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Original Research Article

Microbicidal activity of octenidine oromucosal solution against periodontal bacteria and yeast: an *in vitro* study

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ABSTRACT

Background: Octenidine-containing antiseptic oromucosal solution (OOS) has proven to be effective and safe for temporary bacterial reduction and plaque inhibition in the oral cavity. While its clinical outcomes are encouraging, further research is needed to assess its microbicidal activity against pathogens causing gingivitis and periodontitis.
Methods: We evaluated the *in vitro* microbicidal activity of different product dilutions (v/v) of a commercially available OOS (0.1% (w/v) octenidine dihydrochloride) against 10 periodontopathogen-ic bacteria and three yeast strains using the testing methodology frameworks of DIN EN 13727:2012+A2:2015 (30-s contact time) and DIN EN 13624:2022-08 (60-s contact time), respectively.
Results: The OOS showed high bactericidal activity at 80% (v/v) test concentration, as indicated by the logarithmic reduction factor (lg RF) ≥5. At 50% dilution concentration, bactericidal activity was observed against specific bacteria like *Porphyromonas gingivalis, Prevotella buccalis, Parvimonas micra, Eikenella corrodens, Dialister pneumosintes, Schaalia odontolytica* (*Actinomyces odontolyticus*), and *Campylobacter rectus*. Yeasticidal activity against *Candida albicans* was observed at 80% dilution concentration, whereas *Candida auris* was more susceptible to the OOS and showed lg RF ≥4 even at 50% dilution concentration.
Conclusion: The OOS may be an effective adjunct to periodontal therapy aimed at reducing pathogenic microbial load and inhibiting plaque formation, which may support plaque control strategies.

Keywords: Bactericidal, Mouthrinse, Octenidine dihydrochloride, Oromucosal solution, Periodontopathogens, Plaque inhibition, Yeasticidal

INTRODUCTION

Periodontal diseases, including gingivitis and periodontitis, affect nearly half the global population.[1,2] The onset and progression of periodontal inflammation are associated with dysbiosis, i.e., the shift of the balanced oral microbiota toward pathogenic consortia, including "red-complex" periodontopathogens, such as *Porphyromonas gingivalis, Treponema denticola*, and *Tannerella forsythia*.[2,3] Yeasts, such as *Candida albicans*, have also been detected in the periodontal pockets of patients with chronic periodontitis.[4,5] Additionally, the pathogenesis of these diseases is now understood as the result of three interlinked processes: microbial dysbiosis, the ecological plaque hypothesis, and epigenetic in-fluences.[6,7] Dysbiosis is an imbalance in the resultant community, which contributes to the development of a disease.[7] The ecological plaque hypothesis explains how changes in the local environment, driven by host response, inflammation, and nutrient availability, select for and stabilize these pathogenic communities.[6] Epigenetic influences, such as DNA methylation, histone modifications, and non-coding RNAs, alter host immune responsiveness and partly account for inter-individual differences in disease

susceptibility.[8,9] Taken together, these mechanisms explain how gingivitis, though reversible, may persist and evolve into periodontitis in susceptible individuals, positioning periodontal diseases as the outcomes of complex host–microbe–environment interactions.

The effective management of periodontal diseases requires timely intervention, beginning with accurate assessment of the disease status by a periodontist.[10] This assessment is based on the clinical and radiographic evaluation of gingival inflammation, probing depths, attachment loss, and alveolar bone levels.[11] Although mechanical plaque control is the primary treatment for periodontitis, it does not effectively inhibit plaque formation.[12,13] Hence, adjunctive use of chemical antimicrobial agents, such as mouthrinses, is necessary.[14,15] Such combined strategies aim not only to arrest disease progression but also to promote periodontal health and prevent recurrence, thereby improving both oral and systemic outcomes.

Octenidine dihydrochloride is a well-recognized active ingredient of oral antiseptic preparations.[16-19] It shows broad-spectrum antimicrobial activity owing to its nonspecific mode of action, which also reduces the likelihood of bacterial resistance.[20,21] Clinically, octenidine mouthrinses effectively reduce salivary bacterial counts with minimal toxicity and inhibit plaque formation.[16,17] Further, in orthodontically-treated patients, rinsing with octenidine can significantly reduce the total viable oral bacteria, such as Streptococcus mutans and Lactobacillus species, in saliva.[22] While the clinical results of octenidine are promising, previous studies have focused chiefly on its effects against plaque formation, gingivitis, and total and cariogenic salivary bacteria. Very few studies have evaluated the microbicidal activity of octenidine specifically against periodontopathogens. Therefore, the objective of this study was to evaluate the antimicrobial activity of octenidine dihydrochloride against common periodontopathogens, including both primary organisms, such as the "red-complex" bacteria, and secondary contributors to periodontal diseases. In addition, its efficacy against drug-resistant *Candida auris* was examined to extend its recognized antimicrobial spectrum.

To ensure reproducibility and comparability, the study applied standardized EN 13727/13624 quantitative suspension tests (phase 2/step 1) to oral pathogens, an approach not previously reported in this context. Accordingly, the in vitro microbicidal activity of different dilution concentrations of a commercially available 0.1% octenidine dihydrochloride OOS against a range of periodontal bacteria and yeast strains was investigated using standard testing methods.

METHODS

Test product

A commercial 0.1% (w/v) octenidine dihydrochloride oromucosal solution (octenident® antiseptic, Schülke & Mayr GmbH, Norderstedt, Germany), a clear, colorless, ready-to-use OOS with mint flavor. It was stored in a dark environment at room temperature (approximately 20°C) as per the manufacturer's instructions. The study period was from April 2022 to February 2023, and from September 2022 to March 2023.

Microbial strains

Ten periodontopathogenic bacteria were included in the study (Table 1). These, predominantly anaerobic or microaerophilic bacteria, were cultured using appropriate nutrient media and conditions. The yeast strains tested in the study are listed in Table 2. Two biological and two technical replicates were included for each experiment.

Table 1: Bacterial strains employed in the study and their culture conditions.

Bacteria	Strain	Culture conditions and media laboratory 1	Culture conditions and media laboratory 2
Fusobacterium nucleatum	ATCC 25586, DSM 15643	Anaerobic, 37°C, 2 days, hemin- and vitamin K-enriched medium	Columbia blood agar, anaerobic, 36°C±1°C, 3 days
Aggregatibacter actinomycetemcomitans	ATCC 43717	10% carbon dioxide, 37°C, 2 days, 5% sheep blood agar	Brain heart infusion agar, 36° C±1°C, 3 days, 95% air, 5% carbon dioxide
Porphyromonas gingivalis	ATCC 33277, DSM 20709	Anaerobic, 37°C, 2 days, 5% sheep blood agar	Schaedler agar, anaerobic, 36°C±1°C, 5 days
Prevotella buccalis	ATCC 35310, DSM 20616	Anaerobic, 37°C, 2 days, 5% sheep blood agar	Schaedler agar, anaerobic, 36°C±1°C, 7 days
Dialister pneumosintes	DSM 11619	10% carbon dioxide, 37°C, 4 days, hemin- and vitamin K-enriched medium	Columbia blood agar, anaerobic, 36°C±1°C, 3 days
Campylobacter rectus	ATCC 33238, DSM 3260	10% carbon dioxide, 37°C, 2 days, 5% sheep blood agar	Campylobacter rectus agar, anaerobic, 36°C±1°C, 7 days
Capnocytophaga gingivalis	ATCC 33624, DSM 3290	10% carbon dioxide, 37°C, 3 days, 5% sheep blood agar	Capnocytophaga agar, anaerobic, 36°C±1°C, 3 days

Continued.

Bacteria	Strain	Culture conditions and media laboratory 1	Culture conditions and media laboratory 2
Eikenella corrodens	ATCC 23834, DSM 8340	10% carbon dioxide, 37°C, 2 days, 5% sheep blood agar	Columbia blood agar, microaerophile, 36°C±1°C, 3 days
Parvimonas micra	ATCC 33270, DSM 20468	anaerobic, 37°C, 3 days, 5% sheep blood agar	Columbia blood agar, anaerobic, 36°C±1°C, 3 days
Schaalia odontolytica (Actinomyces odontolyticus)	ATCC 17982	10% carbon dioxide, 37°C, 2 days, 5% sheep blood agar	Columbia blood agar, microaerophile, 36°C±1°C, 2 days

ATCC: American type culture collection, DSM: German collection of microorganisms

Evaluation of bactericidal activity

The DIN EN 13727:2012+A2:2015 standards were followed with some modifications: bacteria comprising the normal oral flora were selected and obtained from DSM and ATCC cultures.[23] A testing environment of 33°C, under clean conditions, was maintained using water baths and room air conditioning.

Table 2: Yeast strains tested in the study.

Yeast	Strain
Candida albicans	ATCC 10231
Candida auris	DSM 21092
Candida auris	DSM 105986

ATCC: American type culture collection, DSM: German collection of microorganisms

Each milliliter of octenident® antiseptic contains 1 mg of octenidine dihydrochloride (0.1% w/v). The test product was diluted with sterile distilled water to obtain the following product test concentrations: 0.01%, 0.1%, 50%, and 80% (v/v). In addition, the ready-to-use formulation was tested at 97% (v/v) in accordance with DIN EN 13727:2012+A2:2015.[23] The bacteria were cultured at two independent laboratories, using specific media and culture conditions to ensure the robustness of the results. The cultures were then examined at both laboratories to identify colonies. If no colonies were visible or if they were too small, the bacteria were cultivated under the same culture conditions for 2 more days and reevaluated.

Quantitative suspension tests for bactericidal activity

Quantitative suspension tests were performed at the temperature of 33°C according to the dilution-neutralization method or membrane filtration method of EN 13727 (5.5.2 or 5.5.3). All tests involved a 30-s contact time, and the necessary validations (control of the test conditions A, control of the inactivator B, and procedure validation C) were within the acceptance limits specified by EN 13727/13624.

Comparative tests for bactericidal activity

Comparative tests were performed according to the EN 13727 (5.5.2.2 or 5.5.3.2) protocol under clean conditions with 0.3 g/l bovine serum albumin (bovine serum albumin fraction V). Further, control procedures were performed according to EN 13727 (5.5.2.3-5.5.2.5 or 5.5.3.3-5.5.3.5).

Dilution-neutralization method for bacteria

After 2 minutes of equilibration between one part interfering substance (organic load: 0.3 g/l bovine se-rum albumin) and one part test organism solution, the two parts were mixed with eight parts of the OOS. At the end of the contact time, an aliquot of 1 ml was transferred to a neutralizer solution of 9 ml. In laboratory 1, the neutralizer comprised polysorbate 80 (30 g/l), lecithin (3 g/l), saponin (30 g/l), and L-histidine (1 g/l) in double distilled water. In Laboratory 2, the neutralizer comprised polysorbate 80 (30 g/l), lecithin (3 g/l), and cysteine (1 g/l); for some preparations, a diluent containing polysorbate 80 (5 g/l) was used instead. After neutralization for 10 s, a sample of 1 ml was taken in duplicate, and agar plates were inoculated.

Membrane filtration method for bacteria

After 2 minutes of equilibration between one part interfering substance (organic load: 0.3 g/l bovine se-rum albumin) and one part test organism solution, the two parts were mixed with eight parts of the OOS. At the end of the contact time, two aliquots of 0.1 ml were transferred into a separate membrane filtration apparatus. The filters were immediately rinsed with at least 150 ml, but no more than 500 ml, of rinsing liquid. The procedure was completed by filtering 50 ml of water. The membranes were then transferred to separate agar plates.

Evaluation of yeasticidal activity

The DIN EN 13624:2022-08 standards were followed with modifications: the testing temperature was maintained at 33°C using water baths and room air conditioning.[24] The load substances included 0.08% mucin Type I-S, 0.25% bovine serum albumin, and 0.35% yeast ex-tract to better simulate oromucosal conditions. The yeast strains were exposed to different OOS concentrations (10%, 50%, and 80%) for 60 s. In case of ready-to-use products, the resulting concentration is 97% (v/v).

Calculation of bactericidal/yeasticidal activity

The bactericidal and yeasticidal activities of the OOS were evaluated based on the logarithmic reduction factor (l g

RF). As per the DIN EN 13727:2009-08, lg RF was calculated using the formula: lg RF = lgN0 – lgNa (lgN0: number of living cfu/ml at the beginning of contact time; ¬lgNa: number of living cfu/ml at the end of contact time). According to the DIN EN standards, the test product was considered bactericidal, if the lg RF was ≥5, and yeasticidal, if the lg RF was ≥4. The lowest dilution concentration demonstrating lg RF ≥5 for each bacterial strain and lg RF ≥4 for each yeast strain was recorded.

RESULTS

Bactericidal activity of octenidine

Data from both the laboratories showed that the OOS exhibited strong bactericidal activity at 80% dilution concentration, with the lg RF exceeding 5 for all bacterial strains, except for *A. actinomycetemcomitans*. This organism showed a lg RF ≥5 in laboratory 1 but narrowly missed the threshold with a lg RF of 4.89 in laboratory 2 (Table 3). However, it was susceptible to the bactericidal effects of the OOS at 97% dilution concentration. Notably, octenidine showed bactericidal activity against the majority of bacterial strains at a 50% concentration as well. The bactericidal effect of the OOS was lowest at 0.01% and 0.1% dilution concentrations for all bacterial strains.

Table 3: Bactericidal activity of the octenidine oromucosal solution.*

Bacterial strain	lg RF (80% dilution concentration) laboratory 1	lg RF (80% dilution concentration) laboratory 2
Capnocytophaga gingivalis	>5.28	>5.06
Porphyromonas gingivalis	>5.23	>5.54
Prevotella buccalis	>5.24	5.06
Parvimonas micra	>5.41	>5.04
Eikenella corrodens	>5.26	>5.05
Aggregatibacter Actinomycetem-comitans	>5.22	4.89
Fusobacterium nucleatum	5.26	>5.06
Dialister pneumosintes	>5.20	>5.49
Schaalia odontolytica (Actinomyces odontolyticus)	>5.09	>5.10
Campylobacter rectus	>5.09	>5.09

lg RF, log reduction factor, *octenident® antiseptic (Schülke & Mayr GmbH, Norderstedt, Germany)

Yeasticidal activity of octenidine

Octenidine displayed strong yeasticidal activity at 80% concentration (Table 4). Additionally, both *C. auris* strains (DSM 21092, DSM 105986) were susceptible to the OOS even at 50% dilution concentration, whereas *C. albicans* did not pass the lg-RF ≥4 threshold at 50% dilution concentration.

Table 4: Yeasticidal activity of the octenidine oromucosal solution.*

Yeast strain	lg RF (80% dilution concentration)
Candida albicans	>4.40
***Candida auris* (DSM 21092)**	>4.74
***Candida auris* (DSM 105986)**	>4.58

lg RF, log reduction factor, *octenident® antiseptic (Schülke & Mayr GmbH, Norderstedt, Germany)

DISCUSSION

This *in vitro* study evaluated the microbicidal activity of a commercially available 0.1% octenidine OOS against 10 periodontopathogenic bacterial strains and three yeast strains using standardized EN 13727/1624 suspension tests across two independent laboratories. The solution demonstrated consistent bactericidal activity at the EN-mandated 80% dilution, achieving lg RF >5 against all tested bacterial strains in laboratory 1 data. Only *A. actinomycetemcomitans* narrowly missed the threshold in laboratory 2; however, it was found effective at 97% dilution. Given the proximity to the threshold, this difference may reflect biological variability rather than a true lack of bactericidal activity. The OOS also demonstrated yeasticidal activity against *C. albicans* and *C. auris* at 80% dilution concentration with a lg RF >4. These findings provide reproducible evidence that octenidine exhibits broad-spectrum antimicrobial activity against organisms relevant to periodontal inflammation.

Periodontal diseases are now understood as the outcomes of microbial dysbiosis, in which a shift from eubiosis toward pathogenic consortia drives gingival inflammation and tissue destruction.[25] Octenidine may therefore serve as an adjunctive therapy that suppresses pathogenic overgrowth, reduces microbial burden, and supports the restoration of eubiosis rather than indiscriminate elimination of the oral micro-biota. Within this ecological framework, the broad-spectrum antimicrobial profile demonstrated here supports the potential utility of octenidine in the management of periodontal inflammation.

The clinical relevance of octenidine is further underscored by evidence comparing it with chlorhexidine, a widely used reference antiseptic. Randomized clinical trials and systematic reviews have reported that 0.1% octenidine mouthrinses are at least as effective as chlorhexidine in reducing plaque formation and gingival inflammation.[22,26,27] While chlorhexidine remains the benchmark oral antiseptic, its long-term use is limited by side effects, including tooth discoloration, mucosal irritation, supragingival calculus formation, cytotoxicity,

and taste alteration.[22] In contrast, octenidine has been consistently reported as well-tolerated with minimal or no side effects, while achieving comparable antiplaque and antimicrobial efficacy, supporting its potential as a clinically viable alternative.[16,22] Thus, the current findings support the potential of octenidine as a viable alternative to chlorhexidine, particularly for patients requiring prolonged antiseptic use where reduced side effects are clinically advantageous.

Further, in addition to the bacterial complexes, the periodontal pocket also serves as a niche for yeast strains.[28,29] *C. auris* is an emerging multidrug-resistant nosocomial pathogen that has also been isolated from the pharynx, nasal passages, and trachea.[30] Its inclusion in the study provides a preemptive, and therefore precautionary, approach aimed at extending the antimicrobial spectrum assessed for octenidine and addressing potential oropharyngeal transmission risks in immunocompromised patients. It should be noted, however, that this does not imply that the OOS is intended to treat nosocomial infections; rather, its oromucosal application may help reduce colonization burden in the oral cavity.

The broad-spectrum microbicidal action of octenidine dihydrochloride is attributable to its ability to dis-rupt the cell membrane of bacteria and yeast.[20] Octenidine (N, N′-(1,10 decanediyl-di-1[4H]-pyridinyl-4-ylidene) bis-(1-octanamine) dihydrochloride) is a quaternary ammonium compound of the bipyridine family, and its amino-pyridine components contribute to the mesomeric distribution of cationic charge.[21] The two cationic pyridine components are separated by 10 methylene groups, with two terminal hydrophobic octanyl groups. Due to this structure, octenidine is an amphipathic molecule that resembles membrane-active antimicrobial peptides.[31,32] Its cationic and hydrophobic character contributes to its interaction with the bacterial cell membrane. Being positively charged, octenidine binds to the negatively charged microbial cell membrane and disrupts its structural integrity.[33] On adhering to the bacteria, octenidine neutralizes the bacterial surface charge through electrostatic interactions and immediately penetrates the thick cell wall to reach the cell membrane. Further, the hydrophobic hydrocarbon chains of octenidine interfere with the fatty acyl chains of the cell membrane and significantly disturb the packing order of bacterial phospholipids. As octenidine does not distinguish between these lipids, its action mechanism lacks selectivity toward microorganisms with varying cell envelope structures and compositions. This nonspecific mode of action involving purely physical interactions may explain the strong and broad-spectrum activity of octenidine.[20,21] Moreover, the rapid bactericidal mechanism of octenidine targets critical membrane properties, reducing the likelihood of bacterial resistance.[34] In fact, it was found to effectively destroy the preformed biofilms of *S. aureus*, methicillin-resistant *S. aureus*, and vancomycin-resistant *S. aureus in vitro*.[35] The broad-spectrum activity of OOS against periodontal bacterial complexes observed in the present study is consistent with its proposed mechanism of action.

Different clinical studies have reported the antiplaque efficacy of octenidine dihydrochloride. A randomized, placebo-controlled, clinical trial of 201 healthy adults demonstrated the efficacy of octenidine mouthrinse in reducing salivary bacterial counts, inhibiting plaque formation over 5 days, and reducing gingival inflammation.[16] In a randomized, placebo-controlled trial of 90 patients with gingivitis, octenidine mouthrinse was found to significantly reduce salivary bacterial counts while showing low toxicity.[17] In addition, octenidine dihydrochloride has a sustained effect on the skin and in the oral cavity.[36] A recent systematic review revealed that rinsing with 0.1% octenidine for 30–60 s inhibited plaque formation by 38.7%–92.9% (within 4 days to 3 months of use), which was either equal to or greater than that achieved with chlorhexidine gluconate (36.4–68.37%).[22] Furthermore, rinsing with 0.1% octenidine reduces microbial growth by up to 5.3 CFU/ml (log10), with superior efficacy over chlorhexidine gluconate preparations.[22] However, research on the antimicrobial activity of octenidine specifically against periodontopathogens is limited. The results of the present study demonstrate the microbicidal activity of octenidine against periodontopathogens, indicating its potential application as an adjunct therapy in periodontitis.

These in vitro experimental conditions do not fully replicate the complex environment of the oral cavity. Under physiological conditions, continuous flow of gingival crevicular fluid and saliva, along with innate and adaptive immune responses, dynamically influence microbial colonization and biofilm persistence. However, the quantitative suspension method provides a standardized, reproducible assessment of anti-microbial efficacy under controlled conditions, allowing direct comparison with European Norm acceptance criteria. Furthermore, suspension tests do not capture biofilm-associated tolerance, which is particularly relevant given that periodontal pathogens predominantly exist in biofilm communities; future work should test mature multispecies biofilms or *ex-vivo* plaque models. Further, the microbial strains utilized in the study were sourced from the oral flora of healthy individuals, potentially limiting the applicability of our findings to patients with gingivitis and periodontitis.[37]

Nevertheless, given the broad-spectrum activity inherent to octenidine and its action mechanism that mitigates antimicrobial resistance, the outcomes of this study hold promise for translation into clinical practice. Future investigations should address these real-world complexities by evaluating the efficacy of octenidine in a microbial environment closely mimicking the natural periodontal ecosystem. Further research could involve the use of mixed cultures comprising bacteria and yeast strains obtained from individuals with diverse periodontal statuses.

CONCLUSION

The study provides a comprehensive microbial coverage, encompassing both primary and secondary periodontopathogens, including multidrug-resistant *C. auris*. By applying standardized EN 13727/13624 quantitative suspension tests, the study ensures reproducibility and regulatory comparability, thereby filling an important gap in the current literature. Octenidine demonstrated in vitro microbicidal activity against a panel of periodontopathogens at 80% dilution concentration, highlighting its potential as an adjunct to mechanical periodontal therapy. Importantly, the OOS has the potential to reduce colonization burden of multidrug-resistant *C. auris* in the oropharyngeal cavity, as suggested by its *in vitro* yeasticidal activity. However, clinical use should follow product labeling and professional guidance.

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