JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2019; 3:184-187
https://doi.org/10.30621/jbachs.2019.745

Original investigation

Antimicrobial Effect of Piceatannol, a Resveratrol Metabolite, on Staphylococcus Aureus

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Received: 09.08.2019; **Accepted:** 04.09.2019; **Available Online Date:** 30.09.2019

Cite this article as: Güldaş N, Uysal T, Ellidokuz H, Başbınar Y. Antimicrobial Effect of Piceatannol, a Resveratrol Metabolite, on Staphylococcus Aureus. J Basic Clin Health Sci 2019; 3:184-187.

This study has been presented in 24th European Congress of Clinicial Microbiology and Infectious Diseases (ECCMID) , Barcelona, Spain May 10-13, 2014 as a poster.

ABSTRACT

Objectives: *Staphylococcus aureus* (*S. aureus*) is one of the major human pathogens in both community acquired and nosocomial infections. Heavy increase of antibiotic resistance between *S. aureus* strains became an important public health problem in progress of time. In this study, the antimicrobial effects of piceatannol on *S. aureus* growth was investigated.

Patients and Methods: The antimicrobial effect of piceatannol on a standard *S. aureus* (DSMZ 6148) strain and two clinical *S. aureus strains* (C1 and C2) was tested in vitro at concentrations between 0 and 750 µg/ mL. Tigecycline and gentamicin were used as positive controls. For each strain, the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) values of piceatannol and the control antibiotics were determined separately using the broth microdilution method according to CLSI (Clinical and Laboratory Standards Institute) standards at 24 and 48 h.

Results: After 24 and 48 h of treatment with piceatannol, the average MIC for all tested strains was 283 µg/mL and 383 µg/mL, respectively. Bactericidal activity increased as piceatannol concentration increased for one of the three strains. After 24 and 48 h of treatment with piceatannol, the average MBC for all strains was 717 µg/ mL and 583 µg/ mL, respectively. The *S. aureus* strains were found to be susceptible to tigecycline and gentamicin.

Conclusion: Piceatannol has antimicrobial effect against *S. aureus*; however, more data regarding the effects of this compound on other microorganisms and its bioavailability are needed.

Keywords: Piceatannol, *Staphylococcus aureus*, antimicrobial effect

INTRODUCTION

Staphylococcus aureus is one of the most frequently isolated pathogens among both community-and hospital-acquired infections all around the world (1). *S. aureus* causes serious infections, including skin and soft tissue infections, endocarditis, osteomyelitis, pneumonitis and bloodstream infections (2). In recent years, increasing antibiotic resistance has caused treatment challenges, which has spurred research into novel antimicrobial agents (3–7). In addition to the development of new antibiotics, there is an extensive research on antimicrobial compounds from natural sources. In this context, resveratrol has been used to inhibit the growth of some pathogenic microorganisms, including Gram-positive and Gram-negative bacteria and fungi (8). Specifically, resveratrol has been shown to inhibit growth of *Propionibacterium acnes*, *Helicobacter pylori, Neisseria gonorrhoeae, Neisseria meningitidis* and *Haemophilus ducreyi* (9–15).

Resveratrol, which is a polyphenolic compound (3, 4′, 5-trihydroxystilbene), is synthesized by many plants and is considered as a plant-derived antibiotic. The main sources of resveratrol in the human diet are grapes, red wine and peanuts (16). Piceatannol (3, 3′, 4′, 5-tetrahydroxystilbene) is an analog of resveratrol that has an additional phenolic group at the 3′ position

(17). Piceatannol is a plant-based stilbene derivative (18). It is a main resveratrol metabolite generated in the liver as a result of cytochrome P450 activity. Therefore, resveratrol can be thought of as a pro-drug for piceatannol (19). Piceatannol is structurally similar to resveratrol, and both have similar biological activities (20). It is rare and valuable compound because of its health-enhancing properties (18). Piceatannol, like resveratrol, has strong antioxidant, anti-proliferative and anti-inflammatory effects but has not been as extensively studied (17). In this study, we aimed to investigate the antibacterial activity of piceatannol against *S. aureus.*

MATERIALS AND METHODS

Chemicals

Piceatannol was purchased from Sigma-Aldrich (P0453). Gentamicin and tigecycline were used as positive controls for the susceptibility experiments.

Bacteria strains

In this study, a standard *S. aureus* strain (DSMZ 6148) and two clinical *S. aureus* strains that were isolated from blood (C1 and C2) were used.

Determination of minimum inhibitory concentration and minimum bactericidal concentration

The MIC (minimum inhibitory concentration) and MBC (minimum bactericidal concentration) values of piceatannol against the *S. aureus* strains were measured in cation-adjusted Mueller Hinton Broth (MHB) medium using the broth micro dilution method according to CLSI standards after 24 and 48 h (21). The culture media were obtained from Oxoid (Basingstoke, Hampshire, England). The strains were cultured for 18–24 h on blood agar plates at 37 °C. Colonies from the blood agar plates were used to inoculate MHB medium, which was adjusted to a concentration that yielded an absorbance similar to a 0.5 McFarland standard (1–2 x 10^8 cfu/mL). First, sterile MHB medium was evenly distributed to the wells of an microtiter plate, which were prepared separately for gentamicin, tigecycline and piceatannol. Next, two-fold dilutions of the antimicrobials were added. Lastly, the bacteria suspensions were distributed. Since piceatannol is not water soluble, it was dissolved in dimethyl sulphoxide (DMSO), and the final concentration of DMSO was adjusted to 0.2%. Then, piceatannol was added to the wells of the microtiter plates at concentrations of 0–750 µg/mL. After incubation at 37 °C, the plates were evaluated in a spectrophotometric plate reader at 450 nm at 24^{th} and 48^{th} h. For each antimicrobial agent, spectrophotometric evaluations at every concentration were repeated three times. Control wells containing DMSO without any antimicrobial agents were also tested. The MIC values were determined as the lowest antimicrobial agent concentration that inhibits microorganism replication. The MBC was determined as the lowest antimicrobial agent concentration capable of causing a reduction of more than 99.9% of the initial inoculum growth as assessed by subculture on agar medium.

RESULTS

All of the tested drugs inhibited replication of the tested *S. aureus* strains (Table 1). After 24 h and 48 h of treatment with piceatannol, the average MIC for all of the tested strains was 283 µg/mL and 383 µg/mL, respectively. The tigecycline average MIC value for all strains was 0.125 µg/mL for 24 h and 0.166 µg/mL for 48 h; the gentamicin average MIC value for all strains was 1.66 µg/mL for 24 h and 4 µg/mL for 48 h.

In this study, the bactericidal activity of piceatannol was also examined. Bactericidal activity against one of the three tested strains was observed at high concentrations of piceatannol. After 24 h and 48 h of treatment with piceatannol, the average MBC for all of the tested strains was 717 µg/mL and 583 µg/mL, respectively. On all tested strains, the average gentamicin MBC value was 8 µg/mL for 24 h and 7 µg/mL for 48 h. The average tigecycline MBC value was 128 µg/mL for 24 h on all strains and was 128 µg/mL for 48 h for the C2 isolate but was greater than 128 µg/mL for 48 h on the other strains.

DISCUSSION

In the present study, we examined the antimicrobial activity of piceatannol on three *S. aureus* strains in comparison to gentamicin and tigecycline. Bacterial infections are significant contributors to morbidity and mortality worldwide, and many infections can be attributed to *S. aureus* (22). Antibacterial therapy is a critical tool for the treatment of *S. aureus* infections. However, in recent years, microorganisms have developed resistance to antimicrobials. For this reason, there is strong interest in identifying novel agents with antimicrobial activities (8). In this context, resveratrol, which is a phytoalexin, has been a focus of antimicrobial research. It is also reported that resveratrol shows bacteriostatic activity against certain Gram-positive bacteria, including *Bacillus cereus, Staphylococcus aureus*, and *Enterococcus faecalis* (14). Conversely, Docherty et al. have shown in an *in vitro* study that resveratrol inhibits *Propionibacterium acnes* and has bactericidal activity at the highest tested concentration (200 µg/mL) (9). In similar studies, resveratrol has been shown to inhibit many clinically important bacteria, including *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Helicobacter pylori,* and *Haemophilus ducreyi* (11–13). In addition to the antibacterial activity of resveratrol, the antifungal and antiviral effects of this compound were also studied. Chan et al stated that resveratrol is not effective against cultures of *S. aureus* and *Pseudomonas aeruginosa* on agar plates, but they did show that it inhibits many human pathogenic dermatophytes. They concluded that resveratrol represents a new type of antifungal agent (23). In addition, Jung et al. have observed fungicidal effects of resveratrol on pathogenic fungi (24). Also, Ma et al carried out a study on antibacterial activity of resveratrol on foodborne pathogens. The results of their review paper reveal that because of its chemical properties (phytoalexin and phytopathogen infection response product), it has an antibacterial activity on food pathogens including *Campylobacter jejuni, Escherichia coli, Listeria monocytogenes, S. aureus* and *Vibrio cholerae* (25).

Piceatannol is an analog of resveratrol that has an additional at 3'-OH position. It is more active in terms of anticancer and antioxidant effects than resveratrol. Resveratrol has shown to be beneficial to human health, but its low bioavailability and rapid metabolism restricts its usage during chronic diseases. Piceatannol has more biological activity and has greater bioavailability than resveratrol (20). However, piceatannol has not been as extensively studied as resveratrol (17). In one study which examined the antibacterial activities of resveratrol and piceatannol, the piceatannol IC_{50} value against *P. acnes* strains at 24 h was found as 123 µg/mL, and the IC_{100} value was found as 234 µg/mL (9). In our study, the piceatannol MIC value on *S. aureus* strains at 24 h was found to be 283 µg/mL, which is close to the IC_{100} value of *P. acnes*. At the same time, the tested strains were found to be susceptible to tigecycline and gentamicin. Piceatannol is a less well-known congener of resveratrol. Many *in vitro* studies have confirmed the antioxidant properties, anti-inflammatory effects and chemopreventive potential of piceatannol (17). In addition, there are some publications that state that piceatannol has antileishmanial and antiplasmodial activities (26–28). Our results showed that piceatannol inhibited *S. aureus* and was bactericidal at the highest tested concentration. This study is the first report describing the research and evidence that piceatannol exhibits in vitro antimicrobial activity against *S. aureus*. However, more data on the biological features of piceatannol and its effects on other microorganisms are necessary. In addition, further study is needed to determine if piceatannol is suitable for use as an antimicrobial agent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - NG, YB; Design - NG, YB; Supervision - NG, YB; Fundings - NG, YB, HE; Materials - NG, YB, TU; Data Collection and/or Processing - NG, YB, TU; Analysis and/or Interpretation - NG, YB, TU, HE; Literature Search - NG, YB, TU, HE; Writing Manuscript - NG, YB, TU, HE; Critical Review - NG, YB, TU, HE

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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