ORIGINAL ARTICLE

Antimicrobial activity of hydroxyapatite toothpaste against *staphylococcus aureus* and *candida albicans*: an experimental study

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Received: 20 May 2026
Revised: 29 June 2026
Accepted: 20 July 2026
Published: 31 July 2026
DOI: 10.24198/pjd.vol38no2.69817

p-ISSN 1979-0201
e-ISSN 2549-6212

Citation:
Maulana, IN, Kurniawan, F, Octarina, O, Lauw, ML. Antimicrobial activity of hydroxyapatite toothpaste against *staphylococcus aureus* and *candida albicans*: an experimental study. Padjadjaran J. Dent. July 2026;38(2):286-293

ABSTRACT

Introduction: Hydroxyapatite is widely used in toothpaste formulations because of its biocompatibility and its role in supporting enamel remineralization; however, its direct antimicrobial activity against oral microorganisms remains unclear. This study aimed to analyze the antimicrobial activity of hydroxyapatite toothpaste against *Staphylococcus aureus* and *Candida albicans*. **Methods:** An *in vitro* experimental study was conducted using the well diffusion method. The tested materials included hydroxyapatite toothpaste at concentrations of 1%, 3%, and 5%, sterile distilled water as a negative control, commercial toothpaste as a positive control, and chloramphenicol 100 ppm and nystatin 5,000 mg/L as comparator controls for *S. aureus* and *C. albicans*, respectively. Inhibition zones were measured after incubation for 24 hours at 37 °C. **Results:** Hydroxyapatite toothpaste at all tested concentrations did not produce inhibition zones against either *Staphylococcus aureus* or *Candida albicans*, whereas the comparator controls demonstrated clear inhibitory effects. Statistical analysis using the Kruskal-Wallis test revealed significant differences among treatment groups for *Staphylocossus aureus* ($p = 0.0005$) and *Candida albicans* ($p = 0.028$). **Conclusion:** Hydroxyapatite toothpaste did not demonstrate direct antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* when assessed using the well diffusion method. These findings indicate that hydroxyapatite is not optimal as a sole antimicrobial agent and should be combined with other active ingredients to enhance antimicrobial effectiveness.

KEYWORDS

Hydroxyapatite, toothpaste, antimicrobial activity, staphylococcus aureus, candida albicans

INTRODUCTION

Dental caries remains one of the most prevalent oral diseases and continues to be a significant public health concern.[1] This highlights the continuing need for effective prevention and control strategies. The development of dental caries begins with the demineralization of hard dental tissues caused by acid production resulting from microbial metabolic activity within dental biofilms.[2]

Repeated acid exposure leads to progressive enamel demineralization characterized by mineral loss, increased porosity, and reduced surface hardness. Microorganisms such as *Staphylococcus aureus* and *Candida albicans* are known to colonize tooth surfaces and participate in the formation of resistant biofilms, thereby contributing to changes in the oral microbial environment and potentially accelerating enamel demineralization.[3,4]

Plaque accumulation is commonly controlled through regular toothbrushing using toothpaste.[5] In addition to its mechanical plaque removal function,

toothpaste formulations are developed with the incorporation of active ingredients designed to inhibit microbial growth and maintain the integrity of hard dental tissues.[6,7] Advances in dental material research have encouraged the use of active agents that not only assist in plaque removal but also contribute to the prevention of enamel demineralization.[8,9,10] Therefore, hydroxyapatite, a commonly used active ingredients in oral-care formulations, requires scientific evaluation to determine its potential in inhibiting the growth of microorganisms involved in biofilm formation.

Hydroxyapatite (HA) is a biomimetic material with high biocompatibility due to its composition and structure which resemble those of the primary mineral component of hard dental tissues, particularly enamel.[11,12] It plays a role in the remineralization process by providing calcium and phosphate ions and promoting the formation of a mineral layer on the tooth surface.[13] Several studies have reported that hydroxyapatite may influence microbial adhesion and biofilm formation through modification of enamel surface characteristics.[14,15,16] However, studies specifically evaluating the antimicrobial activity of hydroxyapatite-based toothpaste against *Staphylococcus aureus* and *Candida albicans* remain limited. To evaluate the potential antimicrobial activity of hydroxyapatite, this study was conducted using an in vitro experimental design with *Staphylococcus aureus* and *Candida albicans* cultures as test microorganisms. Hydroxyapatite toothpaste at concentrations of 1%, 3%, and 5% was used as the treatment formulations and compared with sterile distilled water and commercial toothpaste as control groups.[17,18]

Chloramphenicol at a concentration of 100 ppm for *Staphylococcus aureus* and nystatin at a concentration of 5,000 mg/L for *Candida albicans* were used as standard antimicrobial reference agents to assess microbial susceptibility. As these agents were not formulated as toothpaste, they were not intended to serve as positive controls with equivalent formulation, but rather as biological benchmarks for antimicrobial activity. Antimicrobial activity was assessed based on inhibition zone formation as an indicator of microbial growth suppression.[19,20]

The novelty of this research lies in evaluating the direct antimicrobial activity of hydroxyapatite-based toothpaste against *Staphylococcus aureus* and *Candida albicans*, thereby providing additional insight beyond its well-established remineralization properties and expanding its potential role in oral care. Therefore, this study aimed to analyze the antimicrobial activity of hydroxyapatite toothpaste against these two microorganisms using an in vitro experimental approach.

METHODS

This study was an *in vitro* laboratory experimental study conducted at the Biotechnology Laboratory, Directorate of Laboratory Management, Research Facilities, and Science and Technology Areas, National Research and Innovation Agency (BRIN), Indonesia. The test microorganisms were *Staphylococcus aureus* ATCC 25923 and *Candida albicans* ATCC 10231. Mueller–Hinton Agar (MHA) was used for *S. aureus*, while Sabouraud Dextrose Agar (SDA) was used for *C. albicans*.

The toothpaste base was prepared by gradually mixing 18 g of calcium carbonate ($CaCO_3$) with 3 g of gum arabic under continuous stirring until a homogeneous mixture was obtained. Subsequently, 1 g of sodium carbonate (Na_2CO_3) and 1 g of sodium fluoride (NaF) were added sequentially and mixed thoroughly. Saccharin powder (0.39 g) was then incorporated, followed by the addition of two drops of peppermint oil as a flavoring agent. The mixture was then stirred until a uniform toothpaste base was obtained.[17]

Hydroxyapatite powder with a particle size of <150 mesh was weighed at 0.10 g, 0.30 g, and 0.50 g. The toothpaste base was divided into three portions of 10 g each. Each amount of hydroxyapatite was incorporated into one portion of the toothpaste base and mixed until homogeneous, resulting in toothpaste formulations containing hydroxyapatite at concentrations of 1%, 3%, and 5%.[17]

Microbial suspensions were prepared by transferring isolated colonies into 0.9% physiological saline and adjusting the turbidity to a 0.5 McFarland standard (approximately 1.5×10^8 CFU/mL). A volume of 0.1 mL of the microbial suspension was evenly spread onto the surface of the agar medium. Wells with a diameter of 6 mm were then prepared, and each well was filled with 50 µL of the test materials, consisting of sterile distilled water as a negative control, commercial hydroxyapatite-based toothpaste as a positive control, and hydroxyapatite toothpaste at concentrations of 1%, 3%, and 5%. In addition, chloramphenicol at a concentration of 100 ppm was used as a reference antimicrobial agent for *Staphylococcus aureus*, and nystatin at a concentration of 5,000 mg/L was used as a reference antimicrobial agent for *Candida albicans*. All plates were incubated at 37 °C for 24 hours. Each treatment was performed in triplicate (n=3).[18]

After incubation, the inhibition zones formed around the wells were observed and measured using a caliper. The inhibition zone width was calculated using the formula W = T − D, where W represents the width of the inhibition zone, T represents the diameter of the clear zone, and D represents the diameter of the well.

Statistical analysis was performed using SPSS software. Data normality was assessed using the Shapiro–Wilk test. As the data did not meet the assumption of normal distribution, differences among groups were analyzed using the Kruskal–Wallis test, followed by the Mann–Whitney test for pairwise comparisons when a statistically significant differences were observed ($p < 0.05$).

RESULTS

The antimicrobial activity assay against *Staphylococcus aureus* and *Candida albicans* was performed using the agar well diffusion method. The observations showed that sterile distilled water used as the negative control did not produce an inhibition zone against either test microorganism. Hydroxyapatite toothpaste at all tested concentrations (1%, 3%, and 5%) also did not exhibit the formation of inhibition zones against either microorganism. In contrast, the reference antimicrobial agents, including chloramphenicol at 100 ppm for *Staphylococcus aureus* and nystatin at 5,000 mg/L for *Candida albicans*, produced clearly defined inhibition zones.

Table 1. Inhibition zone test results against *Staphylococcus aureus*

No	Sample		Inhibition Zone (mm) *Staphylococcus aureus* ATC 25923			
			1	2	3	Mean ± SD
1	Commercial Toothpaste		9.72	10.31	11.15	10.39 ± 0.72
2	Hydroxyapatite Toothpaste 1%		0	0	0	0
3	Hydroxyapatite Toothpaste 3%		0	0	0	0
4	Hydroxyapatite Toothpaste 5%		0	0	0	0
5	Sterile Distilled		0	0	0	0
6	Chloramphenicol	100 ppm	24.64	23.30	25.75	24.56 ± 1.23

The normality test was performed using the Shapiro–Wilk test. The results showed that several treatment groups had p-values < 0.05, indicating that the data were not normally distributed. Therefore, nonparametric statistical analyses were performed. The Kruskal Wallis test showed a p-value of 0.005 ($p<0.05$), indicating a statistically significant difference among the treatment groups in terms of their inhibitory effects against *Staphylococcus aureus*. Post hoc analysis using the Mann Whitney test further revealed significant differences between specific treatment groups ($p < 0.05$).

Table 2. Mean **Inhibition zone measurement against *candida albicans***

No	Sample	Inhibition Zone (mm)			
		Candida albicans ATC 10231			
		1	2	3	Mean ± SD
1	Commercial Toothpaste	6.90	5.42	3.04	5.12 ± 1.95
2	Hydroxyapatite Toothpaste 1%	0	0	0	0
3	Hydroxyapatite Toothpaste 3%	0	0	0	0
4	Hydroxyapatite Toothpaste 5%	0	0	0	0
5	Sterile Distilled	0	0	0	0
6	Nystatin 5.000 mg/L	11.88	12.52	12.35	12.25 ± 0.33

The normality test was performed using the Shapiro-Wilk test. The results showed that several groups had a p-values of < 0.05, indicating that the data were not normally distributed. Therefore, nonparametric statistical analyses were applied. The Kruskal Wallis test showed a p-value of 0.028 ($p<0.05$), indicating a statistically significant difference among treatment groups in term of their inhibitory effects against *Candida albicans*. Post hoc analysis using the Mann Whitney test further revealed statistically significant differences between specific treatment groups ($p<0.05$).

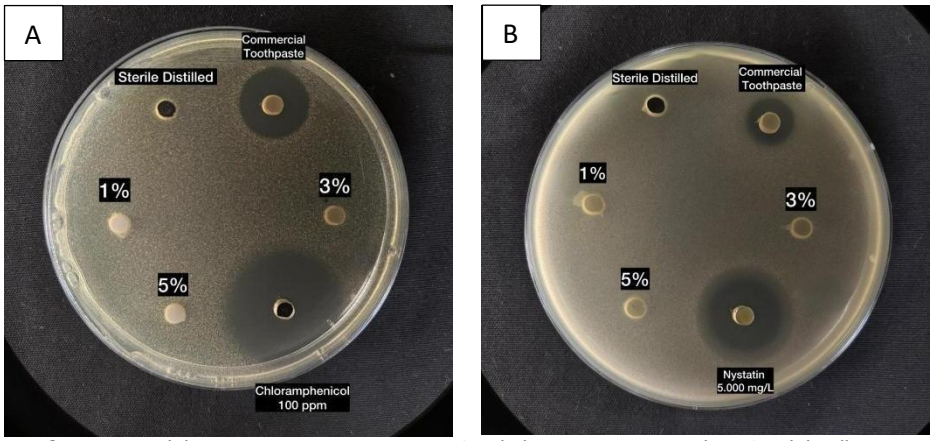

Figure 1. Inhibition zone assay against A. *Staphylococcus aureus* and B. *Candida albicans*

Figure 1 shows the inhibition zone assay results obtained using the well diffusion method against (A) *Staphylococcus aureus* cultured on Mueller-Hinton agar and (B) *Candida albicans* cultured on Sabouraud Dextrose Agar. Hydroxyapatite toothpaste at concentrations of 1%, 3%, and 5% did not produce any inhibition zones, whereas clear inhibition zones were observed in the reference control groups, specifically chloramphenicol against *Staphylococcus aureus* and nystatin against *Candida albicans*.

DISCUSSION

The results of this study demonstrate that toothpaste containing hydroxyapatite at all tested concentrations (1%, 3%, and 5%) did not produce any inhibition zones against *Staphylococcus aureus* or *Candida albicans* when evaluated using the well diffusion method. This observation is presented in Figure 1 and supported by the quantitative data in Table 1 and Table 2, in which all hydroxyapatite-containing toothpaste groups showed inhibition zone measurement of 0 mm. These findings are consistent with previous studies

showing that hydroxyapatite-based oral care products do not exhibit direct antibacterial or antifungal activity when evaluated using agar diffusion methods. Instead, hydroxyapatite primarily contributes to enamel remineralization, reduces bacterial adhesion, and influence biofilm formation rather than directly inhibiting microbial growth. Therefore, the absence of inhibition zones observed in the present study is consistent with the established mechanism of action of hydroxyapatite and with previous experimental findings.[24,25,27,28]

In contrast, the commercial toothpaste used as a positive control produced measurable inhibition zones, while the reference antimicrobial agents, chloramphenicol at 100 ppm against *Staphylococcus aureus* and nystatin at 5,000 mg/L against *Candida albicans*, produced substantially larger inhibition zones.[19,20] These findings suggest that hydroxyapatite in toothpaste formulations does not exhibit direct antimicrobial activity against the tested microorganisms when evaluated by the well diffusion method.

The inhibition zones observed in the commercial toothpaste group (Table 1 and Table 2) are attributed to its active components, including sodium monofluorophosphate, sodium lauryl sulfate, and other supporting compounds. This finding is consistent with previous studies demonstrating that commercial dentifrices containing fluoride compounds and surfactants exhibit measurable antimicrobial activity against oral microorganisms because these formulations contain multiple active ingredients with complementary antimicrobial properties.[5,6,7,21]

Sodium monofluorophosphate interferes with microbial enzymatic activity and reduces acid production, thereby inhibiting microbial growth. In addition, surfactants such as sodium lauryl sulfate disrupt microbial cell membrane integrity, leading to increased permeability and cell lysis. These findings are consistent with previous studies reporting that dentifrices containing fluoride and surfactants exhibit measurable antimicrobial activity against oral microorganisms.[5,21] Therefore, the antimicrobial activity observed in the commercial toothpaste group may reflect the combined effects of multiple active ingredients rather than the presence of hydroxyapatite alone.

The lack of inhibition zones in the hydroxyapatite toothpaste formulations (1%, 3%, and 5%) can be explained by the relatively low antimicrobial activity of hydroxyapatite, which does not act directly to inhibit microbial growth.[22,23] Instead, hydroxyapatite works by modifying the surface properties of dental enamel, thereby reducing the ability of the microorganism to adhere. This modification hinders biofilm formation, an early stage in the development of dental plaque and caries.[24,25] Therefore, despite not forming inhibition zones in antimicrobial tests, hydroxyapatite contributes to oral health by reducing the potential for microbial colonization on enamel surfaces.[26]

Several studies have shown that hydroxyapatite does not function as a bactericidal or fungicidal agent but exhibits indirect antimicrobial activity.[27,28] This activity is related to its ability to enhance the remineralization of demineralized enamel, which not only repairs existing damage but also strengthens the enamel surface, making it more resistant to microbial colonization.[29,30] In addition, hydroxyapatite reduces microbial adhesion and biofilm formation on tooth surfaces, thus preventing microbial colonization during the early stages of biofilm formation. Therefore, although it does not directly kill microorganisms, hydroxyapatite plays a significant role in reducing further microbial colonization and the risk of plaque formation, which may eventually lead to caries.[31,32]

Based on these findings, it can be shown that hydroxyapatite cannot function as a sole antimicrobial agent in toothpaste formulations when assessed solely for direct antimicrobial activity. Therefore, the development of hydroxyapatite-based toothpaste formulations should consider the addition of other active ingredients with direct antimicrobial effects, such as zinc, to enhance microbial growth control in the oral cavity. Zinc works by disrupting microbial cell membranes, inhibiting metabolic enzymes, and reducing the ability of microbes to form biofilm.[33,34]

Combining these two ingredients in toothpaste formulations may improve antimicrobial effectiveness by utilizing the remineralization benefits of hydroxyapatite and the antimicrobial properties of zinc.[35] Thus, these two ingredients can work synergistically to provide enhanced protection and support oral health.

Overall, the results of this study demonstrate that hydroxyapatite does not exhibit direct antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* under the experimental conditions employed, as indicated by the absence of inhibition zones in Tables 1 and 2. These findings are consistent with previous evidence showing that the primary role of hydroxyapatite in oral care is to promote enamel remineralization and reduce microbial adhesion rather than to directly inhibit microbial growth. Consequently, hydroxyapatite provides indirect support for oral health through biofilm modulation rather than direct antibacterial or antifungal activity.[27,32]

These findings confirm that hydroxyapatite alone does not exhibit direct antimicrobial activity in toothpaste formulations when evaluated using the well diffusion method. However, these findings also highlight the need for the development of more complex formulations that combine hydroxyapatite with other active ingredients, such as zinc, to enhance antimicrobial activity and control microbial growth in the oral cavity.[36]

This study is limited by the use of an *in vitro* model, which does not fully replicate the dynamic conditions of the oral cavity, including the presence of saliva and pH fluctuations that may affect the effectiveness of hydroxyapatite. Therefore, further research using *in vivo* models that account for these factors is necessary to assess its effectiveness under more representative oral conditions.

CONCLUSION

Hydroxyapatite toothpaste did not demonstrate direct antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* as assessed by the well diffusion method. Hydroxyapatite may provide indirect antibacterial benefits, primarily through mechanisms related to reducing microbial adhesion and supporting enamel remineralization. Therefore, hydroxyapatite may be less suitable as a sole active ingredient for direct antimicrobial purposes and should be combined with other active agents that possess direct antimicrobial properties.

The implication of these findings is that hydroxyapatite should be positioned as a supportive bioactive agent in toothpaste formulations, contributing mainly to remineralization and potentially supporting biofilm control, while effective antimicrobial action should be achieved through the incorporation of complementary agents with proven direct antimicrobial properties.

Acknowledgement: The authors would like to express their sincere appreciation to Direktorat Jenderal Riset dan Pengembangan, Kementerian Pendidikan Tinggi, Sains, dan Teknologi for funding this research through the Program Hibah Penelitian BIMA 2025.

Author Contributions: "Conceptualization, I.N.M. and F.L.K.; methodology, I.N.M. and F.L.K.; software, I.N.M.; validation, F.L.K. and O.O; formal analysis, I.N.M.; investigation, I.N.M.; resources, F.L.K.; data curation, I.N.M.; writing original draft preparation, I.N.M.; writing review and editing, F.L.K. and O.O; visualization, I.N.M.; supervision, F.L.K.; project administration, O.O; funding acquisition, F.L.K. All authors have read and agreed to the published version of the manuscript."

Funding: "This research was funded by Direktorat Jenderal Riset dan Pengembangan, Kementerian Pendidikan Tinggi, Sains, dan Teknologi through the Program Hibah Penelitian BIMA 2025, grant number 124/C3/DT.05.00/PL/2025 and 1014/LL3/AL.04/2025."

Institutional Review Board Statement: "The study was conducted in accordance with the Declaration of Helsinki. Prior to the implementation of the research, the Ethics Committee of the Faculty of Dentistry, Universitas Trisakti, issued an Ethical Exemption Letter (Reference number 923/S1/KEPK/FKG/6/2025)."

Informed Consent Statement: "Informed consent was not applicable because the study did not involve human participants."

Data Availability Statement: "The data are unavailable due to privacy or ethical restrictions."

Conflicts of Interest: "The authors declare no conflict to interest."

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