expressing of *Lux s* by RT-qPCR (Relative gene expression [2ΔCt] approaches, in this technique the appearance level of *Lux s* gene in test sample was higher from control sample as show in Figure (4). Current study displayed that *Lux s* was upregulated and greatly expressed in patients with UTI caused by *Proteus mirabilis* than the control. The appearance of *Lux s* is significant among UTIs due to its participation in numerous features of UTI pathogenesis figure. (4). Moreover, the existing study initiate that the expression of *Lux s* gene improved in UTI patient with *Proteus mirabilis* when associated with the control group, so the appearance gene is increased more than in average fold change when link with control group, as show in Figure (5).

Table 5: Cycle threshold (Ct) values and relative luxS expression determined by RT-qPCR.

Group	Sample	16S rRNA average Ct	luxS average Ct	ΔCt	ΔΔCt	Average fold change
Control	1	19.23	26.58	7.35	0.160	0.895
Control	2	17.24	24.36	7.12	-0.070	1.050
Control	3	17.68	24.78	7.1	-0.090	1.064
High-virulence P. mirabilis	1	20.77	26.38	5.61	-1.580	2.990
High-virulence P. mirabilis	2	18.31	23.75	5.44	-1.750	3.364
High-virulence P. mirabilis	3	15.44	19.98	4.54	-2.650	6.277
Control	**Average**					**1.00**
High-virulence P. mirabilis	**Average**					**3.98**

Note: Fold-change values and group averages were reorganized into a journal-style summary while preserving the source numbers.

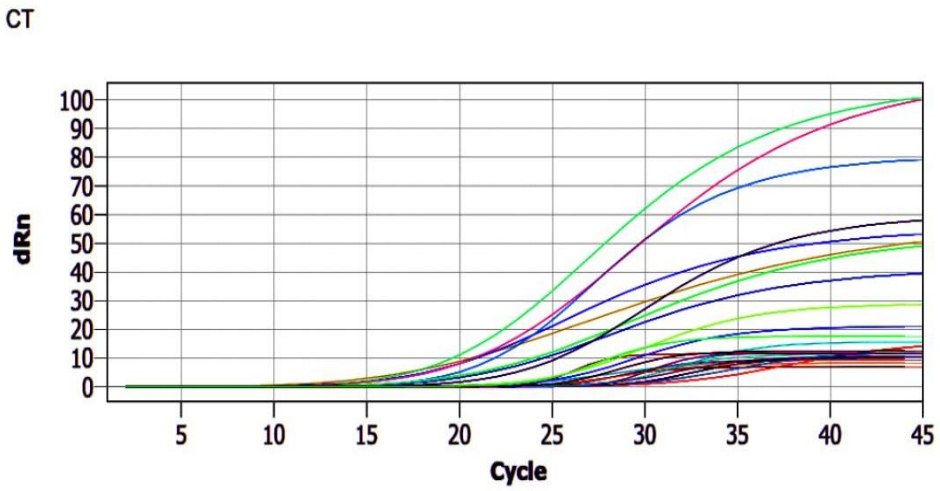

Figure (4): Real time -PCR threshold curves for the amplification of*16s RNA and lux S genes of proteus mirablis* .

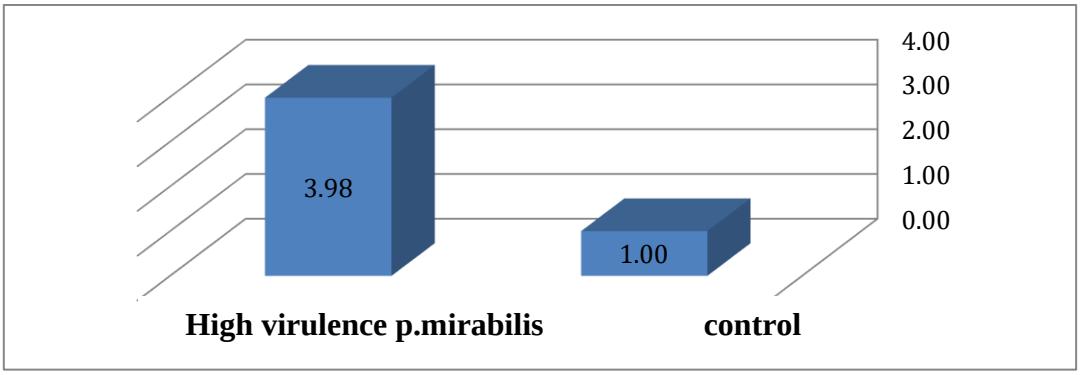

Figure (5): *Lux s* gene expression fold among control and UTI patients versus *16sRNA*.

The levels expression of the aim genes detected by standardizing the cycle threshold (Ct) values against the 16S rRNA reference gene. After that, calculate The comparative mRNA expression by the 2^{-\Delta\Delta Ct} way, accounting for PCR efficacy and mean crossing point deviations among the controls and samples. Detection the level of gene appearance in ordinary tissue is essential for the investigation and clarification of outcomes of gene. By the RT reverse transcription-PCR method, which allows to notice the amplification degree throughout the procedure, calculation of the quantity of gene transcription is accurate and fast (47) Current result approve by (48) which detect the *LuxS* is a transcription of structural operon lux CDABF that is accountable for manufacture of auto inducer 2 (AI-2) which mainly contributes in cell to cell signing in bacteria. After *luxS* is created, AI-2 cast's signs that are used to sense inter species communication and its own cell density in a multi microbial community that has essential part in the virulence factors regulation (49).

CONCLUSION

1- The proteus mirabilis was the important pathogen can cause infection.

2- The occurrence of virulence genes such as *luxS* ,*ureR* and *RbsA* lead to increase pathogenic ability.

RECOMMENDATION

1- Make more research on the antibiotic have high resistance rate such as Nitrofurantoin and Trimethoprim/ Sulfamethoxazole .

2- Study the role of "quorum-sensing inhibitors", such as directing the *luxS* gene, to interrupt bacterial communication.

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