

Comparative In Vitro Antifungal Activity of 0.2% Chlorhexidine Gluconate and 1% Povidone-Iodine Oral Antiseptic Solutions Against *Candida albicans*

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Abstract

Alterations in the oral microbiota of mechanically ventilated intensive care unit (ICU) patients increase the risk of *Candida albicans* colonization, which may contribute to prolonged hospitalization and higher morbidity. Chlorhexidine gluconate and povidone-iodine are commonly used oral antiseptics; however, direct evidence comparing their antifungal activity at clinically used concentrations remains limited. This study compared the in vitro antifungal activity of 0.2% chlorhexidine gluconate and 1% povidone-iodine against *Candida albicans*. This laboratory experimental study used a post-test-only control group design. Antifungal activity was assessed using the Kirby–Bauer disk diffusion method with a standardized *Candida albicans* suspension adjusted to the 0.5 McFarland standard. Sterile normal saline served as the negative control. Inhibition zone diameters were measured after 24 hours of incubation at 37°C. Data from 20 replicates per group were analyzed using the Mann–Whitney U test. The 0.2% chlorhexidine gluconate group produced a significantly larger median inhibition zone than the 1% povidone-iodine group [20 mm (range, 19–20 mm) vs. 11 mm (range, 10–11 mm); $p < 0.001$], while the negative control showed no inhibition. These findings indicate that 0.2% chlorhexidine gluconate has greater in vitro antifungal activity against *Candida albicans* than 1% povidone-iodine. Further MIC/MFC, biofilm-based, and clinical studies are recommended.

Keywords: *Candida albicans*; povidone-iodine; chlorhexidine gluconate; oral antiseptic; in vitro

INTRODUCTION

Critically ill patients requiring mechanical ventilation often experience alterations in their oral microbiota due to reduced mechanical stimulation, decreased salivary flow, and microbial colonization associated with medical devices. These conditions promote the proliferation of opportunistic pathogens such as *Candida albicans* (Carpenter, 2020). The use of oral antiseptics plays a crucial role in maintaining oral hygiene and preventing ventilator-associated pneumonia (VAP). Oral antiseptic agents, particularly chlorhexidine gluconate and povidone-iodine, are commonly used in intensive care units (ICUs) at varying concentrations to reduce microbial colonization. The most frequently used concentrations are 0.2% for chlorhexidine gluconate and 1% for povidone-iodine; however, evidence regarding their effectiveness remains inconsistent

(Zhao et al., 2020). Furthermore, studies specifically evaluating the antifungal activity of these concentrations against *Candida albicans* are still limited.

ICU patients with poor oral hygiene are at increased risk of *Candida* spp. Overgrowth. The increasing morbidity and mortality associated with *Candida* infections contribute substantially to healthcare costs. These infections account for approximately 31.1% of hospitalization costs among fungal diseases and are associated with prolonged hospital stays (Benedict et al., 2019). Patients with *Candida* infections have an average hospital stay of 11.7 days, compared to 5.4 days in non-infected patients (Rayens & Norris, 2022). Colonization by *Candida* spp. may progress to esophageal candidiasis and, in cases of mucosal barrier disruption, may lead to invasive candidiasis, including candidemia and deep organ infections. Treatment remains challenging due to the limited classes of antifungal agents—polyenes, azoles, and echinocandins—as well as their toxicity and limited selectivity, which are related to the biological similarities between fungal and mammalian eukaryotic cells (Vila et al., 2020).

Chlorhexidine gluconate is a broad-spectrum antiseptic effective against Gram-positive bacteria, Gram-negative bacteria, and *Candida* spp., and is widely used due to its ease of application, safety, and cost-effectiveness. However, its effectiveness in reducing fungal colonization, particularly on the skin and oral mucosa, remains limited (Nascimento et al., 2024). Povidone-iodine is also widely used due to its strong bactericidal properties; however, its antifungal activity is less well established. Previous studies have shown that oropharyngeal colonization was significantly reduced in patients receiving 0.12% chlorhexidine gluconate compared to placebo on day 3 (Imakiire et al., 2024). In contrast, a meta-analysis concluded that chlorhexidine gluconate at various concentrations was not effective in reducing VAP and is not recommended for routine use (De Cassai et al., 2024). Both chlorhexidine gluconate and povidone-iodine demonstrate comparable effectiveness as skin antiseptics; however, chlorhexidine gluconate exhibits a lower minimum inhibitory concentration (MIC) against bacterial growth compared to povidone-iodine (Smock et al., 2018).

Although chlorhexidine gluconate and povidone-iodine are widely used as oral antiseptics in ICU settings, existing evidence has mainly focused on their effects on bacterial colonization, oral hygiene, and VAP prevention. Direct evidence comparing the *in vitro* antifungal activity of clinically used oral concentrations, particularly 0.2% chlorhexidine gluconate and 1% povidone-iodine, against *Candida albicans* remains limited. Therefore, it remains unclear which of these two oral antiseptics provides greater inhibitory activity against *Candida albicans* under laboratory conditions. To address this gap, the present *in vitro* study directly compared the antifungal activity of 0.2% chlorhexidine gluconate and 1% povidone-iodine against *Candida albicans* by measuring the diameter of inhibition zones. This *in vitro* study provides preliminary laboratory evidence on the comparative antifungal activity of two commonly used oral antiseptic concentrations against *Candida albicans*.

METHOD

This *in vitro* experimental study employed a post-test-only control group design to compare the antifungal activity of 0.2% chlorhexidine gluconate and 1% povidone-iodine against *Candida albicans*. The independent variable was the type of oral antiseptic, whereas the dependent variable was antifungal activity, expressed as the diameter of the inhibition zone in millimeters. A clinical isolate of *Candida albicans* was obtained from the culture collection of the Microbiology Laboratory of Sultan Agung Islamic Teaching Hospital, Semarang, Indonesia. The isolate had originally been recovered from an oral mucosal swab of an ICU patient with a Candida score of ≥ 3 . The Candida score was calculated based on the following variables: total parenteral nutrition = 1, surgery = 1, multifocal Candida colonization = 1, and severe sepsis = 2. Only a pure Candida

albicans culture free from contamination by other oral microorganisms was included. Fresh cultures less than three days old were used, and all culture media were sterile. The fungal suspension was adjusted to the 0.5 McFarland standard using a densitometer. The number of replicates was determined using Federer's formula. Based on this calculation, the required number of replicates was rounded to 20 replicate assays per treatment group. Accordingly, 20 replicate assays were performed for the 0.2% chlorhexidine gluconate group and 20 replicate assays for the 1% povidone-iodine group. Sterile normal saline was used as the negative control.

Oral mucosal swab collection was performed in accordance with the swab sampling procedure established by the Microbiology Laboratory of Sultan Agung Islamic Teaching Hospital. *Candida albicans* was confirmed through presumptive identification on CHROMagar Candida medium, Gram staining, and germ tube testing. The identification results were compared with the reference strain *Candida albicans* ATCC® 10231™, and species-level identification was further validated using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Antifungal activity was evaluated using the Kirby–Bauer disk diffusion method. Inhibition zones were measured in two perpendicular directions using a caliper, and the mean diameters were recorded in millimeters. The study was conducted in March 2026 at the Microbiology Laboratory of Sultan Agung Islamic Teaching Hospital, Semarang, Indonesia.

Statistical analysis was performed using SPSS software. Differences between groups were analyzed using the Mann–Whitney U test because the data did not meet the normality assumption required for an independent-samples t-test. Statistical significance was set at $p < 0.05$. This study was approved by the Health Research Ethics Committee of Sultan Agung Islamic Teaching Hospital, Semarang, Indonesia, with approval number 21/KEPK-RSISA/II/2026. Permission to conduct the study was also obtained from the Director of Sultan Agung Islamic Teaching Hospital.

RESULTS AND DISCUSSION

This study was conducted in March 2026 at the Microbiology Laboratory of Sultan Agung Islamic Teaching Hospital, Semarang. The aim of this study was to determine the difference in effectiveness between 0.2% chlorhexidine gluconate and 1% povidone-iodine against the growth of *Candida albicans* in vitro. The *Candida albicans* isolate used in this study was obtained from the Microbiology Laboratory of Sultan Agung Islamic Teaching Hospital, collected from oral mucosal swabs of intensive care unit patients. Identification of *Candida albicans* was performed using Gram staining, the germ tube test, Chromogenic Candida agar (CHROMagar Candida), and confirmation by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). The results of Gram staining, the germ tube test, and CHROMagar Candida are presented in Figure 1.

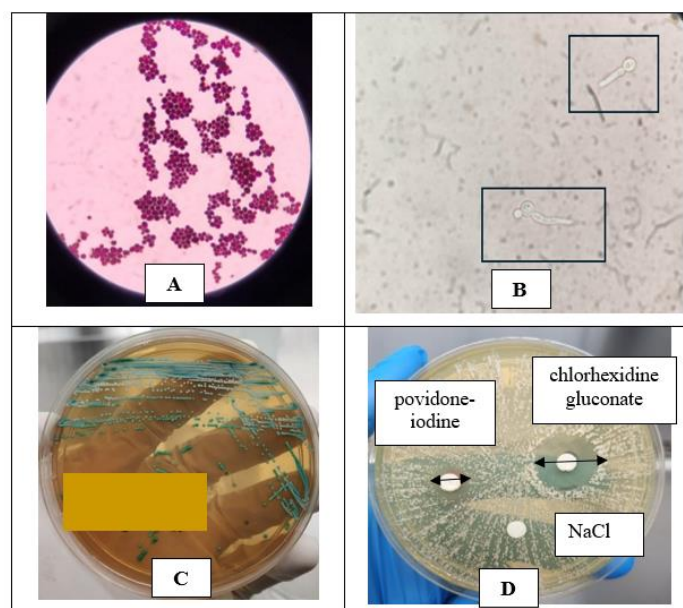


Figure 1. Results of Gram staining (A), Germ tube test (B), CHROMagar Candida (C), and inhibition zone test using chlorhexidine gluconate and povidone-iodine (D).

Gram staining revealed oval, purple yeast cells that were larger than bacterial cells, with some showing budding (A). The germ tube test was performed by incubating the fungal isolate in serum at 37°C for 2 hours. The results demonstrated germ tube formation, appearing as short hyphae-like extensions emerging directly from the yeast cells, which is consistent with the characteristics of *Candida albicans* (B). Growth on CHROMagar Candida medium showed green-turquoise colonies, consistent with the characteristic appearance of *Candida albicans* (C). The inhibition zone test results showed that chlorhexidine gluconate produced a larger inhibition zone than povidone-iodine (D). MALDI-TOF MS confirmed the isolate as *Candida albicans* with a score value of 2.00, indicating reliable species-level identification. The negative control (sterile normal saline) produced no measurable inhibition zone (0 mm), confirming that the observed inhibition was attributable to the test agents. Table 1 summarizes the inhibitory activity of 0.2% chlorhexidine gluconate and 1% povidone-iodine against the growth of *Candida albicans*.

Table 1. Inhibitory activity of 0.2% chlorhexidine gluconate and 1% povidone-iodine against the growth of *Candida albicans*

No	Inhibition Zone of <i>Chlorhexidine</i> <i>gluconate</i> 0.2%	Inhibition Zone of (<i>Povidone</i> <i>Iodine</i> 1%)	<i>p</i>
1.	20 mm	10 mm	<0.001*
2.	20 mm	11 mm	
3.	20 mm	11 mm	
4.	20 mm	10 mm	
5.	20 mm	11 mm	
6.	19 mm	10 mm	
7.	19 mm	11 mm	
8.	20 mm	11 mm	
9.	20 mm	11 mm	
10.	19 mm	10 mm	
11.	20 mm	11 mm	
12.	20 mm	11 mm	
13.	19 mm	11 mm	
14.	19 mm	10 mm	
15.	20 mm	11 mm	
16.	20 mm	11 mm	
17.	20 mm	11 mm	
18.	20 mm	10 mm	
19.	20 mm	10 mm	
20.	19 mm	10 mm	
Median (min–max)	20 (19-20) mm	11(10-11) mm	

* Data were analyzed using the Mann–Whitney U test.

Based on the analysis of inhibition zone diameters, 0.2% chlorhexidine gluconate demonstrated greater effectiveness compared to 1% povidone-iodine against the growth of *Candida albicans*. This was evidenced by the median inhibition zone diameter of chlorhexidine, which was 20 mm (range: 19–20 mm), higher than that of povidone-iodine, which had a median value of 11 mm (range: 10–11 mm). Although a statistically significant difference was observed between the two groups, both agents were classified within the same category of “strong” antimicrobial activity according to the classification of Davis and Stout, as they exhibited inhibition zone diameters ranging from 10 to 20 mm. The inhibition zone, or clear area surrounding the test disc, reflects the antimicrobial potential of the tested agent (Hossain, 2024). The larger inhibition zone observed with chlorhexidine indicates a stronger antifungal activity compared to povidone-iodine, which may be attributed to its mechanism of action involving disruption of cell membrane permeability. Chlorhexidine induces the leakage of intracellular components, including calcium and magnesium ions, as well as the loss of potassium ions, and is also capable of inhibiting biofilm formation (Brookes et al., 2020).

The wider inhibition zone produced by chlorhexidine can be explained by fundamental differences in the mechanism of action and physicochemical behaviour of the two agents. Chlorhexidine gluconate is a cationic bisbiguanide that, at physiological pH, carries a strong positive charge and binds electrostatically to the negatively charged phosphate and carboxyl groups of the *Candida albicans* cell wall mannoproteins and to the phospholipids of the cytoplasmic membrane (Garcia-Rubio et al., 2020). This high binding affinity confers substantivity, allowing the molecule to remain bound and to be released gradually, so that antifungal contact is sustained throughout the diffusion assay. Once bound, chlorhexidine increases membrane permeability and causes leakage of intracellular potassium together with displacement of calcium and magnesium ions, and at higher local concentrations it precipitates cytoplasmic contents. Beyond direct membrane disruption, sub-lethal concentrations of

chlorhexidine have been shown to inhibit *Candida albicans* by disrupting reactive oxygen species and iron–copper homeostasis, triggering mitochondrial dysfunction and apoptosis-like cell death, while also impairing adhesion and biofilm formation (Jiang et al., 2023). This multi-step fungicidal cascade, combined with residual surface activity, accounts for the larger zone of inhibition. In contrast, the antifungal activity of povidone-iodine depends on the release of free molecular iodine from the polyvinylpyrrolidone carrier, which oxidizes proteins, nucleotides and membrane fatty acids in a multitarget manner (Lepelletier et al., 2020). However, free iodine is highly reactive and short-lived, is rapidly consumed by organic material, lacks substantivity, and diffuses unevenly through the agar; moreover, the 1% oral formulation contains only approximately 0.1% available iodine. These factors limit sustained diffusion and produce a smaller, more sharply demarcated inhibition zone despite the intrinsic broad-spectrum activity of the agent.

Previous studies have demonstrated that oral antiseptic chlorhexidine gluconate at a higher concentration (4%) is capable of rapidly killing *Staphylococcus xylosus*, whereas povidone-iodine at a higher concentration (5%) can also eliminate the same bacteria but requires a longer killing time of approximately 2 minutes. The same study reported that 4% chlorhexidine gluconate was able to eradicate *Methicillin-resistant Staphylococcus aureus* (MRSA) within 2 minutes and achieved complete colony reduction within 15 minutes (Anagnostopoulos et al., 2018). Another study comparing 0.2% chlorhexidine gluconate with a combination of 0.2% chlorhexidine gluconate and herbal extracts against *Streptococcus mutans*, using dilution methods to determine minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), reported MIC and MBC values ranging from 1.25–2.5 µg/mL and 15–>25 µg/mL, respectively. Pure chlorhexidine exhibited higher antibacterial activity compared to chlorhexidine gluconate combined with herbal extracts (Mensitieri et al., 2023). These findings suggest that chlorhexidine gluconate possesses both antibacterial and antifungal properties.

Studies on povidone-iodine have shown that a 2% concentration can reduce salivary viral load in COVID-19 patients (Nazrine et al., 2023). Similarly, povidone-iodine at a concentration of 7% diluted to 1:30 (0.23%) has been demonstrated in vitro to exhibit bactericidal effects against *Klebsiella pneumoniae* and *Streptococcus pneumoniae*, as well as virucidal activity against Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Influenza A (H1N1), and rotavirus (Eggers et al., 2018). Furthermore, 10% povidone-iodine has been shown to inhibit the growth of *Streptococcus spp.*, *Methicillin-resistant Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Porphyromonas gingivalis* in the oropharynx of mechanically ventilated patients for up to 3 hours without disrupting the balance of oral microbiota (Tsuda et al., 2020). These findings confirm that povidone-iodine exhibits broad-spectrum antibacterial and antiviral activity. In the present study, povidone-iodine also demonstrated antifungal activity; however, the resulting inhibition zone was smaller than that of chlorhexidine gluconate, indicating comparatively lower efficacy.

The present findings are consistent with previous international studies evaluating antifungal activity. Dehghani Nazhvani et al., (2016) in Iran reported that chlorhexidine mouthwash exerted a stronger inhibitory effect against *Candida* strains colonizing the oral cavity of liver transplant recipients than azole-based rinses. Similarly, (Chavarría-Bolaños et al., 2021) in Costa Rica found that commercial chlorhexidine mouthwashes produced inhibition zones against *Candida albicans* that were proportional to their chlorhexidine concentration, and demonstrated that, among eight commercially available mouthwashes, chlorhexidine-based formulations showed the most consistent combined antibacterial and antifungal activity against oral microorganisms. An in vivo study by Hugar et al., (2024) further confirmed the efficacy of chlorhexidine against both *Streptococcus mutans* and *Candida albicans*. For povidone-iodine,

Amtha & Kanagalingam, (2020) noted that its standalone antifungal role is less well established and that its anti-*Candida* effect, including biofilm eradication, becomes more pronounced when combined with an antifungal such as fluconazole; this is in line with the comparatively smaller inhibition zone observed for povidone-iodine when used alone in the present study. Differences in the magnitude of inhibition reported across studies can be attributed to methodological factors. Many earlier studies employed higher concentrations (4% chlorhexidine; 5–10% povidone-iodine), different *Candida* strains, or dilution-based methods (MIC/MFC), whereas the present study deliberately used the concentrations clinically applied for oral care (0.2% and 1%), making the results directly relevant to ICU practice but not directly comparable in absolute zone size. Furthermore, the disk diffusion method reflects both intrinsic antimicrobial potency and diffusibility; a transient, poorly diffusing agent such as free iodine may therefore under-represent its true fungicidal capacity relative to a highly diffusible and substantive agent such as chlorhexidine (Gajic et al., 2022).

Chlorhexidine gluconate has been widely recognized in several clinical studies as the gold standard oral antiseptic for inhibiting microbial growth (James et al., 2017). A Cochrane review reported that oral hygiene care using chlorhexidine mouthrinse or gel probably reduces ventilator-associated pneumonia (VAP) incidence compared with placebo or usual care, although it may have little or no effect on mortality, duration of mechanical ventilation, or ICU length of stay (Ochoa et al., 2025). These findings carry several implications for oral care in the ICU. Oropharyngeal and respiratory colonization by *Candida albicans* is common in mechanically ventilated patients and is regarded as a marker of poor prognosis; it frequently occurs within polymicrobial biofilms, such as those formed with *Pseudomonas aeruginosa*, which are highly resistant and contribute to ventilator-associated pneumonia (Liu et al., 2025). Reducing the fungal burden is therefore a relevant component of comprehensive oral hygiene in critically ill patients. The superior and sustained anti-*Candida* activity of 0.2% chlorhexidine gluconate observed in this study suggests that it may be preferable to 1% povidone-iodine when antifungal coverage is a specific goal of ICU oral care, but this requires clinical confirmation. Nevertheless, these in vitro results should be interpreted with caution. Clinical evidence remains mixed: while some studies report that chlorhexidine-based oral hygiene reduces VAP incidence (Ochoa et al., 2025), a network meta-analysis concluded that chlorhexidine was not effective in preventing VAP and raised concerns regarding mucosal irritation, taste alteration and staining with prolonged use (Desai et al., 2015). In addition, the two agents should not be combined within the same oral-care regimen, because anionic–cationic incompatibility may reduce the activity of chlorhexidine; a single agent should be selected. Finally, the oral environment–saliva dilution, organic load, established biofilms and limited contact time is likely to attenuate the efficacy seen under controlled in vitro conditions, so these results require confirmation through in vivo studies and clinical trials.

This study has several limitations. First, it was conducted entirely in vitro; therefore, the findings may not fully reflect the complex oral environment of critically ill patients, where saliva dilution, organic load, host immune factors, contact time, and interactions with other microorganisms may influence antiseptic activity. Second, this study used the disk diffusion method, which provides inhibition zone diameters but does not determine the minimum inhibitory concentration (MIC) or minimum fungicidal concentration (MFC), nor does it capture time-kill kinetics. Third, mature *Candida* biofilms were not evaluated, although biofilm formation is clinically important in oral colonization and may reduce susceptibility to antiseptic agents. Fourth, only one clinical isolate of *Candida albicans* and one *Candida* species were tested, limiting the generalizability of the findings to other *Candida albicans* isolates or non-*albicans* *Candida* species. Finally, only one concentration of each antiseptic was evaluated. Future studies using dilution-based MIC/MFC methods, multiple *Candida albicans* isolates and other *Candida* species,

mature biofilm models, and in vivo or clinical designs are needed to confirm whether the superior in vitro activity of chlorhexidine translates into reduced *Candida* colonization and improved outcomes in critically ill patients.

CONCLUSION

In conclusion, 0.2% chlorhexidine gluconate exhibited significantly greater *in vitro* antifungal activity against *Candida albicans* than 1% povidone-iodine. Scientifically, this study provides direct comparative laboratory evidence on two oral antiseptic concentrations that are used in clinical practice but have rarely been compared head-to-head against *Candida albicans*, thereby helping to address the limited and inconsistent evidence regarding their antifungal effects. Clinically, these findings suggest that 0.2% chlorhexidine gluconate may be considered when antifungal coverage is a specific objective of oral hygiene in intubated ICU patients at risk of *Candida* colonization, with the practical caveat that a single agent should be selected rather than combining the two. Future research should confirm these findings through dilution-based assays, such as MIC and MFC testing, to quantify fungistatic and fungicidal thresholds, as well as through testing of multiple *Candida albicans* isolates and other *Candida* species, evaluation against mature biofilms, and in vivo or clinical studies assessing whether the superior *in vitro* activity of chlorhexidine translates into reduced fungal colonization and improved patient outcomes.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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