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Systematic Review

The effect of mouthrinses on severe acute respiratory syndrome coronavirus 2 viral load

A systematic review

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Supplemental material is available online.

ABSTRACT

Background. Considering that the oral cavity is a major entryway and reservoir for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the aim of the authors was to perform a systematic review of in vivo and in vitro studies to assess the effectiveness of mouthrinses on SARS-CoV-2 viral load.

Types of Studies Reviewed. The authors searched PubMed, Web of Science, Scopus, MedRxiv, and bioRxiv databases, including in vitro and in vivo studies assessing the virucidal effect of mouthrinses on SARS-CoV-2 or surrogates. From a total of 1,622 articles retrieved, the authors included 39 in this systematic review.

Results. Povidone-iodine was the most studied mouthrinse (14 in vitro and 9 in vivo studies), frequently showing significant reductions in viral load in in vitro assays. Similarly, cetylpyridinium chloride also showed good results, although it was evaluated in fewer studies. Chlorhexidine gluconate and hydrogen peroxide showed conflicting results on SARS-CoV-2 load reduction in both in vitro and in vivo studies.

Practical Implications. Povidone-iodine–based mouthrinses appear to be the best option as an oral prerinse in the dental context for SARS-CoV-2 viral load reduction. Although the results of primary studies are relevant, there is a need for more in vivo studies on mouthrinses, in particular, randomized controlled clinical trials, to better understand their effect on SARS-CoV-2 viral load and infection prevention.

Key Words. Saliva; COVID-19; decision making; microbiology; public health; infection control.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus. Beyond the SARS-CoV-2 outbreak, betacoronaviruses have been associated with 2 other outbreaks, namely, severe acute respiratory syndrome and Middle East respiratory syndrome.[1,2]

Binding of SARS-CoV-2 to human cells mainly occurs via the angiotensin-converting enzyme 2 receptor,[3,4] which is highly expressed in the oral cavity, mainly in the epithelium of the tongue but also in gingival tissue, particularly on the buccal surface of the sulcular epithelium. Considering that the oral cavity may represent a major entryway and a reservoir of SARS-CoV-2,[5-7] the scientific community adjusted disinfection protocols and preprocedural protocols for dental practice. Widespread use of protective suits was advised, and use of goggles and shoe covers was reinforced, as well as stricter patient triage ahead of the appointment.[8]

Preprocedural gargling with a mouthrinse was hypothesized to act possibly as an additional protective measure, reducing the oral load of SARS-CoV-2.[9] Even before the COVID-19 pandemic, preprocedural gargling was used in dentistry to reduce microbial load before surgeries or routine procedures.[9] There are published guidelines advising the use of some mouthrinses aiming to reduce SARS-CoV-2 salivary viral load before dental appointments, in particular, the use of hydrogen peroxide (H_2O_2) mouthrinses.[10-14] However, supporting evidence on the effectiveness of mouthrinses on SARS-CoV-2 viral load is still scarce, with no systematic reviews analyzing the evidence from both

in vitro and in vivo studies on this question, to the best of our knowledge.[15,16] Thus, our study aimed to assess the effectiveness of mouthrinses in reducing SARS-CoV-2 viral load.

METHODS

Protocol and registration

We conducted this review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist[17] and registered it on the PROSPERO website (CRD42021237418).

Eligibility criteria

Inclusion criteria included in vitro and in vivo studies assessing the virucidal effect of mouthrinses on SARS-CoV-2 or surrogates. Exclusion criteria included reviews, letters to the editor, personal opinions, product news, book chapters, case reports, congress abstracts, protocol suggestions, editorials, correspondence articles, recommendations, trial designs, hypotheses, and studies with animals.

Information sources and search strategy

To develop this review, we performed searches in MEDLINE (via PubMed), Scopus, and Web of Science databases. We conducted searches on January 13, 2021, with an update on November 23, 2021. This search was complemented with a manual search on MedRxiv and bioRxiv preprint databases. Full query is described in eTable 1. Given that the first scientific publications on SARS-CoV-2 concern the year 2020, we limited the search to articles published in 2020 and 2021.

Study selection

After removing duplicates, 2 reviewers (A.S.) and (M.A.) independently reviewed the titles and abstracts of retrieved publications. Studies not excluded in the screening phase were fully read, with full-text analysis also independently performed by the 2 investigators. Any divergence was solved via a discussion with a third reviewer.

Data extraction

The 2 reviewers independently extracted data using a purposely built online form. Any inconsistency in data collection was resolved through discussion with a third author (B.S.M.). The following variables were retrieved from each primary study: author, title, year, country, type of study, sample number and type, patient characterization, intervention and control group, virus strain, type of mouthrinse, concentration, number of mouthrinses per day, rinsing duration, treatment duration, and decrease in viral load. For in vitro studies, the cell lineage used and existence of interfering substances were also assessed.

Risk of bias (RoB) in individual studies

The 2 reviewers independently carried out assessment of the RoB of included randomized controlled trials (RCTs) according to the Cochrane Collaboration tool for assessing RoB.[18] Disagreements between reviewers were resolved after discussion and analysis. No RoB assessment was performed on in vitro studies or observational before-and-after studies owing to a lack of consensually accepted tools for assessing RoB in those specific studies.

Summary measures

We considered all outcome measures directly evaluating SARS-CoV-2 viral load. Main outcome measures presented in our systematic review are viral load expressed in logarithmic (log) reduction value, copies per milliliter, and relative light units. When primary studies used a mouthrinse with known concentration and presented the viral load decrease in logarithmic scale, we interpreted such results following the European Norm EN-14476, which recognizes antiseptics' virucidal capacity when achieving a reduction on viral load equal to or greater than 4 $\log_{10}$.[19] Therefore, we classified the results of the primary in vitro studies when expressed in log scale according to 3 levels considering virucidal activity (viral load reduction): high efficacy (≥ 4 $\log_{10}$; +), moderate efficacy (≥ 3 $\log_{10}$ and < 4 $\log_{10}$; ±), and low efficacy (< 3 $\log_{10}$; −). To simplify the comparison between studies, we converted results expressed in molars to percentages (%, g/100 mL). We converted results presented as a percentage of inactivation or fold reduction to a logarithmic scale.

ABBREVIATION KEY

CHX: Chlorhexidine gluconate.
CPC: Cetylpyridinium chloride.
Ct: Cycle threshold.
H_2O_2: Hydrogen peroxide.
NA: Not applicable.
PCR: Polymerase chain reaction.
PVP-I: Povidone-iodine.
RCT: Randomized controlled trial.
RoB: Risk of bias.
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

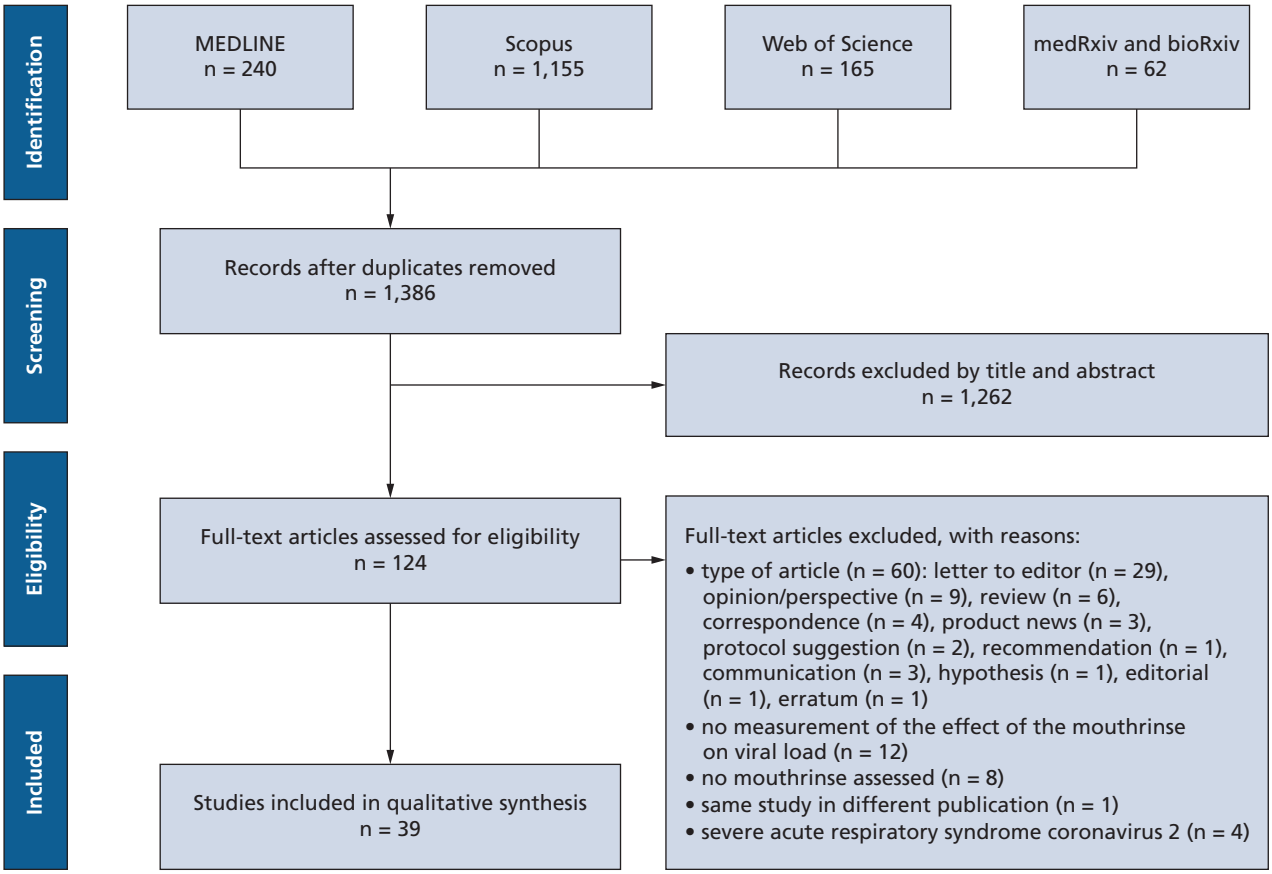

Figure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses study selection flowchart. *Source: Moher and colleagues.*[17]

Synthesis of results

Owing to methodological diversity of included primary studies, it was not possible to carry out a meta-analysis.

RESULTS

Study selection

We retrieved a total of 1,560 articles from bibliographic databases (MEDLINE, Scopus, Web of Science) and 62 from preprint databases. The study selection process is described in the figure.

Study characteristics

Of the 39 included studies, 33 were published as peer-reviewed articles, and 6 were preprints (eTable 2, available online at the end of this article).[20-58] Twenty-four of the published articles were performed in vitro, and 9 were in vivo, 5 of which were RCTs, whereas the remaining were uncontrolled before-and-after studies. Five of the included preprints were performed in vitro, and 1 was in vivo.

In vivo studies included COVID-19–positive hospitalized patients[20-28] and home-isolated patients.[23,29] All in vivo studies quantified SARS-CoV-2 viral load via polymerase chain reaction (PCR), targeting genes E,[20-23,25] RNA-dependent RNA polymerase,[21,23,25] nucleocapsid,[23-25,27,28] S, and R.[24] Three in vivo studies used water as a control,[22,25,28] and 1 used RNA from guanidinium thiocyanat-inactivated virus.[27] One used a similar solution regarding aspect and content but without virucidal components.[29] In vivo studies evaluated the reduction of SARS-CoV-2 in viral titers: 4 presented the results with cycle threshold (Ct) fold changes,[22,24,25,28] 3 in the form of a logarithmic reduction value,[21,23,26] 1 in the form of a logarithmic reduction percentage scale,[29] 1 in a percentage scale,[27] and 1 in copies per mL.[19]

Table 1. Povidone-iodine in vitro effect on severe actute respiratory syndrome coronavirus 2 oral viral load.*

CONCENTRATION, %	CONTACT TIME, S	BIDRA AND COLLEAGUES[30]	PELLETIER AND COLLEAGUES[32]	FRANK AND COLLEAGUES[33]	HASSANDARVISH AND COLLEAGUES[56]	ANDERSON AND COLLEAGUES[45]	BIDRA AND COLLEAGUES[34]
≈ 0.5[‡§]	15	+	NA[§]	±	+	NA	±
	30	±	NA	±	+	+	±
	60	NA	+	NA	+	NA	NA
0.75	15	NA	NA	NA	NA	NA	±
	30	NA	NA	NA	NA	NA	±
	60	NA	+	NA	NA	NA	NA
1.0	15	NA	NA	NA	+	NA	NA
	30	NA	NA	NA	+	+	NA
	60	NA	NA	NA	+	NA	NA
1.25	15	+	NA	±	NA	NA	NA
	30	±	NA	±	NA	NA	NA
	60	NA	+	NA	NA	NA	NA
1.5	15	+	NA	NA	NA	NA	±
	30	±	NA	NA	NA	NA	±
	60	NA	+	NA	NA	NA	NA
2.5	15	NA	NA	±	NA	NA	NA
	30	NA	NA	±	NA	NA	NA
	60	NA	+	NA	NA	NA	NA
> 2.5[¶]	15	NA	NA	NA	NA	NA	NA
	30	NA	NA	NA	NA	+	NA
	60	NA	NA	NA	NA	NA	NA

* Results interpreted according to European Norm-14476, considering a reduction on viral load ≥ 4 $\log_{10}$ as a high efficacy (+), a reduction ≥ 3 $\log_{10} < 4$ $\log_{10}$ as a moderate efficacy (±), and a reduction < 3 $\log_{10}$ as a low efficacy (−). † Preprint article. ‡ Ranging from 0.45%-0.58%. § NA: Not applicable. ¶ Concentrations up to 10%.

Regarding SARS-CoV-2 strains used across in vitro studies, several used well-characterized strains, the most used being USA-WA1/2020.[30-38] Four studies used a SARS-CoV-2 strain directly obtained from an infected patient,[39-42] whereas 1 study did not report the strain used.[43] In vitro studies were performed under dirty,[44-48] clean,[30,32-36,38-40,42,43,49-55] or both conditions,[37,41,56,57] with the terms *dirty* and *clean* referring to the existence of interfering substances. Two in vitro studies did not provide information about the existence of interfering substances.[31,58]

In vivo and in vitro studies applied the intervention solution for a predetermined period—mouthrinse contact time, most commonly ranging from 15 through 120 seconds. Seven in vitro studies included periods of application of 5 minutes or more.[31,35,42,43,52,54,58]

RoB within studies

Two RCTs were marked as high RoB studies,[22,28] whereas the other 3 were marked as low RoB studies[25,27,29] (eTable 3, available online at the end of this article). The other 5 in vivo studies were uncontrolled before-and-after studies that included a low number of participants and for which the assessment of RoB was not feasible.

Results of individual studies

Five in vivo studies showed the virucidal efficacy of povidone-iodine (PVP-I) solutions on SARS-CoV-2 (eTable 4, available online at the end of this article). Seneviratne and colleagues[22] conducted an RCT and reported that a 30-second rinse with 0.5% PVP-I conducted on a group of 4

Table 1 (Continued)

CONCENTRATION, %	MEISTER AND COLLEAGUES[46]	MEYERS AND COLLEAGUES[44]	STATKUTE AND COLLEAGUES[47,†]	DAVIES AND COLLEAGUES[50]	JAIN AND COLLEAGUES[40]	KARIWA AND COLLEAGUES[53]	SHET AND COLLEAGUES[54]
≈ 0.5[‡§]	NA	NA	NA	NA	NA	NA	+
	NA	NA	NA	NA	NA	±	+
	NA	NA	NA	+	NA	± +	+
0.75	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
1.0	NA	NA	NA	NA	NA	NA	NA
	–	NA	NA	NA	–	NA	NA
	NA	NA	NA	NA	±	NA	NA
1.25	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
1.5	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
2.5	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
> 2.5[¶]	NA	NA	NA	NA	NA	NA	± +
	NA	±	–	NA	NA	NA	± +
	NA	± +	NA	NA	NA	NA	± +

hospitalized patients resulted in a significant reduction of viral load 6 hours after rinsing compared with water. However, no significant differences were found 5 minutes and 3 hours after rinsing. After using the same concentration of PVP-I but by performing 2 consecutive 30-second rinses, Chaudhary and colleagues[27] verified a 61% reduction on viral load after 15 minutes and a 97% reduction after 30 minutes. The RCT conducted by Elzein and colleagues[25] found a significant mean Ct difference increase between the paired samples before and after a 30-second 1% PVP-I rinse. In an uncontrolled before-and-after clinical study, Lamas and colleagues[23] reported that a 60-second 1% PVP-I rinse led to a significant drop (≈ 5 $\log_{10}$) in viral load in 1 of the 4 patients evaluated, sustained for at least 3 hours. Jayaraman and colleagues[26] found that 1% PVP-I could reduce the mean (standard deviation) viral load in saliva up to 1.8 (1.1) $\log_{10}$. Significant reductions were observed after 20 and 60 minutes.

In vitro studies reported that PVP-I–containing mouthrinses have a virucidal effect on SARS-CoV-2 (eTable 5, available online at the end of this article). Table 1 summarizes the results found in different studies with application times up to 60 seconds and interpreted following EN-14476. Concentrations up to 0.75% showed moderate to high efficacy in reducing SARS-CoV-2 viral load.[30,32-34,45,50,53,54,56] The 60-second application of PVP-I with concentrations from 0.5% through 0.58% had high efficacy results in the 4 studies evaluating this condition.[32,50,54,56] Concentrations of PVP-I from 1.25% through 2.5% consistently showed moderate to high efficacy results.[30,32-34] Applying concentrations of PVP-I greater than 2.5% showed low[47] (PVP-I at 7.5%), moderate[44,54] (PVP-I at 5% and 7.5%), and high efficacy[45,54] (PVP-I at 7.5% and 10%) within 15 through 30 seconds. The 60-second application also reached moderate to high efficacy results (PVP-I concentrations ranging from 5% to 10%).[44,54]

Table 2. Hydrogen peroxide, chlorhexidine gluconate, and cetylpyridinium chloride mouthrinses in vitro effect on severe acute respiratory syndrome coronavirus 2 oral viral load.*

MOUTHRINSE	CONCENTRATION, %	CONTACT TIME, S	BIDRA AND COLLEAGUES[30]	MEYERS AND COLLEAGUES[44]	DAVIES AND COLLEAGUES[50]	MEISTER AND COLLEAGUES[46]	STEINHAUER AND COLLEAGUES[43]	STATKUTE AND COLLEAGUES[47,†]
Hydrogen Peroxide	1.5	15	–	NA[‡]	NA	NA	NA	NA
		30	–	–	NA	NA	NA	NA
		60	NA	–	–	NA	NA	NA
	3	15	–	NA	NA	NA	NA	NA
		30	–	NA	NA	NA	NA	NA
Chlorhexidine Gluconate	≤0.16[§]	15	NA	NA	NA	NA	–	NA
		30	NA	NA	NA	NA	–	NA
		60	NA	NA	NA	NA	–	NA
	0.2	30	NA	NA	NA	–	NA	NA
		60	NA	NA NA	–	NA	NA	NA
Cetylpyridinium Chloride	≤0.3[¶]	20	NA	NA	NA	NA	NA	NA
		30	NA	± +	NA	NA	NA	+
		60	NA	± +	NA	NA	NA	NA

* Results interpretated according to European Norm-14476, considering a reduction on viral load ≥ 4 log_{10} as a high efficacy (+), a reduction ≥ 3 log_{10} and < 4 log_{10} as a moderate efficacy (±), and a reduction < 3 log_{10} as a low efficacy (–). † Preprint article. ‡ NA: Not applicable. § Includes concentrations of 0.08%, 0.1%, 0.12%, and 0.16%. ¶ Includes concentrations of 0.04%, 0.05%, 0.07%, 0.075%, 0.1%, and 0.3%.

Regarding H_2O_2, Gottsauner and colleagues[20] conducted an in vivo study assessing virucidal efficacy of a 30-second H_2O_2 (1%) rinse. No significant difference was found between baseline and the viral load 30 minutes after rinsing. Chaudhary and colleagues[27] found that 2 consecutive 30-second H_2O_2 (1%) rinses led to a 90% reduction after 15 and 30 minutes. Jayaraman and colleagues[26] reported that a 30-second H_2O_2 (1.5%) rinse could decrease the mean (standard deviation) viral load up to 1.6 (1.5) log_{10} after 60 minutes. A 60-second H_2O_2 (1.5%) rinse led to a significant reduction on viral load immediately after and 30 minutes after rinsing but not after 60 minutes.[28] In vitro studies on the virucidal effect of H_2O_2 showed very limited success (Table 2 and eTable 5, available online at the end of this article).

The virucidal efficacy of chlorhexidine gluconate (CHX) mouthrinses was evaluated with in vivo and in vitro studies (eTables 4 and 5, available online at the end of this article). In an RCT, Seneviratne and colleagues[22] studied the effect of CHX mouthrinses in a group of 6 patients and found no reduction of viral load. Another RCT by Elzein and colleagues[25] reported a mean Ct increase of 5.7 after a 30-second CHX (0.2%) rinse. Eduardo and colleagues[28] conducted an RCT to study the effect of a 30-second CHX (0.12%) rinse and found a significant reduction in viral load 60 minutes after rinsing. One other RCT, by Chaudhary and colleagues,[27] reported that CHX (0.12%) achieved a 90% decrease in viral load 15 minutes after 2 consecutive 30-second rinses but only a 70% decrease after 30 minutes. Yoon and colleagues[21] performed an uncontrolled before-and-after clinical study on the effect of a 30-second CHX (0.12%) rinse in 2 hospitalized patients. The authors observed a transient decrease in viral load for 2 hours after rinsing. In 1 patient, 1 hour after rinsing, no decrease on viral load was observed. Jayaraman and colleagues[26] also reported a limited decrease in viral load in saliva after 90 minutes. Considering application times of up to 60 seconds (Table 2), in vitro application of CHX with concentrations lower than 0.16% showed low efficacy within 15, 30, and 60 seconds.[43] However, 1 study reported moderate efficacy within 30 seconds,[40] and another reported high efficacy after 30 and 60 seconds.[41] The use of 0.2% CHX also showed low efficacy after 30 seconds[46] and 60 seconds.[50] One preprint article reported that CHX (0.12%) achieved low, moderate, and high efficacy, depending on

Table 2 (Continued)

MOUTHRINSE	GREEN AND COLLEAGUES[49,†]	KOCH-HEIER AND COLLEAGUES[51]	JAIN AND COLLEAGUES[40]	MUÑOZ-BASAGOITI AND COLLEAGUES[57]	KOMINE AND COLLEAGUES[55]	TIONG AND COLLEAGUES[41]	ANDERSON AND COLLEAGUES[37,†]
Hydrogen Peroxide	NA	NA	NA	NA	NA	NA	NA
	NA	–	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA
Chlorhexidine Gluconate	NA	NA	NA	NA	NA	NA	NA
	NA	–	±	NA	–	+	NA
	NA	NA	NA	NA	NA	+	NA
	NA	NA	±	NA	NA	NA	– ± +
	NA	NA	NA	NA	NA	NA	NA
Cetylpyridinium Chloride	NA	NA	NA	NA	± +	NA	NA
	±	–	NA	–	+	NA	NA
	±	NA	NA	±	NA	NA	NA

the viral strain used.[37] Meister and colleagues[46] reported low efficacy results after a 30-second rinse with a CHX mouthrinse with unknown concentration.

Cetylpyridinium chloride (CPC) in vivo virucidal activity was studied in an RCT by Seneviratne and colleagues[22] on a group of 4 hospitalized patients (eTable 4, available online at the end of this article). CPC 0.075% mouthrinse significantly reduced viral load within 5 minutes of use. Compared with the control group, the viral load reduction with CPC was maintained for 3 and 6 hours. In vitro studies have found that CPC-containing mouthrinses have a virucidal effect on SARS-CoV-2 (eTable 5, available online at the end of this article). Considering application times between 30 and 60 seconds (Table 2), concentrations of up to 0.3% showed low to high efficacy.[44,47,49,51,55,57] The 20-second application of CPC had moderate to high efficacy.[55] Meyers and colleagues[44] reported that a 120-second application of 0.07% CPC showed moderate to high efficacy. Muñoz-Basagoiti and colleagues[39] reported moderate results with a 120-second application of CPC at a concentration of up to 10 mmol (0.3%).

Other mouthrinses, either more complex or with less frequently used active compounds, were studied in vivo and in vitro by several authors (eTables 4 and 5, available online at the end of this article). Carrouel and colleagues[29] studied the effect of a 60-second rinse with a mouthrinse containing citrox and ß-cyclodextrin. This study reported a significant decrease in viral load of approximately 13% when using the mouthrinse compared with a 7% decrease observed in the placebo group. Eduardo and colleagues[28] conducted an RCT to study the effect of performing a 60-second H_2O_2 (1.5%) (Peroxyl; Colgate) rinse, combined with a 30-second CHX (0.12%) (PerioGard; Colgate) rinse. This combined rinse only achieved minor in Ct values compared with the placebo group. However, when rinsing with a mouthrinse containing CPC (0.075%) and zinc lactate (0.28%), a significant decrease in salivary viral load was achieved for up to 60 minutes. In an uncontrolled before-and-after study, Schürmann and colleagues[24] studied the effect of a 60-second Linola Sept (Dr. Wolff) rinse and reported a mean increase in Ct values of 3.1 (basal versus after rinsing).

In vitro studies included a diversity of complex mouthrinses. Listerine (Johnson & Johnson) mouthrinses were studied by several authors, although each formulation was assessed only in 1 study, apart from Listerine Cool Mint, which was assessed in 2 studies. Listerine mouthrinses showed variable efficacy (Table 3).[44,46,47,50]

Table 3. Other mouthrinses in vitro effect on severe acute respiratory syndrome coronavirus 2 oral viral load.*

MOUTHRINSE	CONTACT TIME, S	MEYERS AND COLLEAGUES[44]	MEISTER AND COLLEAGUES[46]	STATKUTE AND COLLEAGUES[47,†]	DAVIES AND COLLEAGUES[50]	STEINHAUER AND COLLEAGUES[43]
Listerine Antiseptic (Johnson & Johnson)	30	+	NA[‡]	NA	NA	NA
	60	+	NA	NA	NA	NA
Listerine Ultra (Johnson & Johnson)	30	–	NA	NA	NA	NA
	60	–	NA	NA	NA	NA
Listerine Cool Mint (Johnson & Johnson)	30	NA	–	–	NA	NA
Listerine Advanced Gum Treatment (Johnson & Johnson)	30	NA	NA	+	NA	NA
Listerine Advanced Defence Sensitive (Johnson & Johnson)	60	NA	NA	NA	± +	NA
Listerine Total Care (Johnson & Johnson)	60	NA	NA	NA	+	NA
Equate	30	–	NA	NA	NA	NA
	60	–	NA	NA	NA	NA
Antiseptic Mouthrinse (CVS)	30	–	NA	NA	NA	NA
	60	–	NA	NA	NA	NA
Dequonal	30	NA	–	NA	NA	NA
Octenident (Schülke & Mayr)	30	NA	–	NA	NA	NA
ProntOral (B. Braum)	30	NA	–	NA	NA	NA
Corsodyl (GlaxoSmithKline)	30	NA	NA	–	NA	NA
SCD Max	30	NA	NA	–	NA	NA
Octenisept (Schülke & Mayr)	15	NA	NA	NA	NA	+
	30	NA	NA	NA	NA	+
	60	NA	NA	NA	NA	+
OraWize+ (Aqualution Systems)	60	NA	NA	NA	– +	NA
Mouthrinse Containing Ethanol (15.7%), Other Ingredients	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Mouthrinse Containing Zinc Sulfate Heptahydrate, Other Ingredients	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Mouthrinse Containing a Mix of Amyloglucosidase, Other Ingredients	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Essential Iodine Solution	60	NA	NA	NA	NA	NA
ViruProx (Dr. Wittmann & Co)	30	NA	NA	NA	NA	NA
BacterX Pro (EMS)	30	NA	NA	NA	NA	NA
Solution of CPC[§] (0.05%) and CHX[¶] (0.1%)	30	NA	NA	NA	NA	NA
Dental Gel: Anionic Iron Tetracarboxyphthalocyanine (1%)	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA

* Results interpretated according to European Norm-14476, considering a reduction on viral load ≥ 4 $\log_{10}$ as a high efficacy (+), a reduction ≥ 3 $\log_{10}$ and < 4 $\log_{10}$ as a moderate efficacy (±), and a reduction < 3 $\log_{10}$ as a low efficacy (–). eTable 5, available online at the end of this article, can be consulted for assessment of the ingredients of test solutions. † Preprint article. ‡ NA: Not applicable. § CPC: Cetylpyridinium chloride. ¶ CHX: Chlorhexidine gluconate.

Table 3 (Continued)

GREEN AND COLLEAGUES[49,†]	ZOLTAN AND COLLEAGUES[36]	KOCH-HEIER AND COLLEAGUES[51]	SANTOS AND COLLEAGUES[42]	KOMINE AND COLLEAGUES[55]	SHEWALE AND COLLEAGUES[38]	TIONG AND COLLEAGUES[41]	MEISTER AND COLLEAGUES[48]
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
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–	NA	NA	NA	NA	NA	NA	NA
–	NA	NA	NA	NA	NA	NA	NA
–	NA	NA	NA	NA	NA	NA	NA
NA	–	NA	NA	NA	NA	NA	NA
NA	NA	–	NA	NA	NA	NA	NA
NA	NA	–	NA	NA	NA	NA	NA
NA	NA	–	NA	NA	NA	NA	NA
NA	NA	NA	+	NA	NA	NA	NA
NA	NA	NA	+	NA	NA	NA	NA

Table 3. Other mouthrinses in vitro effect on severe acute respiratory syndrome coronavirus 2 oral viral load.*

MOUTHRINSE	CONTACT TIME, S	MEYERS AND COLLEAGUES[44]	MEISTER AND COLLEAGUES[46]	STATKUTE AND COLLEAGUES[47,†]	DAVIES AND COLLEAGUES[50]	STEINHAUER AND COLLEAGUES[43]
Mouthrinse: Anionic Iron Tetracarboxyphthalocyanine (0.1%)	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
GUM PAROEX (Sunstar Suisse), CHX (0.06%) and CPC (0.05%); GUM PAROEX, CHX (0.12%) and CPC (0.05%)	30	NA	NA	NA	NA	NA
GUM PerioShield (Sunstar)	30	NA	NA	NA	NA	NA
ClōSYS Ultra Sensitive Rinse (Rowpar Pharmaceuticals), Sensitive Rinse, Oral Spray, Fluoride Toothpaste	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Colgate Plax Fruity Fresh (Colgate-Palmolive)	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Thymol	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Bactidol (Johnson & Johnson [Philippines])	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Salt Water (2%)	30	NA	NA	NA	NA	NA
	60	NA	NA	NA	NA	NA
Carragelose (1.2 mg/mL), Kappa-Carrageenan (0.4 mg/mL), Sodium Chlorite	30	NA	NA	NA	NA	NA
Sodium Chlorite (0.9%), Panthenol	30	NA	NA	NA	NA	NA
Xylometazolin Hydrochloride (1 mg/mL), Dexpanthenol (50 mg/mL); Sodium Hypochlorite (< 0.08%), Lithium Magnesium Sodium Silicate	30	NA	NA	NA	NA	NA
Xylometazolin Hydrochloride (0.1%)	30	NA	NA	NA	NA	NA
Hydroxypropyl Methyl Cellulose, Succinic Acid, Disodium Succinate	30	NA	NA	NA	NA	NA
Galphimia, Luffa Operculate, Sabadilla	30	NA	NA	NA	NA	NA
Zincum Aceticum, Zincum Gluconium	30	NA	NA	NA	NA	NA
Anise Oil, Eucalyptus Oil, Levomenthol, Myrrh Extract, Clove Oil, Peppermint Oil Ratanhia Root Extract, Tormentil Root Extract	30	NA	NA	NA	NA	NA

DISCUSSION

Summary of evidence

In this systematic review, we included primary studies assessing the virucidal effect of mouthrinses regarding SARS-CoV-2 that had a diverse set of methodologies and assessed a wide range of mouthrinses. PVP-I was the most frequently studied mouthrinse, with most in vitro studies showing some promising results. The results of in vivo studies also pointed to a positive effect of PVP-I on oral viral load reduction, although limitations were found in their methodologies. Similarly, CPC showed positive preliminary results. The use of H_2O_2 and CHX showed conflicting results on SARS-CoV-2 load reduction in both in vitro and in vivo studies.

To the best of our knowledge, our systematic review is the first to analyze information from both in vivo and in vitro studies. A previous systematic review had assessed in vitro studies, with results consistent with those reported in our study.[15]

Considering mouthrinses as antiseptics, they should follow regulating norms. The International Organization for Standardization defines in ISO-16408:2015 the chemical and physical properties of

Table 3 (Continued)

GREEN AND COLLEAGUES[49,†]	ZOLTAN AND COLLEAGUES[36]	KOCH-HEIER AND COLLEAGUES[51]	SANTOS AND COLLEAGUES[42]	KOMINE AND COLLEAGUES[55]	SHEWALE AND COLLEAGUES[38]	TIONG AND COLLEAGUES[41]	MEISTER AND COLLEAGUES[48]
NA	NA	NA	–	NA	NA	NA	NA
NA	NA	NA	–	NA	NA	NA	NA
NA	NA	NA	NA	+	NA	NA	NA
NA	NA	NA	NA	+	NA	NA	NA
NA	NA	NA	NA	NA	–	NA	NA
NA	NA	NA	NA	NA	–	NA	NA
NA	NA	NA	NA	NA	NA	+	NA
NA	NA	NA	NA	NA	NA	+	NA
NA	NA	NA	NA	NA	NA	–	NA
NA	NA	NA	NA	NA	NA	–	NA
NA	NA	NA	NA	NA	NA	+	NA
NA	NA	NA	NA	NA	NA	+	NA
NA	NA	NA	NA	NA	NA	–	NA
NA	NA	NA	NA	NA	NA	–	NA
NA	NA	NA	NA	NA	NA	NA	–
NA	NA	NA	NA	NA	NA	NA	–
NA	NA	NA	NA	NA	NA	NA	–
NA	NA	NA	NA	NA	NA	NA	–
NA	NA	NA	NA	NA	NA	NA	–
NA	NA	NA	NA	NA	NA	NA	–
NA	NA	NA	NA	NA	NA	NA	± +

oral rinses, as well as their test methods, but guidelines for microbiological analysis are specific to mold, bacteria, and yeast, lacking virus instructions.[59] There seems to be a lack of standardization on the evaluation of mouthrinses regarding virucidal properties. According to the EN-14476, an antiseptic is effective when it reduces viral load by 4 $\log_{10}$ or more.[19] Although EN-14476 is not specific toward oral rinses, owing to the lack of more appropriate regulation, we decided to compare our results in light of this European Norm for assessing mouthrinse virucidal properties.

Included primary studies had substantial diversity in their methodologies and results presentation, limiting our capacity to compare different mouthrinses. PVP-I—based mouthrinses appear to have potential for reducing SARS-CoV-2 in the oral cavity. Nonetheless, these results must be interpreted cautiously. The RCT conducted by Elzein and colleagues[25] had a low RoB and reported a significant decrease in viral load after using mouthrinse. However, neither the RCT conducted by Seneviratne and colleagues,[22] which had a high RoB and included just 16 patients, nor the RCT conducted by Chaudhary and colleagues[27] revealed such a significant decrease. Jayaraman and colleagues[26] did not find a significant decrease in an uncontrolled before-and-after study. It also

seems that a dose-response relationship (that is, studies assessing the effect of higher PVP-I concentrations on SARS-CoV-2 viral load do not appear to obtain better results) or a time-response relationship does not exist.

The use of CPC mouthrinses for reducing the viral load also showed encouraging results. CPC has been shown to also be capable of inactivating influenza viruses both in vitro and in vivo but only after 10 minutes of contact time.[60]

In the included primary studies, H_2O_2- and CHX-based mouthrinses produced varied effects on SARS-CoV-2 viral load. As the effect of these mouthrinses was inconclusive, recommending their use may not be adequate. CHX and H_2O_2 already are used in some oral health care products, with CHX displaying broad-spectrum antimicrobial activity,[61] including against anaerobic oral bacteria.[62] Worldwide government agencies and professional associations advise the use of preprocedural rinse with H_2O_2 mouthrinses to reduce oral SARS-CoV-2 viral load,[10-14] so there may be a need to reconsider these directives.

Some complex mouthrinses like Listerine Total Care, Listerine Advanced, and Listerine Antiseptic showed promising results in reducing SARS-CoV-2 viral load in the oral cavity, although they were evaluated in only 1 or 2 studies each. Using these mouthrinses as a coadjutant in oral health care is well established, contributing to the reduction of dental biofilm and gingivitis.[63]

The included primary studies have the limitation of only evaluating the presence of viral particles and not their viability or infectious capacity, and, therefore, other techniques such as viability-PCR could be used to study the infectious potential of the virus. The US Environmental Protection Agency, the Centers for Disease Control and Prevention, and the Lawrence Livermore National Laboratory are developing a rapid viability-reverse transcription PCR to evaluate SARS-CoV-2 viability on surfaces and objects.[64] Analyzing aerosols also could be a realistic way to study the impact of dental procedures on the dissemination of viral particles. Choi and colleagues[65] performed a study on aerosol sampling in the emergency department of a university hospital, collecting a total of 44 samples, 12 of which were positive to known respiratory viruses—influenza A, influenza D, and adenovirus. Lednicky and colleagues[66] reported the generation of aerosols containing SARS-CoV-2 virions by patients with COVID-19 respiratory manifestations even in the absence of aerosol-generating procedures, which can lead to virus transmission. The authors also were able to quantify the generated viral particles detected from a distance of 2 m or more. These results highlight the importance of preventive measures such as prerinse antiseptic mouthrinse but also a rubber dam isolation, given that both strategies can reduce aerosol pathogen load significantly.[66,67]

In addition to the wide diversity of methodologies and results presentations of the included studies, a major limitation of our systematic review is the small number of included RCTs, with only 5 meeting eligibility criteria.[22,25,27-29] The validity of the conclusions is affected by the bias of the included primary studies, in this case, regarding the high RoB of 2 of the RCTs. Furthermore, the other 5 in vivo studies had important limitations in their designs, including the absence of randomization or even a control group and a relatively low number of included patients, which prompts a low level of evidence and hampers the precision of their estimates, respectively. Although in vitro studies are part of the tests proposed by EN-14476,[19] their results cannot be transposed directly to in vivo application of these mouthrinses. In vivo studies should be RCTs that are conducted with a better study design, include a higher number of patients, include a control solution, and express their results as virus logarithmic reduction, allowing a better interpretation of results with a greater level of evidence.

A recurrent inadequacy found in the selected studies was the inclusion of times of application not feasible in clinical practice. Some in vitro studies had application times of 30 minutes,[31] and 1 preprint article also considered an application with a duration of 72 hours.[52] We find these application times unrealistic and not adequate for clinical practice because patients normally are able to gargle only for a short period,[68] usually up to 60 seconds.

Suggestions for future studies

There is a need for more in vivo and in vitro studies on different mouthrinses that consider adequate and realistic application times of up to 60 seconds. A well-designed RCT with a larger number of patients should be considered a priority when it comes to design of in vivo studies. On the basis of results from already published primary studies, future studies should focus mainly on mouthrinses based on PVP-I and CPC. Furthermore, the studies should present their results in the form of a

logarithmic reduction that can be compared according to EN-14476. Studying mouthrinse-induced cytotoxicity should be a concern when assessing virucidal properties of different mouthrinses with different concentrations. Studying viral viability after rinsing and viral presence in aerosols should be considered to better assess the real impact of virus dissemination in the dental setting. Overall, guidelines for the standardized evaluation of the effect of mouthrinses on viruses are needed.

CONCLUSIONS

Considering the current knowledge, using PVP-I–based solutions as a preprocedural rinse in the dental setting appears to be potentially effective in reducing SARS-CoV-2 oral load. There are no powerful arguments for considering the use of H_2O_2 and CHX to be effective regarding SARS-CoV-2 virus, and their use as preprocedural mouthrinses aiming to reduce SARS-CoV-2 oral load should be revised. More RCTs together with in vitro studies are needed to further evaluate mouthrinses based on PVP-I and CPC and test other commercially available mouthrinses showing potential results on SARS-CoV-2 load reduction. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2021.12.007.

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1. Abebe EC, Dejenie TA, Shiferaw MY, Malik T. The newly emerged COVID-19 disease: a systemic review. *Virol J*. 2020;17(1):96.
2. Astuti I. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. *Diabetes Metab Syndr*. 2020;14(4):407-412.
3. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci U S A*. 2020;117(21):11727-11734.
4. Scialo F, Daniele A, Amato F, et al. ACE2: The major cell entry receptor for SARS-CoV-2. *Lung*. 2020;198(6):867-877.
5. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12(1):8.
6. Sakaguchi W, Kubota N, Shimizu T, et al. Existence of SARS-CoV-2 entry molecules in the oral cavity. *Int J Mol Sci*. 2020;21(17):6000.
7. Huang N, Perez P, Kato T, et al. SARS-CoV-2 infection of the oral cavity and saliva. *Nat Med*. 2021;27(5):902-903.
8. Mahdi SS, Ahmed Z, Allana R, et al. Pivoting dental practice management during the COVID-19 pandemic: a systematic review. *Medicina (Kaunas)*. 2020;56(12):644.
9. Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission routes of 2019-nCoV and controls in dental practice. *Int J Oral Sci*. 2020;12(1):1-6.
10. COVID-19: Procedimentos em clínicas, consultórios ou serviços de saúde oral dos C-cuidados de S-saúde P-primários, setor social e privado. Direção Geral de Saúde. Accessed May 12, 2021. https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/orientacao-n-0222020-de-01052020-pdf.aspx
11. Considerations for the provision of essential oral health services in the context of COVID-19. World Health Organization. Accessed May 13, 2021. https://www.who.int/publications/i/item/who-2019-nCoV-oral-health-2020.1
12. Gurzawska-Comis K, Becker K, Brunello G, Gurzawska A, Schwarz F. Recommendations for dental care during COVID-19 pandemic. *J. Clin. Med*. 2020;9(6):1833.
13. ADA COVID-19 risk management guidance; 2020. Australian Dental Association. Accessed May 13, 2021. https://staging.ada.org.au/Covid-19-Portal/Files/pdf/COVID-19-Risk-Management-Guidance.aspx
14. Versaci MB. ADA adds frequently asked questions from dentists to coronavirus resources. *ADA News*. March 12, 2020. American Dental Association. Accessed July 22, 2021. https://www.ada.org/en/publications/ada-news/2020/march/ada-adds-frequently-asked-questions-from-dentists-to-coronavirus-resources
15. Tadakamadla J, Boccalari E, Rathore V, Dolci C, Tartaglia GM, Tadakamadla SK. In vitro studies evaluating the efficacy of mouth rinses on Sars-Cov-2: a systematic review. *J Infect Public Health*. 2021;14(9):1179-11785.
16. Vergara-Buenaventura A, Castro-Ruiz C. Use of mouthwashes against COVID-19 in dentistry. *Br J Oral Maxillofac Surg*. 2020;58(8):924-927.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-269.
18. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
19. Eggers M, Schwebke I, Suchomel M, et al. The European tiered approach for virucidal efficacy testing: rationale for rapidly selecting disinfectants against emerging and re-emerging viral diseases. *Euro Surveill*. 2021;26(3):2000708.
20. Gottsauner MJ, Michaelides I, Schmidt B, et al. A prospective clinical pilot study on the effects of a hydrogen peroxide mouthrinse on the intraoral viral load of SARS-CoV-2. *Clin Oral Investig*. 2020;24(10):3707-3713.
21. Yoon JG, Yoon J, Song JY, et al. Clinical significance of a high SARS-CoV-2 viral load in the saliva. *J Korean Med Sci*. 2020;35(20):e195. https://doi.org/10.3346/jkms.2020.35.e195
22. Seneviratne CJ, Balan P, Ko KKK, et al. Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: randomized control trial in Singapore. *Infection*. 2020;49(2):1-7.
23. Lamas LM, Dios PD, Rodríguez MTP, et al. Is povidone iodine mouthwash effective against SARS-CoV-2? First in vivo tests. *Oral Dis*. Published online July 2, 2020. https://doi.org/10.1111/odi.13526

24. Schürmann M, Aljubeh M, Tiemann C, Sudhoff H. Mouthrinses against SARS-CoV-2: anti-inflammatory effectivity and a clinical pilot study. *Eur Arch Otorhinolaryngol*. 2021;278(12):5059-5067.

25. Elzein R, Abdel-Sater F, Fakhreddine S, et al. In vivo evaluation of the virucidal efficacy of chlorhexidine and povidone-iodine mouthwashes against salivary SARS-CoV-2: a randomized-controlled clinical trial. *J Evid Based Dent Pract*. 2021;21(3):101584.

26. Jayaraman BG, Rajan G, Kannian P, et al. Povidone iodine, hydrogen peroxide and chlorhexidine mouthwashes reduce SARS-CoV2 burden in whole mouth fluid and respiratory droplets. medRxiv. Preprint. Posted online March 1, 2021. Withdrawal status: active. https://doi.org/10.1101/2021.02.25.21252488

27. Chaudhary P, Melkonyan A, Meethil A, et al. Estimating salivary carriage of severe acute respiratory syndrome coronavirus 2 in nonsymptomatic people and efficacy of mouthrinse in reducing viral load: a randomized controlled trial. *JADA*. 2021;152(11):903-908.

28. Eduardo FP, Corrêa L, Heller D, et al. Salivary SARS-CoV-2 load reduction with mouthwash use: a randomized pilot clinical trial. *Heliyon*. 2021;7(6):e07346. https://doi.org/10.1016/j.heliyon.2021.e07346

29. Carrouel F, Valette M, Gadea E, et al. Use of an antiviral mouthwash as a barrier measure in the sars-cov-2 transmission in adults with asymptomatic to mild COVID-19: a multicenter, randomized, double-blind controlled trial. *Clin Microbiol Infect*. 2021;27(10):1494-1501.

30. Bidra AS, Pelletier JS, Westover JB, Frank S, Brown SM, Tessema B. Comparison of in vitro inactivation of SARS CoV-2 with hydrogen peroxide and povidone-iodine oral antiseptic rinses. *J Prosthodont*. 2020;29(7):599-603.

31. Xu C, Wang A, Hoskin ER, et al. Differential effects of antiseptic mouth rinses on sars-cov-2 infectivity in vitro. *Pathogens*. 2021;10(3):11-14.

32. Pelletier JS, Tessema B, Frank S, Westover JB, Brown SM, Capriotti JA. Efficacy of povidone-iodine nasal and oral antiseptic preparations against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). *Ear Nose Throat J*. 2020;100(suppl 2):192S-196S.

33. Frank S, Brown SM, Capriotti JA, Westpver JB, Pelletier JS, Tessema B. In vitro efficacy of a povidone-iodine nasal antiseptic for rapid inactivation of SARS-CoV-2. *JAMA Otolaryngol Head Neck Surg*. 2020;146(11):1054-1058.

34. Bidra AS, Pelletier JS, Westover JB, Frank S, Brown SM, Tessema B. Rapid in-vitro inactivation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using povidone-iodine oral antiseptic rinse. *J Prosthodont*. 2020;29(6):529-533.

35. Mantlo E, Evans A, Patterson-Fortin L, Boutros J, Smith R, Paessler S. Efficacy of a novel iodine complex solution, CupriDyne, in inactivating SARS-CoV-2. bioRxiv. Preprint. Posted online May 8, 2020. Withdrawal status: active. https://doi.org/10.1101/2020.05.08.082701

36. Zoltán K. Efficacy of "Essential Iodine Drops" against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2). *PLoS One*. 2021;16(7):e0254341. https://doi.org/10.1371/journal.pone.0254341

37. Anderson ER, Patterson EI, Richards S, et al. Virucidal activity of CPC-containing oral rinses against SARS-CoV-2 variants and are active in the presence of human saliva. bioRxiv. Preprint. Posted online September 22, 2021. Withdrawal status: active. https://doi.org/10.1101/2021.08.05.455040

38. Shewale JG, Gelhaus HC, Ratcliff JL, Hernandez-Kapila YL. In vitro antiviral activity of stabilized chlorine dioxide containing oral care products. *Oral Dis*. Published online October 12, 2021. https://doi.org/10.1111/odi.14044

39. Muñoz-Basagoiti J, Perez-Zsolt D, León R, et al. Cetylpyridinium chloride-containing mouthwashes reduce in vitro SARS-CoV-2 infectivity. bioRxiv. Preprint. Posted online December 21, 2020. Withdrawal status: active. https://doi.org/10.1101/2020.12.21.423779

40. Jain A, Grover V, Singh C, et al. Chlorhexidine: an effective anticovid mouth rinse. *J Indian Soc Periodontol*. 2021;25(1):86-88.

41. Tiong V, Hassandarvish P, Abu Bakar S, et al. The effectiveness of various gargle formulations and salt water against SARS-CoV-2. *Sci Rep*. Published online October 15, 2021. https://doi.org/10.1038/s41598-021-99866-w

42. Santos C, da Fonseca Orcina B, Brito Reia VC, et al. Virucidal activity of the antiseptic mouthwash and dental gel containing anionic phthalocyanine derivative: in vitro study. *Clin Cosmet Investig Dent*. 2021;13:269-274.

43. Steinhauer K, Meister TL, Todt D, et al. Comparison of the in-vitro efficacy of different mouthwash solutions targeting SARS-CoV-2 based on the European Standard EN 14476. *J Hosp Infect*. 2021;111:180-183.

44. Meyers C, Robison R, Milici J, et al. Lowering the transmission and spread of human coronavirus. *J Med Virol*. 2021;93:1605-1612.

45. Anderson DE, Sivalingam V, Kang AEZ, et al. Povidone-iodine demonstrates rapid in vitro virucidal activity against SARS-CoV-2, the virus causing COVID-19 disease. *Infect Dis Ther*. 2020;9(3):669-675.

46. Meister TL, Brüggemann Y, Todt D, et al. Virucidal efficacy of different oral rinses against severe acute respiratory syndrome coronavirus 2. *J Infect Dis*. 2020;222(8):1289-1292.

47. Statkute E, Rubina A, O'Donnell VB, Thomas DW, Stanton RJ. Brief report: the virucidal efficacy of oral rinse components against SARS-CoV-2 in vitro. bioRxiv. Preprint. Posted online November 18, 2020. Withdrawal status: active. https://doi.org/10.1101/2020.11.13.381079

48. Meister TL, Todt D, Brüggemann Y, et al. Virucidal activity of nasal sprays against severe acute respiratory syndrome coronavirus 2. *J Hosp Infect*. Published online November 6, 2021. https://doi.org/10.1016/j.jhin.2021.10.019

49. Green A, Roberts G, Tobery T, Vincent C, Barili M, Jones C. In vitro assessment of the virucidal activity of four mouthwashes containing cetylpyridinium chloride, ethanol, zinc and a mix of enzyme and proteins against a human coronavirus. bioRxiv. Preprint. Posted online October 28, 2020. Withdrawal status: active. https://doi.org/10.1101/2020.10.28.359257

50. Davies K, Buczkowski H, Welch SR, et al. Effective in vitro inactivation of SARS-CoV-2 by commercially available mouthwashes. *J Gen Virol*. 2021;102(4):001578.

51. Koch-Heier J, Hoffmann H, Schindler M, Lussi A, Planz O. Inactivation of SARS-CoV-2 through treatment with the mouth rinsing solutions ViruProX(R) and BacterX(R) Pro. *Microorganisms*. 2021;9(3):521.

52. Almanza-Reyes H, Moreno S, Plascencia-Lopez I, et al. Evaluation of silver nanoparticles for the prevention of SARS-CoV-2 infection in health workers: in vitro and in vivo. *PLoS One*. 2021;16(8):e0256401. https://doi.org/10.1371/journal.pone.0256401

53. Kariwa H, Fujii N, Takashima I. Inactivation of SARS-CoV-2 by povidone-iodine products: implications for effective mouth rinsing and gargling. *Japan J Veterinary Res*. 2021;69(3):183-187.

54. Shet M, Hong R, Igo D, Cataldo M, Bhaskar S. In vitro evaluation of the virucidal activity of different povidone—iodine formulations against murine and human coronaviruses. *Infect Dis Ther*. 2021;10(4):2777-2790.

55. Komine A, Yamaguchi E, Okamoto N, Yamamoto K. Virucidal activity of oral care products against SARS-CoV-2 in vitro. *J Oral Maxillofac Surg Med Pathol*. 2021;33(4):475-477.

56. Hassandarvish P, Tiong V, Mohamed NA, et al. In vitro virucidal activity of povidone iodine gargle and mouthwash against SARS-CoV-2: implications for dental practice. *Br Dent J*. Published online December 20, 2020. https://doi.org/10.1038/s41415-020-2402-0

57. Muñoz-Basagoiti J, Perez-Zsolt D, León R, et al. Mouthwashes with CPC reduce the infectivity of SARS-CoV-2 variants in vitro. *J Dent Res*. 2021;100(11):1265-1272.

58. Santos PSD, Orcina BD, Machado RRG, et al. Beneficial effects of a mouthwash containing an antiviral phthalocyanine derivative on the length of hospital stay for COVID-19: randomised trial. *Sci Rep*. Published online October 7, 2021. https://doi.org/10.1038/s41598-021-99013-5

59. Ortega K, Rech B, El Haje G, Ballo CB, Pérez-Sáyans M, Braz-Silva PH. Do hydrogen peroxide mouthwashes have a virucidal effect? A systematic review. *J Hosp Infect*. 2020;106(4):657-662.

60. Popkin DL, Zilka S, Dimaano M, et al. Cetylpyridinium chloride (CPC) exhibits potent, rapid activity against influenza viruses in vitro and in vivo. *Pathog Immun*. 2017;2(2):253-269.

61. Mathurasai W, Thanyasrisung P, Sooampon S, Ayuthaya BIN. Hydrogen peroxide masks the bitterness of chlorhexidine mouthwash without affecting its antibacterial activity. *J Indian Soc Periodontol*. 2019;23(2):119-123.

62. Nobahar M, Razavi MR, Malek F, Ghorbani R. Effects of hydrogen peroxide mouthwash on preventing ventilator-associated pneumonia in patients admitted to the intensive care unit. *Brazil J Infect Dis*. 2016;20(5):444-450.

63. Charles CA, Amini P, Gallob J, Shang H, McGuire JA, Costa R. Antiplaque and antigingivitis efficacy of an alcohol-free essential-oil containing mouthrinse: a 2-week clinical trial. *Am J Dent*. 2012;25(4):195-198.

64. Development of rapid viability-reverse transcriptase PCR (RV-RTPCR) method for detection of viable SARS-CoV-2 from environmental aamples. United States Environmental Protection Agency. Accessed April 19, 2021. https://www.epa.gov/covid19-research/development-rapid-viability-reverse-transcriptase-pcr-rv-rtpcr-method-detection

65. Choi JY, Zemke J, Philo SE, Bailey ES, Yondon M, Gray GC. Aerosol sampling in a hospital emergency room setting: a complementary surveillance method for the detection of respiratory viruses. *Front Public Health*. 2018;6:174.

66. Lednicky JA, Lauzard M, Fan ZH, et al. Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients. *Int J Infect Dis*. 2020;100:476-482.

67. Kohn WG, Collins AS, Cleveland JL, et al.; Centers for Disease Control and Prevention (CDC). Guidelines for infection control in dental health-care settings: 2003. *MMWR Recomm Rep*. 2003;52(RR-17):1-61.

68. Eggers M, Koburger-Janssen T, Eickmann M, Zorn J. In vitro bactericidal and virucidal efficacy of povidone-iodine gargle/mouthwash against respiratory and oral tract pathogens. *Infect Dis Ther*. 2018;7(2):249-259.

eTable 1. Database search strategy.

DATABASE	QUERY
MEDLINE (via PubMed)	(mouthwash* OR "mouth rinse" OR "oral rinse" OR rinse OR gargl* OR "gargle lavage" OR "oral irrigation" OR "oral lavage") AND (COVID-19 OR COVID19 OR sars-cov-2 OR 2019-nCoV OR COVID OR coronavirus)
Scopus	(mouthwash* OR "mouth rinse" OR "oral rinse" OR rinse OR gargl* OR "gargle lavage" OR "oral irrigation" OR "oral lavage") AND (covid-19 OR covid19 OR sars-cov-2 OR 2019-ncov OR covid OR coronavirus)
Web of Science	TS=((mouthwash* OR "mouth rinse" OR "oral rinse" OR rinse OR gargl* OR "gargle lavage" OR "oral irrigation" OR "oral lavage") AND (COVID-19 OR COVID19 OR sars-cov-2 OR 2019-nCoV OR COVID OR coronavirus))
MedRxiv and bioRxiv	COVID-19 AND mouthwash

eTable 2. Studies characterization.

STUDY	IN VITRO	IN VIVO	
		Randomized Controlled Trials	Uncontrolled Before-and-After Studies
Peer-Reviewed			
Anderson and colleagues,[45] 2020	Yes	No	No
Bidra and colleagues,[30] 2020	Yes	No	No
Bidra and colleagues,[34] 2020	Yes	No	No
Frank and colleagues,[33] 2020	Yes	No	No
Gottsauner and colleagues,[20] 2020	No	No	Yes
Hassandarvish and colleagues,[56] 2020	Yes	No	No
Lamas and colleagues,[23] 2020	No	No	Yes
Meister and colleagues,[46] 2020	Yes	No	No
Pelletier and colleagues[32] 2020	Yes	No	No
Seneviratne and colleagues[22] 2020	No	Yes	No
Yoon and colleagues[21] 2020	No	No	Yes
Almanza-Reyes and colleagues,[52] 2021	Yes	No	No
Carrouel and colleagues,[29] 2021	No	Yes	No
Chaudhary and colleagues,[27] 2021	No	Yes	No
Davies and colleagues,[50] 2021	Yes	No	No
Eduardo and colleagues,[28] 2021	No	Yes	No
Elzein and colleagues,[25] 2021	No	Yes	No
Jain and colleagues,[40] 2021	Yes	No	No
Kariwa and colleagues,[53] 2021	Yes	No	No
Koch-Heier and colleagues,[51] 2021	Yes	No	No
Komine and colleagues,[55] 2021	Yes	No	No
Meister and colleagues,[48] 2021	Yes	No	No
Meyers and colleagues,[44] 2021	Yes	No	No
Muñoz-Basagoit, and colleagues,[57] 2021	Yes	No	No
Santos and colleagues,[42] 2021	Yes	No	No
Santos and colleagues,[58] 2021	Yes	No	No
Schürmann and colleagues,[24] 2021	No	No	Yes
Shewale and colleagues,[38] 2021	Yes	No	No
Shet and colleagues,[54] 2021	Yes	No	No
Steinhauer and colleagues,[43] 2021	Yes	No	No
Tiong and colleagues,[41] 2021	Yes	No	No
Xu and colleagues,[31] 2021	Yes	No	No
Zoltán,[36] 2021	Yes	No	No
Preprint			
Green and colleagues,[49] 2020	Yes	No	No
Mantlo and colleagues,[35] 2020	Yes	No	No
Muñoz-Basagoiti and colleagues,[39] 2020	Yes	No	No
Statkute and colleagues,[47] 2020	Yes	No	No
Anderson and colleagues,[37] 2021	Yes	No	No
Jayaraman and colleagues,[26] 2021	No	No	Yes

eTable 3. Risk of bias assessment.

STUDY	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALEMENT	SELECTIVE REPORTING	OTHER SOURCES OF BIAS	BLINDING (PARTICIPANTS AND PERSONNEL)	BLINDING (OUTCOME ASSESSMENT)	INCOMPLETE OUTCOME DATA
Seneviratn, and Colleagues,[22] 2020	⊕*	⊕	⊕	?†	⊕	⊖‡	⊕
Carrouel and Colleagues[29] 2021	⊕	⊕	⊕	⊕	⊕	⊕	?
Chaudhary and Colleagues,[27] 2021	?	⊕	?	?	⊕	⊕	?
Eduardo and Colleagues,[28] 2021	⊕	⊕	⊕	⊕	⊖	⊕	⊕
Elzein and Colleagues,[25] 2021	?	⊕	⊕	?	⊕	⊕	⊕

* ⊕: Low risk of bias. † ?: Unclear risk of bias. ‡ ⊖: High risk of bias.

eTable 4. In vivo efficacy of different mouthrinses on severe acute respiratory syndrome coronavirus 2 viral load.

STUDY	STUDY DESIGN	SETTING	INCLUDED PARTICIPANTS, NO.	ASSESSMENT OF VIRAL LOAD	PRODUCT, DURATION OF RINSE, S	COMPARISON	RESULSTS
Gottsauner and Colleagues,[20] 2020	Uncontrolled before-and-after study	Hospitalized patients with a positive test for SARS-CoV-2* within the past 72 h with a median age of 55 y. Single rinse performed in a single day.	10	Oropharyngeal swab, via RT-PCR†	H_2O_2‡ (1%), 30	NA§	Viral load decrease of 0.3×10^3 copies per mL. No significant differences were observed between the baseline viral load and viral load 30 min after the 1% H_2O_2 mouthrinse ($P = .96$).
Lamas and Colleagues,[23] 2020	Uncontrolled before-and-after study	Hospitalized and home-isolated patients with positive RT-PCR for SARS-CoV-2 in nasopharyngeal exudate with a median age of 63.5 y. Single rinse performed in a single day.	4	Nasopharyngeal swab and saliva (method not explained), via RT-PCR	PVP-I¶ (1%), 60	NA	In 2 of 4 patients, PVP-I resulted in a significant drop ($\approx 5 \log_{10}$ and $\approx 2 \log_{10}$ reductions in salivary viral load in each patient), which remained for at least 3 h.
Seneviratne and Colleagues,[22] 2020	RCT#	Hospitalized patients with a nasal swab and saliva RT-PCR positive for SARS-CoV-2. Mean (SD**) age per group: PVP-I (n = 4), 40.7 (11.5) y; CHX†† (n = 6), 43.6 (8.6) y; CPC‡‡ (n = 4), 35.7 (8.5) y; water (n = 2), 36 (14.1) y. Single rinse performed in a single day.	16	Saliva (passive drool), via RT-PCR	PVP-I (0.5%), 30 CHX (0.2%), 30 CPC (0.075%), 30	Water	Ct§§ values detected in all 16 patients were within the range of 15.6-34.5, with a mean (SD) value of 27.7 (4.8); results are presented in form of fold change calculated as a ratio between Ct value at different time points and Ct value at baseline. PVP-I: significant increase in fold change was obtained only at 6 h (ratio = 1) postrinsing with PVP-I in comparison with water ($P < .01$). In comparison with the water group, the PVP-I group patients had higher fold increases in Ct value after 5 min (ratio = 1.1) and 3 h (ratio = 1.2) of postrinsing, but no significance was achieved. CHX: patients showed a varied effect among saliva Ct values after 5 min rinsing, and hence further studies with a larger sample size are required to determine its significance. CPC: significant increase in fold change of Ct value at 5 min (ratio = 1) and 6 h (ratio = 0.9) was observed postrinsing with CPC mouthrinse compared with the water group patients ($P < .05$). Although the fold changes in Ct values were higher at 3 h (ratio = 0.9) in the CPC group, no significance was achieved ($P = .20$).
Yoon and Colleagues,[21] 2020	Uncontrolled before-and-after study	Hospitalized patients with a diagnosis of COVID-19 with a median age of 55.5 y. One rinse per day on 2 nonconsecutive days (days 3 and 6 of the study).	2	Saliva (method not specified), via RT-PCR	CHX (0.12%), 30	NA	The viral load in the saliva decreased transiently for 2 h after using the CHX mouthrinse, but it increased again at 2-4 h postmouthrinse. On day 3, viral load was not detected at 1 h and 2 h postrinse, on both patients. One of the patients showed a baseline viral load of 6.9 $\log_{10}$ and the other of 4.9 $\log_{10}$. On day 6, 1 h after using the mouthrinse, there was no reduction in viral load in 1 patient.

* SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. † RT-PCR: Reverse transcription polymerase chain reaction. ‡ H_2O_2: Hydrogen peroxide. § NA: Not applicable. ¶ PVP-I: Povidone-iodine. # RCT: Randomized clinial trial. ** SD: Standard deviation. †† CHX: Chlorhexidine gluconate. ‡‡ CPC: Cetylpyridinium chloride. §§ Ct: Cycle threshold. ¶¶ CDCM: Mouthrinse containing ß-cyclodextrin and citrox. ## RT-PCR: Reverse transcription polymerase chain reaction.

eTable 4. Continued

STUDY	STUDY DESIGN	SETTING	INCLUDED PARTICIPANTS, NO.	ASSESSMENT OF VIRAL LOAD	PRODUCT, DURATION OF RINSE, S	COMPARISON	RESULSTS
Carrouel and Colleagues,[29] 2021	RCT	Home-isolated patients with a diagnosis of COVID-19. Mean (SD) age per group: placebo (n = 88), 44.08 (16.16) y; CDCM[¶¶] (n = 88), 42.06 (14.97) y. 3 rinses per day, for 7 days	176	Saliva (method not specified), via (rt)RT-PCR	CDCM: ß-cyclodextrin (0.1%) and citrox (0.1%), 60 s	Similar appearance and content solution without antiviral components	Day 1: A significant difference was observed in viral load reduction in the before-and-after comparison of the same patients receiving CDCM versus no difference for the placebo group from T1 (first sample other than basal on day 1) to T2 (second sample other than basal on day 1) ($P = .036$). The percentage median decrease (log_{10} copies/mL) was −12.6% (−29.6% to −0.2%) (CDCM) versus −6.7% (−21.2% to10.4%) (placebo). At T3 (third sample other than basal on day 1), the salivary viral load decreases were significant for both groups compared with T1 (CDCM: $P < .001$; placebo: $P = .002$) but with no significant difference between the 2 groups. 7 days: continuous decrease for the CDCM group and the placebo group was observed for 7 days. On day 7, no significant difference between patients receiving CDCM and those receiving placebo ($P = .388$). In both groups, the viral load was significantly lower on day 7 than on day 1 T1 ($P < .001$)
Chaudhary and Colleagues,[27] 2021	RCT	Hospitalized symptomatic adults (aged 21-80 y) with a diagnosis of COVID-19 via PCR. Median (range) age, 64 (25-82) y. Each mouthrinse group consisted of 10 participants. 2 consecutive rinses on a single day.	40	Saliva (passive drool), via PCR	PVP-I (0.5%), 30 s and 30 s H_2O_2 (1%), 30 s and 30s CHX (0.12%), 30 s and 30 s Normal saline, 30 s and 30 s	RNA from trizol-inactivated virus as positive control	After 15 min, CHX (0.12%), H_2O_2 (1%), and normal saline reduced viral load by 90%. However, PVP-I (0.5%) only reduced the viral load by approximately 61% 15 min after the rinse. After 30 min, H_2O_2 (1%) and normal saline reduced the viral load by approximately 90%, whereas CHX (0.12%) led to an approximately 70% reduction. However, PVP-I (0.5%) led to a 97% reduction on viral load 30 min after the rinse.

eTable 4. Continued

STUDY	STUDY DESIGN	SETTING	INCLUDED PARTICIPANTS, NO.	ASSESSMENT OF VIRAL LOAD	PRODUCT, DURATION OF RINSE, S	COMPARISON	RESULSTS
Eduardo and Colleagues,[28] 2021	RCT	Hospitalized (for up to 3 d) adults (aged 18-80 y), previously received a diagnosis of COVID-19 via nasal swab qualitative RT-PCR[##] with mild to moderate symptoms. Median (range) age per group: placebo (n = 9), 59 (36-85) y; CPC and zinc lactate (n = 7), 46 (34-88) y; H_2O_2 (n = 7), 62 (40-87) y; CHX (n = 8), 53.5 (49-88) y; H_2O_2 + CHX (n = 12), 53 (40-72) y. Single rinse performed in a single day. The H_2O_2 and CHX group performed 2 consecutive rinses, with different gargling times.	43	Saliva (passive drool), via PCR	0.075% CPC (0.075%) + zinc lactate (0.28%) mouthrinse (Colgate Total 12), 30 s H_2O_2 (1.5%) (Peroxyl), 60 s CHX (0.12%) (PerioGard), 30 s H_2O_2 (1.5%) (Peroxyl), 60 s and CHX (0.12%) (PerioGard), 30 s	Distilled water	Significant difference in the mean (SD) Ct value was observed for CPC and zinc lactate (20.4 [3.7]-fold reduction), H_2O_2 (15.8 [0.08]-fold reduction), and H_2O_2 and CHX (2.1 [0.5]-fold reduction) immediately after the rinse (T1), when compared with baseline. 30 min after rinsing (T2), H_2O_2 had a significant mean (SD) reduction in viral load (6.5 [3.4]-fold reduction). CPC and zinc lactate had a significant reduction in mean (SD) Ct values up to 60 min (T3) after the rinsing (6.5 [3.4]-fold reduction), which was not observed after rinsing with H_2O_2 (0.3 [1.3]-fold reduction). CHX achieved a greater than 2-fold mean (SD) reduction (T1, 2.1 [1.5]-fold; T2, 6.2 [3.8]-fold; T3, 4.2 [2.4]-fold reductions). H_2O_2 and CHX and the placebo presented minor changes in mean (SD) Ct values across all time points assessed (T1, 2.1 [0.5]-fold reduction; T2, 1.6 [0.2]-fold reduction; T3, 3.9 [0.3]-fold reduction). CPC and zinc lactate mouthrinse and CHX led to a significant reduction in the SARS-CoV-2 viral load in saliva up to 60 min, whereas H_2O_2 provided a significant reduction up to 30 min after rinsing.
Elzein and Colleagues,[25] 2021	RCT	Hospitalized patients with a diagnosis of COVID-19. Mean (SD) age per group: PVP-I group (n = 27), 39.9 (14.2) y; CHX group (n = 25), 47 (15.4) y; distilled water group (control) (n = 9), 57.2 (22.5) y. Single rinse performed in a single day.	61	Saliva (passive drool), via rRT-PCR	PVP-I (1%), 30 s CHX (0.2%), 30 s	Water	Baseline: mean (SD) Ct value of human ribonuclease P in saliva samples before mouthrinse was 25.4 (2.5) (range, 18.4-32.2); 5 min after for CHX and PVP-I: mean (SD) Ct value of human ribonuclease P in saliva samples after mouthrinse was 26 (2.7) (range, 19.4-32.5). No significant difference was found between the mean Ct values of human ribonuclease P in the 2 groups ($P = .332$). PVP-I: significant mean (SD) difference between the paired samples before (29.9 [6.2]; median, 30.8) and after mouthrinse (34.4 [6.3]; median, 34.2) with 1% PVP-I ($P < .0001$). CHX: higher significant difference of means was found in paired samples using CHX 0.2% ($P < .0001$). The mean Ct increased 5.7 after mouthrinse. The mean (SD) Ct of pre- and postmouthrinse was 27.7 (7.2) (median, 27.1) and 33.9 (7.1) (median, 33.1), respectively.

eTable 4. Continued

STUDY	STUDY DESIGN	SETTING	INCLUDED PARTICIPANTS, NO.	ASSESSMENT OF VIRAL LOAD	PRODUCT, DURATION OF RINSE, S	COMPARISON	RESULSTS
Jayaraman and Colleagues,[26] 2021	Uncontrolled before-and-after study	Hospitalized patients with a diagnosis of COVID-19. Single rinse performed in a single day.	36	Saliva (passive drool) and exhaled respiratory droplets, via RT-PCR	PVP-I (1%); H_2O_2 (1.5%); CHX (0.2%) Duration of the rinse not available	NA	The mean (SD) reduction was significantly higher in respiratory droplets (92%) than in whole saliva samples (50%; $P = .008$). PVP-I: -saliva 20 min: 1.8 (1.1) $\log_{10}$ reduction 60 min: 1.3 (0.9) $\log_{10}$ reduction - respiratory droplets 20 min: 2.5 (0.4) $\log_{10}$ reduction 60 min: 1.6 (1.9) $\log_{10}$ reduction H_2O_2: -saliva 20 min: 1.2 (0.3) $\log_{10}$ reduction 60 min: 1.6 (1.6) $\log_{10}$ reduction 90 min: 1.5 (1.5) $\log_{10}$ reduction 180 min: 0.9 (0.8) $\log_{10}$ reduction -respiratory droplets 20 min: 3.5 (3.7) $\log_{10}$ reduction 60 min: 2.5 (2.8) $\log_{10}$ reduction 90 min: 1.9 (1.6) $\log_{10}$ reduction 180 min: 3.0 (0.03) $\log_{10}$ reduction CHX: -saliva 90 min: 1.6 (1.2) $\log_{10}$ reduction 180 min: 0.4 (1.5) $\log_{10}$ reduction -respiratory droplets 90 min: 1.2 (0.8) $\log_{10}$ reduction 180 min: 0.6 (1.7) $\log_{10}$ reduction
Schürmann and Colleagues,[24] 2021	Uncontrolled before-and-after study	Hospitalized patients with a diagnosis of COVID-19. Single rinse performed in a single day.	34	Pharyngeal swab, via RT-qPCR	Linola Sept (Dr. Wolff) (analogous composition to Biorepair Zahnmilch: aqua, sorbitol, xylitol, zinc hydroxyapatite, cellulose gum, zinc pyrrolidone carboxylic acid, aroma, peg-40, hydrogenated castor oil, sodium lauryl sulfate, sodium myristoyl sarcosinate, sodium methyl, cocoyl taurate, lactoferrin, sodium hyaluronate, sodium saccharin, sodium benzoate, phenoxyethanol, benzyl alcohol), 60 s	NA	The mean (SD) of Ct values before rinsing was 26.0 (5.8). The overall mean (SD) of Ct values after rinsing was 29.1 (6.1). Mean (SD) values showed an increase of the Ct values of 3.1 (3.6), which translated into a significant reduction of the viral load in the pharynx of about 90%. Most patients exhibited a 10-fold reduction of viral load, independently of the initial viral load. The viral load required approximately 6 h to recover to the initial viral load. Moreover, highly infectious patients were able to restore their initial viral load during this time, whereas less infectious patients were not able to restore their initial infectivity 6 h after gargling.

eTable 5. In vitro efficacy of different mouthrinses on severe acute respiratory syndrome coronavirus 2 viral load.

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
PVP-I†						
Anderson and colleagues,[45] 2020	hCoV-19/Singapore/2/2020; Vero E6	Antiseptic solution: PVP-I (10); antiseptic skin cleanser: PVP-I (7.5); gargle and mouthrinse: PVP-I (1.0), 1:2 dilution; throat spray: PVP-I (0.45)	PBS‡	Dirty (0.3 g/L BSA§)	30 s	≥ 4 $\log_{10}$ reduction of SARS-CoV-2 titers, for all the products
Bidra and colleagues,[30] 2020	USA-WA1/2020; Vero 76	PVP-I (0.5, 1.25, 1.5)	Water; ethanol (70%)	Clean	15 s 30 s	15 s: > 4.3 $\log_{10}$ reduction of the infectious virus for all concentrations 30 s: > 3.6 $\log_{10}$ reduction of the infectious virus for all concentrations
Bidra and colleagues,[34] 2020	USA-WA1/2020; Vero 76	PVP-I (0.5, 0.75, 1.5)	Water; ethanol (70%)	Clean	15 s 30 s	15 s: the solutions reduced > 3 $\log_{10}$ of the viral load 30 s: the tested solutions reduced > 3.3 $\log_{10}$ of the viral load
Frank and colleagues,[33] 2020	USA-WA1/2020; Vero 76	PVP-I (0.5, 1.25, 2.5)	Water; ethanol (70%)	Clean	15 s 30 s	15 s: the solutions tested were effective at reducing the viral load > 3 $\log_{10}$ for all concentrations 30 s: the solutions were effective at reducing the viral load > 3.3 $\log_{10}$ for all concentrations
Hassandarvish and colleagues,[56] 2020	SARS-COV-2/MY/UM/6-3, TIDREC; Vero E6	PVP-I (0.5, 1)	Water	Clean; dirty (3.0 g/L BSA and 3 mL/L human erythrocytes)	15 s 30 s 60 s	15 s: 1% PVP-I reduced > 5 $\log_{10}$ viral titers. 0.5% PVP-I reduced > 4 $\log_{10}$ viral load 30 s: 0.5% and 1% PVP-I reduced > 5 og_{10} viral titers 60 s: 0.5% and 1% PVP-I reduced > 5 $\log_{10}$ viral titers
Meister and colleagues,[46] 2020	BetaCoV/Germany/Ulm/01/2020, BetaCoV/Germany/Ulm/02/2020, UKEssen; Vero E6	Iso-Betadine mouthrinse 1.0%: PVP-I (1)	Cell culture medium	Dirty (100 μL mucin type I-S, 25 μL BSA Fraction V, and 35 μL yeast extract)	30 s	Iso-Betadine mouthrinse reduced viral infectivity to up to 3 $\log_{10}$
Pelletier and colleagues,[32] 2020	USA-WA1/2020; Vero 76	Oral rinse PVP-I antiseptic (0.5, 0.75, 1.5)¶	Water; ethanol (70%)	Clean	60 s	After incubation with each nasal/oral antiseptic, viral load decrease of > 4 $\log_{10}$ infectious viruses for all concentrations
Statkute and colleagues,[47] 2020#	England 2; Vero E6	Videne: PVP-I (7.5)	NA**	Dirty (100 μL mucin type I-S, 25 μL BSA Fraction V, and 35 μL yeast extract)	30 s	Videne had an effect of ≈ 3 $\log_{10}$ reduction
Davies and colleagues,[50] 2021	England 2; Vero E6	Povident: PVP-I (0.58)	PBS	Clean	60 s	≥ 4.1 $\log_{10}$ reduction or†† ≥ 5.2 $\log_{10}$ reduction
Jain and colleagues,[40] 2021	SARS-CoV-2 strain used was isolated from a patient; Vero E6	PVP-I (1)	NA	Clean	30 s 60 s	30 s: 99.8% inactivation 60 s: > 99.9% inactivation

* SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. † PVP-I: Povidone-iodine. ‡ PBS: Phosphate buffered saline. § BSA: Bovine serum albumin. ¶ A nasal PVP-I antiseptic (0.5%, 1.25%, 2.5%) was studied as a complement to the oral antiseptic. # Preprint article. ** NA: Not applicable. †† Depending on initial viral concentration (higher, lower). ‡‡ RLU: Relative light units. §§ H_2O_2: Hydrogen peroxide. ¶¶ CHX: Chlorhexidine gluconate. ## CPC: Cetylpyridinium chloride. *** pfu/mL: Plaque forming units per milliliter. ††† $TCID_{50}$/mL: Median tissue culture infectious dose per milliliter. ‡‡‡ SD: Standard deviation. §§§ ppm: Parts per million. ¶¶¶ APD: Anionic.

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Kariwa and colleagues,[53] 2021	WK-521; Vero E6	Isodine Gargle (ethical product) at 2 different concentrations: PVP-I (0.23) and PVP-I (0.47) Isodine Gargle (consumer product): PVP-I (0.23) Isodine Gargle C (consumer product): PVP-I (0.35) Isodine Nodo Fresh (consumer product): PVP-I (0.45)	NA	Clean	30 s 60 s	Isodine Gargle (ethical product) PVP-I (0.23%): 30 s: > 3.1 $\log_{10}$; 60 s: > 3.6 $\log_{10}$ Isodine Gargle (ethical product) PVP-I (0.47%): 30 s: > 3.2 $\log_{10}$; 60 s: > 4.0 $\log_{10}$ Isodine Gargle (consumer product) PVP-I (0.23%): 30 s: > 3.1 $\log_{10}$; 60 s: > 3.6 $\log_{10}$ Isodine Gargle C (consumer product) PVP-I (0.35%): 30 s: > 3.2 $\log_{10}$; 60 s: > 3.4 $\log_{10}$ Isodine Nodo Fresh (consumer product) PVP-I (0.45%): 30 s: > 3.8 $\log_{10}$; 60 s: > 3.8 $\log_{10}$
Meyers and colleagues,[44] 2021	HCoV 229e; HUH7	Betadine 5%: PVP-I (5)	NA	Dirty (200 μL of 5% BSA)	30 s 60 s 120 s	30 s: Decrease in viral load between > 3 $\log_{10}$ and < 4 $\log_{10}$ 60 s: Decrease in viral load between > 3 $\log_{10}$ and > 4 $\log_{10}$ 120 s: > 4 $\log_{10}$ reduction in viral load

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Shet and colleagues[54] 2021	Coronavirus strain OC43, coronavirus strain NL63, and coronavirus strain 229E; MRC-5, Vero CCL-81, and HCT-8 cells	PVP-I solution (0.5, 10) PVP-I scrub (7.5) Placebo solution (0.5) Placebo scrub (7.5)	Authors did not mention placebo composition.	Clean	< 15 s 15 s 30 s 60 s 5 min	PVP-I (0.5%) solution: OC43 strain: 4 $\log_{10}$ reduction (< 15 s); ≥ 5.75 $\log_{10}$ reduction (15 s, 30 s, 60 s, and 5 min); NL63 strain: 4.75 $\log_{10}$ reduction (< 15 s); ≥ 5.25 $\log_{10}$ reduction (15 s, 30 s, 60 s, and 5 min); 229E strain: 3.75 $\log_{10}$ reduction (< 15 s); 4.25 $\log_{10}$ reduction (15 s); ≥ 5.25 $\log_{10}$ reduction for contact times of 15 s, 30 s, 60 s, and 5 min PVP-I 7.5% scrub: OC43 strain: 2.5 $\log_{10}$ reduction (< 15 s); 3 $\log_{10}$ reduction (15 s); 3.75 $\log_{10}$ reduction (30 s, 60 s, and 5 min); NL63 strain: 3.25 $\log_{10}$ reduction (< 15 s, 15 s, 30 s, 60 s, and 5 min); 229E strain: 3.50 $\log_{10}$ reduction (< 15 s, 15 s, 30 s, 60 s, and 5 min) PVP-I 10% solution: OC43 strain: 4.50 $\log_{10}$ reduction (< 15 s); ≥ 5.75 $\log_{10}$ reduction (15 s, 30 s, 60 s, and 5 min); NL63 strain: ≥ 5.25 $\log_{10}$ reduction (< 15 s, 15 s, 30 s, 60 s, and 5 min); 229E strain: 4 $\log_{10}$ reduction (< 15 s); 4.25 $\log_{10}$ reduction (15 s); 4.50 $\log_{10}$ reduction (30 s, 60 s, and 5 min) Placebo 0.5%: OC43 strain: 0.25 $\log_{10}$ reduction (< 15 s); 0.50 $\log_{10}$ reduction (15 s and 60 s); 0.75 $\log_{10}$ reduction (30 s); 1.25 $\log_{10}$ reduction (5 min); NL63 strain: 0.25 $\log_{10}$ reduction (< 15 s, 15 s); 0.50 $\log_{10}$ reduction (60 s and 5 min); no reduction at 30 s; 229E strain: 0.25 $\log_{10}$ reduction (< 15 s); 0.75 $\log_{10}$ reduction (30 s, 60 s, and 5 min); 1 $\log_{10}$ reduction (15 s) Placebo 7.5%: OC43 strain: 1.25 $\log_{10}$ reduction (< 15 s, 15 s); 1.75 $\log_{10}$ reduction (30 s); 3.75 $\log_{10}$ reduction (60 s, 5 min); NL63 strain: 1.25 $\log_{10}$ reduction (< 15 s) 1.75 $\log_{10}$ reduction (15 s); 2 $\log_{10}$ reduction (30 s); 3.25 $\log_{10}$ reduction (60 s, 5 min); 229E strain: 1.5 $\log_{10}$ reduction (< 15 s); 1 $\log_{10}$ reduction (15 s); 2 $\log_{10}$ reduction (30 s); 3.25 $\log_{10}$ reduction (60 s), 3.5 $\log_{10}$ reduction (5 min)
Xu and colleagues,[31] 2021	USA-WA1/2020; HEK293T, HeLa	PVP-I (10) at different final dilutions (5, 0.5, and 0.05)	NA	No information available	30 min	Only the 5% dilution of PVP-I was effective in inactivating the viruses (0 RLU[‡‡])
H_2O_2[§§]						
Bidra and colleagues,[30] 2020	USA-WA1/2020; Vero 76	H_2O_2 (1.5, 3)	Water; ethanol (70%)	Clean	15 s 30 s	15 s: H_2O_2 (1.5%) reduced 1.3 $\log_{10}$ infectious virus. H_2O_2 (3%) reduced 1.0 $\log_{10}$ infectious virus 30 s: H_2O_2 (1.5%) reduced 1.0 $\log_{10}$ infectious virus. H_2O_2 (3%) reduced 1.8 $\log_{10}$ infectious virus

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Koch-Heier and colleagues,[51] 2020	SARS-CoV-2 Isolate "FI-100"; Vero E6	H_2O_2 (1.5)	Nonvirucidal medium control of SARS-CoV-2 with infection medium; no-virus control containing infection medium and test solution	Clean	30 s	H_2O_2 (1.5%) showed no effective reduction of the virus titer
Meister and colleagues,[46] 2020	BetaCoV/Germany/Ulm/01/2020, BetaCoV/Germany/Ulm/02/2020, UKEssen; Vero E6	Cavex oral rinse: H_2O_2 (concentration unknown)	Cell culture medium	Dirty (100 μL mucin type I-S, 25 μL BSA Fraction V, and 35 μL yeast extract)	30 s	Viral load decrease between 0.3 $\log_{10}$ and 1.8 $\log_{10}$
Davies and colleagues,[50] 2021	England 2; Vero E6	Peroxyl: H_2O_2 (1.5)	PBS	Clean	60 s	Reduction of the virus titer by 0.2 $\log_{10}$
Meyers and colleagues,[44] 2021	HCoV 229e; HUH7	Peroxide Sore Mouth Cleanser: H_2O_2 (1.5); H_2O_2 solution diluted to 1.5% in PBS: H_2O_2 (1.5); Orajel Antiseptic Rinse: H_2O_2 (1.5); menthol (0.1)	NA	Dirty (200 μL of 5% BSA)	30 s 60 s 120 s	Virus load reduction between < 1 $\log_{10}$ and 2 $\log_{10}$ for all concentrations and contact times
Xu and colleagues,[31] 2021	USA-WA1/2020; HEK293T, HeLa	Colgate Peroxyl: H_2O_2 (1.5) at different dilutions (0.75, 0.075, and 0.0075)	NA	No information available	30 min	Colgate Peroxyl (0.75% and 0.075%) was effective in inactivating the viruses (0 RLU)
CHX[¶¶]						
Koch-Heier and colleagues,[51] 2020	SARS-CoV-2 Isolate "FI-100"; Vero E6	CHX (0.1)	Nonvirucidal medium control of SARS-CoV-2 with infection medium; no-virus control containing infection medium and test solution	Clean	30 s	CHX (0.1%) showed no effective reduction of the virus titer
Meister and colleagues,[46] 2020	BetaCoV/Germany/Ulm/01/2020, BetaCoV/Germany/Ulm/02/2020, UKEssen; Vero E6	Chlorhexamed Forte: CHX (concentration unknown); Dynexidin Forte 0.2%: CHX (0.2%)	Cell culture medium	Dirty (100 μL mucin type I-S, 25 μL BSA Fraction V, and 35 μL yeast extract)	30 s	Viral load decrease between 0.3 $\log_{10}$ and 1.8 $\log_{10}$
Anderson and colleagues,[37] 2021[#]	USA-WA1/2020, Alpha isolate: hCoV-19/England/204820464/2020, Beta isolate: hCoV-19/South Africa/KRISP-EC-K005321, and Gamma isolate: hCoV-19/Japan/TY7-503/2021; Vero E6	CHX (0.2) with flavor	Ethanol (70%)	Clean; dirty (human saliva)	30 s	USA-WA1/2020: CHX (0.2%) led to a 1.26 $\log_{10}$ reduction; alpha isolate: 3.11 $\log_{10}$ reduction; beta isolate: 4.11 $\log_{10}$ reduction; gamma isolate: 3.36 $\log_{10}$ reduction
Davies and colleagues,[50] 2021	England 2; Vero E6	CHX antiseptic mouthrinse: CHX (0.2); Corsodyl (alcohol-free mint flavor): CHX (0.2)	PBS	Clean	60 s	CHX antiseptic mouthrinse: 0.5 $\log_{10}$ reduction Corsodyl: 0.4 $\log_{10}$ reduction
Jain and colleagues,[40] 2021	SARS-CoV-2 strain used was isolated from a patient; Vero E6	CHX (0.12) and CHX (0.2)	NA	Clean	30 s 60 s	For 30 s and 60 s: CHX (0.12%) led to a 99.9% inactivation. CHX (0.2%) led to a $>$ 99.9% inactivation
Komine and colleagues,[55] 2021	JPN/TY/WK-521 strain; VeroE6/TMPRSS2	GUM PAROEX: CHX (0.12)	PBS, ethanol (70%)	Clean	30 s	GUM PAROEX (0.12%) led to a 0.2 $\log_{10}$ reduction
Steinhauer and colleagues[43] 2021	No available information	CHX (0.1 and 0.2) used in different dilutions (0.08 and 0.16)	Formaldehyde	Clean	15 s 30 s 60 s 5 min 10 min	Both formulations had $>$ 1 $\log_{10}$ reduction of the viral load after 60 s and 5 min (CHX 0.2%) and after 10 min (CHX 0.1%)

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Tiong and colleagues,[41] 2021	SARS-CoV-2 strain used was isolated from a patient, SARS-COV-2/MY/UM/6-3 TIDREC (virus stock); Vero E6	Oradex: CHX (0.12)	Culture cell medium	Clean; dirty (0.3 g/L BSA a 3 mL/L human erythrocytes)	30 s 60 s	Reduction of 4 $\log_{10}$ for all test times and conditions
Xu and colleagues,[31] 2021	USA-WA1/2020; HEK293T, HeLa	CHX (0.12) used in different final dilutions (0.06, 0.006, and 0.0006)	NA	No information available	30 min	CHX (0.06%) was effective in inactivating the viruses (0 RLU). CHX (0.006%) had a moderate anti-viral effect ($>$ 2 x 10^4 RLU)
CPC[##]						
Green and colleagues,[49] 2020[#]	HCoV-SARS 229E; MRC-5	Mouthrinse containing CPC (0.07), sodium fluoride, and flavor oil	NA	Clean	30 s 60 s	Viral load decrease of 3.1 $\log_{10}$ for all contact times
Koch-Heier and colleagues,[51] 2020	SARS-CoV-2 Isolate "FI-100"; Vero E6	CPC (0.05)	Nonvirucidal medium control of SARS-CoV-2 with infection medium; no-virus control containing infection medium and test solution	Clean	30 s	CPC (0.05%) reduced virus titer by 5.6 $\times$ 10^6 pfu/mL[***] (0.7 $\log_{10}$)
Muñoz-Basagoiti and colleagues,[39] 2020[#]	SARS-CoV-2 isolated from a nasopharyngeal swab; Vero E6	Vitis CPC Protec: 2.063 mM of CPC; CPC: 10 mM of CPC diluted in distilled water	Culture cell media	Clean	120 s	Viral load decreased by 3 $\log_{10}$ for all test solutions
Statkute and colleagues,[47] 2020[#]	England 2; Vero E6	Dentyl Dual Action: CPC (0.05-0.1). Other active ingredients: isopropyl myristate, mentha arvensis extract Dentyl Fresh Protect: CPC (0.05-0.1). Other active ingredients: xylitol	NA	Dirty (100 μL mucin type I-S, 25 μL BSA Fraction V, and 35 μL yeast extract)	30 s	Dentyl mouthrinses completely eliminated the virus ($>$ 5 $\log_{10}$ reductions)
Anderson and colleagues,[37] 2021[#]	USA-WA1/2020, Alpha isolate: hCoV-19/England/204820464/2020, Beta isolate: hCoV-19/South Africa/KRISP-EC-K005321, and Gamma isolate: hCoV-19/Japan/TY7-503/2021; Vero E6	CPC (0.07), with flavor and mix of herbal extracts; CPC (0.07), with flavor	Ethanol (70%)	Clean; dirty (human saliva)	30 s	USA-WA1/2020: both CPC mouthrinses led to a $\geq$ 4 $\log_{10}$ reduction; Alpha isolate: both mouthrinses led to a 3.11 $\log_{10}$ reduction; Beta isolate: both mouthrinses led to a 4.11 $\log_{10}$ reduction; Gamma isolate: both mouthrinses led to a 3.36 $\log_{10}$ reduction
Komine and colleagues,[55] 2021	JPN/TY/WK-521 strain; VeroE6/TMPRSS2	GUM WELL PLUS Dental paste: CPC (0.0125); GUM MOUTHWASH HERB 2020: CPC (0.04); GUM WELL PLUS dental rinse (alcoholic type): CPC (0.05); GUM WELLPLUS dental rinse (nonalcoholic type): CPC (0.05); GUM Oral Rinse: CPC (0.075); GUM disinfection spray for mouth/throat: CPC (0.3)	PBS, ethanol (70%)	Clean	20 s 30 s 3 min (dental paste)	20 s: GUM MOUTHWASH HERB 2020 (0.04%) led to $>$ 4.4 $\log_{10}$ reduction; dental rinse (alcoholic type) (0.05%) led to a 4.2 $\log_{10}$ reduction, and GUM WELLPLUS dental rinse (nonalcoholic type) (0.05%) led to a 4.1 $\log_{10}$ reduction. GUM disinfection spray for mouth/throat (0.3%) achieved a $>$ 3.4 $\log_{10}$ reduction 30 s: GUM Oral Rinse (0.075%) led to a $>$ 4.3 $\log_{10}$ reduction 3 min: GUM WELL PLUS dental paste (0.0125%) led to a 3.3 $\log_{10}$ reduction
Meyers and colleagues,[44] 2021	HCoV 229e; HUH7	Crest Pro-Health: CPC (0.07)	NA	Dirty (200 μL of 5% BSA)	30 s 60 s 120 s	Crest Pro-Health decreased viral load by at least 3 $\log_{10}$ to $>$ 4 $\log_{10}$ for all contact times

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Muñoz-Basagoiti and colleagues,[57] 2021	SARS-CoV-2 D614G (isolated from a nasopharyngeal swab) and SARS-CoV-2 B.1.1.7; Vero E6	Vitis Encias: with 1.47 mM of CPC (or 0.05); Vitis CPC Protect with 2.063 mM of CPC (or 0.07); CPC, 10 mM	Vehicles containing the same formulation but without CPC; virus mixed with 1 mL of media as positive control	Clean; dirty (saliva)	30 s 60 s 120 s	30 s: Vitis CPC decreased 10-fold (1 $\log_{10}$) the $TCID_{50}$/mL[†††] of the B.1.1.7 SARS-CoV-2 variant (compared with untreated virus) 60 s: There was a reduction of infectivity above 1,000 (> 3 $\log_{10}$) times regardless of the variant used or the duration of exposure to Vitis CPC 120 s: High doses of CPC (10 mM) effectively suppressed viral infection. CPC-containing mouthrinses decreased approximately 1,000 times the $TCID_{50}$/mL of SARS-CoV-2, whereas vehicles had no impact on SARS-CoV-2 infectivity when compared with untreated virus
Other Mouthrinses						
Green and colleagues,[3] 2020[#]	HCoV-SARS 229E; MRC-5	Mouthrinse containing ethanol (15.7), sodium fluoride, and flavor oil. Mouthrinse containing zinc sulfate heptahydrate (0.2), sodium fluoride, and flavor oil Mouthrinse containing a mix of amyloglucosidase, glucose oxidase, lysozyme, colostrum, lactoferrin, lactoperoxidase, sodium fluoride, and flavor oil	NA	Clean	30 s 60 s	Contact with ethanol, zinc, and enzyme and protein mouthrinses did not provide a substantial reduction in viral counts. Zinc: after 30 s, mean (SD[‡‡‡]) reduction of 1.2 (0.4) $\log_{10}$; after 60 s, mean (SD) reduction of 1.8 (0.1) $\log_{10}$; enzymes and proteins: after 30 s, mean (SD) reduction of 0.3 (0.3) $\log_{10}$; after 60 s, mean (SD) reduction of 0.3 (0.3) $\log_{10}$; ethanol: after 30 s, mean (SD) reduction of 0.2 (0.3) $\log_{10}$; after 60 s, mean (SD) reduction of 0.3 (0.3) $\log_{10}$
Mantlo and colleagues,[35] 2020[#]	USA-WA1/2020; Vero Cells	CupriDyne: iodine and cuprous iodide (250 ppm,[§§§] 25 ppm, 2.5 ppm)	Water (boiling and at room temperature)	Clean	10 min 30 min 60 min	CupriDyne (25 ppm or 2.5 ppm) was not found to cause a significant difference in SARS-CoV-2 titers; CupriDyne (250 ppm) was shown to effectively inactivate the virus to a significant extent after 10, 30, and 60 min. After incubation with undiluted (250 ppm) CupriDyne for 10 min, viral titers dropped by 1 $\log_{10}$. Viral titers dropped 2 $\log_{10}$ after incubation with undiluted CupriDyne for 30 min. Further incubation with undiluted CupriDyne for 60 min reduced viral titers below the limit of detection.
Meister and colleagues,[46] 2020	BetaCoV/Germany/Ulm/01/2020, BetaCoV/Germany/Ulm/02/2020, UKEssen; Vero E6	Dequonal: dequalinium chloride, benzalkonium chloride; Listerine Cool Mint: ethanol, essential oils; Octenident mouthrinse: octenidine dihydrochloride; ProntOral mouthrinse: polyaminopropyl biguanide (polyhexanide)	Cell culture medium	Dirty (100 μL mucin type I-S, 25 μL BSA Fraction V, and 35 μL yeast extract)	30 s	Dequonal and Listerine Cool Mint significantly reduced viral infectivity to up to 3 $\log_{10}$. Octenident virucidal activities could be observed with reduction factors ranging between 0.3 $\log_{10}$ and 1.8 $\log_{10}$. With ProntOral, 1 strain was only moderately reduced, and the other 2 strains were inactivated.
Muñoz-Basagoiti and colleagues,[39] 2020[#]	SARS-CoV-2 isolated from a nasopharyngeal swab; Vero E6	Perio Aid Intensive Care: 1.47 mM of CPC and 1.33 mM of CHX	Culture cell media	Clean	120 s	No impact on SARS-CoV-2 infectivity, when compared with untreated virus

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Statkute and colleagues,[47] 2020[#]	England 2; Vero E6	Corsodyl: ethanol (7), CHX (0.2); other active ingredient, peppermint oil Listerine Cool Mint: ethanol (21); other active ingredients: thymol (0.064), eucalyptol (0.092), methyl salicylate (0.060), and menthol (0.042) Listerine Advanced Gum Treatment: ethanol (23); other active ingredient: ethyl lauroyl arginate hydrochloride (0.147) SCD Max: CPC (0.07-0.1), sodium citric acid (0.05); other active ingredient: sodium monofluorophosphate	NA	Dirty (100 μL mucin type I-S, 25 μL BSA Fraction V, and 35 μL yeast extract)	30 s	Listerine Advanced Gum Treatment eliminated the virus ($>$ 5 $\log_{10}$ reduction). SCD Max and Listerine Cool Mint had a moderate effect ($\approx$ 3 $\log_{10}$ reduction). Corsodyl was relatively ineffective ($<$ 2 $\log_{10}$ reduction).
Almanza-Reyes and colleagues,[52] 2021	SARS-CoV-2 NL/2020 (BetaCoV/Netherlands/01); Vero E6	Argovit silver nanoparticles (0.0004-0.5)	Culture cell media	Clean	72 h	Argovit (0.3%) led to an 80% viral inactivation
Davies and colleagues,[50] 2021	England 2; Vero E6	Listerine Advanced Defence Sensitive: dipotassium oxalate (1.4) Listerine Total Care: eucalyptol, thymol, menthol, sodium fluoride, zinc fluoride OraWize+ Aqualution Systems: stabilized hypochlorous acid (0.01-0.02)	PBS	Clean	60 s	Listerine Advanced Defence Sensitive: $\geq$ 3.5 $\log_{10}$ or[††] $\geq$ 4.2 $\log_{10}$ Listerine Total Care: $\geq$ 4.1 $\log_{10}$ reduction or[††] $\geq$ 5.2 $\log_{10}$ OraWize+: $\geq$ 5.5 $\log_{10}$ or[††] 0.4 $\log_{10}$
Koch-Heier and colleagues,[51] 2021	SARS-CoV-2 Isolate "FI-100"; Vero E6	ViruProX: CPC (0.05) and H_2O_2) (1.5) BacterX pro: CHX (0.1), CPC (0.05), and fluoride anion (0.005) Solution of CPC (0.05) and CHX (0.1)	Nonvirucidal medium control of SARS-CoV-2 with infection medium; no-virus control containing infection medium and test solution	Clean	30 s	Incubation with ViruProX reduced the virus titer by $\geq$ 6.8 $\times$ 10^6 pfu/mL ($\geq$ 1.9 $\log_{10}$) versus the medium control, whereas BacterX pro reduced by $\geq$ 8.4 $\times$ 10^6 pfu/mL ($\geq$ 2.0 $\log_{10}$) CHX (0.1%) and CPC (0.05%) reduced the virus titer by 6.7 $\times$ 10^6 pfu/mL (1.2 $\log_{10}$)
Komine and colleagues,[55] 2021	JPN/TY/WK-521 strain; VeroE6/TMPRSS2	CPC + CHX mouthrinse: 2 formulations: GUM PAROEX, CHX (0.06) + CPC (0.05); GUM PAROEX, CHX (0.12) + CPC(0.05) GUM PerioShield: delmopinol hydrochloride (0.2) mouthrinse	PBS, ethanol (70%)	Clean	30 s	30 s: Both CPC and CHX mouthrinse formulations led to a $>$ 4.3 $\log_{10}$ reduction. The delmopinol hydrochloride mouthrinse (0.2%) led to a $>$ 5.3 $\log_{10}$ reduction.

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Meister and colleagues,[48] 2021	SARS-CoV-2 hCoV-19/ Germany/BY-Bochum-1/ 2020; Vero E6	Oral sprays: (A) Carragelose (1.2 mg/mL), kappa-carrageenan (0.4 mg/mL), sodium chlorite; (B) Sodium chlorite (0.9), panthenol; (C) Xylometazolin hydrochloride (1 mg/mL), dexpanthenol (50 mg/mL); (D) Sodium hypochlorite (< 0.08), lithium-magnesium-sodium-silicate; (E) Xylometazolin hydrochloride (0.1%); (F) Hydroxypropyl methyl cellulose, succinic acid, disodium succinate; (G) Galphimia, *Luffa operculate*, sabadilla Nasal sprays: (H) Zincum aceticum, zincum gluconium; (I) Anise oil, eucalyptus oil, levomenthol, myrrh extract, clove oil, peppermint oil, ratanhia root extract, tormentil root extract	Cell culture medium	Dirty (substance mimicking nasal secretion)	30 s	In general, oral sprays led to a > 1 $\log_{10}$ reduction: (A) 0.53 $\log_{10}$ reduction; (B) 0.13 $\log_{10}$ reduction; (C) 0.09 $\log_{10}$ reduction; (E) 0.20 $\log_{10}$ reduction; (F) 0.18 $\log_{10}$ reduction. Oral spray (G) led to no reduction, whereas oral spray (D) led to a 2.21 $\log_{10}$ reduction. Nasal spray (H) led to no reduction on viral load. Nasal spray (I) led to a ≥ 3.03 $\log_{10}$ or ≥ 4.69 $\log_{10}$ reduction (large volume plating, to reduce cell toxicity)
Meyers and colleagues,[44] 2021	HCoV 229e; HUH7	Listerine Antiseptic: eucalyptol (0.092), menthol (0.042), methyl salicylate (0.06), thymol (0.064) Listerine Ultra: eucalyptol (0.092), menthol (0.042), methyl salicylate (0.06), thymol (0.064) Equate: eucalyptol (0.092), menthol (0.042), methyl salicylate (0.06), thymol (0.064) Antiseptic mouthrinse (CVS): eucalyptol (0.092), menthol (0.042), methyl salicylate (0.06), thymol (0.064)	NA	Dirty (200 μL of 5% BSA)	30 s 60 s 120 s	Listerine Antiseptic decreased viral load by > 4 $\log_{10}$. After incubation times of 60 s and 120 s, no remaining infectious virus was detected. Listerine Ultra, Equate, and antiseptic mouthrinse showed lower efficacy (particularly after 30 s). However, these latter mouthrinses decreased infectious virus titers by > 2 $\log_{10}$.
Muñoz-Basagoiti and colleagues,[57] 2021	SARS-CoV-2 D614G (isolated from a nasopharyngeal swab) and SARS-CoV-2 B.1.1.7; Vero E6	Perio Aid Intensive Care (1.47 mM of CPC and 1.33 mM of chlorhexidine)	Vehicles containing the same formulation but without CPC; virus mixed with 1 mL of media as the positive control	Clean; dirty (saliva)	30 s 60 s 120 s	120 s: High doses of CPC (10 mM) effectively suppressed viral infection. CPC-containing mouthrinses decreased approximately 1,000 times the $TCID_{50}$/mL of SARS-CoV-2, whereas vehicles had no impact on SARS-CoV-2 infectivity when compared with untreated virus
Santos and colleagues,[42] 2021	SARS-CoV-2 strain used was isolated from a patient; Vero ATCC CCL-81	Dental gel: APD[¶¶¶] (1) Mouthrinse: APD (0.1)	Viral solution + cellular system as positive control. Cellular system only as the negative control	Clean	30 s 60 s 5 min	Dental gel APD (1%): 99.99% (4 $\log_{10}$) reduction for all contact times Mouthrinse APD (0.1%): 90% (1 $\log_{10}$) reduction for all contact times
Santos and colleagues,[58] 2021	SARS.CoV2/ SP02.2020.HIAE. Br; Vero CCL-81	APD derivative: 1 mg/mL (1:2), 0.5 mg/mL (1:4), 0.25 mg/mL (1:8), 0.125 mg/mL (1:16), 0.0625 mg/mL (1:32), 0.03125 mg/mL (1:64), 0.01562 mg/mL (1:128)	NA	No information available	30 min	Significant reduction in viral load when compared with the positive control at the 1:2 (99.96%, < 4 $\log_{10}$), 1:4 (99.88%, < 3 $\log_{10}$), 1:8 (99.84%, < 3 $\log_{10}$), and 1:16 (92.65%, < 2 $\log_{10}$) titers. Minor viral neutralization was observed at the 1:32 (77.42%) and 1:64 (11.06%) titers. No virus neutralization was observed below the 1:128 titer.

eTable 5. Continued

STUDY	SARS-COV-2* STRAIN, CELLULAR LINE	TEST MOUTHRINSES, CONCENTRATION (%)	COMPARISON	INTERFERING SUBSTANCES	CONTACT TIME	RESULTS
Shewale and colleagues,[38] 2021	USA-WA1/2020; Vero E6	ClōSYS Ultra sensitive rinse, Sensitive rinse, Oral Spray: stabilized chlorine dioxide (0.1) ClōSYS fluoride toothpaste: stabilized chlorine dioxide (0.04)	PBS	Clean	30 s 60 s 120 s	30s: Ultra sensitive rinse led to a 1.96 log_{10} reduction; Sensitive rinse led to a 1.81 log_{10} reduction; Oral Spray led to a 2.98 log_{10} reduction. 60s: Ultra sensitive rinse led to a 1.39 log_{10} reduction; Sensitive rinse led to a 1.71 log_{10} reduction; Oral Spray led to a 2.67 log_{10} reduction. Sensitive fluoride toothpaste achieved a 2.26 log_{10} reduction with application times of 30 s, 60 s, and 120 s.
Steinhauer and colleagues,[43] 2021	No available information	octenisept: octenidine dihydrochloride (0.1) and phenoxyethanol (20), used in 20% (volume/volume) and 80% (v/v) concentrations	Formaldehyde	Clean	15 s 30 s 60 s	Reduction of titers by $\geq$ 4.4 log_{10} was observed for both concentrations and all contact times
Tiong and colleagues,[41] 2021	SARS-CoV-2 strain used was isolated from a patient, SARS-COV-2/MY/UM/6-3 TIDREC (virus stock); Vero E6	Colgate Plax Fruity Fresh: CPC (0.075), 0.05% sodium fluoride (0.05) XepaThymol: thymol (0.05) Bactidol: hexetidine (0.1),ethanol (9) Salt water: 2% (0.34 M), sodium chloride	Culture cell medium	Clean; dirty (0.3 g/L BSA and 3 mL/L human erythrocytes)	30 s 60 s	Colgate Plax Fruity Fresh: 5 log_{10} reduction for all test times and conditions. Xepa Thymol: 0.75 log_{10} reduction after 60 s (clean conditions), 0.5 log_{10} reduction after 30 s (clean conditions), and after 30 s and 60 s (dirty conditions). Bactidol: 5 log_{10} reduction for all test times and conditions. Salt water: no effect on SARS-CoV-2 viral load.
Xu and colleagues,[31] 2021	USA-WA1/2020; HEK293T, HeLa	PVP-I (10) at different final dilutions (5, 0.5, and 0.05)	NA	No information available	30 min	Only the 5% dilution of PVP-I was effective in inactivating the viruses (0 RLU)
Zoltán,[35] 2021	USA-WA1/2020; Vero 76	200 μg elemental iodine/mL at 3 dilutions (1:1; 2:1, and 3:1)	Water; ethanol (70%)	Clean	60 s 90 s	60 s: 3:1 dilution reduced viral titer by 2 log_{10}, and 2:1 dilution reduced viral titers by 1.7 log_{10} 90 s: 1:1 dilution reduced viral titer by 2 log_{10}