Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Oct 07; 10(F):690-696.
https://doi.org/10.3889/oamjms.2022.10662
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Systematic Review Article*

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Mouthwashes and the Effect on the Viral Load of SARS-CoV-2 in Saliva: A Literature Review

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Edited by: Eli Djulejic
Citation: Pizarro MO, Mejia CR, Rodríguez-Díaz DR, Herrera YM, Cabrejo AB, Alarcon VS. Mouthwashes and the Effect on the Viral Load of SARS-CoV-2 in Saliva: A Literature Review. Open-Access Maced J Med Sci. 2022 Oct 07; 10(F):690-696. **https:**//doi.org/10.3889/oamjms.2022.10662
Keywords: SARS-CoV-2; COVID-19; Mouthwash; Saliva
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Received: 10-Jul-2022
Revised: 03-Aug-2022
Accepted: 27-Sep-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: At present, several active ingredients have been investigated in mouthwashes having certain virucidal properties, which could reduce the viral load of SARS-CoV-2 to avoid contamination in medical or dental practice.

AIM: The objective of this review is to analyze the available evidence regarding mouthwashes and their effect on the salivary viral load of SARS-CoV-2.

METHODS: Records were retrieved from databases such as PubMed, Scopus, Web of Science, and Virtual Health Library up to June 21, 2022. Randomized or non-randomized clinical trials were included where saliva samples and laboratory or *in vitro* studies were used in the presence of saliva.

RESULTS: After a systematic selection process, 11 clinical studies that evaluated at least one mouthwash within clinical protocols and three laboratory studies that evaluated the virucidal efficacy against SARS-CoV-2 in the presence of saliva were finally included.

CONCLUSION: There are oral disinfectants with virucidal action in saliva samples, under clinical and laboratory conditions, capable of reducing the viral load of SARS-CoV-2. Cetylpyridinium chloride, chlorhexidine, and povidone-iodine present the best results so far. However, it was also possible to find active principles of recent appearance that, based on favorable exploratory results, needs further investigation on their efficacy and possible adverse events.

Introduction

The coronavirus disease-19 (COVID-19) is caused due to human infection by SARS-CoV-2, which spread rapidly throughout the world. In March 20202, the WHO declared COVID as a new pandemic, generating a great impact in all areas of health [1], [2]. After more than 2 years of its appearance, the most effective measures to prevent the transmission of severe acute respiratory syndrome by coronavirus 2 (SARS-CoV-2) continue to be public health interventions, in this case immunization and social distancing [1], [2]. In the meantime, progress in the clinical treatment of COVID-19 patients has not yet achieved the goals set by the researchers, due to most drugs that had antiviral efficacy *in vitro* were found to be ineffective in the clinical treatment of COVID-19 [3].

Various studies have identified health professionals as a significant percentage of patients hospitalized for COVID-19, highlighting the fact that dental surgeons and ophthalmologists present a greater risk due to the close proximity of the face during the activities they perform [4], [5].

Once the virus has enters the human body, SARS-CoV-2 infects the nasopharyngeal and salivary secretions of affected patients and its spread has been shown to be predominantly respiratory. At present and worldwide, there is still no consensus on the acceptance and practice of clinical guidelines based on scientific evidence regarding specific standards that dental surgeons should have for public and private professional practice [6], [7]. Taking into account that saliva plays a key role in the transmission of this disease, a possible method to reduce the load of SARS-CoV-2 in saliva could be through the use of a mouthwash, since some of its components could affect the outer lipid membrane of the virus [6], [8], [9].

The objective of this review is to analyze the available bibliographic evidence regarding mouthwashes and their effect on the viral load of SARS-CoV-2 in saliva.

Methods

This literature review was carried out according to the methodology indicated for evidence-based clinical practice [10]. The research question was based on the PICO model, it is aimed at evaluating the current knowledge of the role that mouthwashes could play in the context of SARS-CoV-2 infection (problem), how its use (intervention) can promote a reduction in viral load in saliva (result), reported in clinical trials and in laboratory studies, compared to a control or placebo group (comparator).

The present review used a selection method according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. An electronic bibliographic search was carried out in the following databases: PubMed, Scopus, Web of Science, and the Virtual Health Library. Likewise, the bibliographic recovery period included publications until June 21, 2022. Bibliography in English and Spanish was retrieved using the terms MeSH, non-MeSH, and DeCS used in search expressions presented in Table 1 The publications included were clinical studies and *in vitro* studies, which evaluated the effect of a mouthwash or oral rinse on the viral load in saliva. The following were excluded from the review: Systematic reviews, literature reviews, study protocols, clinical cases, letter to the editor, books, newsletters, and announcements.

Table 1: Database search strategies

Database	Search expression
PubMed	((((mouth rinse*[Title/Abstract]) OR (mouthwash*[Title/Abstract])) OR (oral rinse*[Title/Abstract])) AND ((SARS-CoV-2[Title/Abstract]) OR (COVID-19[Title/Abstract]))) AND (saliva*[Title/Abstract])
Scopus	(TITLE-ABS-KEY (saliva*) AND TITLE-ABS-KEY ((covid-19 OR sars-cov-2) AND (mouthwash OR “oral rinse”)))
Web of Science	((TS=(SARS-CoV-2 OR COVID-19)) AND TS=(“oral rinse” OR mouthwash OR “mouth rinse”)) AND TS=(saliva*)
Virtual Health Library	((COVID-19) AND (enjuague oral OR colutorio)) AND (saliva)

Two independent reviewers (MOP and VSA) screened all record titles retrieved from the databases followed by an assessment of the abstract titles relevant to the review. Abstracts that fulfilled the selection criteria were selected and any disagreement about the selection was resolved through the involvement of a third reviewer (CRM). All duplicates were removed using the Zotero reference manager, after verifying the registry with a more recent and complete version. Subsequently, the full-text studies corresponding to the selected abstracts were retrieved and examined in detail to verify that the studies fulfilled the inclusion criteria. A Microsoft Excel data collection form was designed to extract the relevant data fields from each included study. Data extraction was performed by the two reviewers independently (MOP and VSA) and in duplicate. Where necessary, the corresponding author of studies was contacted by email to obtain any missing information of interest.

Results

A total of 185 articles were retrieved from the following databases: 56 records for PubMed, 68 for Scopus, 43 for Web of Science, and 18 for the Virtual Health Library. Duplicate records were removed, keeping a total of 99 publications. The selected records were screened by title and abstract, followed by a full-text review applying the exclusion criteria to obtain the 14 articles on which the present review was based, according to the flowchart described in Figure 1.

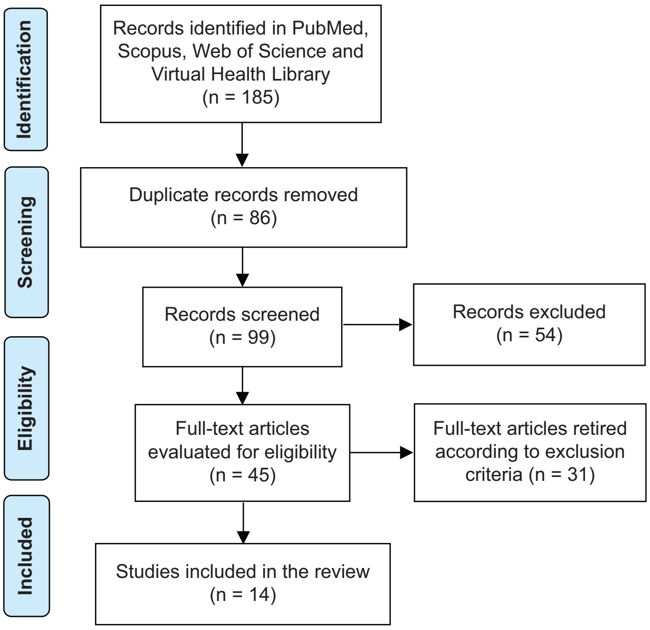

Figure 1: Flowchart showing systematic sequence for included studies

Review

High-risk clinical practice and viral load

Dental physicians and surgeons are continually at risk of possible COVID-19 infection due to the procedures they perform by being in close proximity to the patients with and without symptoms [4], [11]. Clinically, severe COVID-19 infection has been described by the appearance of certain events such as a strong inflammatory response from the immune system, lymphopenia, thrombocytopenia, and coagulopathies [3]. Several collection sites have been described in the literature to study the viral load in COVID-19, including nasopharynx, sputum, saliva, plasma, urine, and feces. Saliva viral load has shown significant positive correlations with IL-18 and IFNλ, both of which are associated with disease severity and mortality, in addition to progressive depletion of lymphocytes [5], [12].

Despite currently having a reduction in mortality rates, asymptomatic COVID-19 patients continue to be a challenge for the dental profession, as it has been shown that the infection continues to be transmitted through saliva with a significant viral load in dental practice environments through aerosol generation [6], [13], [14]. This context has forced the search and testing of numerous approaches to reduce the viral load in saliva produced by COVID-19, among which the use of mouthwashes stands out due to its ease of use and application within daily practice [1], [6], [15].

Effectiveness of oral mouthwashes against SARS-CoV-2 in saliva

Recent research has aimed to determine whether providing mouthwashes with antimicrobial agents before or during a dental procedure might have a concrete benefit in preventing the transmission of COVID-19 [15], [16]. Table 2 describes the characteristics of the clinical and laboratory investigations where various agents were tested as mouthwashes in saliva samples or in the presence of saliva.

Discussion

Povidone-iodine

Povidone-iodine is an antiseptic agent that has been shown to have broad activity against a series of pathogenic microorganisms, including coronaviruses, so its use has been proposed to reduce the viral load in otorhinolaryngology surgical practices, as described by studies [17], [18]. In the context of the COVID-19 pandemic, it has been widely studied due to certain advantages such as its ease of preparation, cost, relatively safe use, and its potential to reduce SARS-CoV-2 viral titers [19], [20], [21].

The virucidal activity varies according to the concentration or formulation, where the 0.5% and 10% solutions presented the best results along with some adverse events such as burning sensation, localized irritation, and itching that can last from a few minutes to hours [22]. However, there is a consensus to affirm that povidone-iodine does not present cytopathic and/or non-cytotoxic effects, in addition to rarely reported allergic reactions, dental stains, or stains in general [22], [23]. On the other hand, recent studies have evaluated molecular iodine as the true microbicide agents in aqueous and alcoholic solutions through their forms $I_2 \cdot HO$ or $I_2 \cdot C_2H_5OH$. However, knowledge about the relationship between the structural configurations of molecular iodine and its antimicrobial activities is still unclear [24].

Cetylpyridinium chloride

Cetylpyridinium chloride (CPC) is a cationic quaternary ammonium with an important spectrum against oral microorganisms and is widely used in various over-the-counter mouthwashes, with a concentration that range from 0.05% to 0.1% [25], [26]. Recent studies postulate that CPC is an active agent against SARS-CoV-2, based on *in vitro* experiments and randomized clinical trials, where it has been observed that CPC induces the disorganization and rupture of viral membrane proteins in saliva [18], [25], [26], [27], [28]. Adverse events reported with the use of CPC are quite few which includes numbness of the tongue, decreased taste or bitter taste, sublingual swelling, tooth sensitivity, and tooth staining [29], [30]. Although, the esthetic impact it would have with respect to dental staining would be less than chlorhexidine [31].

Chlorhexidine

Chlorhexidine is a commercially available dicationic biguanide, available in concentrations of 0.02%, 0.05%, 0.12%, 0.2%, and 0.5% with significant residual antimicrobial activity that is not affected by the presence of fluids and blood [32]. The use of chlorhexidine has been demonstrated in various *in vitro* studies and in clinical trials, heterogeneous results with respect to the reduction of the viral load of SARS-CoV-2 have been reported [17], [27], [33]. However, most studies reviewed report to chlorhexidine as an option to consider after povidone-iodine and cetylpyridinium chloride in their results, in addition to taking into account the adverse events related to its use, such as a burning sensation and dryness, alteration of taste, and dental staining [18], [25], [26].

Hydrogen peroxide

Hydrogen peroxide solutions have a biocidal activity due to the generation of hydroxyl radicals and other oxygenated oxidants capable of reacting with lipids, proteins and nucleic acids, disrupting the structure of the pathogen [34]. Recent studies indicate that under acidic pH conditions, due to the addition of coformulations, hydrogen peroxide can be considered an active agent for the inactivation of SARS-CoV-2 virus [27], [34], [35].

Octenidine hydrochloride plus phenoxyethanol

Octenidine hydrochloride (OCT) is a cationic bipyridine that has been widely used for wound disinfection due to its efficacy against bacteria and fungi and recently has been tested against the SARS-CoV-2 virus in many *in vitro* and clinical studies, while phenoxyethanol is an ethanol derivative which serves as a preservative component of OCT and that improved the antimicrobial efficacy [36], [37]. However, there are still few clinical studies that can provide more

Table 2: Characteristics of included studies

Author (year)	Methods	Sample/specimens	Intervention: Mouthwash	Assessment/follow-up	Conclusion
Gottsauner *et al*. [43], 2020	Clinical pilot study	10 patients positive for SARS-CoV-2, who served as their own controls	1% hydrogen peroxide	Baseline and 30 minutes after rinsing	Rinsing with hydrogen peroxide did not decrease viral load in patients positive for SARS-CoV-2
Carrouel *et al*. [39], 2021	Clinical (RCT)	GC: 88 GT: 88	GC: Placebo GT: CDCM	For 7 days in salivary samples	CDCM significantly reduced the salivary viral load of SARS-CoV-2 in asymptomatic or mild cases, 4 h after the initial dose. In the long term, the effect is limited
Chaudhary *et al*. [19], 2021	Clinical (RCT)	40 symptomatic individuals	GC: Normal saline GT1: 1% hydrogen peroxide GT2: 0.12% CHX GT3: 0.5% povidone-iodine	Baseline, 15 min and 45 min after using the solutions	All the mouthwashes tested reduced the salivary load of SARS-CoV-2. The reduction at 15 and 45 min was not different between mouthwashes
Costa *et al*. [33], 2021	Clinical (RCT)	GC:50 GT: 50	GC: Placebo GT: 0.12% CHX	Baseline, 5 min and 60 min after using the solutions	The patients who used chlorhexidine gluconate had an effect on the decrease in salivary viral load of SARS-CoV-2 during all the observation times
Eduardo *et al*. [27], 2021	Randomized clinical pilot trial	GC: 12 GT1: 12 GT2: 12 GT3: 12 GT4: 12	GC: Distilled water GT1: 0.075% CPC + 0.28% Zinc lactate GT2: 1.5% hydrogen peroxide GT3: 0.12% CHX GT4: 1.5% Hydrogen peroxide + 0.12% CHX	Baseline, immediately after rinsing, 30 min and 60 min later	CPC + Zinc and CHX significantly reduced the viral load of SARS CoV-2 up to 60 minutes, while Hydrogen Peroxide significantly reduced up to 30 min after use
Elzein *et al*. [17], 2021	Clinical (RCT)	GC: 9 GT1: 27 GT2: 25	G1: Distilled water GT2: 0.2% CHX GT3: 1% Povidone-iodine	Baseline, immediately after rinsing and 5 min later	Gargling with povidone-iodine or chlorhexidine rinsing significantly reduce the viral load of SARS-CoV-2 in saliva
Ferrer *et al*. [44], 2021	Clinical (RCT)	GC: 15 GT1: 15 GT2: 15 GT3: 15 GT4: 15	GC: Distilled water GT1: 2% povidone-iodine GT2: 1% hydrogen peroxide GT3: 0.07% CPC GT4: 0.12% CHX	Baseline, 30, 60 and 120 min after rinsing	The SARS-CoV-2 load in saliva was not significantly affected by any of the four mouthwashes tested
Guimaraes *et al*. [35], 2021	Clinical (non-RCT)	GC: 15 GT1: 12 GT2: 12 GT3: 12 GT4: 12	GC: Sterile water GT1: 1.5% hydrogen peroxide GT2: 0.12% CHX GT3: 0.1% sodium hypochlorite GT4: 1.5% hydrogen peroxide + 0.12% CHX	Baseline, immediately after rinsing, 15 and 30 minutes after rinsing	Compared to baseline values, sodium hypochlorite and hydrogen peroxide produced a significant reduction. No experimental group demonstrated a significant reduction in viral load compared to control
Muñoz-Basagoiti *et al*. [25], 2021	*In vitro*	800 μL of mouth rinse was mixed with 200 μL of SARS-CoV-2 and 200 μL of sterilized saliva	GC: Distilled water G1: 1.47 mM CPC G2: 1.47 mM CPC + 1.33 mM CHX G3: 2.063 mM CPC	60 s of incubation and the experiments were carried out in triplicate. Virucidal activity was measured in contact with sterillized saliva for 30 s	Cetylpyridinium chloride inhibited viral fusion, at concentrations where there is no cytotoxic effect. The virucidal activity was equally effective in presence of saliva
Seneviratne *et al*. [18], 2021	Clinical (RCT)	GC: 2 GT1: 4 GT2: 6 GT3: 4	GC: Sterile water G1: 0.5% povidone–iodine G2: 0.2% CHX G3: 0.075% CPC	Baseline, 5 min, 3 h and 6 hours after rinsing	Cetylpyridinium chloride and povidone iodine had a significant effect in reducing the viral load of SARS-CoV-2 in saliva, compared to the control group
Alemany *et al*. [28], 2022	Clinical (RCT)	GC:40 GT: 40	GC: Distilled water GT: 0.07% CPC	Baseline, 1 h, and 3 h after rinsing	In SARS-CoV-2 positive asymptomatic or mildly symptomatic patients, CPC produced a significant increase in salivary nucleocapsid protein, an indicator of viral disruption
Anderson *et al*. [26], 2022	*In vitro*	800 μL of mouthwash was added to 100 μL of human saliva mixed with 100 μL of SARS-CoV-2	GC−: Distilled water GC+: 70% ethanol in distilled water G1: 0.2% CHX G2: 0.07% CPC	30 s of incubation and the experiments were carried out in duplicate. Virucidal activity was measured in contact with human saliva for 5 min	Cetylpyridinium chloride but not chlorhexidine, completely inactivated SARS-CoV-2 (Alpha, Beta, Gamma, Delta) The presence of saliva did not affect the results
Smeets *et al*. [36], 2022	Exploratory clinical study	6 samples were collected from 8 patients with active SARS-CoV-2 infection	5% Octenidine Hydrochloride + phenoxyethanol	Baseline and 1 min, 30 min, 60 min, 240 min, and 360 min after rinsing	The rinse based on Octenisept + phenoxyethanol could temporarily reduce SARS-CoV-2 RNA load in saliva with rapid onset of effects
Teagle *et al*. [45], 2022	*In vitro*	0.5 ml SARS-CoV-2 virus strain (USA-WA1/2020) provided by EIB resources and 5% human saliva	100 ppm MIOR	The evaluations were made at 30 and 60 s	MIOR is effective in reducing the infectivity of SARS-CoV-2, in the presence of human saliva

GC: Control group, GT: Treatment group, RCT: Randomized controlled trial, CPC: Cetylpyridinium chloride, CHX: Chlorhexidine, CDCM: β-cyclodextrin and citrox, MIOR: Molecular iodine oral rinse, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

information about their effectiveness as mouthwashes as well as adverse events.

β-*cyclodextrin*

Cyclodextrins are natural cyclic oligosaccharides composed of six to eight D-glucose linked to other units (α-, β-, and γ-CD) [38]. *In vitro* studies showed a reduction of cholesterol by cyclodextrin in cell models, and in particular of methyl beta-cyclodextrin, are capable of altering the way receptors are distributed throughout the membrane, making it impossible for SARS-CoV-2 virus to enter [38], [39]. In Japan, they are even considered natural products and their use in food is widespread [40]. Cyclodextrins can be considered safe for ingestion because they are not generally absorbed from the gastrointestinal tract, and are currently used in conjunction with remdesivir, a drug approved by the Food and Drug Administration (FDA) against COVID-19 [40], [41].

Sodium hypochlorite

Sodium hypochlorite solutions have many advantages as they are inexpensive, easy to prepare, and generally have a broad spectrum of activity against microbes and viruses. The mechanism observed was the degeneration of the particles, since there were a dramatic morphological change and a loss of structure within the virus particles, its efficacy against SARS-CoV-2 having been demonstrated during hand hygiene, in two concentrations of 0.05% and 0.25% [35]. However, it has limitations like the instability with the temperature variations and the sunlight, and the skin and mucous membranes irritation [42].

Conclusion

Based on the evidence found in clinical and *in vitro* studies, it can be concluded that currently, the rinses with the best results in reducing viral load in saliva samples or in the presence of saliva are in the following order: Cetylpyridinium chloride, chlorhexidine, and povidone-iodine; and may be considered for use as mouthwashes against SARS-CoV-2. Hydrogen peroxide-based mouthwashes showed the most contradictory results in the included studies. According to the criteria established for this review, no studies were found that evaluated essential oils. According to the studies included in this review, adverse events associated with the use of the evaluated mouthwashes are rare or otherwise not reported, which prevents a conclusive assessment of the safety of their use. Emerging studies evaluating octenidine hydrochloride plus phenoxyethanol, β-cyclodextrin, and sodium hypochlorite have shown encouraging results in exploratory designs and need to be tested in more studies to find more alternatives to prevent the risk of cross-infection in medical and dental settings.

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