



## Evaluation of Antimicrobial and Quorum Sensing Inhibitory Activities of *Umbilicaria deusta* Extract against *Staphylococcus aureus*

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**Abstract:** Lichens are recognized as a rich resource of bioactive secondary metabolites, and therefore, there is growing interest in their potential antivirulence properties. *Staphylococcus aureus* is a major pathogen of both human and veterinary importance, responsible for persistent infections like bovine mastitis and skin infections in other animals. This study examines the biological activity of the acetone extract from *Umbilicaria deusta* for its antimicrobial effects and quorum sensing (QS) inhibition properties against *S. aureus*. Lichen thalli were collected and identified using ITS rDNA sequencing, and extracted by maceration. Antimicrobial activity was evaluated against *S. aureus* ATCC 25923 using microdilution assays, while QS inhibition was evaluated in USA300-derived *agr* P2-GFP and P3-GFP reporter strains. The *U. deusta* extract did not exhibit antimicrobial or growth inhibitory effects at the tested concentrations. However, the extract presented a clear reduction in QS activity in both reporter systems without affecting bacterial growth, with approximately 60% inhibition for each promoter. These results indicate that *U. deusta* is unlikely to act as a conventional antimicrobial against *S. aureus* but may represent a promising source of antivirulence compounds targeting QS pathways in clinically relevant MRSA strains.

**Keywords:** Lichen secondary metabolites; *Umbilicaria deusta*; antivirulence activity; quorum sensing inhibition; *Staphylococcus aureus*; MRSA.

## *Umbilicaria deusta* Ekstraktının *Staphylococcus aureus*'a Karşı Antimikrobiyal ve Korum Algılama İnhibitör Aktivitelerinin Değerlendirilmesi



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**Öz:** Likenler, biyolojik olarak aktif sekonder metabolitler açısından zengin bir kaynak olarak tanınmakta ve potansiyel antivirülans özelliklerine yönelik ilgi giderek artmaktadır. *Staphylococcus aureus*, hem insan hem de veteriner hekimlik açısından büyük öneme sahip bir patojen olup, özellikle sığırlarda mastitis ve hayvanlarda deri enfeksiyonları gibi kalıcı enfeksiyonlara neden olmaktadır. Bu çalışmada, *Umbilicaria deusta*'dan elde edilen aseton ekstraktının biyolojik aktivitesi; antimikrobiyal etkileri ve *S. aureus*'ta quorum sensing (QS) inhibisyon potansiyeli yönünden incelenmiştir. Toplanan liken talusları, ITS rDNA dizilemesi kullanılarak tanımlanmış ve maserasyon yöntemiyle özütleri elde edilmiştir. Antimikrobiyal aktivite, *S. aureus* ATCC 25923 suşu ile mikrodilüsyon testleriyle değerlendirilmiş ve QS inhibisyonu USA300 kökenli *agr* P2-GFP ve P3-GFP raporlayıcı suşlarda analiz edilmiştir. *U. deusta* ekstraktı, test edilen konsantrasyonlarda saptanabilir bir antimikrobiyal ya da büyüme baskılayıcı etki göstermemiştir. Fakat, bakteri büyümesini etkilemeden her iki raporlayıcı suşta da QS aktivitesinde yaklaşık %60 oranında belirgin bir azalma gözlenmiştir. Elde edilen bulgular, *U. deusta*'nın *S. aureus*'a karşı konvansiyonel bir antimikrobiyal ajan olarak etki göstermesinin olası olmadığını; ancak klinik açıdan önemli MRSA suşlarında QS yollarını hedefleyen antivirülans bileşikler için potansiyel bir kaynak olabileceğini göstermektedir.

**Anahtar kelimeler:** Liken sekonder metabolitleri; *Umbilicaria deusta*; antivirülans aktivite; quorum sensing inhibisyonu; *Staphylococcus aureus*; MRSA.

### INTRODUCTION

*Staphylococcus aureus* is a clinically relevant pathogen that causes high morbidity and mortality rates in health-care settings across the globe. It can cause a variety of infections, especially in immunocompromised patients, including soft tissue infections, sepsis, endocarditis, bone

infections, lung infections, and urinary system infections. *S. aureus* is significant in both human and veterinary medicine, responsible for a wide range of infections, including mastitis in dairy animals and skin and soft tissue infections in livestock and companion animals, often with chronic and recurrent courses that complicate treatment (Song et al., 2024). *S. aureus* can develop resistance against different

types of antibiotics, which makes its treatment harder. Methicillin-Resistant *S. aureus* (MRSA) is a particular concern for its pathogenic behaviors. Bovine mastitis caused by *S. aureus* remains a persistent challenge in dairy herds worldwide, with high prevalence of MRSA and agr-positive isolates (Eidaros et al., 2025). The World Health Organisation (WHO) included MRSA in the 2024 WHO Bacterial Priority Pathogens List as a high-priority pathogen and defines it as one of the most prevalent drug-resistant pathogens (WHO, 2024). Moreover, the WHO also suggests continued investment in R&D for prevention and control.

*S. aureus* is a high-burden pathogen with its multidrug resistance, even in nonfatal cases. Therefore, alternative approaches are needed in its treatment. Antivirulence approaches have gained attention in this regard, as they target microbial pathogenicity rather than bacterial viability. One of the most prominent antivirulence methods is quorum sensing (QS) inhibition. QS is a regulatory mechanism that bacteria sense their population density via the accumulation of signaling molecules. Gram-negative bacteria secrete small molecules called autoinducers (AIs). As their population grows, the molecules diffuse back into the cell to bind to their specific regulator and start the expression of multiple virulence factors. On the other hand, Gram-positive bacteria produce autoinducing peptides (AIPs), which are recognized by membrane-bound receptor proteins. This interaction activates a phosphorylation cascade that leads to the expression of virulence-associated genes (Bhatt, 2019).

*S. aureus* has a specific QS system controlled by its *agr* locus and *sarA* pathway that regulates most of its virulence factors, including biofilm formation (Novick, 1999). The *agr* locus produces an AIP derived from AgrD, which is exported by AgrB. Accumulation of extracellular AIP leads to activation of the receptor AgrC and subsequent phosphorylation of AgrA, which in turn drives transcription from the P2 and P3 promoters. While P2 reinforces the *agr* operon expression, P3 produces RNAIII. RNAIII is the central effector molecule of the *S. aureus* QS system and functions as a multifunctional regulatory RNA. It functions to repress genes involved in adhesion and colonization, and to activate the expression of exotoxins, proteases, and hemolysins. It drives the transition from colonization to invasive infection (Hallier et al., 2024). On the other hand, the *sarA* pathway also regulates adhesins, exoenzymes, and immune evasion factors through agr-independent pathways, and plays a critical role in biofilm formation by repressing extracellular protease production (Kuai et al., 2024). Hence, there is a strong necessity for the identification of QS inhibitors. Interference with QS signaling represents an attractive antivirulence strategy that attenuates pathogenicity without exerting direct bactericidal pressure.

*Umbilicaria deusta* is a saxicolous lichen of the family Umbilicariaceae, commonly found on exposed siliceous rocks in boreal, alpine, and montane regions of Europe, Asia, and North America, and is characterized by its dark brown to black thallus with a roughened, isidiate surface (Schmull, 2008). *Umbilicaria* species have demonstrated that organic solvent extracts are rich in phenolic secondary metabolites, particularly depsides and tridepsides that have antioxidant and antimicrobial activities (Buçukoglu, Albayrak, Halici, & Tay, 2013). Studies show that lichen extracts may interfere with QS pathways, suggesting potential antivirulence applications (Gökalsın et al., 2020).

Therefore, this study aims to evaluate the QS inhibitory potential of *U. deusta* extract, providing insight into its potential as a natural antivirulence agent against *S. aureus*.

## MATERIAL AND METHOD

**Sample collection and identification:** Lichen samples were collected from exposed rock surfaces in Uludağ, Bursa, at an altitude of 1775m (40°05'35.6"N 29°17'25.8"E). The samples were taxonomically identified based on morphological characteristics at Marmara University, Türkiye, by Prof. Dr. Gülşah Çobanoğlu. Collected materials were air-dried at room temperature, cleaned of debris, and stored in sterile containers until extraction.

For molecular confirmation, genomic DNA was extracted from collected lichen thalli using QIAamp DNA Kit (Qiagen). ITS1 and ITS2 regions of ribosomal DNA were amplified via PCR using universal fungal primers ITS1F and ITS4. Amplification conditions were: initial denaturation at 95 °C for 5 min, 30 amplification cycles of 95 °C for 30 s, 55 °C for 30 s, 72 °C for 60 s, and a final extension of 72 °C for 10 min (Manter & Vivanco, 2007). Amplification products were visualized on a 1.5% agarose gel, purified, and sequenced commercially via Sanger sequencing. Obtained sequences were compared against reference sequences in the NCBI GenBank database using BLASTn, after trimming low-quality base reads (Q<20). Species-level identification was evaluated based on sequence similarity. For phylogenetic analysis, ITS sequences of related species from the *Umbilicaria* genus were retrieved from GenBank and were aligned using MUSCLE. To identify the nucleotide substitution model, "Find Best DNA/Protein Models (ML)" function was utilized in MEGA 11. Phylogenetic relationships were inferred using the Maximum Likelihood (ML) method under the selected model (K2). The robustness of the inferred clades was evaluated by bootstrap analysis with 1000 replicates.

**Extraction:** Dried and powdered lichen samples were macerated with acetone at a 1:20 (w/v) ratio. The mixture was incubated at room temperature with shaking for 24h in dark conditions. It was then filtered and the solvent was removed using a rotary evaporator (Ranković, Kosanić, & Stanojković, 2011). This procedure was repeated 3 times. Obtained crude extracts were stored at -20°C.

**Antimicrobial assay:** The antimicrobial activity of the *U. deusta* extract was assessed using the broth microdilution method in accordance with Clinical and Laboratory Standards Institute guidelines, document M07 (CLSI, 2024). The *U. deusta* extract was dissolved in dimethyl sulfoxide (DMSO), and using a 96-well plate, serial two-fold dilutions of the extract were prepared in Mueller–Hinton broth (MHB) and tryptic soy broth (TSB) to achieve final concentrations of 160, 80 and 40 µg/ml, in triplicate. The wells were then inoculated with wild-type *S. aureus* ATCC 25923 with a final OD 600 nm of 0.01 to obtain approximately 10<sup>7</sup> CFU/ml. The plate was then incubated at 37°C for 20h with shaking. The growth inhibition was observed visually, in addition to optical density measurement (OD 600nm) in a microplate reader (Cytation 3, Agilent). Vancomycin was used as a positive control, and diluted DMSO at the corresponding concentration were used as the solvent control. Higher concentrations of the extract could not be tested due to limited aqueous solubility and crystallization in broth medium. Final DMSO concentration did not exceed 1% (v/v).

**QS inhibition assay:** QS inhibition was determined quantitatively using the biomonitor strains *S. aureus* USA300agr P2::GFP and USA300agr P3::GFP, kindly provided by James et al. (2013). The strains were constructed from community-acquired pulsed-field type USA300 CA-MRSA (Voyich et al., 2005). These reporter constructs contain the green fluorescent protein (GFP) gene, under the control of the agr P2 and P3 promoters, respectively, allowing real-time monitoring of agr promoter activity in response to QS signals. The GFP gene is integrated at the *geh* locus, while leaving the native agr operon intact. The assay was performed according to the slightly modified method of Bjarnsholt et al. (2010). Briefly, two-fold serial dilutions of the lichen extracts were prepared in black, clear-bottom 96-well microtiter plates with TSB, and bacterial cultures were added to achieve a final OD 600nm = 0.1. Plates were incubated at 37 °C for 20h with continuous shaking, measuring every 30 min. Bacterial growth was monitored by measuring absorbance at 600 nm, while QS activity was assessed by quantifying GFP fluorescence using an excitation wavelength of 485 nm and an emission wavelength of 535 nm according to optimizations in TSB. Background fluorescence from TSB with the corresponding DMSO concentration was measured and subtracted from all

fluorescence values before analysis. At the 20th hour, GFP fluorescence values were normalized to OD 600nm to take growth into account, and the inhibition percentages were calculated.

**Statistical Analysis:** All experiments were performed in at least three independent replicates. Data at the 20th hour are presented as mean values ±SD. The normality of the data was assessed using the Shapiro-Wilk test. However, due to the small sample size, non-parametric tests were preferred. Statistical significance of inhibition was determined using the Kruskal-Wallis test, followed by Dunn's post-hoc test for multiple comparisons. The IC50 value was calculated via log-transformed linear regression analysis by plotting log<sub>10</sub> of concentrations against inhibition percentage. All analyses were performed with a confidence interval of 95%.

## RESULTS

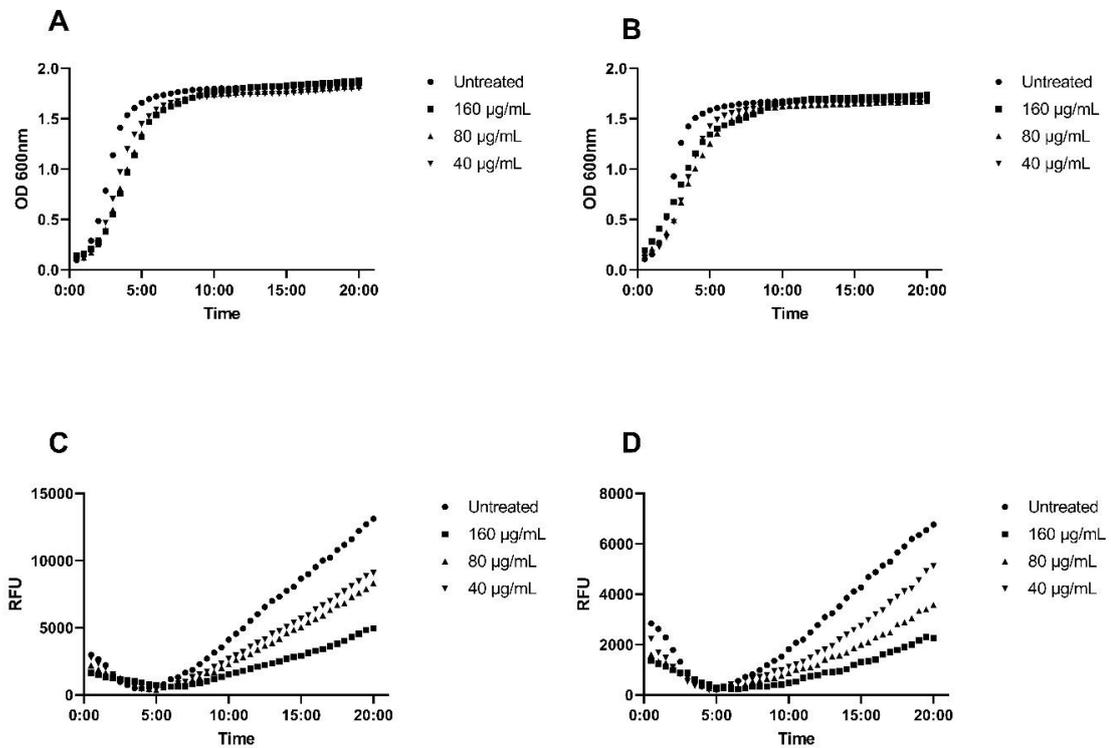
**Molecular identification:** PCR amplification of the ITS1–ITS2 region from the extracted lichen genomic DNA yielded a clear amplicon of the expected size, as confirmed by agarose gel electrophoresis. Following purification and Sanger sequencing, high quality ITS sequences were obtained after trimming low quality bases (Q < 20). Sequence analysis followed by BLASTn comparison against the NCBI GenBank database showed a total score of 569, with 96% query coverage, an E-value of 5 × 10<sup>-157</sup>, and 96.07% sequence identity to *U. deusta* reference sequences. The sequence was deposited in GenBank under accession number GenBank: PX780781.1 (Sequence S1). Moreover, the obtained phylogenetic tree separated *U. deusta* from other closely related species within the genus (Figure S1). These results support the taxonomic identification of the collected lichen material.

**Antimicrobial activity:** No antimicrobial or growth inhibitory activity was observed for the extract under the tested conditions. In MHB, *S. aureus* ATCC 25923 has shown similar growth profiles as the untreated control across all tested concentrations (160, 80, and 40 µg/ml). Higher concentrations could not be evaluated due to the limited solubility of the extract in aqueous medium and visible crystallization at increased doses. Optical density measurements at 600 nm indicated that bacterial growth was not affected by the presence of the extract in either medium. Growth comparisons are shown in supplemental Figure S2.

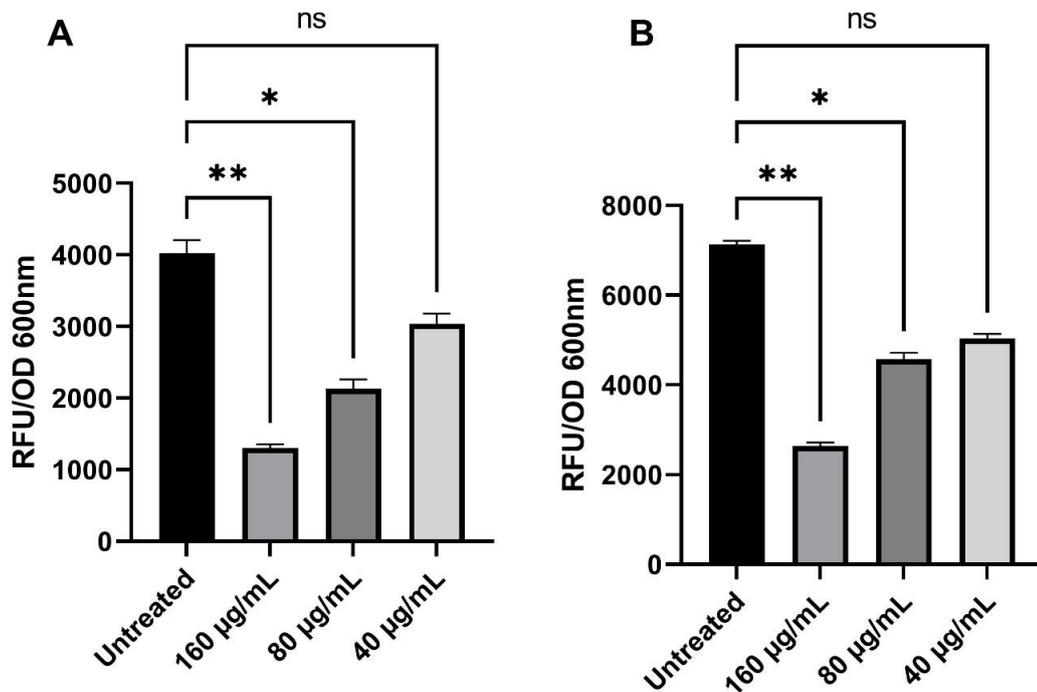
**QS inhibitory activity:** Treatment with the extract at sub-inhibitory concentrations did not significantly affect bacterial growth of the *S. aureus* biomonitor strains USA300agr P2::GFP and USA300agr P3::GFP, as indicated by OD 600nm values relative to the untreated control (Figure 1A and 1B). In contrast, GFP fluorescence measurements revealed a concentration-dependent reduction in agr-driven

reporter activity (Figure 1C and 1D). Both P2 and P3 associated expression levels were decreased. A decrease of  $62.96\% \pm 1.04$  for P2 and a decrease of  $67.68\% \pm 1.36$  for P3

were observed after correction for growth for 160  $\mu\text{g/ml}$  (Figure 2). According to the regression model ( $y = -71.61x + 189.86$ ), the  $IC_{50}$  value was determined as 89.73  $\mu\text{g/ml}$ .



**Figure 1.** Effects of *U. deusta* extracts on *agr*-mediated QS in *S. aureus*. Growth curves of *S. aureus* USA300agr P2::GFP (A) and P3::GFP (B) reporter strains cultured in concentrations of *U. deusta* extract; GFP fluorescence measurements reflecting *agr* P2 (C) and P3 (D) driven reporter activity.



**Figure 2.** QS inhibition by *U. deusta* extract against *S. aureus* *agr* USA300 reporter strains at 20 h. (A) *agr* P2 promoter activity and (B) *agr* P3 promoter activity expressed as RFU/OD 600nm. Data represent three independent experiments. Statistical significance was evaluated compared to the untreated control (\*:  $p < 0.05$ , \*\*:  $p < 0.01$ ; ns, not significant).

## DISCUSSION

This study explored the biological activity of *U. deusta* extract based on prior reports suggesting that lichen-derived secondary metabolites may exert antimicrobial effects. Several *Umbilicaria* species, including *U. cylindrica*, *U. crustulosa*, and *U. decussata*, have previously demonstrated antimicrobial effects against both Gram-positive and Gram-negative bacteria (Buçukoglu et al., 2013; Manojlovic et al., 2012; B. Ranković et al., 2007). However, under the experimental conditions tested, the extract did not exhibit detectable antimicrobial or growth inhibitory effects in either MHB or TSB. This absence of detectable antimicrobial activity in *U. deusta* does not conflict with earlier reports but instead reflects the well known variability in lichen bioactivity across species and conditions. Secondary metabolite profiles in lichens vary with species, geographic origin, environmental factors, substrate, and extraction method (Poulsen-Silva et al., 2025). Recent antimicrobial screening of hydroalcoholic lichen extracts, including *U. crustulosa*, demonstrated measurable antibacterial activity for some species, while others showed limited effects, reinforcing species specific differences in bioactivity (Sevinç et al., 2024). Even within the same genus, differences in metabolite composition and abundance can lead to distinct biological outcomes. Thus, the lack of antimicrobial activity observed here likely results from the specific chemical characteristics of *U. deusta*.

Following the lack of growth inhibition, the study's focus shifted toward evaluating effects on bacterial virulence regulation. Using *agr* P2 and P3-GFP reporter strains derived from the clinically relevant MRSA USA300 lineage, *U. deusta* extract significantly reduced *agr*-mediated QS activity by approximately 60% without affecting bacterial growth. The *agr* system is a master regulator of virulence in *S. aureus*, controlling the expression of toxins, proteases, and other pathogenicity-associated factors (Bodine & Muir, 2025). These findings suggest possible interference with *agr* related signaling rather than indirect effects related to growth inhibition. The observed QS inhibition in an MRSA background highlights the potential relevance of this approach for difficult-to-treat *S. aureus* infections.

The widespread use of antibiotics in cattle, especially for bovine mastitis, contributes significantly to antimicrobial resistance (AMR), thus the need for better control measures and alternative non-antibiotic treatment strategies (Touza-Otero et al., 2024). Selective inhibition of QS without bactericidal activity aligns with the concept of antivirulence strategies, which aim to attenuate pathogenic behavior while minimizing selective pressure for resistance development. Targeting regulatory pathways such as QS is increasingly considered a promising

alternative or complement to conventional antibiotics, particularly for multidrug-resistant pathogens (Song et al., 2025).

Natural secondary metabolites from plants, fungi, and lichens have been shown to interfere with bacterial communication through different mechanisms, including disruption of signal–receptor interactions and suppression of QS-controlled gene expression (Boban et al., 2023; Gökalsın et al., 2019). While direct evidence for lichen-mediated QS inhibition in *S. aureus* remains limited, studies have also shown that lichen metabolites such as evernic acid, in addition to crude extracts, can modulate QS in bacterial pathogens, supporting the relevance of lichens as sources of antivirulence compounds. (Gökalsın et al., 2020; Gökalsın & Sesal, 2016). In this context, the present findings contribute novel evidence that *U. deusta* extracts can modulate QS pathways in *S. aureus*.

A practical limitation encountered in this study was the hydrophobic nature of the crude *U. deusta* extract. Many lichen secondary metabolites are poorly soluble in aqueous media, which limits observable biological effects in water-based assays (Dresler et al., 2025). We were unable to test higher concentrations due to poor solubility and crystallization in aqueous media, which limited assay compatibility. This limitation may have explained the lack of antimicrobial activity and could also have underestimated the QS inhibitory potential of the extract. Future studies using improved formulations, such as better solvents or delivery systems, may help overcome these limitations and allow a more complete evaluation of the antivirulence potential of *U. deusta* extracts.

In conclusion, this study suggests that *U. deusta* may represent a promising source of antivirulence agents against *S. aureus*. *S. aureus* is a common cause of chronic infections such as bovine mastitis and other livestock diseases, and where conventional antibiotic therapy is often ineffective due to antimicrobial resistance. By selectively targeting QS in a clinically relevant MRSA background without affecting bacterial growth, lichen-derived extracts may offer an alternative strategy for mitigating *S. aureus* pathogenicity while reducing the risk of resistance development.

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