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RESEARCH ARTICLE OPEN ACCESS

Chlorhexidine vs. Cetylpyridinium chloride: Impacts on salivary biomarkers linked to early oral squamous cell carcinoma detection

Chlorhexidine vs. CPC: Salivary biomarkers in early OSCC

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Abstract

Objective: This study aimed to evaluate the effects of chlorhexidine (CHX) and cetylpyridinium chloride (CPC) mouthwashes on salivary biomarkers associated with early detection of oral squamous cell carcinoma.

Method: The research investigated how daily use of chlorhexidine (CHX) and cetylpyridinium chloride (CPC) affects salivary biomarkers, which help detect early OSCC. The study included 150 participants who received equal distribution between the CHX and CPC groups and a control group for 14 days of observation. The researchers evaluated inflammatory cytokines IL-6 and IL-8, TNF-α and MMP-9 and oxidative stress markers ROS, MDA and TAC in saliva samples taken at three time points.

Result: The use of CHX led to a significant decrease in pro-inflammatory cytokines and MMP-9 levels and improved oxidative stability through reduced ROS and MDA and elevated TAC levels. The biochemical changes from CPC treatment were similar to those from CHX but at a lower intensity. The control group showed no important changes in biomarkers. The study results showed CHX produces more extensive and stronger changes in all measured biomarkers.

Conclusion: The study demonstrates that using antiseptic mouthwashes containing CHX for routine oral care will create detectable biochemical changes, which could hide early signs of OSCC in saliva tests. The implementation of pre-sampling protocols and washout periods becomes necessary to maintain accurate diagnostic results in clinical practice and research settings.

Keywords: Oral squamous cell carcinoma; salivary biomarkers; chlorhexidine; MMP-9; oxidative stress.

Plain English Summary

The research was conducted to determine the ability of regular antiseptic mouthwashes to change saliva biomarkers to detect oral squamous cell carcinoma (OSCC) in its early stage. One hundred and fifty of them were subjected to 14 days of chlorhexidine (CHX) or cetylpyridinium chloride (CPC), or nothing. Many biomarkers of inflammatory and oxidative stress were quantified in saliva samples. The findings revealed that chlorhexidine had a significant impact on modifying most biomarkers related to the early detection of cancer, whereas CPC had lesser effects. Such findings indicate that the use of the mouthwash should also be put into consideration in the event of taking saliva samples to make a diagnosis.

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Introduction

Oral squamous cell carcinoma (OSCC) represents the main malignant tumour of the oral cavity because it causes 90% of all oral cancer cases globally, yet creates major clinical and public health issues despite better diagnostic methods (1, 2). Patients fail to recognise OSCC development at its early stages until their condition advances to an untreatable stage (1). Scientists created non-invasive biomarkers because current diagnostic methods need new approaches to identify molecular alterations which occur before patients show clinical signs.

Scientists have recognised saliva as an essential biological fluid which tracks both internal and external body systems. Scientists use saliva biochemical elements, which contain cytokines, enzymes, nucleic acids and oxidative stress products to identify tumour markers before clinical symptoms appear without needing tissue biopsy procedures (3, 4). Research shows that IL-6, IL-8 and TNF-α inflammatory cytokines and MMP-9, ROS and MDA oxidative stress markers exhibit measurable changes at the time of oral cancer onset (2, 5, 6). The proposed OSCC screening biomarkers need appropriate control of environmental factors which impact their stability and concentration levels.

The reliability of salivary biomarkers depends on oral hygiene products, but antiseptic mouthwashes represent a vital yet often disregarded element. The antimicrobial and anti-inflammatory properties of chlorhexidine (CHX) make it the preferred chemical plaque control agent, yet these effects modify saliva biochemical content (7, 8). The dental practice implementation of CHX as a standard procedure results in bacterial reduction and gum inflammation control and body-wide inflammatory responses, which produce major changes in salivary cytokine levels and oxidative stress markers (9, 10). The modifications in biomarkers resulting from these changes could generate incorrect test results, which either conceal or exaggerate the initial indicators of cancer progression.

Cetylpyridinium chloride (CPC) shows antimicrobial activity by damaging cell membranes, although its ability to fight infections is limited to specific microorganisms when compared to chlorhexidine (CHX). Research shows that CPC creates modifications in salivary biochemical indicators, although these changes remain less significant than those produced by CHX (11, 12). The methodological problem emerges because mouthwash tests for OSCC screening biomarkers in uncontrolled settings, which produce inaccurate diagnostic outcomes.

The research investigated how daily CHX and CPC mouthwash application affects the biomarkers which indicate OSCC detection. The research evaluates IL-6, IL-8 and TNF-α inflammatory cytokines and MMP-9 enzyme and ROS, MDA and TAC oxidative stress markers to determine if these oral antiseptics create detectable biochemical changes that affect saliva-based screening tests. The research needs an understanding of these interactions to develop standardised protocols for OSCC surveillance population salivary sampling.

The research investigated how two common antiseptic mouthwashes with chlorhexidine (CHX) and cetylpyridinium chloride (CPC) affect salivary biomarkers, which function as OSCC screening tools for early-stage oral squamous cell carcinoma (OSCC). The research studied how CHX and CPC mouthwashes affect IL-6 and IL-8 and TNF-α inflammatory cytokines, MMP-9 enzyme, ROS, MDA and TAC oxidative stress markers. The researchers studied biomarker changes between the CHX and CPC groups relative to control participants to establish if these mouthwashes create biochemical changes that affect OSCC screening outcomes through saliva analysis.

Materials and Methods

The research employed a randomised controlled clinical design to study the effects of CHX and CPC mouthwashes on OSCC detection biomarkers in saliva throughout a 14-day study period.

Study Population

The study included 150 nonsmoking healthy participants who received equal distribution between three groups using CHX mouthwash, CPC mouthwash and a no-rinse control group. The participants followed standard oral hygiene instructions while avoiding any new products, and they had no antibiotic or anti-inflammatory drug exposure during the study period.

The three groups started with equal conditions because their demographic information revealed no substantial variations between them.

Randomization

The subjects were randomly allocated into the three groups (chlorhexidine, cetylpyridinium chloride, and control) through a computer-generated randomisation sequence. The approach was used to guarantee equal allocation and reduce bias in allocating to the study groups.

Intervention Protocol
The CHX group participants received 0.12% chlorhexidine gluconate solution (10 mL) twice daily, while CPC group participants used 0.05% cetylpyridinium chloride solution with the same application frequency. The control participants underwent water rinsing as their only procedure without receiving any additional treatment. Participants needed to avoid food consumption and liquid intake and toothbrushing for thirty minutes following each rinse session.

Saliva Collection
The research team collected unstimulated whole saliva samples at three different time points, which included baseline (T0) and days 7 and 14 (T1 and T2). The researchers obtained saliva samples during the 8:00 AM to 10:00 AM time period to reduce daily variations before storing them at –80°C for future analysis.

Biochemical Analysis
The researchers used ELISA and spectrophotometric assays to test salivary biomarkers by following established laboratory procedures. The research analysed IL-6, IL-8, and TNF-α inflammatory cytokines together with MMP-9, ROS, MDA and TAC as oxidative stress markers.

Statistical Analysis
The research team used paired t-tests to evaluate changes within groups and one-way ANOVA with Tukey post-hoc testing to evaluate differences between groups. The results show mean values with standard deviations, while the study uses $p > 0.05$as its significance threshold.

Results
The study achieved its goal when 150 participants finished without any protocol violations while their age and sex distribution remained equal between the CHX, CPC and control groups ($p > 0.05$). The biomarker changes throughout the study resulted from intervention effects because the study population showed no demographic differences.

Inflammatory Cytokines
Daily use of chlorhexidine led to a substantial decrease in the IL-6, IL-8, and TNF-α levels both on day 7 and day 14 over the baseline ($p < 0.01$). The CPC group exhibited minimal reductions in cytokine expression, with IL-6 and IL-8 displaying moderate decreases while TNF-α levels remained relatively stable. The control group, in contrast, showed no significant changes in cytokine concentrations throughout the study period. These results suggest that CHX exerts a more potent anti-inflammatory effect on the salivary milieu than CPC. Table 1 summarises the temporal variations in all cytokine levels among the study groups at each time point. Figure 1 specifically illustrates the progressive decline in IL-6 levels across the three time points, while Figure 2 shows the corresponding trends for IL-8 and TNF-α throughout the study period.

Table 1. Temporal changes in salivary biomarkers across the three study groups.

Biomarker	Time	Control (Mean ± SD)	CHX (Mean ± SD)	CPC (Mean ± SD)	p-value (Between Groups)
IL-6 (pg/mL)	T0	5.2 ± 1.1	5.1 ± 1.0	5.3 ± 1.2	—
	T1	5.1 ± 1.0	4.2 ± 0.9	4.8 ± 1.0	<0.05
	T2	5.3 ± 1.2	3.8 ± 0.8	4.5 ± 0.9	<0.01
IL-8 (pg/mL)	T0	12.3 ± 2.5	12.1 ± 2.4	12.2 ± 2.6	—
	T1	12.1 ± 2.4	10.0 ± 2.0	11.0 ± 2.2	<0.05
	T2	12.4 ± 2.6	9.5 ± 1.8	10.7 ± 2.0	<0.01
TNF-α (pg/mL)	T0	6.0 ± 1.2	6.1 ± 1.1	6.0 ± 1.2	—
	T1	6.0 ± 1.1	5.0 ± 0.9	5.5 ± 1.0	<0.05
	T2	6.1 ± 1.2	4.6 ± 0.8	5.3 ± 0.9	<0.01
MMP-9 (ng/mL)	T0	95 ± 10	94 ± 11	95 ± 10	—
	T1	94 ± 11	80 ± 9	87 ± 10	<0.05
	T2	96 ± 12	75 ± 8	84 ± 9	<0.01
ROS (μM)	T0	120 ± 15	118 ± 14	119 ± 15	—
	T1	119 ± 14	105 ± 12	112 ± 13	<0.05
	T2	121 ± 15	98 ± 10	108 ± 12	<0.01
MDA (nmol/mL)	T0	3.2 ± 0.5	3.1 ± 0.5	3.2 ± 0.5	—
	T1	3.1 ± 0.5	2.5 ± 0.4	2.8 ± 0.4	<0.05
	T2	3.2 ± 0.5	2.3 ± 0.4	2.7 ± 0.4	<0.01
TAC (mM)	T0	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	—

	T1	1.5 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	<0.05
	T2	1.5 ± 0.2	1.7 ± 0.2	1.6 ± 0.2	<0.05

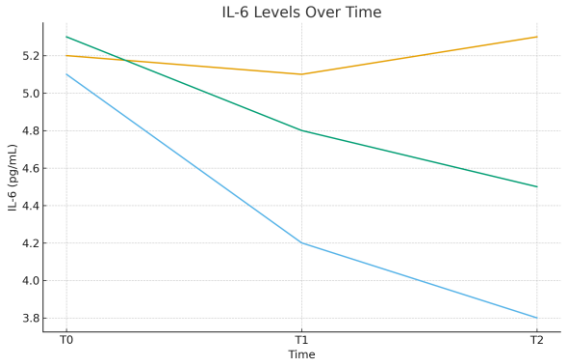


Figure 1. Temporal changes in IL-6 levels in the CHX, CPC, and control groups at baseline, day 7, and day 14.

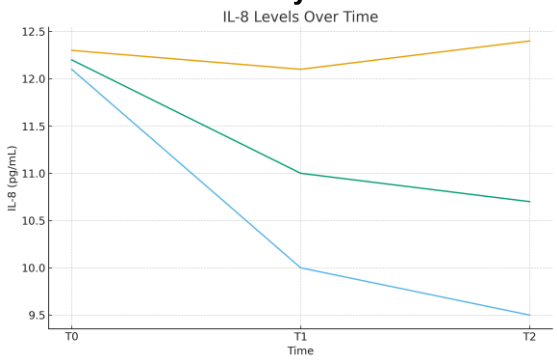


Figure 2. Trends in IL-8 (A) and TNF-α (B) concentrations across the study period.

The pattern of salivary MMP-9 resembled that of inflammatory cytokines. The CHX group recorded a substantial decrease in the concentration of MMP-9 at day 14 in comparison to baseline levels ($p < 0.01$). On the contrary, the CPC group only exhibited a medium reduction, whereas the control group did not experience any detectable changes throughout the study period. These results indicate that CHX can affect biochemical processes related to the extracellular matrix remodelling. Figure 3 shows the comparative changes in the MMP-9 concentrations of the study groups. Matrix Metalloproteinase-9 (MMP-9).

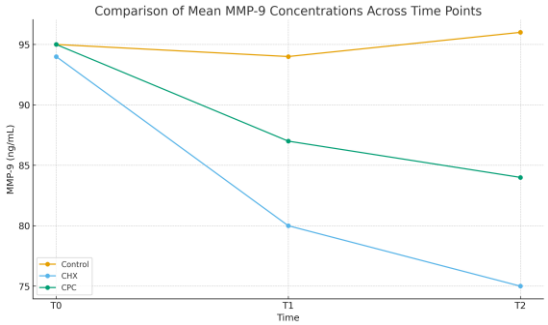


Figure 3. Comparison of mean MMP-9 concentrations across time points for all study groups

Oxidative Stress Markers

The application of chlorhexidine led to a substantial decrease in oxidative stress markers, such as ROS and MDA, at both time points of evaluation ($p <$ 0.05). Parallel to the above, total antioxidant capacity (TAC) rose with time in the CHX group. The CPC group showed a slight decrease in the levels of oxidative stress biomarkers, and the

control group showed a stable level of biomarkers throughout the course of the study. The above findings suggest that CHX has a greater modulatory impact on the oxidative environment of the salivary environment relative to CPC. Figure 4 shows variations in the oxidative stress markers during the study period.

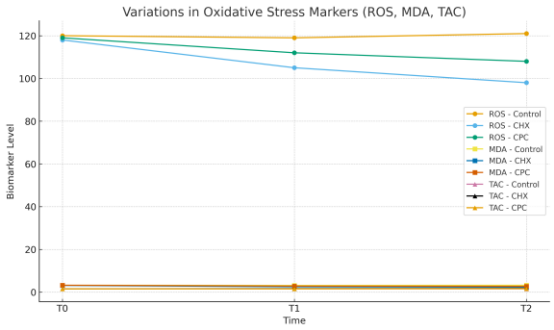


Figure 4. Variations in oxidative stress markers (ROS, MDA, TAC) following exposure to CHX and CPC.

Comparisons Between CHX and CPC

A direct comparison of the two mouthwash interventions showed that CHX led to significant modulation of all tested biomarkers compared with CPC. There were statistically significant differences between groups of IL-6, IL-8, MMP-9, ROS and MDA ($p < 0.05$). These results also confirm that CHX has a greater biochemical effect on salivary inflammatory and oxidative patterns. A direct comparison of the effects of CHX and CPC on all biomarkers is shown in Table 2. The overall percentage change in each biomarker from baseline to day 14 is illustrated in the heatmap in Figure 5

Table 2. Comparative influence of CHX and CPC on inflammatory and oxidative biomarkers.

Biomarker	CHX Effect	CPC Effect	Interpretation
IL-6	Significant ↓	Moderate ↓	Stronger anti-inflammatory effect with CHX
IL-8	Significant ↓	Mild ↓	CHX provides a greater reduction
TNF-α	Significant ↓	Mild ↓	CHX may influence diagnostic assessments
MMP-9	Significant ↓	Moderate ↓	CHX more effectively suppresses matrix activity
ROS	Significant ↓	Mild ↓	CHX reduces oxidative stress more robustly
MDA	Significant ↓	Mild ↓	Greater impact on lipid peroxidation with CHX
TAC	Moderate ↑	Mild ↑	CHX slightly enhances antioxidant status

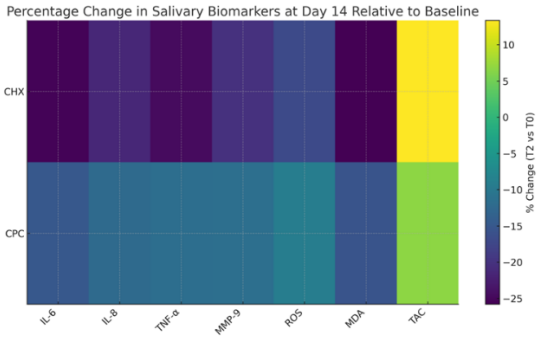


Figure 5. Heatmap illustrating the percentage change in salivary biomarkers at day 14 relative to baseline.

Discussion

This paper shows that antiseptic mouthwash, especially chlorhexidine (CHX), has profound effects on the concentration of major salivary biomarkers suggested to be used in the detection of early oral squamous cell carcinoma (OSCC). The results also suggest that CHX has a significant impact on the reduction of pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) and matrix metalloprotease-9 (MMP-9) and also changes the

markers of oxidative stress, such as ROS, MDA and TAC, more significantly than cetylpyridinium chloride (CPC). The findings of this study demonstrate that saliva has a strong biochemical response to antimicrobial mouthwashes that can affect the validity of salivary biomarkers as early OSCC screening and diagnostic studies (1, 2).

Modulation of Inflammatory Cytokines: Impact on Diagnostic Reliability

The IL-6, IL-8 and TNF-α levels in CHX users decreased according to studies, which show chlorhexidine has anti-inflammatory and broad-spectrum antimicrobial effects. CHX antimicrobial properties damage bacterial membranes and reduce microbial populations, which leads to decreased epithelial stimulation and lower cytokine production and ultimately reduces inflammatory signalling in the oral cavity [8]. The cytokines function as both inflammatory indicators and tumorigenesis promoters, which stimulate cell growth and blood vessel formation, and tumour spread in OSCC (2). The CHX treatment method produces lower cytokine levels, which might hide initial disease indicators that would decrease the reliability of salivary biomarkers for screening purposes.

The use of CPC resulted in small decreases in IL-6 and IL-8, but it did not affect TNF-α levels. The limited antimicrobial range of CPC prevents effective bacterial membrane attachment, which results in weak bacterial control and minimal impact on inflammation (11). The biochemical characteristics of oral antiseptics determine their impact on salivary immune markers, so researchers need to assess cytokine-based diagnostic tests while taking into account recent mouthwash use.

MMP-9 Suppression and Its Implications for Tumour Biology

The CHX group showed a major decrease in MMP-9 levels, which requires immediate assessment. The body enables tumour cells to spread throughout the body because MMP-9 breaks down the extracellular matrix through its degradation process (5). The reduction of MMP-9 levels caused by drugs might mask the first signs of matrix remodelling pathway changes, which appear during the initial stages of OSCC development. The proposed use of salivary MMP-9 as an early malignant transformation indicator would become less accurate because any treatment that reduces its natural variations.

The biochemical effects of CPC produced a less intense response, which indicates that this compound affects matrix-related enzymes through limited mechanisms that protect their natural fluctuations. The therapeutic application of CHX produces major biomarker interference, which affects diagnostic test results.

Oxidative Stress Dynamics and Redox Regulation

The process of carcinogenesis leading to cancer development depends on oxidative stress because high ROS and MDA levels result in elevated lipid peroxidation rates and genetic instability (3). The research findings demonstrated that CHX treatment reduced ROS and MDA levels while simultaneously boosting total antioxidant capacity. The three measured parameters indicate that CHX treatment creates an oral environment with elevated antioxidant levels because it decreases microbial metabolism and leukocyte-generated oxidative reactions. The oral health benefits of this redox state modulation come with a risk of reducing the biochemical signals that help identify early malignant or pre-malignant redox imbalances.

The minimal oxidative effects of CPC prove that it works well for studies that need redox-based diagnostic markers.

Integrative Interpretation: How CHX and CPC Alter the Diagnostic Landscape

The biological pathways of OSCC development show a significant impact from CHX through its effects on cytokine, proteolytic and oxidative profiles. CHX produces biological effects, which include inflammatory signalling, extracellular matrix remodelling, and oxidative stress that together promote tumour development and growth. The multiple applications of CHX create chemical patterns that match healthy oral environments, which might reduce the accuracy of saliva tests for screening purposes.

CPC shows minimal impact on all biomarker categories, although it does not completely lack effect. The research results confirm medical studies, which show CPC produces minimal changes to body chemistry compared to CHX (12). The use of CPC as an antiseptic for diagnostic saliva collection becomes more suitable when patients require saliva sample collection. The duration of CHX washout needs to be longer when patients need to collect their saliva samples.

Study Limitations

There are a number of limitations in this study. The duration of the observation was also rather brief (14 days), and the study population comprised healthy individuals rather than patients with oral pathology. Thus, it is possible that the response to biomarkers

can vary in clinical populations with premalignant lesions or malignant lesions. Also, the long-term biochemical consequences of the use of the mouthwash were not examined. Future research ought to examine these biomarkers in patients with oral potentially malignant disorders and provide more follow-up time.

Conclusion

The research shows that CHX produces major changes in OSCC-related salivary biomarkers, but CPC produces minimal changes to these biomarkers. The research shows that doctors need to consider antiseptic mouthwash usage when reading saliva-based diagnostic results and supports the use of standardised washout protocols or methodological controls to maintain biomarker screening accuracy.

List of Abbreviations:

CHX: Chlorhexidine
CPC: Cetylpyridinium Chloride
OSCC: Oral Squamous Cell Carcinoma
IL-6: Interleukin-6
IL-8: Interleukin-8
TNF-α: Tumour Necrosis Factor Alpha
MMP-9: Matrix Metalloproteinase-9
ROS: Reactive Oxygen Species

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Institutional Research Ethics Committee and was conducted in accordance with the ethical standards of the Helsinki Declaration. Written informed consent was obtained from all participants before their inclusion in the study.

Consent for Publication

All authors gave their consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 license.

Data Availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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No specific funding was received for this study.

Author Contributions

MMA contributed to the conceptualisation and design of the study, supervised the research process, performed data analysis and statistical evaluation, and participated in manuscript preparation and critical revision.
AJOAQ contributed to study design, clinical investigation, and manuscript preparation.
AZAM participated in the literature search, clinical and experimental investigations, data acquisition, and manuscript editing.
ASHA contributed to the definition of intellectual content, literature review, experimental procedures, statistical support, and critical review of the manuscript.
All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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