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Impact of prodigiosin on staphylococcus aureus isolated from acne vulgaris

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***Abstract*---**Acne is a skin disorder characterized by clogged hair follicles and chronic inflammation of the pilosebaceous follicles. A total of one hundred and five acne swabs were collected from patients with acne vulgaris infection at Baghdad's hospitals. For primary identification, 54 (45%) samples had a positive S. aureus culture on Mannitol salt agar (MSA) for 24 hours at 37°C. In addition, four pre-isolated also identified S. marcescens (pigment producers) which were identified by vitek-2 technique were taken for prodigiosin extraction, mineral salt broth with peptone (0.5 percent) was utilized, followed by pigment extraction, partial purification, also pigment measurement by spectrophotometer. Furthermore, using a microtiter plate assay, the bacterial ability to form biofilms was assessed for 20 S. aureus isolates (multidrug resistant isolates). The results revealed that only 8 strong isolates were biofilm producers, while 5 in addition 7 isolates were moderate also weak biofilm producers. The minimal inhibitory concentration of tetracycline also prodigiosin generated by isolated S. marcescens were determined using the broth microdilution technique for S. aureus isolates (S7 also S8). From overnight cultures of S. aureus (S7 also S8), DNA was effectively extracted. The IcaA, IcaD, FnbpA, also Geh genes were amplified, then the results were confirmed using gel electrophoresis. The IcaA(151bp), IcaD (483), FnbpA (191), also Geh (473) genes were discovered in the study. RNA was isolated from the chosen isolates (S7), which was then treated with prodigiosin (62.5 g/ml) also tetracycline (31.25 g/ml) at their respective sub-MICs. Under the impact of sub-MIC of prodigiosin, quantitative real time PCR revealed a decrease in IcaA, IcaD, Geh, also a modest rise in FnbpA gene expression, while all genes exhibited an increasing in gene expression under the effect of sub-MIC of tetracycline.

***Keywords*---**staphylococcus aureus, prodigiosin, IcaA gene, lipase, biofilm.

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Introduction

Most people between the ages of 12 & 25 are affected with Acne, which is also known as Acne vulgaris., Around 85 percent of persons between the ages of 15 & 24 in the United States are affected by acne. (1) Most often, skin & soft tissue infections are caused by Staphylococcus aureus and Streptococcus pyogenes, the 2 most prevalent bacteria (2). Normal skin flora causes many of these illnesses, & the kind of bacteria & the location where it is inoculated dictate the shape & severity of the infection (3). If the infection is not treated, it can spread to the surrounding tissues, and the tiny lesion grows into a much larger, swollen, cutaneous, inflamed, localized lesion that is walled off by fibrin deposition by the tissue, and the walling off is to prevent the Staphylococcal infection from spreading further (4). So complicated is acne's impact on sufferers' self-esteem & sociability that it may create severe issues. (5). As a result, it has a huge impact on the health-care system (6).

Acne is a multifaceted disease, including both internal & environmental factors, like increased sebum production, ductal hyper cornification, and changes in the microbial ecology, notably colonization with Propionibacterium acnes (P. acnes) (7). One of the most prevalent microbes in the human body is Staphylococcus aureus, a Gram-positive round-shaped bacterium from the Firmicutes genus (8) S. aureus was found to be present in 43 percent of acne patients in cross-sectional research (9). Acne pus is often contaminated with the bacteria S. aureus (10). Antibiotics have played a significant role in the treatment of acne for many years. Antibiotic-resistant bacteria have unfortunately grown in number as a consequence of widespread usage of antibiotics (11). When it comes to prescribing antibiotics to patients, doctors have had to adapt to altering drug sensitivity patterns and the rise of more aggressive bacteria, like MRSA, that are more difficult to treat (12). Many bacterial species produce prodigiosin as a secondary metabolite (13). Temperature, incubation time, pH, nutrient supply, and quorum sensing all have a role in this compound's antibacterial, antiprotozoal, antitumor, and anti-inflammatory properties (14). When compared to previous findings, it has an antibacterial impact on P. aeruginosa, E. coli, and Staphylococcus aureus (15). The aim of this study is to investigate the role of prodigiosin effect on biofilm (polysaccharide adhesion genes) and lipase gene involved in the pathogenicity and persistency of the S. aureus by the following steps:

1. Extraction of prodigiosin pigment and study it ̓s antibacterial and antibiofilm effect against S. aureus isolates
2. Study the effect of prodigiosin and antibiotic on the expression of biofilm gene (IcaA, IcaD, FnbpA) and lipase gene (Geh)

Methods

Collection of *Staphylococcus aureus* isolate

One hundred five acne swab specimens were collected between August and November of 2021. These samples were taken at Al-Yarmouk Teaching Hospital in Baghdad, Al-Kindy Hospital, & Medical Clinics in Baghdad utilizing sterile transport medium (BIOZEK medical) swabs. After that, the samples were grown

on Mannitol salt agar, a selective medium for Staphylococcus spp. A 24-hour incubation period at 37°C in aerobic conditions was then carried out on the samples. Microorganisms isolated on mannitol salt agar and kept at 4°C were transferred to nutrient-agar plates then subculture on slants (16).

Identification of Bacteria

Cultural Characteristics

To be a selective medium, MSA has a high salt content of 7.5%, which only allows staphylococci to grow while limiting the growth of other bacteria. Mannitol has also been employed in this medium as a differential agent. In order to see whether S. aureus can ferment this sugar into acidic byproducts, a yellow halo appears around the colonies, suggesting a decrease in pH. (17).

Microscopic Features

Gram staining was employed on questionable colonies to determine typical bacterial morphology under a light microscope.

Identification of bacterial isolate by Vitek -2 system

The Vitek-2 compact device was utilized to identify the bacteria isolate on nutritional agar. This method is utilized to identify and confirm the presence of *S. aureus* bacteria in bacterial isolate.

Screening for prodigiosin production *by Serratia marcescens* isolates

To select highest yielding *Serratia marcescens* isolate was identified by identification and evaluated for prodigiosin production in liquid culture, as mentioned in the following sections:

Inoculum Preparation

Serratia marcescens isolate were inoculated into a 150ml Erlenmeyer flask containing 20ml of Brain heart broth utilizing a few loopfuls of *S. marcescens* growth from an overnight culture on nutrient agar; this culture was cultivated in an incubator at 30 degrees Celsius.

Method of cultivation

An autoclave of 15 minutes at 121 C with 50 ml of minerals salt broth medium was utilized to create Erlenmeyer flasks (250 ml). A *Serratia* isolate inoculum of 1 ml (2 percent inoculum) was added to each flask. Incubation at 30 degrees Celsius and 200 rotations per minute on an orbital shaker for 48 hours After incubation, samples were collected for prodigiosin analysis.

The synthesis of prodigiosin pigment & its quantification utilizing UV-Vis spectroscopy

the red pigment was measured by measuring absorbance at 530 nm utilizing a twin beam UV-Visible spectrophotometer (18).

Prodigiosin pigment partial purification

Prodigiosin was largely purified by Chen and colleagues with modifications (19).

Antibiotic Resistance

This step was completed utilizing the Vitek system, and it included running a test on bacteria utilizing around 22 antibiotics.

Biofilm formation assay

investigated the production of biofilms by antibiotic-resistant *S. aureus* isolate**.** (20)

Lipase-producing bacteria screening and selection

Following the manufacturer's instructions to make tributyrin agar base (Himedia).
. Samples were grown on TAB and incubated at 37°C for 24 hours.
. A positive outcome for lipase activity is the creation of a clean zone surrounding the bacterial growth in a petri dish, which shows lipid hydrolysis (decomposition).

Minimum inhibitory concentrations of prodigiosin pigment & tetracycline were determined.

The following procedure was utilized utilizing 96-well micro-titer plates: (21).

1. prodigiosin and tetracycline dilutions were made utilizing serial dilutions of concentrations (1000,500,250,125,62.5,31.25,15,625,7.8125) µg/ml.
2. Except for the negative control wells, all wells were infected with 10µ l of bacterial solution equivalent to McFarland standard NO. 0.5 (1.5108 CFU/ml).
3. The microtiter plate was incubated for 24 hours at 37°C.
4. The MIC for each bacterial isolate was defined as the lowest concentration at which no observable growth was observed.

Molecular Analysis

Genomic DNA Extraction

ABIO pure Extraction technique was utilized to separate genomic DNA from bacterial growth .Conventional polymerase chain reaction (PCR) was performed to amplify fragments of genes under study, to detect biofilm and lipase formation genes in S. aureus, The extracted DNA, primers(table1) Go Taq®Green Master Mix

Promega (USA), were Thawed at 4c, vortexed to ensure that the contents are homogeneous, A total volume of PCR mixture stated in table2

Table 1: Primers sequences

Gene	Primer	Sequence 5-3
IcaA	F	GAGGTAAAGCCAACGCACTC
IcaA	R	-CCTGTAACCGCACCAAGTTT
IcaD	F	GAACCGCTTGCCATGTGTTG-
IcaD	R	GCTTGACCATGTTGCGTAACC
FnbA	F	GATACAAACCCAGGTGGTGG-
FnbA	R	TGTGCTTGACCATGCTCTTC
Geh	F	GCACAAGCCTCGG
Geh	R	GACGGGGGTGTAG
16Sr	F	TGTCGTGAGATGTTGGG
16Sr	R	CGATTCCAGCTTCATGT

Table 2: The components of master mix in pcr

Master mix Component	**Volume**	**Final concentration**
		1 sample
Master Mix	10 µl	1X
Forward primer	1 µl	1 µM
Reverse primer	1 µl	1 µM
DNA template	2ng/µl	3ng/µl
Nuclease free dH2O	5 µl	
Final volume	**20µl**	

DNA was amplified in a thermo-cycler PCR device utilizing PCR reaction tubes under the conditions listed in table 3. Gradient PCR was utilized to improve the PCR program's temperature and time.

Table 3: Pcr program

Steps	°C	m:s	Cycle
Initial Denaturation	95	05:00	1
Denaturation	95	00:30	30
Annealing	57.5,60,5 5	00:30	
Extension	72	01:00	
Final Extension	72	07:00	1
Hold	10	10:00	

Gel Electrophoresis

Following PCR amplification, agarose gel electrophoresis was utilized to confirm amplification. The extracted DNA criteria were entirely trustworthy on PCR. 1X TAE buffer, Ethidium bromide (10mg/ml), DNA ladder marker The agarose was made (22), A flask was filled with 100 cc of 1X TAE. The buffer received 1.5 gm (1.5 percent) agarose. In the microwave, the solution was heated to boiling until all of the gel particles were dissolved. The agarose was treated with one liter of ethidium bromide (10mg/ml). The agarose was well mixed and no bubbles formed as a result of the stirring. The solution was allowed to cool to 50-60 degrees Celsius.

RNA Purification protocol procedure

RNA was isolated from sample due to the protocol of TRIzol™ Reagent

Quantitative real-time polymerase chain reaction (qRT-PCR

The RT-PCR reaction should be carried out in a nuclease-free environment. Preparation of RNA sample, as well as the assembling of a reaction mixture, PCR, and analysis of the reaction should be performed in separate areas using GoTaq® 1-Step RT-qPCR system

Result & discussion

Samples Collection, Isolation, Identification, Cultural Characteristics

Al-Yarmouk teaching Hospital in Baghdad, Al-Kandi Hospital, & Medical Clinics in Baghdad all participated in the study of acne swabs obtained from individuals with acne vulgaris. MSA is an excellent culture medium for detecting *Staphylococcus* bacteria, the suspected isolate of *S. aureus* was capable of fermenting mannitol which then creating yellow color owing to acid generation, these findings are comparable to that done by the same method utilized (23). Initially, 54 (51% of the samples tested positive for *S. aureus*) in addition 35 (33% of the samples tested positive for *S. epidermis*) samples were identified utilizing Mannitol salt agar (MSA) for 24 hours at 37°C;

Vitek -2 compact system for bacterial identification

The Vitek -2 compact device was utilized to identify the 105 isolates which were cultivated on mannitol. The findings showed that 54 (51% of the samples) were *S. aureus,* 35 (33% of the samples) were *S. epidermis,* 16 (15% of the samples) were *S. werrneri,*

Screening for prodigiosin production by Serratia marcescens isolates

S1, S2, S3, and S4 were the four red pigment-producing isolates. To ensure reproducibility, all isolate were cultivated under similar circumstances, including the same inoculum size, pH, cell count, incubation period, also shaking speed. The screening was carried out in a mineral salt medium containing peptone (0.5

percent). (24) discovered pigment production when the temperature was elevated to 27°C.

Determination of prodigiosin pigment in UV-visible by spectroscopy

A UV-wavelength scan was utilized to assess the absorbance value of prodigiosin, & the results showed that it had an OD533 UV visible absorbance value. At 530 nm, (25) the Prodigiosin pigment displays a distinctive absorption. Prodigiosin improved from *Serratia* spp. KH-95 showed a maximum absorption spectrum of 535 nm, as illustrated in Figure (1).

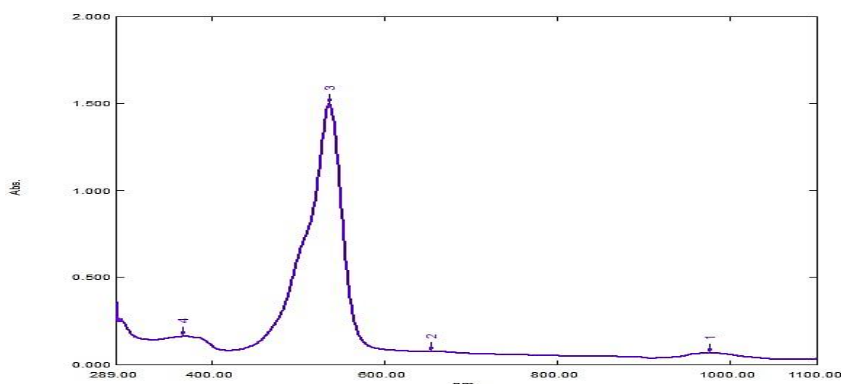

Figure (1): UV prodigiosin pigment -Visible near OD533

Partial purification of prodigiosin

Only the cell pellets were utilized. Prodigiosin's dark red powder was removed and placed in a dark glass plate on the refrigerator owing to its reduced stability in the light (26)

Antibiotic susceptibility test of S. aureus

Amoxicillin, Ampicillin, Imipenem, Amoxicillin Clavulanic acid and Oxacillin were among the 22 antibiotics tested for susceptibility by 54 isolates. Rifampicin and Tobramycin were also tested. Erythromycin, Linezolid, Teicoplanin, Tetracycline, Tigecycline, Nitrofurantoin and Trimethoprim / Sulfamethoxazole, Moxifloxacin, vancomycin There were 54 (100 percent) isolate that were resistant to Amoxicillin, Benzylpenicillin and Imipenem; Ampicillin Clavulanic Acid; Oxacillin Meropenem; Fusidic Acid; Rifampicin; and 50 (90 percent) isolate that were sensitive to Gentamicin, Tobramycin, Tetracycline, Erythromycin, tetracycline, Other antibiotics, on the other hand, have emerged as the most effective treatment, as shown by their 100% maximal sensitivity. Figure 2 reveals this information.

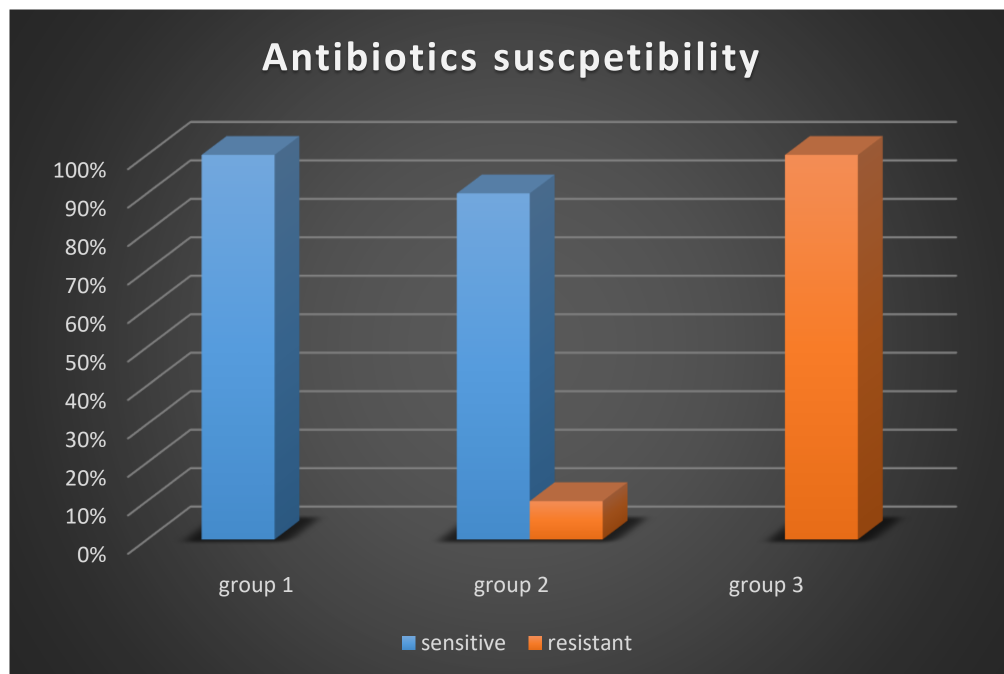

Figure2: The percentage of antibiotics susceptibility against S. aureus

Group1(Amoxicillin, Benzylpenicillin and Imipenem; Ampicillin Clavulanic Acid; Oxacillin Meropenem; Fusidic Acid; Rifampicin
Group2(Gentamicin, Tobramycin, Tetracycline, Erythromycin, tetracycline and Amoxicillin, Benzylpenicillin and Imipenem; Ampicillin Clavulanic Acid; Oxacillin Meropenem; Fusidic Acid; Rifampicin
Group3(Linezolid, Teicoplanin, Tigecycline, Nitrofurantoin, Trimethoprim / Sulfamethoxazole, Moxifloxacin, vancomycin)

Biofilm assay

Many unique methodologies have lately been developed or altered for biofilm research, leading to more thorough knowledge on biofilm physiology, structure, and composition. The production of biofilms is considered an indication that a pathogen is virulent, 96-well polystyrene microtiter plates were employed as a standard test for biofilm biomass exposure in this study to evaluate the ability of S. *Sarena* biofilm-producing isolate (27) It is more sensitive than other methods, therefore crystal violet is utilized to stain just the cells and the slimy components are washed away by subsequent washing processes (28).

To determine the thickness of the biofilm, we utilized a microplate reader to detect absorbance at 630nm. This resulted in a correlation between absorbance values and the biofilm thickness on the surface of microtiter wells. The results were categorized into three groups (weak, moderate, and strong) based on the constraints mentioned in Table (4).

Table (4): Biofilm forming capacity of S. aureus isolate

Strong biofilm isolates	Mean OD630	Moderate biofilm isolates	Mean OD630	Weak biofilm isolates	Mean OD630
S7	1.731	**S6**	0.160	**S2**	0.083
S8	2.079	**S10**	0.149	**S3**	0.077
S9	1.049	**S14**	0.207	**S4**	0.080
S11	0.289	**S15**	0.181	**S5**	0.090
S17	0.469	**S1**	0.193	**S12**	0.076
S18	0.896			**S13**	0.098
S10	0.29			**S16**	0.088
S19	0.891	**C**	0.06		

S: S. aureus; C: control; cut off value 0.05324924

The current study revealed that 8 (16.70%) of *S. aureus* isolate were strong biofilm producers, whereas 5 (60%) and 7 (23.30%) were moderate and weak biofilm producers, respectively, utilizing the characteristics listed in Table 4. Different isolate' capacity to process biofilm, variances in the main number of cells that flourished in adhesion, and differences in the quality and amount of quorum sensing, signaling molecules (autoinducer) generated by each isolate might all contribute to changes in biofilm thickness (29)

Lipase activity

Twenty S. aureus isolate were chosen for lipase activity testing because they were more antibiotic resistant. Lipase synthesis is considered a virulence marker .The ability of *Sarena* lipase-producing isolate was assessed in this investigation utilizing pre-sterilized petri dishes, which were utilized as controls .*S. aureus* isolated were grown on tributyrin agar base (TAB) and incubated for 24 hours at 37 degrees Celsius since this technique is more sensitive than the others .The creation of a clear zone surrounding the bacterial growth, which symbolizes lipid hydrolysis (decomposition) within a petri dish, is a positive result for lipase activity, and all of the isolate were positive. Figure (3)

Figure (3): Lipase formation by S. aureus isolate

S. aureus and *S. epidermidis* secrete lipase enzyme and the positive result is the appearance of a clear zone around the bacterial growth and the study was on the *S. aureus* and *S. epidermidis* bacteria isolated from human facial sebaceous skin (30).

Minimal Inhibitory Concentration Test of (tetracycline, prodigiosin,) for S. aureus isolate

Two *S. aureus* isolate (S7, S8) were evaluated utilizing the Microdilution technique indicated by the clinical trial and laboratory values discovered (31) recommendations to control the minimal inhibitory concentration for tetracycline, prodigiosin against *S. aureus*. The MICs of tetracycline were (62,5µ g/ml) for (S7) and (15.6µ g/ml) for (S8), due to the table (5).

Table (5): Shows MICs of (tetracycline and prodigiosin,) against 2 isolate of S. aureus (S7 and S8)

S. aureus isolate	Tetracycline µ g/ml	prodigiosin µ g/ml
S7	62,5	125
S8	15.6	500

Numerous antibiotic MICs, including tetracycline, where the range was (0.06-8 g /ml) MIC was 4 g /ml for tetracycline. (32) Tetracycline resistance raised from 18 to 25% of isolate between 1994 and 2001 (33).

Molecular Analysis

DNA Extraction

Overnight, DNA from two *S. aureus* isolates (S7, S8) was successfully extracted. the concentration was verified by bio drop to be (10-20) ng/µL, also the intact DNA bands were confirmed using gel electrophoresis.

Detection of genes in S. aureus isolate

PCR was conducted for two isolates (S8 also S7), using the, (*IcaA, IcaD, FnbpA, Geh)* primer to amplify the constitutional gene (*IcaA*, *IcaD, FnbpA, Geh*) also bands were confirmed with gel electrophoresis. The results revealed that (IcaA *IcaD, FnbpA, Geh*) genes (151bp,483bp,191bp,473bp) was detected in two S. aureus isolates (S8 also S7). As shown in figures (4), (5), (6), (7)

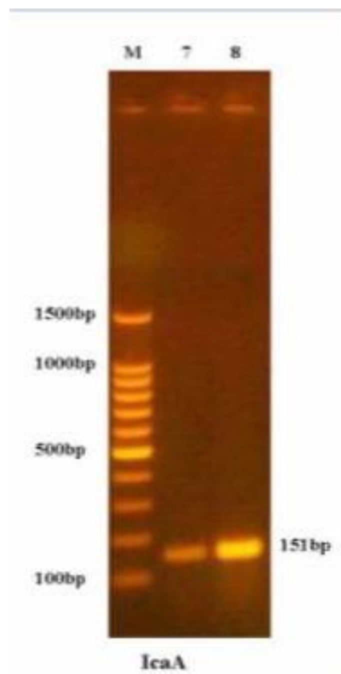

Figure (4): The results of S. aureus isolate' IcaA gene amplification (S7 and S8) were fractionated on 1.5 percent agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker

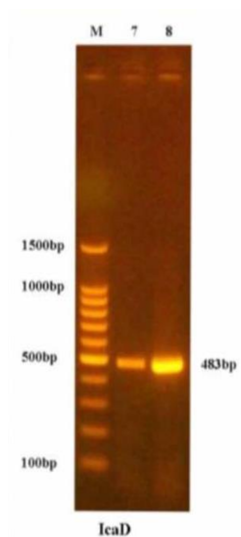

Figure (5): The results of S. aureus isolate' IcaD gene amplification (S7,S8) were fractionated on 1.5 percent agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker

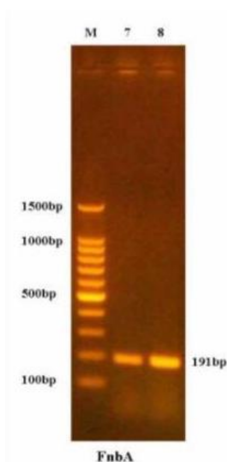

Figure (6): S. aureus isolate S7 and S8 had their FnbpA gene amplification results stained with Eth.Br. M: a 100-base ladder marker

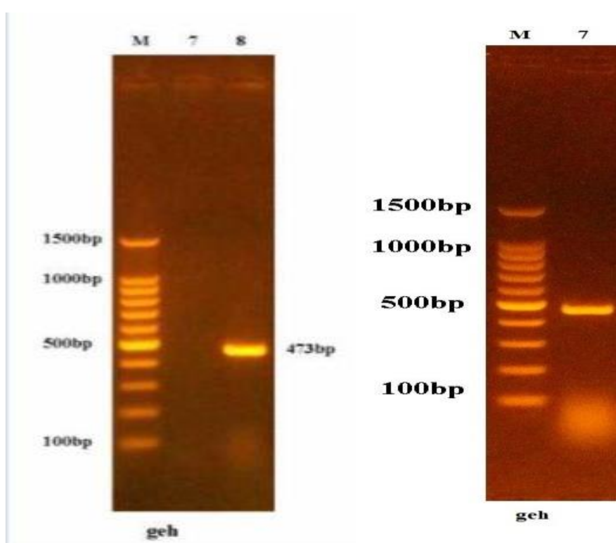

Figure (7): Results of Geh gene amplification of S. aureus isolates (S7, S8) were fractionated on 1.5% agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker.

Real Time-Qpcr

RNA Extraction

RNA was extracted from the selected *S. aurues* isolate (S7) (which was more sensitive to prodigiosin and tetracycline than S8 isolate) which grown in nutrient broth as a control in addition to two treatments in which the isolate was treated with sub-MIC of prodigiosin (62.5 µg/ml) and sub-MIC of tetracycline (31.25 µg/ml). Total RNA of samples was extracted by using TRIzol reagent, and the concentration was ranged between (10 to 20 ng/µl.).

Effect of (prodigiosin and tetracycline) on the expression of S. aureus isolate (S7) genes (IcaA, IcaD, Geh and FnbpA)

quantitative real-time PCR was performed using SYBR green in a one-step RT-PCR technique, in order to determine the effect of sub-MIC prodigiosin and tetracycline on the expression of the *IcaA, IcaD, Geh, FnbpA* gene in *S. aureus* isolates(S7), livak equation 2-ΔΔct was used, which is a simple method for measuring relative changes in gene expression in real-time quantitative PCR experiments (34).

The effect of sub-MIC of prodigiosin showed a decrease in the expression level (down regulation) of the *IcaA, IcaD, Geh* and slight increasing of *FnbpA*, while the result of sub-MIC of tetracycline showed an increase in the expression level(up-regulation) of all genes as shown in table (5) and (6)

Table (5) fold change of (IcaA, IcaD, Geh, FnbpA) genes in S. aureus in presence of sub-MIC of prodigiosin (62.5 µg/ml)

sample	16S	*Fnbp*	DCT	DDCT	Folding
C7	12.7	16.8	4.1	0.0	1.0
P7	15.3	19.3	4.0	-0.1	1.1
sample	16S	*IcaA*	DCT	DDCT	Folding
C7	12.7	19.5	6.8	0.0	1.0
P7	15.3	23.1	7.8	1.0	0.5
sample	16S	*IcaD*	DCT	DDCT	Folding
C7	12.7	19.3	6.6	0.0	1.0
P7	15.3	233	8.0	1.4	0.4
sample	16S	*Geh*	DCT	DDCT	Folding
C7	12.7	22.3	9.6	0.0	1.0
P7	15.3	25.2	9.9	0.4	0.81

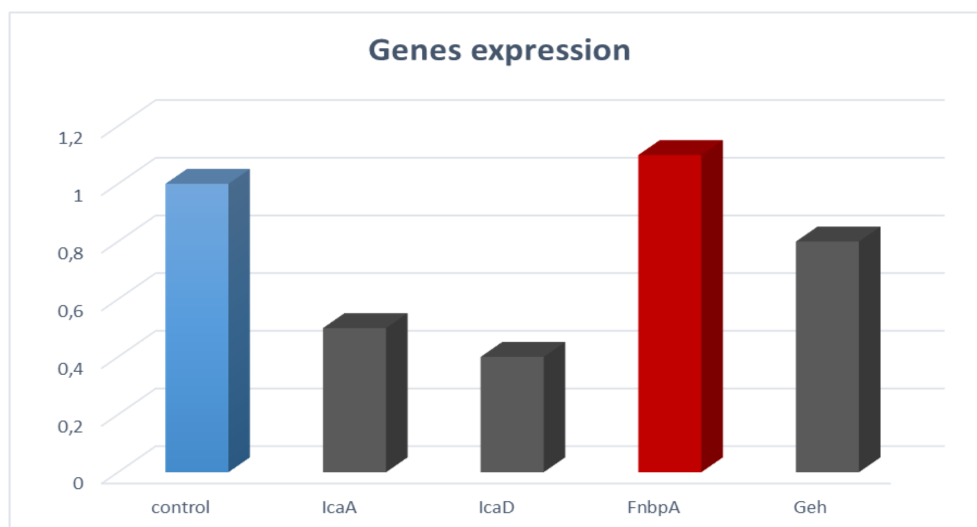

Figure (8) fold change of (IcaA, IcaD, Geh, FnbpA) genes in S. aureus in presence of sub-MIC of prodigiosin (62.5µg/ml)

Table (6) fold change of (IcaA, IcaD, Geh, FnbpA) genes in S. aureus in presence of sub-MIC of tetracycline (31.25µg/ml)

sample	16s	*FnbpA*	DCT	DDCT	Folding
C7	23.69	19.44	-4.25	0.00	1.00
T7	25.80	17.29	-8.51	-4.26	19.17
sample	16s	*IcaA*	DCT	DDCT	Folding
C7	23.69	28.34	4.65	0.00	1.00
T7	25.80	25.93	0.12	-4.53	23.12
sample	16s	*IcaD*	DCT	DDCT	Folding
C7	23.69	29.11	5.42	0.00	1.00
T7	25.80	27.56	1.75	-3.67	12.71
sample	16s	*Geh*	DCT	DDCT	Folding
C7	23.69	27.06	3.37	0.00	1.00
T7	25.80	25.17	-0.64	-4.01	16.08

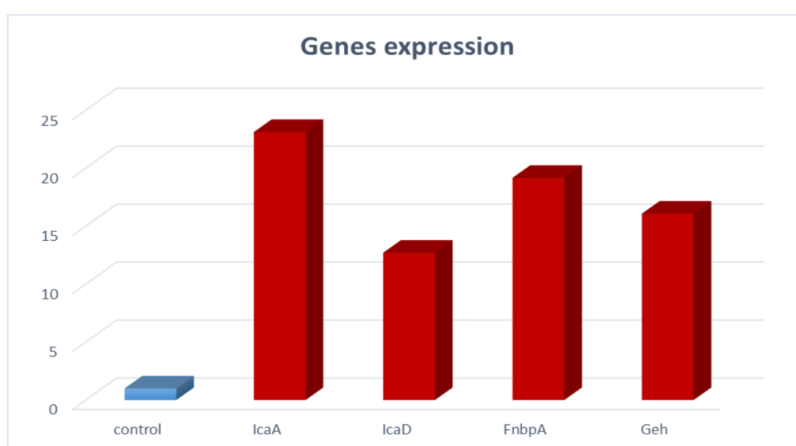

Figure (9) fold change of (IcaA, IcaD, Geh, FnbpA) genes in S. aureus in presence of sub-MIC of tetracycline (31.25 µg/ml)

The findings of this study's qRT-PCR indicated that the expression of the (*IcaA*) gene was (0.5) in the presence of prodigiosin at a concentration of sub-MIC (62.5), while the expression of the (*IcaD*) gene was (0.4), and the expression of the *Geh* gene was (0.8), while the was the *Fnbp* (1.1). As for the sub-MIC of tetracycline (31,25), it exhibited an insight to rise in the expression level for *IcaA,* which was (23.12), *IcaD*, which was (12.71), and *Geh,* which was (16.08). *Fnbp* was (19.17). In keeping with the findings of earlier research (35), found that subinhibitory concentrations of tetracycline and the semisynthetic streptogramin antibiotic quinupristin-dalfopristin enhanced ica expression by a factor of 9 to 11-fold. On the other hand, penicillin, oxacillin, chloramphenicol, clindamycin, gentamicin, ofloxacin, vancomycin In subinhibitory doses of erythromycin, there was a moderate increase in the expression of *ica,* which was measured as a 2.5-fold increase.

Certain antibiotics' sub-inhibitory concentrations (sub-MICs) have the ability to alter the staphylococcal biofilm expression, leading to an increase or induction of

biofilm development (36) antibiotic concentrations can influence the expression of important bacterial virulence factors such as adhesins or toxins (35). When added to culture medium at concentrations below the minimum inhibitory concentration (MIC), antibiotics have the potential to alter bacterial cellular processes (37). Tetracyclines specifically inhibit the 30S ribosomal subunit, hindering the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. When this process halts, a cell can no longer maintain proper functioning and will be unable to grow or further replicate (38).

Prodigiosin due to its hydrophobic properties is proposed to influence the function of biological membranes, Prodigiosin can enter into the cytoplasm of bacterial cells and, at higher concentrations, affects the membrane integrity by depletion of lipopolysaccharide layer of *E. coli* and *B. cereus* (39).The antibacterial activity of prodigiosin (PG) is the result of their ability to pass through the cellular membrane and damaging it and their capacity for inhibiting target enzymes involved in DNA replication, such as topoisomerase IV and DNA gyrase, which inhibit the cell growth (40).

Conclusions

There is a necessity of using other antibiotics other than tetracycline as a drug of choice for *S. aureus* infecting acne, and Prodigiosin is better than tetracycline against *S. aureus*

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