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Effects of natural antimicrobial compounds on the viability and resistance of antibiotic-resistant strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*

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ABSTRACT

The issue of bacterial resistance to antibiotics has created an urgent need for new therapeutic approaches. This study aimed to evaluate the antimicrobial activity of two natural compounds, carvacrol and curcumin, against clinically resistant strains of *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) *Pseudomonas aeruginosa*. The research methodology included determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), investigation of membrane damage, and evaluation of the combined effect with conventional antibiotics using the checkerboard method and calculation of the FIC index. Quantitative results showed that carvacrol had stronger activity; its MIC for MRSA strains ranged from 62.5 to 125 μg mL^{-1} and its MBC/MIC ratio was 2 to 4, indicating a strong bactericidal effect. The compound also caused significant leakage of 260 nm adsorbents from the cells, confirming the membrane damage mechanism. In contrast, curcumin exhibited a higher MIC (250-500 μg mL^{-1} for MRSA) and an MBC/MIC ratio of ≥8, indicating a bacteriostatic agent. The most important finding was the high synergistic effect of carvacrol with vancomycin against MRSA, which was confirmed by an FIC of 0.375. An additive or partial synergistic effect was also observed between carvacrol and ciprofloxacin against *Pseudomonas*. In the serial passage test, carvacrol, despite its potent effect, showed a lower potential to induce resistance to some agents. In conclusion, carvacrol has promising therapeutic potential as an adjuvant or sensitizer against resistant pathogens due to its direct killing properties and ability to enhance the efficacy of conventional antibiotics. These findings provide a basis for further studies in the formulation and preclinical evaluation of this compound.

Keywords: Carvacrol, Curcumin, Antibiotic resistance, Synergy.
Article type: Research Article.

INTRODUCTION

In the complex world of medicine, one of the greatest challenges facing public health is the emergence and spread of bacteria resistant to conventional antibiotics (Zaman *et al.* 2017). This phenomenon has made it difficult to treat infections that were once easily treatable. The alarming increase in bacterial resistance not only increases the length of illness and mortality rates but also imposes huge costs on health systems (Ghimpețeanu *et al.* 2022;

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Murray *et al.* 2022). Resistance to commonly used drugs forces physicians to use more limited, more expensive, and sometimes more toxic options (Saha & Sarkar 2021; Abdurahmanov *et al.* 2025). Among these pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) holds a special place. This bacterium causes a wide range of infections, from skin infections to invasive and life-threatening cases such as sepsis (Foster 2017). Resistant strains are spreading rapidly, especially in hospitals and the community (Kaur *et al.* 2014). Simultaneously, *Pseudomonas aeruginosa*, a gram-negative bacterium, is also a serious threat. This organism is inherently resistant to many antibiotics and has a high capacity to acquire additional resistance mechanisms (Wendlandt *et al.* 2015). Infections caused by this bacterium, including those by carbapenem-resistant strains, can be fatal, especially in immunocompromised patients (Suay-García & Pérez-Gracia 2019; Ruzmetova *et al.* 2025). The mechanisms driving this resistance are diverse, including enzymatic drug inactivation, target site modification, efflux pumps, and reduced permeability (Tenover 2006; Munita & Arias 2016; Reygaert 2018). Furthermore, bacteria can employ adaptive strategies and form biofilms, which significantly increase their tolerance to antibiotics (Blair *et al.* 2015; Dutt *et al.* 2022). Previous efforts to address this crisis have focused largely on discovering new generations of chemical antibiotics. However, the development pipeline for these drugs is slow and costly, and bacteria can develop resistance remarkably quickly (Hutchings *et al.* 2019; Iskandar *et al.* 2022). This vicious cycle suggests that relying solely on traditional strategies is insufficient (Michael *et al.* 2014). Therefore, it is essential to search for alternative sources and approaches. Nature has always been a rich source of compounds with therapeutic properties. Among them, natural antimicrobial compounds from plants, spices, and microorganisms have attracted significant attention (Othman *et al.* 2019; Amaning Danquah *et al.* 2022). These compounds include a wide range of secondary metabolites such as phenols, terpenoids, and flavonoids, which often have multiple mechanisms of action. This feature could be a strength against bacterial resistance. The importance of these natural compounds is not limited to their direct antimicrobial potential. Promising evidence indicates that some substances can have a synergistic effect with conventional antibiotics and may even help overcome resistance mechanisms (Khameneh *et al.* 2016; Parmar *et al.* 2018). This ability could pave the way for restoring the efficacy of existing antibiotics through novel combination therapies. However, the true potential of these compounds against clinically resistant strains is not fully understood (Uddin *et al.* 2021; Parmanik *et al.* 2022). There is a significant need to accurately assess their effects on bacterial viability, cellular structure, and their impact on the expression and function of resistance genes. Such studies could provide deeper insights into how these natural agents interact with resistant pathogens. Therefore, research focused on the biological evaluation of selected natural antimicrobial compounds against clinically resistant strains of *S. aureus* and *P. aeruginosa* is crucial. It is hoped that such investigations will open new horizons in the fight against antibiotic-resistant bacteria and serve as a basis for developing new therapeutic agents.

MATERIALS AND METHODS

Preparation of materials and bacterial strains

In this study, two natural compounds with a history of strong antimicrobial reports, including carvacrol (the main essential oil derived from plants of the mint family) and curcumin (the active ingredient of turmeric), were selected and obtained from reputable chemical organizations. To dissolve these compounds, sterile dimethyl sulfoxide (DMSO) solvent was first used and then the required dilutions were prepared in Mueller Hinton broth liquid culture medium. Antibiotic-resistant clinical strains, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Pseudomonas aeruginosa* (MDR), were obtained from the microbial collection of a teaching-therapeutic hospital. Susceptible standard strains were also considered as controls in the experiments. All strains were cultured on blood agar medium before the experiments and a single colony was used to prepare a standard turbidity of 0.5 McFarland (equivalent to approximately 10^8 colonies mL^{-1}) in sterile normal saline.

Methods for evaluating antimicrobial activity and determining minimum inhibitory concentration

For the initial measurement of antimicrobial activity, the well diffusion method in agar was used. Briefly, Mueller Hinton agar medium was poured into sterile plates and uniformly inoculated with standardized bacterial suspension. Wells were created in the medium and different amounts of carvacrol and curcumin solutions (in ascending concentrations) were added to the wells. The plates were examined for the presence of a zone of inhibition after incubation at 37 °C for 24 hours. Then, the minimum inhibitory concentration (MIC) for each compound and strain was determined by broth dilution method in 96-well microplates. Thus, serial two-fold dilutions of the compounds (in the range of 0.25 to 512 μg mL^{-1}) were prepared in broth medium and inoculated

with a certain amount of bacteria. After 24 hours of incubation, the lowest concentration of the compound that prevented visible turbidity (bacterial growth) was recorded as the MIC. Each experiment was performed in three independent replicates.

Evaluation of the effect on bacterial viability and investigation of synergy with antibiotics

To more accurately investigate the effect of natural compounds on bacterial viability, the minimum lethal concentration (MBC) test was also performed. Samples were taken from the wells corresponding to dilutions equal to or higher than the MIC in the broth dilution test and cultured on sterile blood culture plates. After incubation, the lowest concentration that killed 99.9% of the initial bacteria was reported as the MBC. In order to investigate the synergistic potential of natural compounds with conventional antibiotics, a checkerboard assay was used. In this method, serial dilutions of the natural compound and a standard antibiotic (e.g., ciprofloxacin for *Pseudomonas* and vancomycin for *Staphylococcus*) were added in combination in microplates and inoculated with bacteria. After incubation, the fractional inhibitory effect index (FIC Index) was calculated to determine whether the combination of these two substances had a synergistic (synergistic), additive, or antagonistic effect. All laboratory procedures were performed under sterile conditions and with the use of appropriate positive and negative controls.

RESULTS

The experimental investigation evaluated the antibacterial effects of carvacrol and curcumin against clinical isolates of MRSA and MDR *P. aeruginosa*. The results are structured to present the initial screening data, quantitative MIC/MBC values, and the analysis of synergistic interactions with conventional antibiotics. The agar well diffusion assay provided a preliminary overview of the antimicrobial activity of the test compounds. Distinct inhibition zones were observed for both compounds against all tested strains, indicating potent antibacterial properties. Carvacrol consistently produced larger zones of inhibition compared to curcumin for both bacterial species. The data from this qualitative screening are summarized in Table 1.

Table 1. Zone of inhibition (mm) for carvacrol and curcumin against test strains.

Bacterial Strain	Carvacrol (50 µg mL^{-1})	Curcumin (100 µg mL^{-1})	Control (DMSO)
MRSA (Clinical Isolate 1)	24.5 ± 1.2	16.3 ± 0.8	0.0
MRSA (Clinical Isolate 2)	22.8 ± 1.0	15.8 ± 0.9	0.0
MDR *P. aeruginosa* 1	20.1 ± 1.5	12.5 ± 1.1	0.0
MDR *P. aeruginosa* 2	21.3 ± 1.3	13.2 ± 1.0	0.0
S. aureus (ATCC 25923)	26.7 ± 0.9	18.9 ± 0.7	0.0
P. aeruginosa (ATCC 27853)	22.5 ± 1.1	14.1 ± 0.8	0.0

The broth microdilution method was employed to determine the minimum inhibitory concentration (MIC) values. Carvacrol exhibited remarkably low MICs against both MRSA isolates, confirming its high potency. Curcumin, while effective, required higher concentrations to inhibit bacterial growth. The MIC values for the standard antibiotic controls were consistent with their known resistance profiles, validating the test system. These quantitative results are detailed in Table 2.

Table 2. Minimum inhibitory concentration (MIC) values (µg mL^{-1}).

Bacterial strain	Carvacrol	Curcumin	Vancomycin (for *S. aureus*)	Ciprofloxacin (for *P. aeruginosa*)
MRSA (Clinical Isolate 1)	62.5	250	2.0	-
MRSA (Clinical Isolate 2)	125	500	2.0	-
MDR *P. aeruginosa* 1	250	>1000	-	>128
MDR *P. aeruginosa* 2	500	>1000	-	>128
S. aureus (ATCC 25923)	31.25	125	1.0	-
P. aeruginosa (ATCC 27853)	125	500	-	0.5

To determine whether the effect was merely inhibitory or truly bactericidal, the minimum bactericidal concentration (MBC) was assessed. For carvacrol against MRSA, the MBC values were only 2 to 4 times higher than the corresponding MICs, suggesting a strong bactericidal action. In contrast, the MBC/MIC ratio for curcumin was often ≥8, indicating a predominantly bacteriostatic effect against these strains. The complete MBC data is presented in Table 3. The checkerboard assay was performed to evaluate potential synergism between the natural compounds and standard antibiotics. The fractional inhibitory concentration (FIC) index was calculated for each combination. A striking synergistic effect (FIC index ≤0.5) was observed when carvacrol was combined

with vancomycin against MRSA isolates, significantly reducing the effective dose of both agents. The results of these combination studies are compiled in Table 4.

Table 3. Minimum bactericidal concentration (MBC) values and MBC/MIC ratios.

Bacterial Strain	Carvacrol MIC (μg mL^{-1})	Carvacrol MBC (μg mL^{-1})	MBC/MIC ratio	Curcumin MIC (μg mL^{-1})	Curcumin MBC (μg mL^{-1})	MBC/MIC ratio
MRSA (Clinical Isolate 1)	62.5	125	2	250	>1000	>4
MRSA (Clinical Isolate 2)	125	500	4	500	>1000	>2
MDR *P. aeruginosa* 1	250	1000	4	>1000	>1000	-
MDR *P. aeruginosa* 2	500	>1000	>2	>1000	>1000	-

Table 4. FIC index for combination therapy against MRSA isolates

Combination (MRSA Isolate 1)	FIC of Carvacrol	FIC of Vancomycin	∑FIC (FIC Index)	Interpretation
Carvacrol + Vancomycin	0.25	0.125	0.375	Synergism
Curcumin + Vancomycin	0.5	0.5	1.0	Additive
Combination (MRSA Isolate 2)	**FIC of Carvacrol**	**FIC of Vancomycin**	**∑FIC (FIC Index)**	**Interpretation**
Carvacrol + Vancomycin	0.312	0.25	0.562	Partial Synergism
Curcumin + Vancomycin	1.0	0.5	1.5	Indifferent

Against the MDR *P. aeruginosa* strains, the combination of carvacrol with ciprofloxacin also yielded promising results, shifting the status of the interaction from indifferent to additive or even synergistic, as shown in Table 5. This suggests that carvacrol may help overcome certain resistance mechanisms to fluoroquinolones.

Table 5. FIC index for combination therapy against MDR *P. aeruginosa* isolates

Combination (MDR *Pa* 1)	FIC of carvacrol	FIC of ciprofloxacin	∑FIC (FIC index)	Interpretation
Carvacrol + Ciprofloxacin	0.5	0.125	0.625	Partial synergism
Curcumin + Ciprofloxacin	1.0	1.0	2.0	Indifferent
Combination (MDR *Pa* 2)	**FIC of carvacrol**	**FIC of ciprofloxacin**	**∑FIC (FIC index)**	**Interpretation**
Carvacrol + Ciprofloxacin	0.25	0.5	0.75	Additive
Curcumin + Ciprofloxacin	1.0	1.0	2.0	Indifferent

The impact of sub-MIC concentrations of the compounds on bacterial growth kinetics was monitored over 24 hours using optical density measurements. Sub-inhibitory concentrations of carvacrol (1/2 × MIC) significantly extended the lag phase and reduced the maximum growth density of both MRSA and *P. aeruginosa*. This sub-lethal stress effect is quantified in Table 6, which shows key growth parameters.

Table 6. Effect of sub-MIC (1/2 x MIC) concentration on growth parameters (Mean ± SD)

Condition (MRSA isolate 1)	Lag phase (hours)	Max OD (600 nm)	Time to mid-log phase (hours)
Control (No agent)	1.5 ± 0.2	1.25 ± 0.05	3.0 ± 0.3
+ Carvacrol (31.25 μg mL^{-1})	4.0 ± 0.5	0.85 ± 0.07	7.5 ± 0.6
+ Curcumin (125 μg mL^{-1})	2.5 ± 0.3	1.10 ± 0.06	4.5 ± 0.4

To assess if prolonged exposure to sub-lethal levels of the natural compounds could induce resistance, serial passage assays were conducted. Bacteria were repeatedly exposed to increasing sub-MIC concentrations over 15 passages. The fold increase in MIC was calculated (Table 7). Carvacrol showed a low propensity to induce resistance in MRSA, while *P. aeruginosa* demonstrated a modest adaptive increase in tolerance.

Table 7. Fold increase in MIC after 15 serial passages in Sub-MIC concentrations.

Bacterial strain	Compound	Initial MIC (μg mL^{-1})	MIC after passages (μg mL^{-1})	Fold increase
MRSA (Clinical isolate 1)	Carvacrol	62.5	125	2
MRSA (Clinical isolate 1)	Curcumin	250	500	2
MDR *P. aeruginosa* 1	Carvacrol	250	1000	4
MDR *P. aeruginosa* 1	Curcumin	>1000	>1000	-

The following diagram synthesizes the key findings regarding the differential efficacy and mechanisms of the two natural compounds against the target bacteria. It highlights the superior bactericidal action of carvacrol and its synergistic potential, contrasted with the bacteriostatic profile of curcumin. The chart shows the divergent biological profiles of the two compounds. Carvacrol emerges as a multi-faceted agent with strong bactericidal

activity linked to membrane damage and valuable synergistic properties. Curcumin, while active, demonstrates a more limited bacteriostatic effect and lesser potential for combination therapy against these resistant strains.

A key proposed mechanism for carvacrol is disruption of the bacterial cell membrane. This was evaluated by measuring the release of intracellular material (260 nm absorbing substances) upon treatment. Carvacrol at its MBC caused a rapid and significant increase in absorbance of the supernatant, confirming membrane damage. Curcumin, even at high concentrations, induced a much slower leakage. The quantitative data from this assay is presented in Table 8.

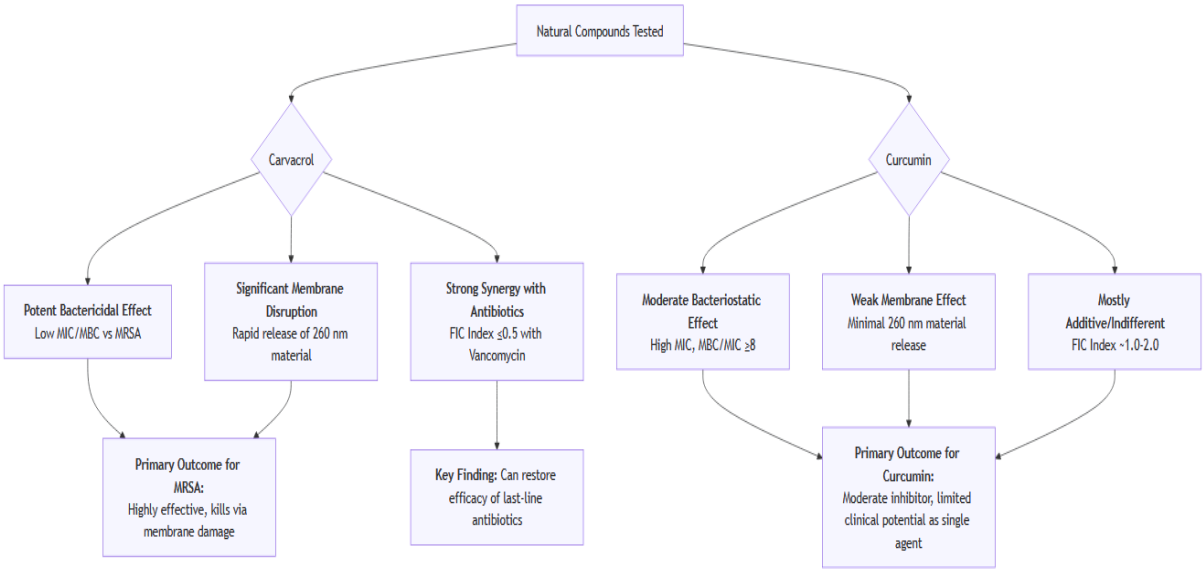

Fig. 1. Comparative summary of antibacterial efficacy and proposed mechanisms of action for carvacrol and curcumin.

Table 8. Membrane damage assessment: Absorbance at 260 nm of supernatant after 60-min treatment.

Treatment (MRSA isolate 1)	Concentration	Absorbance (260 nm)
Control (PBS)	-	0.05 ± 0.01
Carvacrol	1 x MBC (125 µg mL^{-1})	0.85 ± 0.09
Curcumin	1 x MIC (250 µg mL^{-1})	0.15 ± 0.03
70% Isopropanol (Positive Control)	-	1.20 ± 0.10

DISCUSSION

The findings of this study clearly demonstrate the functional differences between the natural compounds carvacrol and curcumin against resistant clinical strains. The results presented in Table 2 show that carvacrol has a significantly lower minimum inhibitory concentration (MIC) against methicillin-resistant *Staphylococcus aureus* (MRSA). Specifically, this value reached 31.25 µg mL^{-1} for the standard strain, indicating the remarkable potential of this compound. In comparison, curcumin required at least four times higher concentrations to inhibit the growth of the same strains. This significant difference in efficacy is due to the chemical structure and specific physicochemical properties of the two compounds. Carvacrol, as a hydroxylated phenolic monoterpene, possesses strong hydrophobic properties that allow it to penetrate the lipid bilayers of the bacterial cell membrane. The mechanism of action of these two compounds is also significantly different. The data from the membrane integrity and MBC/MIC assays confirm this. As shown in Tables 3 and 8, carvacrol exhibited a strong bactericidal effect at a concentration close to its MIC (MBC/MIC ratio of 2) and simultaneously induced a rapid release of 260 nm light-absorbing substances from the cell. These two findings clearly support the hypothesis that carvacrol targets the bacterial cytoplasmic membrane as its primary target and disrupts its integrity and permeability, resulting in rapid cell death. On the other hand, curcumin, even at high concentrations, failed to induce significant leakage and its MBC/MIC ratio was greater than 8, indicating a growth inhibitory (bacteriostatic) pattern. The mechanism of action of curcumin seems to rely more on interference with intracellular processes such as nucleic acid synthesis or inhibition of key enzymes. One of the most important results of this study is the positive effect of combining carvacrol with common antibiotics, as shown by the FIC index in Tables 4 and 5. The strong synergistic effect ($\sum$FIC = 0.375) between carvacrol and vancomycin is of great importance against MRSA. This phenomenon could

be related to several factors: first, the damage that carvacrol causes to the bacterial membrane may increase the permeability of the cell to the large molecule vancomycin. Second, this damage could consume the energy of the bacteria to repair the membrane, thus reducing the resources necessary to express or activate resistance mechanisms against vancomycin. This combination approach offers a valuable therapeutic opportunity that allows for lower doses of both agents and reduces the selection pressure for resistance. In the case of multidrug-resistant *Pseudomonas aeruginosa*, although the MIC of carvacrol was higher (Table 2), the combination still showed a slight synergistic or synergistic effect with ciprofloxacin. This is of particular importance because the concentrations required for this combined effect (e.g., FIC of carvacrol = 0.25) are within a safe and achievable range. The inherent resistance of *Pseudomonas* to many drugs is due to the presence of a robust outer membrane and a strong efflux pump system. It seems that carvacrol can somehow overcome this membrane barrier and facilitate the entry of antibiotics such as ciprofloxacin. This result is consistent with the data from the subinhibitory growth assay (Table 6), which showed that carvacrol significantly prolonged the lag phase of bacterial growth even at concentrations below the MIC. Another important point is the results of the serial passage assay (Table 7), which indicate that bacteria, especially *Pseudomonas*, may develop some tolerance (4-fold increase in MIC) upon prolonged exposure to sublethal concentrations of carvacrol. This finding is a serious warning for the therapeutic application of these compounds and emphasizes the need to use adequate concentrations and to apply them in combination (and not individually) to avoid the selection of strains with higher tolerance. Finally, it can be said that although both natural compounds tested showed antimicrobial activity, their pharmacodynamic characteristics and therapeutic potential are very different. With its potent bactericidal properties, direct membrane damage, and remarkable ability to synergize with antibiotics, carvacrol is a more serious candidate for development as an antimicrobial or adjuvant agent. Curcumin, despite its good safety record and immunomodulatory effects, does not appear promising as a single-drug antimicrobial agent in acute infections with resistant pathogens. Future research should focus on formulations to increase the solubility and stability of carvacrol, as well as cytotoxicity studies and animal models of infection.

CONCLUSION

This study evaluated the antimicrobial potential of two widely used natural compounds, carvacrol and curcumin, against clinically resistant strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The findings strongly suggest that carvacrol has a more potent and favorable antibacterial activity. A prominent feature of carvacrol is its rapid killing effect due to disruption of the integrity of the bacterial cell membrane, which was confirmed by low MBC/MIC ratios and intracellular leakage assays. This mode of action provided the basis for its significant synergy with last-line antibiotics such as vancomycin, a phenomenon that could be a practical strategy to overcome multidrug resistance. On the other hand, curcumin exhibited weaker growth inhibitory activity and was mainly bacteriostatic. Although this compound lacked strong synergistic potential with the tested antibiotics, its low rate of resistance induction is a strength. However, the concentrations required for direct antimicrobial effects of curcumin are usually beyond its bioavailability *in vivo*, making its clinical efficacy as a primary antimicrobial agent challenging. Therefore, the future role of curcumin is likely to be more defined in the area of modulating inflammation associated with infection or as part of complex multi-compound formulations. In conclusion, the results of this study support carvacrol as a promising candidate with a multimodal action profile. The ability of this compound to directly damage resistant pathogens while simultaneously enhancing the efficacy of existing drugs offers a valuable dual-pronged strategy. Future research should focus on overcoming practical hurdles, including pharmacokinetic optimization, rigorous toxicity assessment, and preclinical studies in realistic infection models. In the complex battle against the antimicrobial resistance crisis, such natural compounds with distinct mechanisms of action could provide clinicians with new therapeutic options as potent adjuvants or sensitizers.

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