Review Article

The effectiveness of mouthwash against SARS-CoV-2 infection: A review of scientific and clinical evidence

Ming-Hsu Chen [a], Po-Chun Chang [b,c,d,*]

[a] Department of Otorhinolaryngology, Cathay General Hospital, Taipei, Taiwan
[b] Graduate Institute of Clinical Dentistry, School of Dentistry, College of Medicine, National Taiwan University, Taipei, Taiwan
[c] Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan
[d] School of Dentistry, College of Dental Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

The COVID-19 pandemic, caused by the spread of SARS-CoV-2 infection that is mainly through the airborne transmission, is a worldwide health concern. This review seeks to assess the potential effectiveness of mouthwash in reducing the oropharyngeal load of SARS-CoV-2 based on the available evidence. Articles related to mouthwash and COVID-19 in PubMed were electronically searched in July, 2021. After manually excluding articles lacking sufficient scientific evidence or validation processes, those with inaccessible online full text, those that did not test the effectiveness of mouthwash against SARS-CoV-2, and those not written in English, 17 original and 13 review articles were chosen for this review. The eligible articles revealed that the main virucidal mechanism of mouthwash was via interactions with the viral envelope. Povidone-iodine (PVP-I), cetylpyridinium chloride (CPC), and essential oils with ethanol showed virucidal effects on SARS-CoV-2 *in vitro*, potentially by interfering with the viral envelope. A few clinical studies demonstrated that PVP-I, CPC, hydrogen peroxide, and chlorhexidine reduced the oropharyngeal load of SARS-CoV-2. Although the available evidence is limited, mouthwash containing PVP-I or CPC shows potential for reducing the oropharyngeal load of SARS-CoV-2 and thus may present a risk-mitigation strategy for COVID-19 patients.
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* Corresponding author. Graduate Institute of Clinical Dentistry, School of Dentistry, College of Medicine, National Taiwan University, No. 1 Chang-Te St., Taipei, 10048, Taiwan.
E-mail address: changpc@ntu.edu.tw (P.-C. Chang).

Introduction

The COVID-19 pandemic, caused by the spread of a new coronavirus strain of SARS-CoV-2, has affected more than 200,000,000 individuals and caused more than 4,000,000 deaths worldwide in 2020−2021.[1] The primary routes of disease transmission were respiratory droplets and contact.[2] Clinical evidence showed that the virus was detectable in swabs of the upper respiratory tract and the self-collected saliva of patients infected by SARS-CoV-2.[3,4] Angiotensin-converting enzyme 2 (ACE2), the main host cell receptor of SARS-CoV-2, was highly expressed by the oral mucosal epithelial cells.[5] Because the viral load of SARS-CoV-2 is associated with the severity of COVID-19,[6] reduction of the viral load in the oral cavity may reduce the severity of the disease. Antiviral mouthwash has been proposed as a low-cost and easily implemented strategy against SARS-CoV-2 infection, thereby reducing the risk of viral transmission.[7]

This paper provides an evidence-based review to assist dental and healthcare professionals who consider mouthwashes as an auxiliary strategy in controlling SARS-CoV-2 infection. It explains the potential mechanism by which mouthwashes may control SARS-CoV-2 infection and reviews in vitro and clinical research supporting the virucidal properties of mouthwashes on SARS-CoV-2.

Search strategy for evidence collection

An electronic search of scientific articles in PubMed using the Boolean operators of "(mouthrinse OR mouthwash) AND (COVID OR SARS-CoV-2 OR coronavirus)" was performed on July 23, 2021. 122 articles were included for the subsequent screening, and the exclusion criteria were:

- The full text is inaccessible online.

- The article is a case report, a case series, a clinical study with fewer than 5 participants per group, a letter to the editor, editorial, or a short communication without an experimental section.
- The article is a summary of protocol or hypothesis without any experimental validation.
- The article is a systematic review without any eligible articles for the analysis.
- The tested compounds are not designed for oral use against SARS-CoV-2 infection.
- None of the tested compounds revealed >90% inactivation of SARS-CoV-2 (for the in vitro studies only).
- The article is not written in English.

After excluding the ineligible articles, a total of 30 articles were chosen. The characteristics of in vitro studies (9 articles) are listed in Table 1, clinical studies (8 articles) in Table 2, and 13 review articles (4 systematic reviews and 9 narrative reviews) in the Appendix.

Mouthwashes with virucidal potential against SARS-CoV-2 infection

SARS-CoV-2 is covered with a lipid envelope that is embedded with spike glycoproteins, which interact with ACE2 to penetrate cells.[8] Interfering with the lipid envelope has been reported as a virucidal strategy for enveloped viruses, including coronaviruses.[9,10] Membrane disrupting agents, including 62−71% ethanol, 0.5% hydrogen peroxide (HP), and 0.1% sodium hypochlorite, have been shown to efficiently inactivate SARS-CoV-2 within 1 min of surface disinfection.[11] The primary mechanism of mouthwashes used to reduce the load of active virus in the oropharynx is likely damaging or destroying the viral envelope.[12]

Table 1 The characteristics of the virucidal effectiveness of the tested compounds in the in vitro studies.

Investigated compounds	Minimal incubation period	Virucidal effect[a]	Compounds with virucidal effect	Ref No.
CHX, EOs, HP, PVP-I, dequalinium chloride, octenidine dihydrochloride, polyhexanide	30 s	Undetectable	EOs, PVP-I, dequalinium chloride	24
CPC, EOs, HP, PVP-I	30 s	≥99.9%	CPC, EOs, PVP-I	19
PVP-I	60 s	≥99.99%	PVP-I	20
PVP-I	15 s	≥99.99%	PVP-I	22
CHX, octenidine dihydrochloride	15 s	≥99.99%	octenidine dihydrochloride	35
CHX, PVP-I	30 s	≥99.8%	CHX, PVP-I	21
CHX, CPC, delmopinol hydrochloride	20 s	≥99.9%	CPC	29
CHX, EOs, HP, PVP-I, potassium oxalate, hypochlorous acid	60 s	≥99.99%	EOs, PVP-I, hypochlorous acid	23
CPC	2 min	99.9%	CPC	28

Abbreviations: CHX: chlorhexidine; CPC: cetylpyridinium chloride; EOs: essential oils; HP: hydrogen peroxide; PVP-I: povidone-iodine.
[a] Based on the measurement from tissue culture infectious dose 50 (TCID50) assay. The standard of EN14476 defined the virucidal efficacy success as at least a 4 $\log_{10}$ reduction (≥99.99% virus inactivation) relative to the virus recovery control.

Ethanol

While a high concentration (60—80%) of ethanol showed potent effects in damaging the viral envelope and was suggested as an effective agent against SARS-CoV-2 infection,[12,13] to reduce toxicity and prevent irritation of the oral mucosa, the concentration of ethanol in ethanol-containing mouthwashes is generally 15—25%. This low concentration of ethanol still causes swelling of the phosphatidylcholine vesicles, promotes interdigitation, and leads to leakage in the lipid envelope. The lipid envelope not only stabilizes spike glycoproteins but also regulates viral sensitivity to antibody neutralization. Biophysical changes to the lipid envelope caused by low concentrations of ethanol could only reduce pathogenicity without completely neutralizing the virus.[12]

Evidence as a mouthwash against SARS-CoV-2 infection
Ethanol does not serve as an active ingredient in available mouthwashes but often appears as an inactive ingredient at concentrations below 25%.[13] A 30-s exposure to diluted ethanol-based hand rubs showed that 20% ethanol reduced the infectivity of SARS-CoV-2 by >87%, whereas 30% ethanol reduced the infectivity by >99.99%.[14]

Povidone-iodine (PVP-I)

PVP-I is a broad-spectrum antiseptic agent effectively against bacteria, fungi, protozoans, and viruses. The free iodine released from PVP-I destabilizes the lipid envelope, lyses spike proteins, irreversibly damages the virus by degenerating nucleoproteins and oxidizing the nucleic acids of viral particles, and relieves inflammation by scavenging free radicals.[8,15] PVP-I is commercially available at concentrations of 0.23—10% in the form of scrubs, foams, ointments, nasal sprays, and mouthwashes.[7,8] Previous evidence affirms that 15-s exposure to 0.23% PVP-I reduced the infectivity of the coronaviruses responsible for the 2003 severe acute respiratory syndrome (SARS) and 2012 Middle East respiratory syndrome (MERS) outbreaks, and the infectivity was further reduced to undetectable levels with 1—2 min' exposure.[16,17] However, although the incidence was rare, adverse effects including contact dermatitis, allergies, and thyroid dysfunction, were reported when $\geq$1% PVP-I was utilized.[15,18] Solutions of 4% and 5% PVP-I show toxicity to human keratinocytes and respiratory cells *in vitro*.[18]

Evidence as a mouthwash against SARS-CoV-2 infection
Six *in vitro* studies supported the virucidal effect of PVP-I-containing mouthwash against SARS-CoV-2 infection. Within 30—120 s of incubation with 5% PVP-I, >99.9% of SARS-CoV-2 was inactivated.[19] Pelletier et al. demonstrated that a 60-s incubation with 1—3% PVP-I inactivated >99.99% of SARS-CoV-2, equivalent to 70% ethanol under the same incubation conditions.[20] Jain et al. reported that a 30-s incubation with 1% PVP-I inactivated 99.8% of SARS-CoV-2.[21] Hassan-darvish et al. examined the effect of 15—60 s of incubation with 0.5—1% PVP-I and reported that $\geq$99.99% of SARS-CoV-

Table 2 The characteristics of the virucidal effectiveness of the tested compounds in the clinical studies.

Investigated compounds	Analyzed participants	Rinsing protocol	Summary of results	Ref No.
HP	10	30 s	Viral load was not significantly reduced in oropharyngeal specimens of patients after 30 min.	37
CHX, CPC, PVP-I, water (control)	16	30 s	Viral load was significantly reduced in saliva in CPC group at 5 min and 6 h and in PVP-I group at 6 h.	25
PVP-I, no intervention (control)	24	4/day for 5 days	PVP-I had no significant influence on changes of viral load in the nasopharyngeal swabs over 7 days.	26
CHX, no intervention (control)	121	30 s, 2/day for 4 days	Virus was eliminated from oropharynx in 62.1% patients in CHX group (5.5% in control).	36
HP, water with mint essence (control)	35	30 s, 3/day for 7 days	HP did not significantly reduce the length of hospital stay or COVID-19 related symptoms.	38
hydrocortisone	34	1 min	Viral load in pharyngeal swabs was significantly reduced after 5 min, and the reduction was persistent for 6 h in 90% patients	42
bioflavonoids, placebo	176	1 min, 3/day for 7 days	Compared with placebo, viral load in saliva was significantly reduced in bioflavonoids group after 4 min at the first day and was modest reduced until 7 days.	40
CHX, CPC, HP, CHX + HP, water (control)	36	30—60 s	Viral load in saliva was significantly reduced up to 60 min in CHX and CPC groups and up to 30 min in HP group.	30

Abbreviations: CHX: chlorhexidine; CPC: cetylpyridinium chloride; HP: hydrogen peroxide; PVP-I: povidone-iodine.

2 was inactivated within 15 s.[22] A 1-min incubation with 0.58% PVP-I also inactivated >99.99% of SARS-CoV-2.[23] Meister et al. demonstrated that a 30-s incubation with 0.1% PVP-I immediately reduced 3 strains of SARS-CoV-2 to undetectable levels.[24]

A randomized controlled trial (RCT) conducted in Singapore revealed that in four COVID-19 patients prescribed 0.5% PVP-I mouthwash for 30 s, the load of SARS-CoV-2 was significantly reduced after 6 h of treatment compared with patients prescribed water rinses.[25] Guenezan et al. prescribed 12 COVID-19 patients 1% PVP-I 4 times daily for 5 days with supplemental PVP-I nasal spray but concluded that PVP-I did not significantly influence the change in viral load over 7 days compared with patients receiving a placebo treatment.[26] They also reported that thyroid dysfunction occurred in 42% of the patients receiving PVP-I treatment but spontaneously resolved after 7–12 days.

Cetylpyridinium chloride (CPC)

Quaternary ammonium compounds are widely used antimicrobial agents that interfere with the lipid components on the surface of bacteria, disrupt the integrity of the viral envelope, and are lysosomotropic, destroying the capsid of the virus.[12,27,28] Among these compounds, CPC is "generally regarded as safe" by the Food & Drug Administration and against severe coronaviruses with an effective dose (EC$_{50}$) <5 μM.[8] CPC is currently used in medicated mouthwashes at 0.02–0.075% concentration.[7,12]

Evidence as a mouthwash against SARS-CoV-2 infection

Three *in vitro* studies supported the virucidal effect of CPC-containing mouthwash against SARS-CoV-2 infection. Meyers et al. demonstrated that 0.07% CPC inactivated ≥99.9% of SARS-CoV-2 within 30–120 s of incubation.[19] Komine et al. also demonstrated that mouthwashes containing 0.04–0.075% CPC inactivated >99.99% of SARS-CoV-2 in 20–30 s.[29] Munoz-Basagoiti et al. investigated the antiviral effect of CPC on the D614G and Alpha SARS-CoV-2 variants.[28] They demonstrated that a 2-min incubation with 10 mM (0.35%) CPC suppressed viral fusion by disrupting the viral envelope, thus inhibiting virus entry into target cells. They also demonstrated that a 30-s incubation with 2 mM (0.07%) CPC in the presence of sterilized saliva still inactivated ≥99.9% SARS-CoV-2, even at a dilution ratio of 1:10.

A RCT conducted in Singapore revealed that, compared with COVID-19 patients using water rinses, 4 patients prescribed 30 s of exposure to 0.075% CPC mouthwash exhibited a significantly reduced load of SARS-CoV-2 in 5 min and the effect persisted for 6 h.[25] Eduardo et al. also prescribed 30 s of exposure to 0.075% CPC mouthwash to 7 COVID-19 patients and demonstrated that, compared with the baseline, viral load was significantly reduced for up to 60 min.[30]

Chlorhexidine (CHX)

CHX is a cationic biguanide compound showing broad-spectrum antimicrobial properties and has been considered the gold standard of chemical plaque control.[31–33]

Positively charged CHX reacts with negatively charged microbial surfaces, damaging the cytoplasmic membrane and causing leakage.[12] The virucidal mechanism has not been fully elucidated but is probably related to interaction with the viral envelope.[34] In general, the concentration of CHX in mouthwashes is 0.12–0.2% and the major adverse effects of CHX include tooth pigmentation, supragingival calculus deposition, and taste alteration.[31,32]

Evidence as a mouthwash against SARS-CoV-2 infection

The *in vitro* evidence of CHX against SARS-CoV-2 is controversial. Jain et al. demonstrated that 30–60 s of incubation with 0.12–0.2% CHX inactivated ≥99.9% of SARS-CoV-2.[21] However, Meister et al. reported that a 30-s incubation of 0.2% CHX modestly reduced the load of SARS-CoV-2 (70–90%; <1 log$_{10}$ reduction),[24] and Davies et al. reported similar results with a 1-min incubation period.[23] Komine et al. reported that 30-s incubation with 0.12% CHX achieved only 42.5% virus reduction after 10 min.[29] By further extending the incubation period to 10 min, Steinhauer et al. demonstrated that 0.1–0.2% CHX could only inactivate <90% (<1 log$_{10}$ reduction) of SARS-CoV-2.[35]

Although a small RCT conducted in Singapore did not reveal significant differences in the reduction of SARS-CoV-2 between patients prescribed 30 s of 0.2% CHX exposure and those prescribed water rinses,[25] a larger RCT conducted in the United States demonstrated that by following a 4-day course of 0.12% CHX oropharyngeal rinse (30-s exposure, twice daily), SARS-CoV-2 was eliminated from the oropharynx in 62.1% of COVID-19 patients.[36] Another small RCT conducted in Brazil showed that a 30-s 0.12% CHX rinse significantly reduced the load of SARS-CoV-2 in saliva for up to 60 min.[30]

Hydrogen peroxide (HP)

HP targets the viral envelope by liberating oxygen free radicals and disrupting the lipid structure,[8] and a concentration of about 0.5% is virucidal to enveloped viruses, including coronavirus.[12] Concentrations of HP >5% may induce tissue damage, but 1–3% HP does not pose a significant risk of adverse effects and is generally accepted in mouthwash formulas.[31] Because SARS-CoV-2 is vulnerable to oxidation, 0.1% HP has been recommended as a preprocedural mouthwash to reduce the viral load.[32]

Evidence as a mouthwash against SARS-CoV-2 infection

The included *in vitro* evidence did not support the effectiveness of HP against SARS-CoV-2 infection. A 30-s incubation with 1.5% HP resulted in <90% and 90–99% inactivation of SARS-CoV-2 according to Meister et al. and Meyers et al., respectively.[19,24] With a 60-s incubation, Davies et al. demonstrated only a 0.2 log$_{10}$ reduction of SARS-CoV-2.[23]

A small clinical trial demonstrated that after a 30-s 1% HP oral rinse, the oropharyngeal viral load was not significantly reduced after 30 min.[37] Another study on hospitalized COVID-19 patients demonstrated that daily 1% HP oral rinses (30-s exposure 3 times daily for 7 days) with 0.5% HP nasal spray neither relieved COVID-19 symptoms nor

Table 3 The summary of virucidal mechanisms and current evidence of test compounds against SARS-CoV-2 infection.

Compound	Virucidal mechanisms	Conc. (%)	Exposure time (seconds)	In vitro evidence against SARS-CoV-2 (studies)		Clinical evidence in COVID-19 patients (studies)		Potential adverse effect
				Support	Not support	Support	Not support	
PVP-I	Destabilize viral envelope, lyse spike glycoprotein, degenerate viral particles, and scavenge free radicals	0.5–1	30	6	Nil	1	1	Allergy, thyroid dysfunction
CPC	Interfere with viral envelope, lysosomotropic to destroy the capsid of virus	0.04–0.075	30	3	Nil	2	Nil	Tooth pigmentation, change in taste sensation, burning sensation
HP	Disrupt the lipid structure	1–1.5	30	Nil	3	1	2	Tooth/oral tissue damage, burning sensation
CHX	Interfere with viral envelope	0.12–0.2	30	1	4	2	1	Tooth pigmentation, supragingival calculus formation, change in taste sensation
EOs with low conc. ethanol	Interfere with viral envelope	NA	NA	3	Nil	Nil	Nil	Burning sensation, mucosal irritation, palatal erythema

Abbreviations: CHX: chlorhexidine; CPC: cetylpyridinium chloride; EOs: essential oils; HP: hydrogen peroxide; PVP-I: povidone-iodine; NA: not applicable.

reduced hospitalization time.[38] The data also revealed that adverse effects, mainly mucosal burning sensations, occurred in a few patients and diminished with time. Furthermore, in a small RCT, patients prescribed 60 s of exposure to 1.5% HP mouthwash showed a significant reduction of salivary viral load for up to 30 min.[30] This study also tested a 30-s 0.12% CHX mouthwash following the HP rinse but showed an inferior reduction of the viral load. The authors inferred that the secondary CHX rinse might wash out HP in the oral cavity and reduce the contact time below that required for HP's virucidal effects.

Essential oils (EOs)

EOs are volatile compounds originally extracted from plants. The main compounds of EOs in the mouthwash are terpenes, terpenoids, and phenylpropanoids, and ethanol is included as an inactive ingredient.[8,13] EOs-containing mouthwashes are widely used for professional and home use, and showed virucidal effects on enveloped viruses, including herpes simplex and influenza virus, but not on non-enveloped viruses.[39] The virucidal mechanisms are interference with the phospholipid bilayer and disturbing the viral envelope and spike glycoproteins to prevent viral attachment to target cells.[8,31] The main adverse effects of EOs-containing mouthwashes are mild burning sensations and reversible palatal erythema.[31]

Evidence as a mouthwash against SARS-CoV-2 infection
Three in vitro studies supported the effectiveness of EOs-containing mouthwashes against SARS-CoV-2 infection. Meister et al. reported that SARS-CoV-2 was reduced to undetectable levels after a 30-s EOs incubation.[24] Both Meyers et al. and Davies et al. demonstrated that ≥99.99% of SARS-CoV-2 was inactivated after a 1- to 2-min EO

incubation.[19,23] There are currently no clinical studies investigating EOs-containing mouthwashes against SARS-CoV-2 infection.

Others

Several broad-spectrum antimicrobials, including dequalinium chloride, octenidine dihydrochloride, C31G, and hypochlorous acid, are found in mouthwash formulas and have shown a variety of virucidal effects *in vitro*, but there is no current evidence supporting their clinical effectiveness.[23,24,33] Based on virtual simulation of SARS-CoV-2 inhibition, antiviral bioflavonoids could be of interest to fight SARS-CoV-2.[8] A medium-sized RCT demonstrated that COVID-19 patients prescribed 1 min of bioflavonoid mouthwash 3 times daily for 7 days exhibited significantly reduced salivary viral loads after 4 h on the first day, and the viral load was modestly reduced compared with the placebo group until the seventh day.[40] A small clinical study investigated the applicability of anti-inflammatory hydrocortisone-containing mouthwash in COVID-19 patients to reduce the cytokine storm induced by SARS-CoV-2 infection[41] and found that after 1 min of exposure to hydrocortisone-containing mouthwash, a 90% viral load reduction was achieved for up to 6 h.[42]

Preprocedural rinse to reduce the airborne SARS-CoV-2 transmission

Viral transmission through the aerosolized droplets generated in dental procedures has drawn researchers' attention during the COVID-19 pandemic. To reduce the airborne transmission of SARS-CoV-2, a series of precautions, including the use of a rubber dam, high-volume evacuator (HVE), and preprocedural mouthwash have been recommended to dental professionals.[31,43] As Samaranayake et al. stated, although an HVE is a compulsory requirement during most dental procedures, a preprocedural mouthwash must be utilized to reduce microbe-laden aerosols if possible.[43] They reviewed 7 clinical studies and pointed out that preprocedural rinsing with CHX, CPC, or EOs was effective in reducing bacterial loads in aerosols. Testori et al. reviewed 11 clinical studies and 4 clinical guidelines and suggested preprocedural rinsing with CHX, HP, PVP-I, or CPC to prevent the spread of SARS-CoV-2.[32] However, they also acknowledged that the direct clinical evidence related to SARS-CoV-2 is very limited, and there was high variability in the protocols tested. Based on the results from *in vitro* studies and previous experience controlling coronaviruses, two nationwide interim guidelines recommend a 1–1.5% HP or 0.2% PVP-I preprocedural mouthwash to limit the risk of SARS-CoV-2 infection.[15,16]

Conclusions

Because the oropharynx serves as a reservoir of SARS-CoV-2, the use of mouthwashes could be considered beneficial for COVID-19 patients and to prevent airborne SARS-CoV-2 transmission. However, given that SARS-CoV-2 infection emerged at the end of 2019, extremely small sample sizes and imperfect study designs often lead to inconclusive results from clinical studies. As shown in Table 3, although the available evidence is limited, a 30-s exposure to 0.5–1% PVP-I or 0.04–0.075% CPC appears to reduce the oropharyngeal load of SARS-CoV-2 and present a risk mitigation strategy for COVID-19 patients.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2021.10.001.

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