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Comparison study between *gallic acid* and *curcumin* extracts on the efflux pump inhibition of clinically isolated *staphylococcus aureus*

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ABSTRACT

Background. The increasing incidence of multidrug-resistant bacteria has forced the development of novel techniques to improve antibiotic potency. Bacterial efflux pumps are essential in this resistance as they actively expel detrimental antimicrobial substances from the cell. **Aim.** This study aimed to examine the inhibitory effects of two plant extracts, gallic acid and curcumin, on the efflux pump activity of clinically isolated *Staphylococcus aureus*. **Methods.** The efficacy of different concentrations (100, 200, 400, 800, and 1600 mg/ml) of gallic acid and curcumin extracts was assessed. Cartwheel assays were conducted to evaluate efflux activity before and after treatment, and real-time PCR (qRT-PCR) was utilized to confirm the genetic impact of these extracts on the *norA* gene encoding the efflux pumps. **Results.** The findings indicated substantial decreases in resistance levels and significant inhibition of efflux pump activity, with 400 mg/ml identified as the lowest effective concentration. While curcumin demonstrated a more potent zone of inhibition in growth assays, real-time PCR results revealed that gallic acid was significantly more effective than curcumin in downregulating and inhibiting the expression of the *norA* gene across the tested concentrations (fold change of 0.60 vs 0.66, respectively). **Conclusion.** Both gallic acid and curcumin possess significant potential as plant-derived efflux pump inhibitors (EPIs). However, gallic acid demonstrates superior efficacy in downregulating *norA* gene expression, underscoring its potential as a more effective agent in modifying gene-mediated resistance in multidrug-resistant *Staphylococcus aureus* strains.

Keywords: gallic acid, curcumin, Antibiotic resistance, *norA* gene, Plant extracts.

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INTRODUCTION

Staphylococcus aureus, a prominent human pathogen, this bacteria is present in the normal skin microbiota of animals and humans (1) It is recognized for its capacity to acquire resistance to several antibiotics, primarily attributable to efflux pumps. These membrane proteins actively expel various antibiotic drugs from the bacterial cell, consequently reducing treatment efficiency (2) (3) (4) .

The major facilitator superfamily (MFS) contains significant efflux pump transporters characteristic of Gram-positive bacteria, the intrinsic efflux gene systems are the most significant among these pumps. The chromosomal genes norA , norB, and norC under *s.aureus* encode efflux pumps (5, 6) .

Substances that diminish resistance and inhibit efflux pumps in bacteria are known as efflux pump inhibitors (EPIs). Recent research has focused on the ability of phytochemicals to enhance the effectiveness of antibiotics against resistant bacteria by inhibiting efflux pumps(7).

Plant-derived inhibitors proficiently obstruct various kinds of efflux pumps. Plant EPIs seek to obstruct efflux pump action in bacterial cells, hence augmenting the effectiveness of antibiotics (8).

A possible strategy to address this resistance involves utilizing plant secondary metabolites, which are bioactive molecules generated by plants

that frequently demonstrate antibacterial capabilities, Plant secondary metabolites, including flavonoids, tannins, alkaloids, terpenoids, and phenolic acids, have attracted interest for their capacity to block bacterial efflux pumps (9) .

There are many examples of plant secondary metabolites that act as EPIs. Curcumin is the main component of Curcuma longa (L) and other subspecies' rhizomes (10). It is turmeric's active ingredient. Its bioactivity has led to extensive research on curcumin (11). Antibiotics against *S. aureus* are more efficacious and less virulent with curcumin in animal pathogenicity models.(10)

Potential efflux pump effects of curcumin have been explored. Curcumin may influence efflux pumps, the activity of which can improve antibiotic efficacy against resistant bacteria. According to this study, curcumin help to fight antibiotic resistance by attacking bacteria's efflux pumps. The bacterial cell membrane could be damaged by curcumin, which may impact efflux pumps (11) .

Pomegranates contain gallic acid, which may be healthy. Antimicrobial gallic acid kills many bacteria, fungi, and viruses (12) .

As an efflux pump inhibitor, gallic acid has been explored. Gallic acid may inhibit efflux pumps, boosting antibiotic intracellular abundance and antibacterial action. Bacteria become more sensitive to antibiotics when gallic acid blocks efflux pumps. These properties of gallic acid could help fight antibiotic-resistant bacterial infections, which is global health issue (13) .

MATIRIALS AND METHODS

Collection of bacterial samples

This investigation involved the collection of 105 samples, including burns, wounds, blood, pus, and ear swabs, from the Public Health Laboratory, Medical City Teaching Hospital, AL-Immamain Alkadhimiyan Teaching Hospital, Alyarmook, and the Central Teaching Hospital of Pediatrics in Baghdad. Sample collection occurred from October 17, 2023, to February 1, 2024.

Identification of *S.aureus* isolates

Isolates identified as gram-positive bacteria were evaluated using Gram stain, catalase, oxidase, and coagulase assays.

Antibiotics susceptibility

Disk diffusion was used to determine antibiotic susceptibility according to Clinical and Laboratory Standards Institute (CLSI) criteria. Several bacterial colonies were transferred to a test tube with 5 ml of brain heart infusion broth and cultured at 37°C for 4–6 hours until turbidity was noticed using a disposable wire loop. Turbidity was measured at 1.5×10^8 cells/ml compared to the McFarland standard (No. 0.5) (7). The antibiotics used in this investigation are in Table 1.

Table 1. The antibiotics susceptibility test against *s.aureus* bacteria.

NO	Antibiotic disks	symbol	Disk potency (µg)
1	Azithromycin	AZM	15
2	Cephoxitin	CX	30
3	chloramphenicol	C	30
4	Clindamycin	CD	2
5	Erethromycin	E	15
6	Gentamycin	GEN	10
7	Levofloxacin	LE	5
8	Nitrofurantoin	NIT	30
9	Ofloxacin	OFX	5
10	Trimethoprimesulfanethaxol	COT	25

Detection of Efflux pump by cartwheel method

The agar-based Ethidium bromide method measures *Staphylococcal* efflux pump activity.
1-52 *S. aureus* isolates were grown in 5 mL TSB at 37 °C until they reached 0.6 OD at 600 nm.
2-after autoclaving, Trypton soy agar plates were created. The plates were solidified in a dimly lighted room after cooling to 50°C and applying EtBr concentrations of 0.25, 0.5, 1, 2, 4, and 8 mg/l to the TSA.
3- They were then marked into eight cartwheel-shaped sections.
4-For 18 hours at 37 degrees Celsius, each plate was immersed in 10 microliters of broth for cultivation. All plates were gel-documented following incubation.
5- Each isolate's fluorescent dye accumulation was. at low concentrations, isolates had no efflux pump, a negative outcome. At varying concentrations, a positive result was seen without fluorescence (14) .

plant materials

gallic acid extract (srlchem , india) and curcumin extract (CCOF,USA) were bought , it was ready to use, and it was used according to the procedure in the box.

Preparation of the extracts

Five concentrations of each extract was prepared (100 , 200 , 400 , 800 , 1600) mg\ml for use it in The well diffusion technique to test the antibacterial activity of the extracts. A sterile Petri dishes (90 mm diameter) were used to pour Mueller-Hinton agar. A 6-mm sterile core borer was used to carve a well in the agar. Load 100µl of gallic acid extract and curcumin components into each well of each plate using a micropipette. Rulers measured the inhibitory zone in millimeters after 24 h at 37° C incubation (15) .

Isolation of bacterial DNA

The genomic DNA of the *S.aureus* isolates was isolated using a Genomic DNA purification kit sourced from Elk/China. The purity and concentration were evaluated, and gel electrophoresis was utilized to test the integrity of the DNA.

PCR for *Nor* a gene detection

The efflux pump in *Staphylococcus aureus* isolates was validated by conventional PCR with specific primers for the *Nor a* gene. The Amplicon size and primer sequence are detailed in

Table 2. The program was implemented in PCR analysis of primers for the *Nor a* gene, as illustrated in Table 3.

Isolation of bacterial RNA

RNA was extracted from *Staphylococcus aureus* using a Genomic RNA purification kit from TRIzol™ (Elk, China). The purity and concentration were evaluated, and gel electrophoresis was utilized to test the integrity of the RNA samples.

Real-time PCR for *Nor a* gene expression

The impact of plant extracts on the efflux pump genes of *Staphylococcus aureus* was validated via RT-PCR utilizing specific primers for the *Nor a* gene. The Amplicon size and primer sequence are detailed in Table 2. The program was implemented in PCR analysis of the primer for the Nor a gene, as illustrated in Table 4

Table 2. Primer sequences & amplicon size for bacterial DNA and RNA extractions

Primer Name	Primer Sequence F	Primer Sequence R	Tm.	Product size (bp)	Refrence
Nor-A *For normal PCR	ATGTTGCTGCTGCTCTGTTC	TCAACTGTCAAACGATCACG	60	718	**(16)**
Nor-A *For RT PCR	AATGCCTGGTGTGACAGGTT	TCCACCAATCCCTGGTCCTA	60	121	**(17)**
16 s	GGACAATACAAAGGGCAGCGA	GTGTGTACAAGACCCCGGAAC	60		Primer design

Table 3. The program of *nora primer* amplification using normal PCR analysis (18)

Steps	°C	m: s	Cycle
Initial Denaturation	95	05:00	1
Denaturation	95	00:15	45x
Annealing	60	00:15	
Extension	72	00:15	
Final Extension	72	10:00	1

Table 4. The program of *norA primer* amplification used in RT-PCR analysis

Steps	°C	m: s	Cycle
Initial Denaturation	95	03:00	1
Denaturation	95	00:20	45
Annealing	60	00:20	
Extension	72	00:20	

Analysis Gene Expression

Relative quantification

Folding =2-ΔΔCT

ΔCT =CT gene - CT House Keeping gene

ΔΔCT =ΔCT Treated or Control – Average ΔCT Average Con

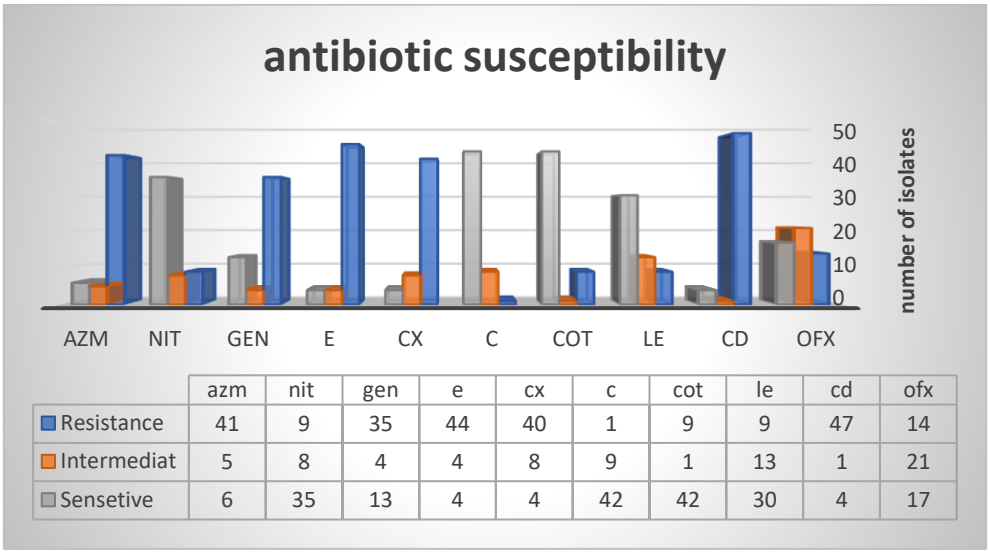
RESULTS

Identification of Staphylococcus aureus

Among 105 individuals, 52 (49.52%) were found to have *Staphylococcus aureus* based on traditional culture and microscopic characteristics. Colonies of 52 isolates on mannitol salt agar were smooth, transparent, creamy, and yellow. Microscopic examination was conducted on gram-positive, non-spore forming, non-motile bacteria arranged in grape-like clusters. In biochemical experiments, 52 bacterial isolates found as mannitol-positive, Gram-positive, oxidase-negative, catalase-positive, and coagulase-positive were classified as *Staphylococcus aureus*.

Antibiotic susceptibility of *s.aureus*

The antibiotic susceptibility profile was established utilizing the disc diffusion method; the 52 Staphylococcus aureus isolates, previously identified using biochemical assays, were specified as follows: The highest resistance level was observed with clindamycin at 90.38% (n=47/52), followed by erythromycin at 84.62% (n=44/52), azithromycin at 78.85% (n=41/52), cefoxitin at 76.92% (n=40/52), gentamicin at 67.31% (n=35/52), ofloxacin at 26.92% (n=14/52), and levofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole at 17.3% (n=9/52), with chloramphenicol at 1.93% (n=1/52) as shown in fig 1 . *Staphylococcus aureus* exhibits the highest resistance to lincosamides and macrolides, primarily due to the *Msr a* and *Mef a* efflux pumps, which are the principal contributors to this resistance (19) . Enzyme modification represents the predominant mechanism of aminoglycoside resistance, particularly in *S. aureus* (20) . Chloramphenicol exhibits reduced resistance due to its diminutive, hydrophobic structure, which facilitates penetration across the bacterial membrane and diminishes susceptibility to active efflux compared to other antibiotics (21) .

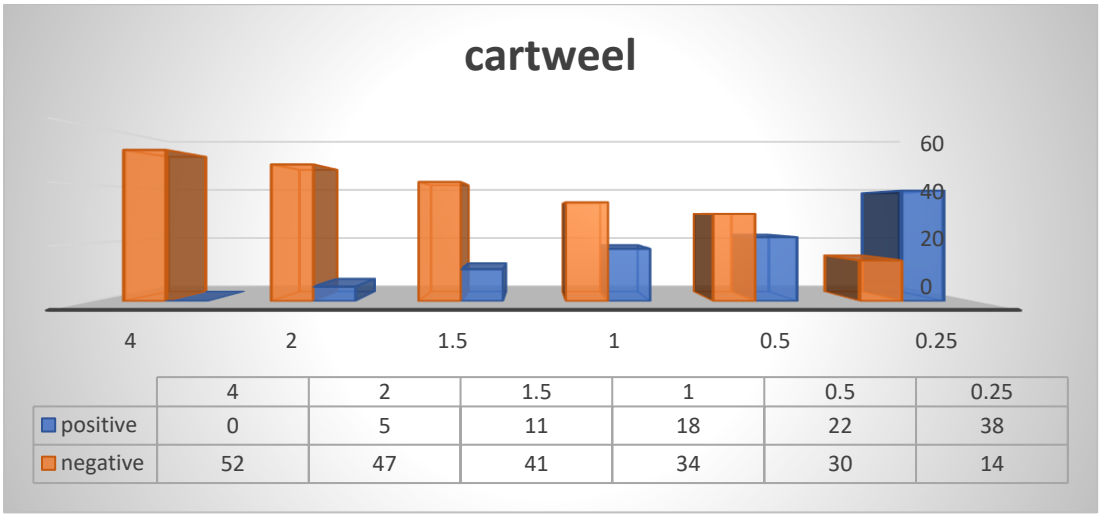


	azm	nit	gen	e	cx	c	cot	le	cd	ofx
Resistance	41	9	35	44	40	1	9	9	47	14
Intermediat	5	8	4	4	8	9	1	13	1	21
Sensetive	6	35	13	4	4	42	42	30	4	17

Fig 1 (antibiotics susceptibility of *Staphylococcus aureus*)

The efflux pump activity of *S.aureus*

S.aureus isolates was validated by EtBr cartwheel assays. All 52 isolates cultured on tryptone soy agar-ethidium bromide plates at concentrations of 0, 0.25, 0.5, 1, 1.5, 2, and 4 mg/L were prepared on the same day by (14) . as shown in fig 2 At low EtBr concentrations (0.25 mg/l) under UV irradiation, 38 out of 52 localized S. aureus isolates exhibited efflux activity, whereas 14 did not. Thirty negative isolates at 0.5 mg/l, 34 at 1.0 mg/l, 41 at 1.5 mg/l, 47 at 2.0 mg/l, and no fluorescence at 4.0 mg/l EtBr.



	4	2	1.5	1	0.5	0.25
positive	0	5	11	18	22	38
negative	52	47	41	34	30	14

Fig 2 (Al-selected isolates of *S. aureus* subjected to different concentrations of EtBr.)

Antibacterial activity of plant extracts.

Five concentrations (100, 200, 400, 800, and 1600 mg/ml) of extracts from gallic acid and curcumin were evaluated for antibacterial efficacy. Concentrations of 100 and 200 proved ineffectual; therefore, we selected 400 as the minimum inactive amount. Both 800 and 1600 were efficient in inhibiting bacterial growth (22) (23) (10) as shown in table 5.

Table 5 Average inhibition zones of gallic acid and curcumin extracts at different concentrations

concentrations	Average of inhibition zone of gallic acid (mm)	Average of inhibition zone of curcumin (mm)
1600 mg\ml	27.3	28.6
800 mg\ml	24	24.6
400 mg\ml	20	19
200 mg\ml	17	13
100 mg\ml	11.3	7.6
Mean	19.93	18.60
P value	= 0.593	

The research demonstrates a definitive correlation between concentration and inhibitory efficacy for both gallic acid and curcumin, increased does not result in greater inhibitory zones, with curcumin demonstrating higher

efficacy Compared to gallic acid at all concentrations. This indicates possible uses for curcumin in antimicrobial therapies, especially at elevated dosages, these results agree with (10) which share thet Curcumin significantly diminished the minimum inhibitory concentration (MIC) of several antibiotics when administered in combination, highlighting its function as an efflux pump inhibitor , and (24) that show impact of gallic acid on the efflux pumps of *Staphylococcus aureus*. The findings demonstrated that gallic acid may augment the antibacterial efficacy of specific antibiotics by obstructing the efflux pump, resulting in a reduced minimum inhibitory concentration (MIC) of ethidium bromide (EtBr) when used in conjunction with gallic acid.

ANOVA (Analysis of Variance) test was used, to compare the means of the two groups. The significant p-value was (0.593) and that means there are no significant differences between the two groups.

Molecular Identification of *Nor a* Gene in *s.aureus*

The Nor a gene was identified using PCR using a specific primer. The critical element of *S.aureus* efflux mechanism, the MFS transport system, is the norA pump. *norA* encodes the efflux pump; Floxacin, quaternary ammonium compounds, biocides, dyes, and antiseptics serve as substrates for the *norA* efflux pump. Studies indicate that 43% of *S. aureus* strains exhibit overexpression of *norA*. Organisms that overexpress *norA* exhibit diverse antibiotic resistance profiles, including resistance to fluoroquinolones (4). The findings revealed that 7 of 10 isolates (70%) tested positive for the nor a gene (718 bp), as shown in Figure 3. This corresponds with local investigations demonstrating that 91.80% of 65 clinical S. aureus isolates carried the *Nor a* gene, as reported by Sabir, N (25) that 91.80% of 65 clinical *S. aureus* isolates possessed the *Nor a* gene.

Fig 3 Gel electrophoresis of *norA* gene.

Gene expression of the *norA* gene.

Quantitative Real-time PCR (qRT-PCR) was employed to assess the gene expression of the *norA* gene following treatment with various quantities of plant extracts. This study included (13) experimental subjects, consisting of (12) distinct concentrations of different concentrations of gallic acid and curcumin extracts and one control group (bacterial sample without adding any treatment). The evaluation of the results and the analysis of gene expression folding for each sample were performed in line with the equations of (26).

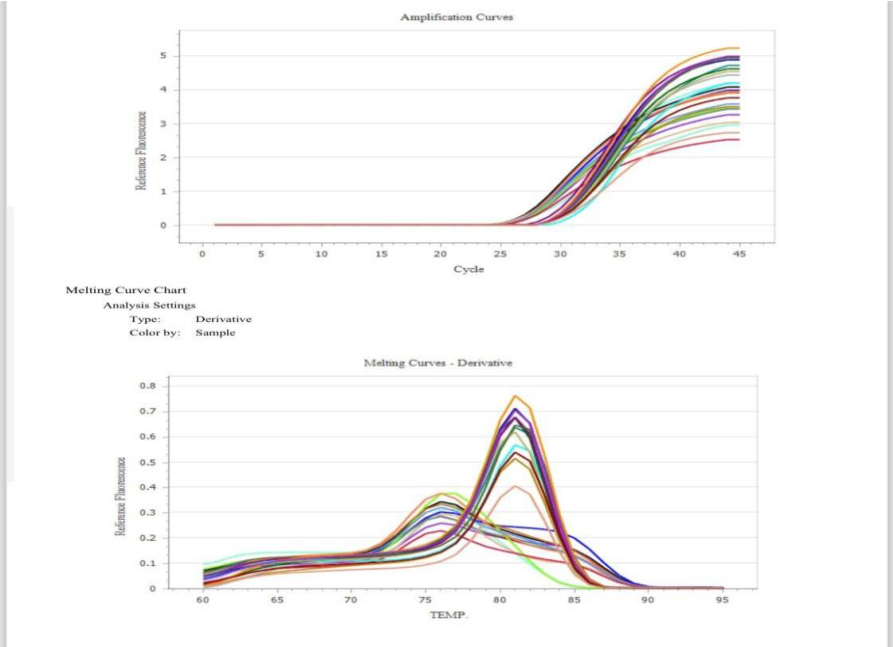


Fig 4 the amplification and melting curves of the *Nor a* gene of different concentrations of study groups using Relative Quantitative Real Time-PCR.

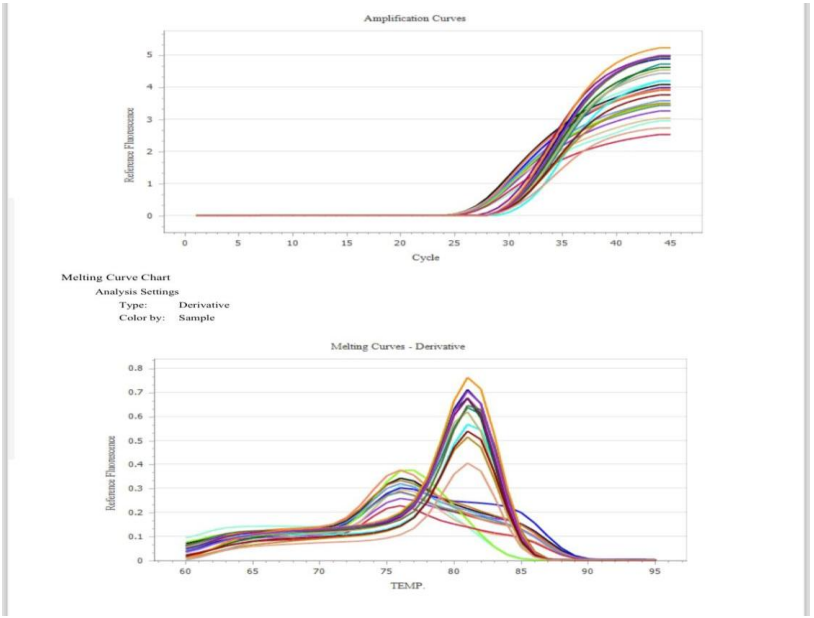


Figure 5 the amplification and Melting Curves of (16 s) housekeeping genes using Relative Quantitative Real Time-PCR.

Table 6: RT PCR equation results for *S.aureus* after treatment with different concentrations of gallic acid and curcumin extracts

Groups	Means Ct of the housekeeping gene	Means Ct of *norA*	Means Δ Ct of *norA*	ΔΔ Ct	A fold of gene expression $2^{-\Delta\Delta Ct}$
Treatment of gallic acid	26.73	25.95	-1.43	0.73	0.60
Treatment of curcumin	28.25	26.22	-1.56	0.60	0.66
Control	28.074	25.914	-2.16	0.00	1.00

Both gallic acid and curcumin treatments led to reduced expression levels of the target gene *norA* in comparison to the control group. Although both treatments positively influenced gene expression compared to the control, the fold changes suggest they may also have a suppressive effect, Gallic acid exhibits a greater inhibitory effect on the expression of nor a than curcumin, as seen by the lower fold change value (0.60 vs. 0.66). This indicates that gallic acid is more efficacious in diminishing the expression of the target gene. this results agree with (27) Which confirmed the impact of secondary metabolites plants extracts in the inhibition of *Nor a* gene .

Discussion

Recent study assessed the antimicrobial inhibitory effects of gallic acid and curcumin, as well as their influence on the expression of the Nor a gene in Staphylococcus aureus. Curcumin exhibited a more potent antibacterial inhibitory effect than gallic acid; nevertheless, gallic acid was more successful in diminishing the expression of the *norA* gene. The fold change study indicated that gallic acid resulted in a more significant decrease of nor A expression than curcumin. This suggests that while curcumin may be a more effective antibacterial drug, gallic acid demonstrates greater efficacy in downregulating norA expression. This contrast underscores the potential for employing both substances in complementary capacities within antibacterial therapies and gene expression modification.

Conclusion.

Both gallic acid and curcumin possess significant potential as plant-derived efflux pump inhibitors (EPIs). However, gallic acid demonstrates superior efficacy in downregulating *norA* gene expression, underscoring its potential as a more effective agent in modifying gene-mediated resistance in multidrug-resistant *Staphylococcus aureus* strains.

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