BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 4

DOI: 10.58240/1829006X-2025.21.4-239

REVIEW ARTICLE

FROM ORAL CARE TO VIRUS CONTROL: BIOMEDICAL APPLICATIONS OF CETYLPYRIDINIUM CHLORIDE – A SYSTEMATIC REVIEW

Rohit Kumar Singh[1*], Deepak Nallaswamy[1], Shanmugam Rajeshkumar[2], Sheeja S Varghese[3], Jayasree Anandan[2]
[1]Department of Prosthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai - 600077, TN, India
[2]Nanobiomedicine Lab, Department of Anatomy, Saveetha Medical college and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai - 602105, TN, India
[3]Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai - 600077, TN, India
***Corresponds to ;**Dr Rohit Kumar Singh PhD Scholar Department of Prosthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai - 600077, TN
Email Id: rks.prosthodontics@gmail.com
Received: *Apr10, 5, 2025;* ***Accepted:*** *May. 10, 2025;* ***Published:*** *May. 18, 2025;*

ABSTRACT

Background: Cetylpyridinium chloride (CPC) is a quaternary ammonium compound extensively used in oral hygiene products for its potent antimicrobial and antiviral activity. Its mechanism involves disruption of microbial cell membranes through electrostatic and hydrophobic interactions. In addition to its oral applications, CPC has gained attention for integration into biomaterials and potential to mitigate SARS-CoV-2 transmission, warranting a comprehensive review of its biomedical relevance.

Materials and Methods:A systematic review was conducted following PRISMA guidelines across PubMed, ScienceDirect, and Google Scholar (1990–2023), using terms related to CPC's antimicrobial, antiviral, and material-incorporation functions. Eligible studies included in vitro, in vivo, and clinical investigations assessing CPC's efficacy, mechanisms, and integration into dental materials. Articles were screened, data extracted, and quality assessed using CONSORT and STROBE tools. Due to heterogeneity, findings were synthesized qualitatively.

Results: Evidence supports CPC's significant antimicrobial efficacy in reducing plaque, gingivitis, and biofilm formation, with up to 30% improvement over controls. It exhibits broad-spectrum bactericidal action, though polymicrobial biofilms show reduced susceptibility. CPC also demonstrates >99.9% inactivation of SARS-CoV-2 in vitro, indicating prophylactic potential. Its incorporation into orthodontic adhesives and resins yields sustained antimicrobial effects, though material strength may decline over time. Emerging resistance and biofilm penetration barriers highlight key limitations.

Conclusion:CPC is a versatile antimicrobial with proven utility in oral care and public health. Its efficacy against bacterial and viral pathogens, including SARS-CoV-2, and potential for biomaterial integration underscore its translational value. However, long-term biocompatibility and resistance development require further research to optimize its application across clinical domains.

Keywords: Cetylpyridinium Chloride (CPC); Antimicrobial Activity; Oral Biofilms; SARS-CoV-2 Inactivation; Biomedical Applications

INTRODUCTION

Cetylpyridinium chloride (CPC) is a quaternary ammonium compound that functions as a cationic surfactant with strong amphiphilic properties. These characteristics allow CPC to interact effectively with microbial cell membranes, disrupting their structural integrity and leading to cell lysis and death. Its mode of action involves the electrostatic attraction between the positively charged pyridinium ion and the negatively charged components of bacterial membranes such as lipopolysaccharides and phospholipids. Additionally, the hydrophobic cetyl chain intercalates into lipid bilayers, causing membrane disorganization, leakage of cytoplasmic contents, and ultimately, microbial death.[1-3]

These properties confer CPC broad-spectrum antimicrobial activity against both gram-positive and gram-negative bacteria, as well as certain fungi and enveloped viruses.[4]

CPC is widely used in a range of oral hygiene products, including toothpastes, mouthwashes, lozenges, and sprays due to its efficacy in reducing dental plaque, gingivitis, halitosis, and bacterial load in the oral cavity.[5-7] Its effectiveness in disrupting oral biofilms has made it a preferred adjunct in both preventive and therapeutic dentistry.[8] Beyond dentistry, CPC has garnered attention for its antiviral activity, particularly against SARS-CoV-2, where studies demonstrated its ability to reduce viral load in saliva by up to 99.9% following short-term exposure[9], making it a valuable candidate for reducing viral transmission risk. Furthermore, emerging research suggests that CPC can be integrated into biomedical materials, such as orthodontic adhesives and denture bases, to provide sustained antimicrobial effects.[10] However, issues such as microbial resistance, material compatibility, and formulation challenges continue to be explored. This systematic review comprehensively analyzes the literature on CPC's biomedical applications, including its antimicrobial efficacy, antiviral capabilities, material incorporation, resistance development, and safety profile. The goal is to provide a well-rounded understanding of CPC's therapeutic value and future potential in healthcare and public health settings.

2. MATERIAL AND METHODS

2.1 Search Strategy and Data Sources

A structured and comprehensive systematic review was performed in accordance with PRISMA guidelines to collate existing literature on the biomedical applications of Cetylpyridinium chloride (CPC). An exhaustive electronic search was conducted across three major scientific databases: PubMed, Google Scholar, and ScienceDirect, covering a publication period from January 1990 to December 2023. The search strategy incorporated Boolean logic and truncation operators using the following terms: "*Cetylpyridinium chloride" OR "CPC" AND "oral biofilm" OR "antimicrobial mouthwash" OR "SARS-CoV-2 CPC" OR "CPC resistance" OR "orthodontic adhesives" OR "CPC dental materials"*. Additionally, manual reference mining of retrieved articles and reviews was performed to ensure inclusion of all pertinent studies.

2.2 Eligibility Criteria

Studies were selected based on pre-defined inclusion and exclusion criteria. Eligible studies included:

- Original experimental research involving in vitro, in vivo, or ex vivo models;
- Clinical investigations such as randomized controlled trials (RCTs), cohort studies, or case-control studies;
- Studies reporting on CPC efficacy, mechanism of action, resistance development, antiviral applications, or material incorporation.

Only articles published in peer-reviewed journals and written in English were considered. Exclusion criteria comprised commentaries, editorials, conference abstracts, duplicate reports, and review articles that did not provide new experimental data or systematic synthesis.

2.3 Study Selection and Data Extraction

All articles were independently screened in two stages by two reviewers (blinded to author identities). First, titles and abstracts were reviewed for relevance. Full texts of potentially eligible studies were then assessed in detail. Discrepancies were resolved through discussion or consultation with a third reviewer. The PRISMA flowchart guided the selection process as illustrated in Figure 1. After removing duplicates, titles and abstracts were screened for relevance. Full-text reviews of eligible studies followed, ensuring compliance with the inclusion criteria. Data were extracted using a standardized data extraction form designed to capture study characteristics, including:

- Authors, publication year, and journal;
- Study design and experimental setting;
- CPC concentration and formulation;
- Microbial or viral targets;
- Quantitative and qualitative outcomes;
- Findings, limitations, and conclusions.

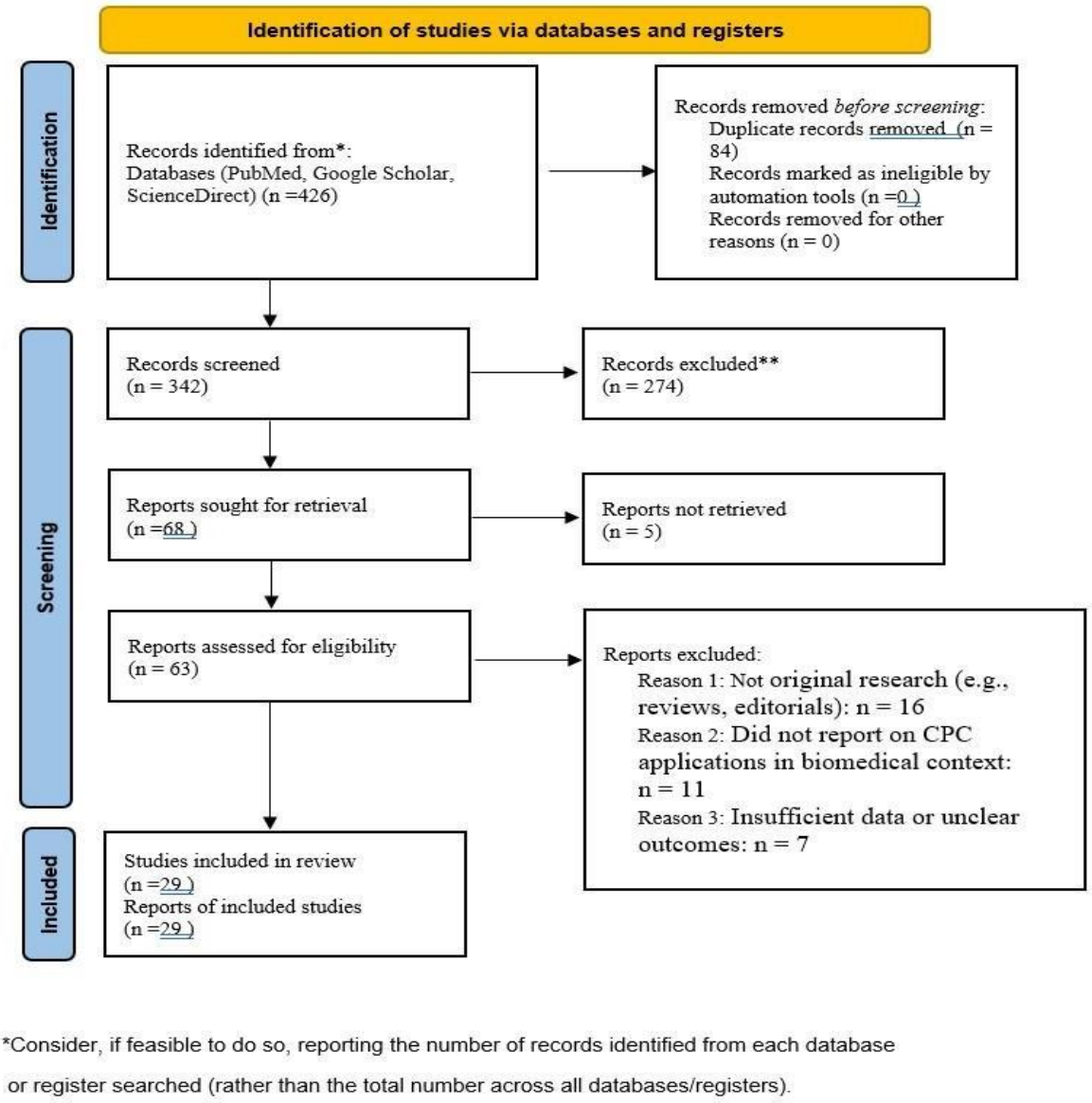

Figure 1. PRISMA flowchart

2.4 Quality and Risk of Bias Assessment

To evaluate the internal validity of included studies, two reviewers independently assessed the risk of bias using established tools:

- CONSORT 2010 checklist for clinical trials;
- STROBE guidelines for observational and laboratory-based studies.

Assessment criteria included randomization, blinding, sample size justification, statistical rigor, reproducibility, and transparency in outcome reporting. Any discrepancies in assessment were resolved through consensus or adjudication by a senior investigator.

2.5 Data Synthesis

Due to the heterogeneity of study designs, interventions, and outcomes, a qualitative synthesis was performed. Results were stratified by application domains (e.g., antimicrobial efficacy, antiviral activity, biomaterial integration, resistance mechanisms) and CPC concentrations. Where applicable, outcome trends were highlighted and compared across studies.

3. RESULT

Table 1. Summary of Key Findings on the Biomedical Applications of Cetylpyridinium Chloride (CPC)

Application Domain	Study/Authors	Model/Setting	CPC Formulation & Dose	Target Organism(s)	Key Findings	Limitations
Antimicrobial (Oral)	Stookey et al. (2005) [5]	RCT (6 months)	0.075% & 0.10% mouthwash	Oral plaque biofilms	~30% reduction in plaque and gingival inflammation	Limited to short-term safety
	He et al. (2012) [6]	Clinical trial	0.07% CPC rinse	Supragingival plaque bacteria	Sustained antimicrobial activity up to 12 hrs	No long-term resistance tracking
	Lotufo et al. (2009) [7]	Clinical study	0.05% CPC rinse	Oral biofilm vs fluoride rinse	29.3% superior plaque reduction vs fluoride	Small sample size
	Rao et al. (2011) [8]	In vitro multi-species biofilm	Alcohol-free CPC rinse	Mixed oral flora	Disruption of oral biofilms	Not validated in vivo
Mechanism of Action	Gilbert & Moore (2005) [2]	Theoretical review	N/A	Gram-positive/negative bacteria	Displacement of Ca^{2+}/Mg^{2+}, membrane disruption, cell lysis	No clinical testing
	Denyer & Stewart (1998) [3]	Microscopy & enzymatic assays	N/A	Bacterial membranes	Induces autolysis, metabolic inhibition	Primarily mechanistic
Resistance Development	Luppens et al. (2008) [11]	In vitro biofilms	0.07% CPC	S. mutans + V. parvula	Dual-species biofilms more tolerant than mono	Specific to species studied
	Smith et al. (2013) [18]	In vitro	Commercial rinses with CPC	MRSA	<60% biofilm reduction	Not effective on resistant strains
	Tattasawart et al. (1999) [17]	Adaptive exposure	Repetitive sub-lethal doses	P. stutzeri	60× MIC increase over 6 weeks	High resistance potential
	Izano et al. (2008) [12]	Enzymatic biofilm disruption	CPC + Dispersin B	A. actinomycetemcomitans	EPS degradation restored CPC efficacy	Only tested one EPS enzyme
Antiviral (SARS-CoV-2)	Anderson (2021) [9]	In vitro plaque assay	CPC mouthrinse (0.075%)	SARS-CoV-2 variants	>99.9% reduction in viral titers after 30 sec	Not tested in vivo

Application Domain	Study/Authors	Model/Setting	CPC Formulation & Dose	Target Organism(s)	Key Findings	Limitations
	Perez-Errazuriz et al. (2021) [14]	In vitro	0.07% CPC rinse	SARS-CoV-2 (P.1, B.1.1.7)	Broad virucidal activity across strains	Pre-clinical only
Material Integration	Al-Musallam et al. (2006) [10]	In vitro resin testing	CPC at 2.5%, 5%, 10% in adhesives	S. mutans	Dose-dependent inhibition; antibacterial resins	DTS reduction over time
	Ganeshnarayan et al. (2009) [13]	Diffusion modeling	CPC transport studies	Poly-N-acetylglucosamine biofilms	EPS blocks CPC diffusion	Limited to laboratory conditions

3.1 Antimicrobial Efficacy of CPC in Oral Applications

A substantial body of clinical and in vitro research confirms the potent antimicrobial activity of Cetylpyridinium chloride (CPC) against diverse oral pathogens. In a large-scale randomized controlled trial, **Stookey et al. (2005)** evaluated two concentrations of CPC mouthwashes—0.075% and 0.10%—over a six-month period and reported statistically significant reductions in plaque accumulation, gingival inflammation, and bleeding indices, with reductions of up to 30% compared to placebo. These findings were corroborated by **He et al. (2012)** and **Rao et al. (2011)**, who demonstrated that both single-use and prolonged application of CPC-containing rinses resulted in substantial suppression of microbial biofilms in the supra-gingival plaque region.

Furthermore, **Lotufo et al. (2009)** found that a 0.05% CPC rinse reduced plaque accumulation by 29.3% more than a fluoride-based control rinse 12 hours post-application. These results confirm that CPC has a broad-spectrum antimicrobial profile, effectively targeting both gram-positive and gram-negative bacterial species implicated in caries, periodontitis, and halitosis. CPC's substantivity—its ability to remain adsorbed on oral surfaces and provide prolonged antimicrobial effects—further contributes to its efficacy.

3.2 Mechanism of Action

The bactericidal action of CPC is primarily attributed to its cationic pyridinium moiety, which disrupts ionic homeostasis by displacing essential divalent cations such as calcium and magnesium from microbial cell surfaces (Gilbert & Moore, 2005). This displacement compromises cell wall integrity, facilitating the insertion of CPC's hydrophobic cetyl chain into the lipid bilayer, which destabilizes membrane structure and induces cell lysis.

Moreover, CPC initiates autolytic enzymatic activity, triggering the degradation of structural proteins and nucleic acids within microbial cells. **Denyer and Stewart (1998)** report that CPC interferes with intracellular metabolic processes, including RNA synthesis and protein folding, contributing to irreversible cell death. Scanning electron microscopy and fluorescence assays have shown clear evidence of membrane disruption and cytoplasmic leakage following CPC treatment.

3.3 Resistance Concerns and Limitations

While CPC is generally effective, emerging studies suggest that biofilm-associated bacteria may exhibit reduced sensitivity to CPC. **Luppens et al. (2008)** demonstrated that dual-species biofilms composed of *Streptococcus mutans* and *Veillonella parvula* exhibited significantly higher tolerance to CPC than single-species biofilms. This suggests synergistic protective mechanisms within polymicrobial communities that hinder CPC penetration or inactivate its surfactant properties.

Likewise, **Smith et al. (2013)** evaluated CPC efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) and reported less than 60% reduction in biofilm viability, suggesting limited effectiveness against certain antibiotic-resistant strains. Furthermore, **Tattasawart et al. (1999)** observed an increase in CPC minimum inhibitory concentrations (MICs) by up to

60-fold in *Pseudomonas stutzeri* after six weeks of repeated sub-lethal exposure, indicating the potential for adaptive resistance.

The extracellular matrix components such as poly-N-acetylglucosamine (PNAG) have also been implicated in CPC resistance. **Izano et al. (2008)** demonstrated that enzymatic degradation of PNAG using dispersin B significantly increased CPC susceptibility in *Aggregatibacter actinomycetemcomitans*, highlighting the barrier role of exopolysaccharides.

3.4 Antiviral Activity Against SARS-CoV-2

Recent investigations have extended the applicability of CPC into virology. In the context of the COVID-19 pandemic, CPC has demonstrated virucidal activity against multiple SARS-CoV-2 variants. **Anderson (2021)** and **Perez-Errazuriz et al. (2021)** reported that CPC-containing mouthrinses achieved a >99.9% reduction in viral titers after only 30 seconds of exposure in vitro plaque assays. These results were consistent across multiple viral lineages, including B.1.1.7 and P.1.

The mechanism involves CPC's ability to disrupt the viral lipid envelope, rendering the virus non-infectious. These findings suggest that routine oral hygiene practices using CPC mouthrinses could serve as a non-invasive strategy to reduce viral load in saliva, potentially limiting transmission in clinical and community settings. Given the high viral load in the oropharynx during early infection, CPC rinses may offer prophylactic benefit to both infected individuals and close contacts.

3.5 Integration into Dental Materials

Beyond topical formulations, CPC has been explored for incorporation into biomaterials used in dental and orthodontic applications. **Al-Musallam et al. (2006)** investigated the antimicrobial efficacy of orthodontic adhesives modified with CPC concentrations of 2.5%, 5%, and 10%. The study found a dose-dependent reduction in bacterial colonization, particularly against *S. mutans*, a key etiological agent in enamel demineralization.

However, material characterization revealed a reduction in diametral tensile strength (DTS) following water aging, particularly at higher CPC concentrations. While polymerization and setting of the material remained unaffected, the mechanical compromise raises questions about long-term durability and biocompatibility. Despite these concerns, the ability to deliver sustained antimicrobial activity makes CPC-modified resins a promising innovation for denture bases, retainers, and intraoral devices, especially in high-risk patients.

DISCUSSION

The findings of this systematic review reinforce the broad-spectrum antimicrobial and antiviral efficacy of Cetylpyridinium chloride (CPC), particularly in applications related to oral health and hygiene. CPC demonstrates potent activity against a range of pathogenic microorganisms, including *Streptococcus mutans*, *Aggregatibacter actinomycetemcomitans*, and other contributors to caries and periodontal diseases.[5,6,10] In monomicrobial environments and controlled in vitro settings, CPC's mechanism of action—disruption of the cell membrane via cationic interaction and lipid bilayer insertion—yields consistently favorable outcomes in reducing biofilm mass, plaque indices, and microbial load.[1-3]

However, microbial biofilms present a formidable barrier to CPC penetration. The extracellular polymeric substances (EPS) within biofilms create a physical and chemical diffusion barrier that reduces CPC's access to inner microbial layers. Studies involving dual-species and polymicrobial biofilms have reported diminished efficacy, as evidenced by *Streptococcus mutans* demonstrating increased tolerance when co-cultured with *Veillonella parvula*.[11] These observations highlight the importance of exploring synergistic combinations, such as CPC with enzymatic agents like dispersin B (DspB), which degrades EPS components and facilitates deeper penetration and antimicrobial action.[12,13] Such combinations may enhance CPC's biofilm-disruptive potential and address limitations in resistant microbial communities.

Beyond its oral health applications, CPC has gained relevance in broader public health contexts, especially during the COVID-19 pandemic. Its demonstrated virucidal activity against SARS-CoV-2 and other enveloped viruses supports its inclusion in antiviral mouthrinses and preventive protocols.[9,14] In addition, CPC's utility has been extended to buccal tablets, hand sanitizers, disinfectant sprays, and edible surface sanitizers. Regulatory bodies such as the FDA and EFSA have approved CPC for use on produce and poultry surfaces, citing its low toxicity and broad antimicrobial spectrum.[15,16]

Despite these promising attributes, long-term safety and biocompatibility concerns must be addressed.

Studies on CPC-integrated dental biomaterials, such as orthodontic adhesives and acrylic resins, report mechanical degradation after aging, raising questions about material stability and suitability for prolonged intraoral use.[10] Furthermore, the potential for resistance development, particularly in hospital and community environments where CPC is frequently used, necessitates ongoing surveillance, resistance profiling, and the development of alternating formulations or rotational use protocols.[11,17-19]

In conclusion, while CPC holds significant promise as a multifunctional antimicrobial agent, its optimal use requires continued innovation in formulation science, strategic combination therapies, and robust clinical validation in long-term settings.

5. CONCLUSION

Cetylpyridinium chloride remains a valuable antimicrobial and antiviral agent, with significant contributions to oral hygiene, disinfection, and infection control. Its future lies in enhanced delivery mechanisms and integration into smart dental materials. Resistance surveillance and formulation stability are crucial in maximizing its therapeutic benefit.

6. DECLARATIONS

Acknowledgement

The authors would like to acknowledge the help and support rendered by the department of prosthodontics and also the management of Saveetha Dental College and hospitals for their constant assistance with the research.

Conflict of interest

All the authors declare that there was no conflict of interest in the present study.

Source of funding:

Self-Funded study

Abbreviation

- *DTS*: Diametral Tensile Strength
- *EPS*: Extracellular Polymeric Substances
- *MIC*: Minimum Inhibitory Concentration
- *RCT*: Randomized Controlled Trial

REFERENCES

1. Mao X, Auer DL, Buchalla W, et al. Cetylpyridinium chloride: Mechanism of action, antimicrobial efficacy in biofilms, and potential risks of resistance. *Antimicrob Agents Chemother*. 2020;64(8).
2. Gilbert P, Moore LE. Cationic antiseptics: diversity of action under a common epithet. *J Appl Microbiol*. 2005;99(4):703–715.
3. Denyer SP, Stewart GS. Mechanisms of action of disinfectants. *Int Biodeterior Biodegradation*. 1998;41(3-4):261–268.
4. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev*. 1999;12(1):147–179.
5. Stookey GK, Beiswanger BB, Mau MS, et al. A 6-month clinical study assessing the safety and efficacy of two cetylpyridinium chloride mouthrinses. *Am J Dent*. 2005;18(2):24A–28A.
6. He S, Wei Y, Fan X, Hu D, Sreenivasan PK. A clinical study to assess the 12-hour antimicrobial effects of cetylpyridinium chloride mouthwashes. *J Clin Dent*. 2012;22(Spec Iss):195–199.
7. Lotufo R, Calil CM, Feng HS, et al. Clinical investigation of the efficacy of a commercial mouthwash containing 0.05% CPC. *J Clin Dent*. 2009;20:50–54.
8. Rao D, Aravanitidou E, Du-Thumm L, Rickard AH. Efficacy of an alcohol-free CPC-containing mouthwash against oral multi-species biofilms. *J Clin Dent*. 2011;22:187–194.
9. Anderson ER. Virucidal activity of CPC-containing oral rinses against SARS-CoV-2 variants. *bioRxiv*. 2021.
10. Al-Musallam TA, Evans CA, Drummond JL, et al. Antimicrobial properties of an orthodontic adhesive combined with cetylpyridinium chloride. *Am J Orthod Dentofacial Orthop*. 2006;129(2):245–251.
11. Luppens SBI, Kara D, Banornas L, et al. Effect of *Veillonella parvula* on the antimicrobial resistance of *Streptococcus mutans* in dual-species biofilms. *Oral Microbiol Immunol*. 2008;23:183–189.
12. Izano EA, Sadovskaya I, Wang H, et al. Poly-N-acetylglucosamine mediates biofilm formation and detergent resistance in *Aggregatibacter actinomycetemcomitans*. *Microb Pathog*. 2008;44(1):52–60.
13. Ganeshnarayan K, Shah SM, Libera MR, et al. Poly-N-acetylglucosamine impedes CPC transport through bacterial biofilms. *Appl Environ Microbiol*. 2009;75(4):1308–1314.

14. Perez-Errazuriz S, Velasco-Ortega E, Jimenez-Guerra A, et al. Cetylpyridinium chloride as a tool against COVID-19. *Int J Odontostomatol*. 2021;15(1):27–30.
15. Wang H, Li Y, Slavik MF. Efficacy of CPC in immersion treatment for reducing bacteria on vegetables. *J Food Prot*. 2001;64(12):2071–2074.
16. Zhang D, Liu CH, Zhang J, et al. Effects of CPC buccal tablets on halitosis. *Nan Fang Yi Ke Da Xue Xue Bao*. 2014;34(9):1386–1389.
17. Tattasawart U, Maillard JY, Furr JR, Russell AD. Resistance to CPC in *Pseudomonas* spp. after repetitive exposure. *J Hosp Infect*. 1999;42(3):219–229.
18. Smith K, Robertson DP, Lappin DF, et al. Commercial mouthwashes are ineffective against oral MRSA biofilms. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115(5):624–629.
19. Leelaporn A, Paulsen IT, Tennent JM, et al. Multidrug resistance to antiseptics in coagulase-negative staphylococci. *J Med Microbiol*. 1994;40(3):214–220.