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Antiviral effect of oral antiseptic solutions commonly used in dentistry practice: A scoping review

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ABSTRACT

Objective: The purpose of this scoping review is to show the evidence available in the literature and provide an overview of the antimicrobial-containing mouthwashes for reducing viral load in order to group the most up-to-date information and make it more accessible to dentists.

Design: A structured electronic search in PubMed (Medline), LILACS, EMBASE and EBSCO without temporal restriction was performed. The studies were selected based on their title, abstract and full reading following a pre-established order based on the inclusion and exclusion criteria. The included studies were those that analyzed the effect of viral load reduction by mouthwashes, primary studies, no reviews and in Spanish, English or Portuguese.

Results: The search resulted in 1881 articles, at the end of the exclusion of duplicates and selection, 71 articles were included in this scoping review. The substances most commonly found were chlorhexidine (CHX), povidone-iodine (PVP-I), essential oils (EO), cetylpyridinium chloride (CPC), hydrogen peroxide (H2O2) and other substances (OTHERS).

Conclusion: Of all the mouthwashes analyzed, the Essential oils, Cetylpyridinium Chloride and Povidone-iodine, showed antiviral potential against common viruses present in the oral cavity, with no significant side effects in short-term use, and are viable options for use as a pre-procedure in clinical routine against SARS-CoV-2 and other types of viruses. The other solutions need further studies to determine their effect and confirm their clinical use.

Introduction

The pandemic of the new coronavirus SARS-CoV-2 revealed a gap in knowledge related to the battle against viruses. During dental treatment, the dentist can be exposed to different microorganisms from different sources, for example contaminated equipment, body fluids, blood, respiratory secretions and saliva. The main factors for this risk of infection are based on the application of disinfection and sterilization procedures that can reuse instruments/equipment, inappropriate use of PPE, as well as the use of diluted or expired disinfectants [1].

The search for substances that reduce viral load is very current and necessary. In dentistry, saliva is a contaminated fluid with numerous viruses and infectious potential that generates a great concern regarding care of biosecurity, both for professionals and patients [2].

Therefore, in this scenario, every patient must be treated as a potential carrier of the disease and source of transmission, in which each service must receive a high level of attention, following all appropriate and recommended procedures to reduce the risk of transmission of pathogens [1].

In addition to all the biosafety control and PPE that reduce the professional's contact with the viruses, it is important for the professional an alternative that reduces the presence of the virus in the oral cavity, being a pre-procedure rinse a viable alternative [3]. The WHO (World Health Organization) suggested the use of mouthwashes as a pre-procedure to provide a safer dental appointment, but there is no established protocol for their use with antiviral evidence of these substances. So it is important for the dentist and other health professionals to know how to reduce viral load with grouped and updated information. With this in mind this scoping review intends to show the evidence available in the literature and provide an overview of the effect of mouthwashes for reducing viral load in the mouth in order to unify the most up-to-date information and make this more accessible to dentists.

Methods

Study design

This is a scoping review to map the literature related with effectiveness of mouthwashes and viruses present in the oral cavity, conducted

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using the PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist [4].

Focused question

This scoping review intends to answer the following research question: Which substances used as mouthwash have antiviral activity against common viruses found in the oral cavity?

Search strategy

An electronic search in PubMed (Medline), LILACS, EMBASE and EBSCO without temporal restriction updated to September 2021, using a combination of the following Medical Subject Headings (MeSH) terms and Boolean operators, was performed: for PubMed - (Mouthwashes OR "Mouthwashes"[Mesh] OR mouthrinse OR gargling OR "oral rinse") AND (virus OR viruses OR viral OR viridae OR "viral load"); and for the other bases - (Mouthwashes OR mouthrinse OR gargling OR "oral rinse") AND (virus OR viruses OR viral OR viridae OR "viral load").

Eligibility criteria

The protocol was prepared after considerations, and pilot searches. Before the beginning of the study, a consensus was reached among all the authors, and a series of inclusion and exclusion criteria were defined.

Inclusion criteria

Studies that evaluated the reduction of viral load by mouthwashes against common viruses present in the oral cavity were selected. Primary studies (studies in humans and in animals, case reports and series, experimental laboratory studies) and letters to the editor that presented results of experimental studies were included. Studies published in English, Spanish or Portuguese were considered and there wasn't a date limit in the search.

Exclusion criteria

Studies where the main topic wasn't the description of reduction of viral load by mouthwashes against common viruses present in the oral cavity, systematic reviews, reviews, duplicate articles, books or book chapters and author comments/opinion articles.

Selection of the manuscripts

Results of literature search were analyzed in Zotero 4.0 software (Digital Scholarship, Vienna, Virginia, USA). Two researchers (ET, LM) independently screened titles/abstracts after duplicates removal from feb./21 to sep./21. Any conflict that arose were resolved by a third reviewer (SH). The same reviewers then evaluated full text articles and developed the charting table. Data was extracted, including the following: study ID (author and year of publication), study design *(in vitro* or *in vivo*), concentration tested, type of virus, methods (type of analysis or test) and results.

Results

The first search (Jan/2021) in the selected databases (PubMed, LILACS, EMBASE and EBSCO) resulted 1684 titles, after removing the duplicates (586), remained 1098 articles for reading the titles, of which 148 were selected for reading the abstract and full article. Two search updates were made (Jun/2021 and Sep/2021) and, in the first update with 136 articles, 35 duplicates were removed resulting in 101 works and 33 selected. The second update resulted in 61 titles, with the 52 duplicates [52] removed, it resulted in 9 articles, being selected 6 studies. In total, 187 works were selected for reading the full article. Of the 187 works, 71 articles were included in the review. A new title update was carried out in May 2022, resulting in a few new titles, all of them were related to SARS-CoV-2 and did not bring new information, so they were not included.

Data extraction was divided by commonly known substances: chlorhexidine (CHX), povidone-iodine (PVP-I), cetylpyridinium chloride (CPC), essential oils (EO), hydrogen peroxide (H2O2) and others (OTHERS) substances that are lesser known were allocated together.

Table 1 shows the distribution of the studies, with CHX and PVP-I were the substances more tested, followed by EO, CPC and H2O2. Table 2 presents the characteristics of the *in vitro* studies that had positive results and Table 3 shows all *in vivo* studies selected for the different substances.

Discussion

Several products are described in the literature with antiviral activity for some strains of viruses that commonly are present in the oral cavity and that possesses a possibility of use as pre-procedure mouthwash, such as Chlorhexidine, Povidone-iodine, Cetylpyridinium chloride, Essential oils, Hydrogen peroxide and other substances. For use in the oral cavity as pre-procedural, it is desirable that the mouthwash has an effect with 30 s to 1 min of exposure, low concentration, and that does not cause side effects. Many substances have been used in mouthwashes and are effective in controlling biofilm, reducing the counts of bacteria, helping to control gingivitis, but the effects in the virus present in the oral cavity is still unknown. The mechanisms of action of these substances have been discussed in others reviews [5–7].

Chlorhexidine

Chlorhexidine is a dicationic molecule that has a high substantivity with slow release and a longer period of action. Thanks to the property of its molecule, it has a great antibacterial action defined in the literature, also acting against fungi, yeasts and enveloped viruses due to virus membrane sensitivity [8–10]. Because of these characteristics and its routine use in the dentist's life, it is a possible option as a mouthwash to reduce the viral load present in the oral cavity.

The chlorhexidine solution at different concentrations was present in 22 articles, most of these studies were tested SARS-CoV-2, with 12 performed. Chlorhexidine has been tested with different concentrations and contact times.

With 30 s of contact time, *in vitro* studies had different results. An inactivation of more than 99.9% of the virus with a concentration of 0.2% was obtained [11], and a complete inactivation of SARS-CoV-2 virus replication and pseudotyped SARS-CoV-2 viruses with 0.12% was observed [12]. However, others studies observed little or no action on virus inactivation, even with 1 min of contact time or more [8,13–18].

The Chlorhexidine solution as a mouthwash was also tested *in vivo* and had divergent results, but most of them with positive results. In a two 2 arm study, most patients, who used 0.12% chlorhexidine mouthwash for 30 s associated with the use of nasal spray of the same solution in a determined protocol, resulted in testing negative in RT-PCR tests when compared to the control group without use. This study promoted the use of the same protective protocol for healthcare workers at one hospital and compared it with another group of workers at another hospital who did not use it, in the group that used the combination did not develop the infection and 50% of workers who did not use it (control group) had the disease [19]. The same concentration of 0.12% also obtained good results when testing the effect of the solution over time in 60 positive patients at different times (baseline, immediately after, 30 and 60 min after) with a significant reduction in viral load up to 60 min later [20]. On the other hand, no antiviral was verified against SARS-CoV-2, after patients gargling CHX at concentrations of 0.1% and 0.2%, respectively [21,22].

Table 1
Description of the number of studies included in the review that tested the different oral antiseptic solutions.

PRODUCT	NUMBER OF STUDIES	NUMBER OF STUDIES *in vitro*	NUMBER OF STUDIES *in vivo*
Chlorhexidine (CHX)	23	17	6
Povidone Iodine (PVP-I)	22	17	5
Essential oils (EO)	10	8	2
Cetylpyridinium chloride (CPC)	8	6	2
Hydrogen peroxide (H2O2)	7	5	2
Others substances (OTHERS)	13	8	5

Table 2
Evidence-based *in vitro* studies on the effect of oral rinses against different viruses.

Substance/ concentration	Viruses	Exposure time (s)	Virucidal effect (%)	Reference
CHX (0.12–0.2%)	SARS-CoV-2	30s	≥99.9	Jain, 2021
PVP-I (0.2–1%)	SARS-CoV-2	15s	>99.99	Hassandarvish et al., 2020
	SARS-CoV-2	30s	≥99.9	Meister et al., 2020
	SARS-CoV-2	30s	>99.99	Bidra et al., 2020
	SARS-CoV-2	30s	>99.99	Anderson, 2020
	SARS-CoV-2	60s	99.9	Jain, 2021
	SARS-CoV-2	60s	>99.99	Pelletier et al., 2021
	SARS-CoV-2	60s	≥99.99	Davies et al., 2020
	SARS-CoV; MERSCoV; Rotavirus; Influenza A	15s	≥99.99	Eggers et al., 2018
	MVA; MERS-CoV; HCoV-EMC/2012	15s	>99.99	Eggers, 2015
	HIV	30s	>99.99	Harbison e Hammer, 1989
	Influenza Herpes HIV	30s	≥ 99.99	Kawana et al., 1997
EO	SARS-CoV-2	30s	>99.9	Statkute et al., 2020
	SARS-CoV-2	30s	99.9	Meister et al., 2020
	SARS-CoV-2	60s	≥99.90	Davies et al., 2020
	HCoV-229E	60s	≥99.99	Meyers et al., 2020
	HIV-1 and HSV-1	30s	≥99.99	Baqui et al., 2001
CPC (0.0125–0.30%)	SARS-CoV-2	20s	≥99.90	Komine et al., 2021
	SARS-CoV-2	30s	≥99.90	Statkute et al., 2020
	HCoV-229E	30s	≥99.90	Green et al., 2020
	HCoV-229E	30s	≥99.90	Meyers et al., 2020
H2O2 (1.5–3.0%)	–	–	–	–
OTHERS				
BT / GT	SARS-CoV-2	10s	≥99.99	Ohgitani, 2021
(OCT) - 0.1%	SARS-CoV-2	15s	≥99.99	Steinhauer et al., 2021
DH - 0.2%	SARS-CoV-2	30s	>99.99	Komine et al., 2021
BKC	SARS-CoV-2	30s	>99.00	Meister et al., 2020
(HOCl) 0.01–0.02%	SARS-CoV-2	60s	≥99.99	Davies et al., 2020

These results show the divergence in the form of application of chlorhexidine solutions, in terms of concentration and contact time, as well as in the authors' conclusions. Although some studies report no antiviral action of Chlorhexidine against SARS-CoV-2 under the conditions tested, it is important to note that other authors have identified the effect of the solution *in vitro* and *in vivo*, being as a stimulus for carrying out studies with a greater number of people, in more controlled situations and testing different concentrations and exposure times.

Other studies used chlorhexidine with different viruses present in the oral cavity. HSV-1 and HIV-1 were investigated in concentrations of 0.12% and 0.2% and exposure time of 30 s, with a conclusion that CHX mouthwashes were effective against the HIV-1 and HSV-1 under the conditions tested [23]. The product completely inactivated the virus at concentrations greater than 0.2%, this effect seemed immediate, since the effectiveness of the antiviral action was not related to the contact time [23]. The use of 20% solution combined or not with administration of acyclovir against HSV-1, resulting in a significant reduction in viral titers with chlorhexidine in combination or not with the antiviral [24]. Another study with HSV-1 tested chlorhexidine *in vitro* and *in vivo*. The CHX solution was used *in vitro* as 0.01%, 0.05%, 0.1% and 0.2% at 0, 10, 20 and 60 min. *In vivo*, the 0.2% solution was used in 51 male albino mice with topical applications 5 times a day for 14 days with collections on day 6 and 8 after infection. The use of chlorhexidine was not effective and there was a significant cytotoxic activity [25]. CHX (concentration not informed) was investigated with different viruses, and products were mixed and incubated for various periods of time, showing inactivation of Rubella, Measles, Mumps virus and HIV, but was not effective against Adenovirus, Poliovirus (types 1 and 3), Rotavirus, Rhinovirus, and Influenza virus [26]. Poliovirus type 1 was also assessed in other two studies, the first with 0.05% concentration and the second without informing the concentration, at times of 15, 30 and 60 min for the first and 3 to 5 min for the other, CHX had no antiviral effect [27,28]. For the other viruses, the results were a little divergent. Only HSV had a considerable antiviral effect in 3 of 4 studies, even though it was only one tested *in vivo*, these results suggest the performance of randomized clinical studies to confirm these results and the possibility of use in clinical routine. HIV had 2 studies indicating an effect, but 2 reporting no effect. Rubella, Measles and Mumps virus only one study tested the effect, even though it is positive, more evidence is needed to indicate its use. For Adenovirus, Poliovirus (types 1 and 3), Rotavirus, Rhinovirus, Influenza virus, Sabin type 1, Human adenovirus, Coxsackie virus and Human coronavirus OC43), the results were negative for the antiviral effect of Chlorhexidine.

Chlorhexidine has antiviral effect against HSV and HIV and little antiviral effect in other viruses commonly present in the oral cavity, clinical studies are necessary to address the effect in reducing virus titer in the oral cavity.

Povidone-iodine

The povidone-iodine is a water soluble molecule composed of a polymer called polyvinylpyrrolidone and iodine. It was developed in the 1950s and it has been widely used as skin antiseptic and mouthwash due to its iodophor properties that confer a broad spec-

Table 3
Evidence-based *in vivo* studies on the effect of oral rinses against different viruses.

Substance/ concentration	Type of study	Participants/ virus	Rinsing protocol	Control	n	Analysis	Main results	Reference
CHX (0.12 - 0.2%)	PRC	SARS-CoV-2 positive	30 s/2x day - 4 days	No intervention	CHX = 66 Control = 55	Qualitative RT-PCR	Negative RT-PCR result CHX = 62,1% Control = 5,5%	Huang and Huang, 2020
	RCT	SARS-CoV-2 positive	30s	Distilled water	CHX = 27 Control = 9	Salivary Δ (Ct) value	CHX had a higher Δ*Ct value* compared to control.	Elzein, 2021
	PRCT	SARS-CoV-2 positive	30s	Distilled water	CHX = 8 Control = 9	Salivary (Ct) *value*/fold changes relative to the placebo and baseline	CHX reduced the viral load after 30 s rinsing and up to 60 min.	de Paula Eduardo, 2021
	RCT	SARS-CoV-2 positive	30s	Tap water	CHX = 6 Control = 2	Salivary (Ct) value	Rinsing with CHX did not reduce viral load.	Seneviratne et al., 2020
	PRCT	SARS-CoV-2 positive	2x day - 7 days	Chlorine dioxide (0.1%)	CHX = 20 Control = 20	Qualitative COVID antigen	Negative antigen result CHX = 8 Control = 12	Avhad et al., 2020
PVP-I (0.2 - 1%)	RCT	SARS-CoV-2 positive	30 s/3x day - 7 days	Tap water	PVP-*I* = 5 Control = 5	(Ct) value	Viral clearance was achieved in 100% using PVP-I, 20% (Tap water)	Mohamed et al., 2020
	RCT	SARS-CoV-2 positive	4x day - 5 days	Tap water	PVP-*I* = 12 Control = 12	Quantitative RT-PCR/viral Titers	PVP-I had no effect on reducing viral RNA over time. Viral titers reduced 75% (95% CI, 43%–95%) after 1 day compared to 32% (95% CI, 10%–65%) in control.	Guenezan et al., 2021
	RCT	SARS-CoV-2 positive	30s	Distilled water	PVP-*I* = 25 Control = 9	Salivary Δ (Ct) value	PVP-I was effective to reduce viral load in saliva, with ΔCt value higher than control.	Elzein, 2021
	RCT	SARS-CoV-2 positive	30s	Tap water	PVP-*I* = 4 Control = 2	Salivary (Ct) value	PVP-I reduced viral load only 6 h after rinsing compared with control.	Seneviratne et al., 2020
	PCP	SARS-CoV-2 positive	60 s/ 2x day	–	1	Qualitative RT-PCR	After 7 days, negative PCR for 1 gene.	Blasi, 2021
EO	RCT	SARS-CoV-2 positive	30 s/3x day - 7 days	Tap water	EO = 5 Control = 5	(Ct) value	Viral clearance was achieved in 80% for EO.	Mohamed et al., 2020
	RCT	Herpes (positive HSV I and HSV II)	30s	Sterile water	EO = 20 Control = 20	Salivary viral quantification - plaque assay (PFU/mL)	Rinsing with EO reduced salivary virus to zero after 30 s and remained at significant reduction at 30 and 60 min after application.	Meiller et al., 2005
CPC (0.0125–0.30%)	PRCT	SARS-CoV-2 positive	30s	Distilled water	CPC = 7 Control = 9	Salivary (Ct) value/fold changes relative to the placebo and baseline	CPC+Zn resulted in better reductions in viral load, with 20.4 ± 3.7-fold reductions after 30 s of rinsing.	de Paula Eduardo, 2021
	RCT	SARS-CoV-2 positive		Tap water	CPC = 4 Control = 2	Salivary (Ct) value	CPC reduced viral load 5 min and 6 h after rinsing compared with control.	Seneviratne et al., 2020
H2O2 (1,0–1,5%)	PRCT	SARS-CoV-2 positive	60s	Distilled water	H2O2 = 7 Control = 9	Salivary (Ct) value/fold changes relative to the placebo and baseline	Rinsing with HP resulted in 15.8 ± 0.08 fold reductions after 30 s.	de Paula Eduardo, 2021
	PCP	SARS-CoV-2 positive	30s	–	H2O2 = 10	Quantitative RT-PCR/Viral Titers	Gargling with 1% hydrogen peroxide did not decrease the intraoral viral load in SARS-CoV-2-positive subjects.	Gottsauner et al., 2020
OTHERS								
Sodium Bicarbonate - 7.5%	PCP	SARS-CoV-2 positive	30 s/7 days	–	10	Qualitative RT-PCR	Negative RT-PCR result after 1, 5 and 7 days of rinsing.	Kumar et al., 2021
Linola Sept® mouthwash	OS	SARS-CoV-2 positive	60s	–	34 = Experimental 5 = Temporal accompaniment	(Ct) value Viral load	The experimental solution reduced the viral load by about 90% in the saliva of most patients.	Schürmann et al., 2021
ARGOVIT1 AgNPs	PR	SARS-CoV-2 positive	15 - 30 s/3x day	Conventional mouthwash	114 = Experimental 117 = Control	Qualitative RT-PCR	The incidence of SARS-CoV-2 infection was lower in the experimental group = 1.8% (2 participants out of 114) compared to control 28.2% (33 participants out of 117).	Almanza-Reyes et al., 2021
Freshclor (CHD - Chlorine dioxide 0.1%)	PRCT	SARS-CoV-2 positive	3x day/7 days	CHD	CHX = 20 Control (CHD) = 20	Qualitative RT-PCR	Negative antigen result CHD = 12 CHX =8	Avhad et al., 2020
CDCM	RCT	SARS-CoV-2 positive	60 s/3x day/ 7 days	–	88 = CDCM 88 = Placebo	Quantitative RT-PCR	There was a greater median percentage decrease in salivary viral load in the CDCM group compared to the placebo group.	Carrouel et al., 2021

Subtitle: RCT - Randomized Controlled Trial; PRC - Prospective Randomized Cohort; PRCT- Pilot Randomized Clinical Trial; PCP - Prospective Clinical Pilot; PRC - Prospective Randomized.

Table 4
General characteristics of included studies that verified the effect of Chlorhexidine in different viruses. *When various substances were tested in the same work and the substance in question did not achieve the best result, the methods were exposed in the solution that achieved this.

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Jain, 2021	*in vitro*	Sigma Aldrich (CHX solution - 0.2% and 0.12%)	SARS-CoV-2	Antiviral assay: 2uL of SARS-CoV-2 virus stock prepared by cultivating virus using VeroE6 (pfu 2×107/mL) was mixed with 18 μL of the test sample. All the samples were incubated for 30 s and 60 s. The analysis of the virus inactivation was based on the quantification of viral RNA (cycle threshold [Ct] profile) present in the culture supernatant using qRT-PCR.	Chlorhexidine digluconate in 0.2% concentration (difference ct=12.5 $\pm$ 0.5) and PVP-I 1 (difference ct=11$\pm$2) inactivated more than 99.9% of SARS-CoV-2, in contact time of 30 s and 60 s respectively.
Steinhauer et al., 2021	*in vitro*	Chlorhexamed fluid 0.1% (CHX - 0.1%); Chlorhexamed forte alkoholfrei (CHX - 0.2%)	SARS-CoV-2	Antiviral assay: SARS-CoV-2 was incubated with medium or various oral rinses (CHX 0,1%, 0,2% and OCT 0,1%) for indicated concentrations (80% and/or 20%) and time-periods (15 s, 30 s, 1 min, 5 min, 10 min). Viral titres were determined upon limited end-point titration on Vero E6 cells. Tissue culture infectious dose 50% (TCID50/mL) was calculated according to Spearman-Karber.	CHX (formulations A and B) had only limited efficacy against SARS-CoV-2, at a concentration of 80% (v/v).The effect only occurs at prolonged time, after 1 min.
Xu et al., 2021	*in vitro*	Chlorhexidine gluconate (CHX - 0.12%)	SARS-CoV-2 / pseudotyped SARS-CoV-2	*	After the 30-min contact time, CHX 0,12% completely inactivated the virus replication of SARS-CoV-2 and of pseudotyped SARS-CoV-2 viruses.
Davies et al., 2020	*in vitro*	Ecolabs - Antiseptic Mouthwash (CHX 1 - 0.2%); GlaxoSmithKline - Corsodyl (CHX 2 - 0.2% Alcohol free)	SARS-CoV-2	*	Two chlorhexidine gluconate-based products were not effective at inactivating SARS-CoV-2.
Statkute et al., 2020	*in vitro*	Corsodyl (CHX - 0.2%)	SARS-CoV-2	*	CHX showed little antiviral effect, with $a < 2$log fold reduction
Komine et al., 2021	*in vitro*	GUM® PAROEX (CHX - 0.12% Mouthwash)	SARS-CoV-2	*	The mouthwash containing only 0.12% CHX as antiseptic did not show a sufficient inactivation effect against SARS-CoV-2 in this study.
Meister et al., 2020	*in vitro*	Chlorhexamed Forte (CHX - Not informed); Dynexidine Forte CHX - 0.2%	SARS-CoV-2	*	CHX mouthwashes were not effective against the virus under the conditions tested.
Avhad et al., 2020	*in vivo*	Guard OR - Mouthwash (CHX - 0.2%)	SARS-CoV-2	*	After 20 patients in each group gargling twice a day for one week, 12 remain positive for SARS-CoV-2 antigen from CHX group compared to 8 from Chlorine group.
Seneviratne et al., 2020	*in vivo*	Pearly White Chlor-Rinse (CHX - 0.2%)	SARS-CoV-2	*	Comparison of salivary Ct values of patients within each group of PI, CHX, CPC and water at 5 min, 3 h and 6 h time points did not show any significant differences.
Huang and Huang, 2020	*in vivo*	CHX comercial mouthwash- 0,12%	SARS-CoV-2	COVID-19 patient: It was a prospective randomized cohort study using CHX as an oral rinse and subsequent oropharyngeal spray in hospitalized patients with COVID-19. For one arm, the study group used 15 ml of 0.12% CHX for 30 s twice daily for 4 days. In the other arm, after rinsing with CHX, the patient used CHX spray in the oropharynx twice a day for 4 days. Treatment efficacy was verified by RT PCR after four days of chlorhexidine use. Healthcare worker: preventive effectiveness of using the same oral rinse regimen with CHX oral rinse and oropharyngeal spray twice a day in healthcare workers compared to healthcare workers from the same hospitals who did not use CHX.	COVID-19 patiente: There was a difference between the proportion of patients who tested negative after the use of chlorhexidine ($n = 66$) (62.1%) in relation to the control group ($n = 55$) (5.5%). Among patients who used a combination of oral rinse and oropharyngeal spray ($n = 93$), 86.0% eliminated oropharyngeal SARS-CoV-2, *versus* 6.2% of control patients ($n = 80$) after 4 days of treatment. Healthcare worker: The group that used chlorhexidine ($n = 15$) as a mouthwash and oropharyngeal spray twice daily did not develop SARS-CoV-2 infection, compared to a 50% rate among healthcare workers at their respective hospitals during the course of this study.

(*continued on next page*)

Table 4 (*continued*)

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Elzein, 2021	*in vivo*	CHX solution - 0.2%	SARS-CoV-2	61 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), randomly assigned to three groups: PVP-I group, CHX group, and distilled water as control group. Saliva samples collected at baseline and at 5 min post-application of mouth rinses/water. Samples subjected to SARS-CoV-2 RTePCR analysis. Outcome = delta Ct - change in cycle threshold (Ct) values of salivary SARS-CoV-2. Evaluation of the efficacy = difference in cycle threshold (Ct) value.	A significant difference was noted between the delta Ct of distilled water wash and each of the 2 solutions Chlorhexidine 0.2% (p=.0024) and 1% Povidone-iodine (p=.012). No significant difference between the delta Ct of patients using Chlorhexidine 0.2% and 1% Povidone-iodine solutions (p=.24). A significant mean Ct value difference (p<.0001) between the paired samples (before and after) in Chlorhexidine group (n = 27) and also in Povidone-iodine group (n = 25) (p<.0001) was found. No significant difference (p=.566) in the control group (n = 9).
de Paula Eduardo, 2021	*in vivo*	Periogard (CHX - 0.12%)	SARS-CoV-2	60 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), randomly assigned to two groups: placebo (oral rinsing with distilled water) group and other groups according to the type of mouthwash (CPC, CHX, HP, CHX-HP). Saliva samples collected at baseline (before rinsing), immediately after rinsing, 30 min and 60 min post-application of mouth rinses/water. Samples subjected to SARS-CoV-2 RTePCR analysis.	Mouthwash with CPC + Zinc and CHX resulted in significant reductions of the SARSCoV-2 viral load in saliva up to 60 min after rinsing, while HP mouthwash resulted in a significant reduction up to 30 mins after rinsing.
Ebrahimi et al., 2014	*in vitro*	Chlorhexidine solution (CHX - 0.001 - 0.002%)	HSV-1	*	CHX had anti-herpetic effect, with log reduction between 2 and 3log in virus titers.
Park, 1991	*in vitro*	Chlorhexidine gluconate solution (CHX - 20%)	HSV-1	Antiviral efficacy: Acyclovir and chlorhexidine (combined or alone) with different concentrations were tested on replication virus. Viral titers were verified by plaque assay technique. Effect on viral DNA synthesis: Vero cell monolayers were infected with HSV-1 F-strain/ cultivated with medium containing 5 umol/L of acyclovir, 10ug/ml chlorhexidine or both and total DNA extracted.	Antiviral efficacy: CHX (5, 8, 10, or 20 pg/ml) in combination with acyclovir resulted in viral titers significantly lower than were those by chlorhexidine or acyclovir alone. Effect viral DNA synthesis: 20 pg/ml of chlorhexidine or 5 pg/ml of acyclovir reduced by 11% and 75%; both acyclovir (5 pg/ml) and chlorhexidine (20 pg/ml), HSV-1 DNA synthesis was inhibited by 87%, whereas cellular DNA synthesis was not altered in comparison with that from the infected cultures receiving acyclovir or chlorhexidine alone.
Park and Park, 1989	*in vitro and in vivo*	Chlorhexidine gluconate solution (CHX - 20%)	HSV-1	Antiviral Assay: The virus titers were determined by plaque assay technique after exposure time (0, 10, 20 or 60 min) with CHX solution (0.01%, 0.05%, 0.1% or 0.2%) at 37 °C. *In vivo* infection: Fifty-one inbred male albino mice was inoculated with a viral solution (50 uL containing 5 × 105 PFU). Infected mice were divided into three equal groups, Group 1, control (no treatment); Group 2, topical application of 0.2% CHX was started 2 h after the viral infection; Group 3, topical application of 0.2% CHX was started 24 h after the viral infection. CHX was applied topically 5 times a day for 14 consecutive days. On days 6 and 8 post-infection, samples were collected and processed to determine viral titers.	CHX inhibited HSV-1 growth in a concentration-dependent manner: the higher the CHX concentration, the greater the inhibition. CHX at concentrations greater than 0.001% (10 bg/ml), showed significant cytotoxic activity. The treatment with CHX was not statistically significant.
Baqui et al., 2001	*in vitro*	Peridex (CHX - 0.12%); Sigma (CHX solution - 20%)	HIV-1 and HSV-1	*	After the 30-s contact time, undiluted 0.12% and 0.2% completely inhibited both HIV-1 and HSV-1. The antiviral effects of 0.12% and 0.2% of CHX were found to be similar.

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Table 4 (*continued*)

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Bernstein et al. 1990	*in vitro*	Peridex (CHX - 0.12%)	Herpes simplex virus (HSV), Cytomegalovirus (CMV), Influenza A, Parainfluenza, Polio, and Hepatitis B (HBV)	Antiviral assay: A mixture of mouthrinse (Peridex) containing 0.12% chlorhexidine gluconate (CH) or a placebo containing only excipients, no CH, were assayed with a virus suspension for 30 s, 5 min and 15 min. Aliquots were diluted and inoculated in appropriated tissue culture for each type of virus. The antiviral efficacy was determined by plaque enumeration stained with 1% crystal violet. For HBV virus, inactivation of the virus was tested by the assay of the virus-associated DNA polymerase activity during contact with active and placebo mouthrinses. The amount of DNA synthesized in a three-hour period was then estimated by the count of radioactivity in the trichloroacetic-acid-insoluble precipitate.	The virucidal effect occurred quite rapidly, with a 30-s exposure showing reductions of 59% for parainfluenza and of 99.7+% for CMV. Parainfluenza showed a 59% reduction at 30 s, a 91% reduction at 5 min, and a 99% reduction at 15 min. The percentage of reductions at 15 min ranged from >98% for influenza to >99.9% for HSV. The placebo had virtually no virucidal effectiveness, except against CMV, which showed a 70% reduction at 15 min. Neither the CHX containing mouthrinse nor the placebo was effective against the polio virus. DNA polymerase activity assays for HBV. This indicated that exposure of HBV to the placebo had little effect on DNA polymerase activity. However, exposure to the 0.12%-CHX mouthrinse significantly reduced HBV-DNA polymerase activity in 30 s (85% reduction), compared with the placebo. After 15 min of exposure to the CHX mouthrinse, HBV-DNA polymerase activity was decreased 99%, compared with the placebo.
Harbison e Hammer, 1989	*in vitro*	(CHX solution 20%)	HIV-1	*	Chlorhexidine gluconate completely inactivated HIV at concentrations of >0.2% (1:100 dilution of laboratory stock; 1:20 dilution of commercial stock). Inactivation appeared to be immediate since no difference in efficacy based on length of exposure to the microbicide was detected. Thus, both microbicides are highly effective at killing HIV *in vitro*.
Kawana et al., 1997	*in vitro*	Hibitane Concentrate (CHX - not informed)	Adenovirus (type 5), Mumps virus, Rotavirus, Poliovirus (type 1 and 3), Coxsackie virus (type B), Rhinovirus (type 14), Herpes virus (type 1), Rubella virus, Measles virus, Influenza virus (type A), HIV (type 1).	*	Rubella virus, Measles, Mumps virus and HIV were inactivated by CHX. CHX was not effective against Adenovirus, poliovirus type 1 and 3, Rotavirus, Rhinovirus and Influenza Virus.
Papageorgiu, Moccé-Llivina and Jofre, 2001	*in vitro*	Hibitane (CHX - not informed)	Poliovirus type 1	*	CHX had no effect on the number of polioviruses tested with either of the procedures.
Boudoma, M; Enjalbert; Didier, J. 1984	*in vitro*	Hibitane 5 (CHX - 0.05%)	Poliovirus type 1	*	After 15, 30 and 60 min, chlorhexidine had no effect on the virus.
Geller et al. 2010	*in vitro*	CHX - not informed	Coronavirus 229E (HCoV 229E)	Antiviral assay: Virus (HCoV 229E) and products (CHX or tested substances) were mixed thoroughly and incubated at RTa. Reductions in titres were measured by MTT and NR assay in L-132 cells.	*Antiviral assay:* CHX showed the best activity, induced a reduction of 0.8, 0.5, 1.4 and 2.1log10 at 10−4 mol/L concentration for contact times of 5, 15, 30 and 60 min, respectively, and 1.4, 2.1, 2.4 and 3 log10 reduction at 10−3 mol/ L for the same contact times (30 and 60 min).

trum of action [29,30]. The antiviral effect of PVP-I occurs when the molecule dissociates and releases free iodine that causes irreversible damage to the membrane, proteins and nucleic acids of microorganisms [29].

The over-the-counter commercial formulations are usually consumed at 1% PVP-I and it can be safely used in the oral mucosa in doses up to 10% [29]. With short-term use of PVP-I, adverse systemic effects are infrequent [31], and it has only a few contraindications, which include iodine allergy, thyroid disease, contact dermatitis, and pregnancy [29,32].

The virucidal efficacy of PVP-I was evaluated in laboratory studies against the coronavirus, mainly SARS-CoV-2. At concentrations ranging from 0,23% [33] to 1% or more, PVP-I solutions reduced >99.99% of viral titers after 30 s of treatment [34–36]. Davies et al. [13] and Pelletier et al. [37] found the same result (> 4log10 reduction of viral titre) after 1 min of treatment, using 0.58% and 1% PVP-I, respectively.

Table 5
General characteristics of included studies that verified the effect of Povidone-iodine in different viruses. *When various substances were tested in the same work and the substance in question did not achieve the best result, the methods were exposed in the solution that achieved this.

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Statkute et al., 2020	*in vitro*	Videne (PVP-I - 0.5%)	SARS-CoV-2	*	During a 30-s exposure, (PVP-I) eliminated the virus by 2–3-log10, but less than the recommended standards EN14476 (> 4-log10 reduction).
Jain, 2021	*in vitro*	PVP-I solution - 1%	SARS-CoV-2	*	PVP-I showed a level of antiviral effectiveness in the test, but less than CHX and showed the smallest relative changes in Ct values at 30 s. PVP-I 1% (difference ct=11±2) inactivated more than 99.9% of SARS-CoV-2, in contact time of 60 s.
Bidra et al., 2020	*in vitro*	Veloce Biopharma (PVP-I - 3.0%, 2.5%, and 1.0%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 15 and 30 s at RTa. Surviving virus from each sample was then quantified by standard endpoint dilution assay and the log reduction value of each compound compared to the negative control was calculated.	After the 15 s and 30 s contact times, PVP-I oral antiseptic rinse at all 3 concentrations of 0.5%, 1.25%, and 1.5% completely inactivated SARS-CoV-2.
Xu et al., 2021	*in vitro*	Povidone-Iodine (PVPI - 10% solution)	SARS-CoV-2 / pseudotyped SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 30 min at 37 °C. To assess the effect of mouth rinses, infection was determined by measuring fluorescence intensity after 24 h for replication competent viruses or luciferase activity after 48 h for pseudotyped viruses in HeLa-hACE2 cells.	After the 30-min contact time with virus, diluted povidone-iodine (0.5%), appeared to have potent antiviral activities, however, showed severe cytotoxicity to cells utilized.
Davies et al., 2020	*in vitro*	Povident (PVP-I - 0.58%) (surfactant-free)	SARS-CoV-2	*	PVP-I reduced SARS-CoV-2 titre by ≥ 4.1 log10 using unconcentrated TCF and ≥ 5.2 log10 using concentrated TCF.
Pelletier et al., 2021	*in vitro*	PVP-I solution - 1%, 1.5% and 3%	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 60 s at RTa. Reductions in titres were measured by standard end point dilution assay.	All concentrations of oral rinse antiseptics evaluated completely inactivated, reducing >4 log10 CCID50 infectious virus, from 5.3 log10 CCID50/0.1 mL to 1 log10 CCID50/0.1 mL or less the SARS-CoV-2 at 60 s of exposure.
Eggers et al., 2018	*in vitro*	Isodine (PVP-I - 7%)	SARS-CoV, MERSCoV, Rotavirus (strain Wa) and Influenza virus A (subtype H1N1)	Viruses (SARS-CoV-2, MERS-CoV, H1N1 and Rotavirus) and products were mixed thoroughly and incubated for 15 s RTa. Defined test conditions, including temperature, contact time and interfering substances, were performed according to virucidal quantitative suspension test EN14476:2013.	All viral titres were reduced by between 4.40 and 6.00 log10 TCID50/ml (corresponding to a reduction in viral titre of ≥ 99.99% for all viruses tested) after 15 s of contact time with PVP-I gargle at a concentration of 0.23% (1:30 *i.e.*, recommended dilution). The lower PVP-I concentrations of 0.023% (1:300 dilution) and 0.0023% (1:3000 dilution) that were tested against rotavirus and influenza did not reach a log10 reduction in viral titre ≥ 4, except for the 0.023% concentration against influenza under clean conditions.
Hassandarvish et al., 2020	*in vitro*	Betadine (PVP-I - 1%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 15, 30 and 60 s at RTa. Viral titres were calculated using the Spearman-Kärber method and reported as median tissue culture infectious dose (TCID50/ml).	The undiluted product (1%) achieved >5 log10 reduction in viral titres compared to the control at 15, 30 and 60 s under both clean and dirty conditions. At a two fold dilution (0.5% PVP-I), the test product demonstrated >4 log10 kill at 15 s and >5 log10 kill at 30 and 60 s in both clean and dirty conditions.
Anderson, 2020	*in vitro*	Betadine antiseptic solution (PVP-I - 10%), Betadine antiseptic skin cleanser (PVP-I - 7.5%), Betadine Gargle and mouthwash (PVP-I - 1.0%) and Betadine throat spray (PVP-I - 0.45%)	SARS-CoV-2 (hCoV-19/Singapore/2/2020)	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 30 s at RTa. Viral titres were calculated using the Spearman–Karber method and reported as median tissue culture infectious dose (TCID50)/mL.	The antiseptic solution, hand sanitiser, throat spray and gargle/mouthwash were non-cytotoxic to the Vero-E6 at dilutions ≥ 1:100 and skin cleanser at dilutions ≥ 1:1000; All four products achieved ≥ 99.99% virucidal activity against SARS-CoV-2, corresponding to ≥ 4 log10 reduction of virus titre, within 30 s of contact.

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Table 5 (*continued*)

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Bidra et al., 2020	*in vitro*	Veloce Biopharma (PVP-I - 0.5%, 1.0% and 1.5%)	(SARS-CoV-2) USA-WA1/2020	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 15 and 30 s at RTa (22 ± 2 ˚C). Surviving virus from each sample was quantified by standard end-point dilution assay and the log reduction value (LRV) of each compound compared to the negative (water) control was calculated.	At 15-s contact time, all of the PVP-I oral rinse antiseptics tested were effective at reducing >3 log10 CCID50 infectious virus (3.67 log10 CCID50/0.1 mL to 0.67 log10 CCID50/0.1 mL or less). At 30-s contact time, once again all of the PVP-I oral rinse antiseptics reduced >3.33 log10 CCID50 infectious virus (4.0 log10 CCID50/0.1 mL to 0.67 log10 CCID50/0.1 mL or less). No cytotoxicity was observed with any of the test compounds.
Meister et al., 2020	*in vitro*	Iso-Betadine mouthwash - Polyvidone-iodine- (PVP-I - 1.0%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly for 30 s at RTa. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay in Vero E6 cells.	The different SARS- CoV-2 strains (1–3) were susceptible to PVD-I, with ≥ 2,5log reduction factor after 30 s exposure.
Eggers, 2015	*in vitro*	Skin cleanser (PVP-I - 4%), Surgical scrub (PVP-I - 7.5%) and Gargle/mouthwash (PVP-I - 1%)	MVA; MERS-CoV-HCoV-EMC/2012	Virus (MERS-CoV, MVA) and product were mixed thoroughly and incubated for 15, 30, and 60 s for MVA, and 15 s for MERS-CoV at RTa. The virucidal activity was determined by the difference of the logarithmic titer of the virus control minus the logarithmic titer of the test virus.	For PVP-I mouthwash formulation, log10 reduction in viral titer ≥4 (99,99%) was demonstrated under clean and dirty conditions after only 15 s exposure undiluted for both viruses (MVA and MERS-CoV).
Meyers et al., 2020	*in vitro*	Betadine (PVP-I - 5%)	HCoV-229E	*	PVP-I was effective against the virus, eliminating 99,9% of virus and within 30 s and 99.99% (> 4log) within 2 min of exposure.
Boudoma, M; Enjalbert; Didier, J. 1984	*in vitro*	PVP-I solution - 5%	Poliovirus type 1	Virus (Poliovirus type 1) and product were mixed thoroughly and incubated for 15, 30, and 60 min at RTa. Titres of 15, 30 and 60 min were compared to the titre of control after 60 min incubation. All titrations were performed with plaque technique on 24-well plates.	PVP-I 5% were rapidly virucidal, reducing 5log10 after 15 min incubation.
Papageorgiu, Moccé-Llivina and Jofre, 2001	*in vitro*	Iodine Solution (IO - 2%)	Poliovirus type 1	Virus (Poliovirus type 1) and products were mixed thoroughly and incubated for 3 to 5 min at 22+- 2 ˚C. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay in Huh7 cells or Counting culturable viruses adsorbed to cellulose nitrate filters (the VIRADEN method).	The Iodine solution did inactivate viruses after exposure.
Harbison e Hammer, 1989	*in vitro*	Betadine solution I (10%), Betadine solution II (5%), Betadine douche (10%), Pharmadine solution (10%), Betadine medicated douche (10%), Betadine antiseptic gel (10%), Betadine standardized solution (10%), Betadine lubricating antiseptic gel (5%), Betadine scrub (7.5%), Betadine scrub II (5%)	HIV-1	Virus (HIV-1) and product were mixed thoroughly and incubated for 30, 60 and 10 min. at RTa. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay.	With the exception of the lubricating antiseptic gel, all povidone-iodine products completely inactivated the virus at concentrations of >0.5% (10- to 20-fold dilutions of stock).
Kawana et al., 1997	*in vitro*	Isodine solution, Isodine gargle, Isodine cream (PVP-I - 0.2 g/mL)	Adenovirus (type 5), Mumps virus, Rotavirus, Poliovirus (type 1 and 3), Coxsackie virus (type B), Rhinovirus (type 14), Herpes virus (type 1), Rubella virus, Measles virus, Influenza virus (type A), HIV (type 1).	Viruses and products were mixed thoroughly and incubated for various times at 25 ˚C. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay.	PVP-I was effective against all the virus species tested. PVP-I drug products, which were examined in these experiments, inactivated all the viruses within a short period of time. Measles had an irregular sensibility to PVP-I and were inactivated only within a long period of time exposure.

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Table 5 (*continued*)

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Mohamed et al., 2020	*in vivo*	Betadine (PVP-I - 1%)	SARS-CoV-2	Patients positive for SARS-CoV-2 (Stage 1 COVID-19), randomly assigned to four groups: PVP-I group, Essential oils group, Tap water group and no intervention as control group using the mouthwashes for 30 s, 3 times/day per 7 days. Nasopharyngeal and oropharyngeal swabs were taken at day 4, 6 and 12 of the intervention. The collected swabs were analyzed by RT-PCR using the commercial kit, LyteStarTM 2019-nCoV RT-PCR Kit 1.0 and following the manufacturer's recommendations	Five confirmed Stage 1 COVID-19 patients were included in each arm. Viral clearance was achieved in 100% using PVP-I, 20% (Tap water) and 0% (Control). There was no reporting of any side effects.
Seneviratne et al., 2020	*in vivo*	Betadine Gargle and Mouthwash (PVP-I - 0.5%)	SARS-CoV-2	*	Comparison of salivary Ct values of patients within each group of PI, CHX, CPC and water. The effect of decreasing salivary load was observed to be sustained at 6 h time point.
Guenezan et al., 2021	*in vivo*	Mylan (PVP-I 1%)	SARS-CoV-2	24 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), randomly assigned to a control group (no intervention, $n = 12$) or an intervention group ($n = 12$). Intervention consisted of 4 successive mouthwashes and gargles with 25 mL of 1% aqueous PI solution each, followed by one 2.5 mL nasal pulverization of the same solution into each nostril using an intranasal mucosal atomization device (4 times a day for 5 days). Follow-up was done on day 1 and then every 2 days until day 7 to assess the efficacy (viral quantification) and safety of the decolonization. Almost all (>95%) of the nasopharyngeal swabs were taken by the same skilled nurse at least 3 h after the last PI application for quantification of viral RNA using RT-PCR, and viral titer using the dilution limit method on Vero cells and the Spearman-Karber approach with a limit of detection of 10 tissue culture infectious dose (TCID50) per mL.	Use of PVP-I had no influence on changes of viral RNA quantification over time. Mean relative difference in viral titers between baseline and day 1 was 75% (95% CI, 43%−95%) in the intervention group and 32% (95% CI, 10%−65%) in the control group. Thyroid stimulating hormone elevation (median [IQR], 3.4 [2.6–4.3] mIU/L *vs* 2.1 [1.4–3.1] mIU/L at baseline) was observed in all patients after 5 days of PI exposure, exceeding the upper normal value in 5 patients, with a return to baseline values 7 to 12 days later. No modification in thyroid hormone (T3, T4) or creatinine levels was observed.
Blasi, 2021	*in vivo*	PVP-I solution - 1%	SARS-CoV-2	1 patient positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR) was told to inhale a 1% aqueous solution of PVP-I through each nostril until the liquid is perceived in the throat, followed by gargling with the same solution for 60 s, twice a day. SARS-CoV-2 real-time PCR tests were conducted: E gene (Pan Coronavirus screening); RdRP/S gene (2019-nCoV specific target gene); N gene (2019-nCoV specific target gene).	After further 24 h, all other symptoms disappeared. One week later, the real-time PCR test was positive only for gene N (2019-nCoV specific target gene).
Elzein, 2021	*in vivo*	PVP-I solution - 1%	SARS-CoV-2	*	A significant difference was noted between the delta Ct of distilled water wash (control) and 1% PVP-I (p=.012). No significant difference between the delta Ct of patients using 1% PVP-I solution (p=.24). A significant mean Ct value difference (p<.0001) between the paired samples (before and after) in the PVP-I group ($n = 25$) (p<.0001) was found. No significant difference (p=.566) in the control group ($n = 9$). PVP-I was effective against the virus under the conditions tested.

Table 6
General characteristics of included studies that verified the effect of Essential oils in different viruses. *When various substances were tested in the same work and the substance in question did not achieve the best result, the methods were exposed in the solution that achieved this.

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Statkute et al., 2020	*in vitro*	Listerine Cool Mint (ethanol 21.7%, thymol 0.064%, eucalyptol 0.092%, methyl salicylate 0.060% and menthol 0.042%), Listerine Advanced Gum Treatment (23% v/v ethanol, ethyl lauroyl arginate HCl (LAE) 0.147% w/w)	SARS-CoV-2	*	During a 30 s of exposure, the rinse containing ethanol/ethyl lauroyl arginate eliminated live virus to EN14476 standards (>4-log10 reduction), while another with ethanol/essential oils eliminated virus by 2–3-log10.
Xu et al., 2021	*in vitro*	Listerine Antiseptic Original (eucalyptol 0.092%, menthol 0.042%, methyl salicylate 0.06%, thymol 0.064%)	SARS-CoV-2 / pseudotyped SARS-CoV-2	Viruses (SARS-CoV-2 and Pseudotyped SARS-CoV-2) and products were mixed thoroughly and incubated for 30 min at 37 °C. To assess the effect of mouthrinses, infection was determined by measuring fluorescence intensity after 24 h for replication competent viruses or luciferase activity after 48 h for pseudotyped viruses in HeLa-hACE2 cells.	After the 30-min contact time, diluted listerine completely inactivated the virus replication of SARS-CoV-2 and of pseudotyped SARS-CoV-2 viruses, with minimal cytotoxicity.
Davies et al., 2020	*in vitro*	Listerine Advanced Defense Sensitive (1.4% dipotassium oxalate); Listerine Total Care (eucalyptol, thymol, menthol, sodium fluoride and zinc fluoride)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 1 min at 20 ± 2 °C. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay in Vero E6 cells.	Both formulations of Listerine (Listerine Advanced Defense Sensitive and alcohol-free Listerine Total Care) reduced SARS-CoV-2 titre to below the limit of detection for the tests after a 1 min treatment: ≥3.5 log10 reduction for Listerine Advanced Defense Sensitive and ≥4.1 log10 reduction for Listerine Total Care, respectively.
Meister et al., 2020	*in vitro*	Listerine Cool Mint (ethanol 21.7%, thymol 0.064%, eucalyptol 0.092%, methyl salicylate 0.060% and menthol 0.042%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly for 30 s at RTa. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay in Vero E6 cells.	Listerine Cool Mint significantly reduced viral infectivity to up to 3 orders of magnitude to background levels after 30 s exposure time.
Meyers et al., 2020	*in vitro*	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%) and Antiseptic Mouthwash (eucalyptol 0.092%, menthol 0.042%, methyl salicylate 0.06%, thymol 0.064%)	HCoV-229E	Virus (HCoV-229e) and product were mixed thoroughly and incubated for 30 s, 1 min, or 2 min at RTa. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay in Huh7 cells.	Listerine Antiseptic was able to decrease the infectious virus levels by greater than 4 log10, or greater than 99.99%. After incubation times of 1 and 2 min we were unable to detect any remaining infectious virus. Listerine Antiseptic, Listerine Ultra, Equate and Antiseptic Mouthwash all showed slightly lower efficacy, particularly at the shorter contact times, and Equate showed the greatest variability. However, the Listerine-like (same composition) mouthwashes/gargles decreased infectious virus titers by greater than 99%.
Yamanaka et al., 1994	*in vitro*	Listerine; Cool Mint Listerine (dilution 50% and 5%)	HIV (HTLV-IIIB)	Virus (HIV) and product were mixed thoroughly and incubated for 10, 20 or 30 s at RTa. Reductions in titres were measured by using the kit HIVAG-1 (P24 ANTIGEN) in CD4 cells.	The results showed that Listerine and Cool Mint Listerine were almost identical. Exposure for 30 s to 50% of Listerine inactivated more than 60% of HIV.
Baqui et al., 2001	*in vitro*	Listerine Antiseptic (LA) and Tartar control Listerine Antiseptic (TLA)	HIV-1 and HSV-1	Viruses (HIV-1 and HSV-1) and products were mixed thoroughly for 30 s at RTa. Reductions in titres were measured by inhibition of the syncytia formation or the cytopathic effect (CPE) for HIV-1 on MT-2 cells and by inhibition of the plaque formation for HSV-1 on Vero cell monolayers.	After the 30-s contact time, LA and TLA completely inhibited both HIV-1 and HSV-1. LA and TLA inhibited HSV-1 up to 1:2 dilution. The antiviral effects of LA and TLA were found to be similar.

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Table 6 (*continued*)

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Dennison et al., 1995	*in vitro*	Listerine Antiseptic (diluted)	HSV-1 (14–012), HSV-2 (333–8–9), Rotavirus (SA-11), Influenza A (H1N1), Adenovirus type 5 (Strain Adenoid 75)	Viruses (Herpes simplex virus type 1 and type 2, Rotavirus, Influenza A virus (H1N1) and Adenovirus type 5) and product were mixed thoroughly and incubated for 30 s, 2 min, and 5 min at 37 ˚C. For assessment of direct toxicity a confluent monolayer of Vero cells was used, and for inhibition of growth a monolayer was used that was 60% to 70% confluent.	Listerine at a dilution greater than or equal to 1:100 did not have a cytopathic effect or inhibit the growth of any of the cells used in the virucidal assays. The number of plaques formed by HSV-1 was reduced by 96.3% when the virus was exposed to Listerine for 30 s. Exposure to Listerine for 2 min resulted in 100% reduction of infective HSV-1, and 5 min of exposure resulted in 97.6% reduction of PFUs per well. Exposure of HSV-2 to Listerine for all time periods tested inactivated the virus. Thus a 100% reduction in HSV-2 plaques was seen at 30 s, 2 min, and 5 min. The number of plaques formed by Rotavirus was reduced by 12.2% when the virus was exposed to Listerine for 30 s. Exposure to Listerine for 2 min reduced the number of plaques by only 5.7%. After 5 min of exposure virus infectivity for the experimental group was higher, with 21.5% more plaques in groups treated with Listerine than in the virus group not treated with Listerine. Exposure of Influenza to Listerine effectively eliminated the infectivity of virus for all Listerine exposure periods tested. Exposure of Adenovirus to Listerine for 5 min resulted in a 33.4% reduction in the vero cell cytopathic effect. Adenovirus infection reduced the confluent vero monolayer of cells from 99.4% -+ 0.9% coverage to 25.1% -+ 15.5% after 3 days; with exposure of the adenovirus to Listerine for 5 min, 49.9% -+ 14.8% of the monolayer remained.
Mohamed et al., 2020	*in vivo*	Listerine® Original	SARS-CoV-2	*	This preliminary study showed that regular gargling with 1% PVP-I and Essential oils formula have the potential for achieving early SARS-CoV-2 viral clearance among stage 1 COVID-19 patients. Viral clearance was achieved in 100%, 80%, 20% and 0% for 1% PVP-I, essential oils, tap water gargle and control group respectively. There was no reporting of any side effects.
Meiller et al., 2005	*in vivo*	Listerine Antiseptic Cool Mint (eucalyptol 0.091%, menthol 0.042%, thymol 0.063%)	HSV-I and HSV-II	Patients with Herpes (direct immunofluorescence of cytological smears of the lesions/oral fluids was used to confirm Herpes simplex virus types I or II), randomly assigned to treatment groups: active ingredient and sterile water as control group. Salivary fluid samples were taken: (1) at baseline; (2) immediately following a 30 s rinse; (3) 30 min. after the 30 s rinse; and (4) on the repeat trial, also at 60 min. after the 30 s rinse. All samples were evaluated for viral titer and results compared.	In both Trials 1 (30 min) and 2 (60 min), recoverable infectious virions were reduced to zero after a 30 s experimental rinse (Listerine); whereas, the control rinse (sterile water) resulted in a non-significant ($p>.05$) reduction. The experimental group also demonstrated a continued significant ($p>.05$) reduction 30 min post rinse when compared with baseline while the control group returned to baseline levels. In Trial 2, the 60 min post rinse follow-up demonstrated a 1–2 log residual reduction from baseline in the experimental group; however, this was not significant.

Table 7
General characteristics of included studies that verified the effect of Cetylpyridinium chloride in different viruses. *When various substances were tested in the same work and the substance in question did not achieve the best result, the methods were exposed in the solution that achieved this.

STUDY	STUDY TYPE	CONCENTRATION	VÍRUS	METHODS	RESULTS
Statkute et al., 2020	*in vitro*	SCD Max (CPC - 0.1%); Dentyl Dual Action (CPC 0.05%–0.1%); Dentyl Fresh Protect (CPC 0.05%–0.1%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 30 s at RTa. Reductions in titres were measured onto VeroE6 cells transduced with Lentivirus vectors expressing ACE2 and TMPRSS2.	During a 30 s exposure, two rinses containing cetylpyridinium-chloride eliminated the live virus to EN14476 standards (>4-log10 reduction).
Muñoz-Basagoiti et al., 2021	*in vitro*	Perio Aid Intensive Care (with 1.47 mM of CPC + 1.33 mM of Chlorhexidine) and Vitis CPC Protect (CPC - 2.063 mM)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 2 min at RTa. Collected viruses were titrated on Vero E6 cells to calculate the Tissue Culture Infectious Dose 50% (TCID50) per ml after each of the treatments.	CPC has antiviral activity against SARS-CoV-2 and CPC-containing mouthwashes have the capacity to reduce 1000 times the infectivity of a viral stock when treated at a 1:1 ratio for 2 min.
Komine et al., 2021	*in vitro*	GUM® WELL PLUS Dental rinse (alcoholic type)(CPC - 0.05%); GUM® WELL PLUS Dental rinse (non-alcoholic type)(CPC - 0.05%); GUM® WELL PLUS Dental paste [CPC toothpaste - 0.05% (1/4 slurry with ultrapure water: 0.0125% CPC]; GUM® Disinfection spray for mouth/throat (CHX - 0.06% + CPC 0.05% mouthwash); GUM® PAROEX (CHX 0.12% + CPC 0.075% mouthwash); GUM® Oral Rinse (CPC - 0.075%); GUM® MOUTHWASH HERB 2020 (CPC - 0.04%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 20 s, 30 s or 3 min at 25 °C. The viral infectivity titer was expressed in PFU/mL. Three independent experiments were performed.	All the products containing 0.0125 to 0.30% CPC inactivated SARS-CoV-2 with a reduction of 3.3 to >4.4Log10 PFU/mL regardless of dosage form.
Green et al., 2020	*in vitro*	CPC solution - 0.07%	HCoV-229E	Virus (Human CoV-SARS 229E) and product were mixed thoroughly and incubated for 30 s and 1 min at RTa. The post exposure infectivity TCID50 (50% tissue culture infectious dose) was determined using the Quantal test (Spearman -Kärber method) - mean log10 reduction as the difference in TCID50.	After 30 s and 1 min of exposure, only 0.07% CPC induced a reduction in viral count (≥99.9%) of Human CoV-SARS 229E in this *in vitro* test.
Meyers et al., 2020	*in vitro*	Crest Pro-Health (CPC - 0.07%)	HCoV-229E	*	After the contact time, Crest Pro-Health (mouthwash containing CPC) decreased infectious virus by at least 3 log10 to greater than 4 log10, or 99.9% to more than 99.99%.
Alvarez et al., 2020	*in vitro*	CPC solution (CAS 123–03–5, Merck)	HSV-1 (KOS); HSV-1 (K26-GFP); HSV-2 (333) ZAG GFP	For assessing the antiviral effect of CPC on the formation of PFUs, Vero cells or gingival fibroblasts were cultured in 24-well plates and infected with HSV-1, HSV-2, ACVR-HSV-1 or ACVR-HSV-2 for 1 h and then immediately after treated with CPC for 10 min. PFUs were determined directly in the cultures at 24 h.p.i. using a fluorescence microscope.	After the contact time (10 min) CPC treatment reduced the amount of HSV-1 and HSV-2 genome copies in Vero cells and gingival fibroblasts. Cells infected with either virus and then treated with CPC produced significantly less PFUs and viral titers after HSV-1 and HSV-2 infection, when compared to untreated cells.
Seneviratne et al., 2020	*in vivo*	Colgate Plax mouthwash (CPC - 0.075%)	SARS-CoV-2	16 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), randomly assigned to four groups: PVP-I group ($n = 4$), CHX group ($n = 6$), CPC group ($n = 4$) and water as control group ($n = 2$). Saliva samples collected at baseline and at 5 min, 3 h, and 6 h post-application of mouth rinses/water for 30 s. Samples subjected to SARS-CoV-2 RTePCR analysis.	There was no statistically significant difference when comparing the salivary Ct values of the patients within each test and water group in the times. However, when the change in Ct value in each of the patients in the CPC group was compared with the patients in the water group at the respective time points, a significant increase was observed in the patients in the CPC group at 5 min and 6 h.
de Paula Eduardo, 2021	*in vivo*	Colgate Total 12 (CPC - 0.075% + Zinc lactate 0.28%)	SARS-CoV-2	60 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), randomly assigned to two groups: placebo (oral rinsing with distilled water) group and other groups according to the type of mouthwash (CPC, CHX, HP, CHX-HP). Saliva samples collected at baseline (before rinsing), immediately after rinsing, 30 min and 60 min post-application of mouth rinses/water. Samples subjected to SARS-CoV-2 RTePCR analysis.	Mouthwash with CPC + Zinc resulted in significant reductions of the SARS-CoV-2 viral load in saliva up to 60 mins after rinsing.

Table 8
General characteristics of included studies that verified the effect of Hydrogen Peroxide in different viruses. *When various substances were tested in the same work and the substance in question did not achieve the best result, the methods were exposed in the solution that achieved this.

STUDY	STUDY TYPE	CONCENTRATION	VÍRUS	METHODS	RESULTS
Bidra et al., 2020	*in vitro*	H2O2 solution - 1.5% and 3%	SARS-CoV-2	*	The H2O2 solutions at concentrations of 1.5% and 3.0% showed minimal virucidal activity after 15 s and 30 s of contact time.
Xu et al., 2021	*in vitro*	Colgate Peroxyl (H2O2 - 1.5%)	SARS-CoV-2 / pseudotyped SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated (the time depends on the product). Reductions in titres were measured by CellTiter 96® AQueous One Solution Cell Proliferation Assay in HeLa-hACE2 and TR146 cells.	After the 30-min contact time with virus, diluted Colgate Peroxyl, significantly inactivated viruses but their antiviral effects were associated with severe cytotoxicity.
Davies et al., 2020	*in vitro*	Peroxyl (H2O2 - 1.5%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 1 min at 20 ± 2 °C. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay in Vero E6 cells.	Peroxyl was ineffective in reducing virus titer after 1 min of exposure
Meister et al., 2020	*in vitro*	Cavex Oral Pre Rinse (H2O2 - 1.5%)	SARS-CoV-2	Virus (SARS-CoV-2) and product were mixed thoroughly and incubated for 30 s at RTa. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay by crystal violet staining and subsequent scoring of the amounts of wells displaying cytopathic effects in Vero E6 cells.	Cavex Oral pre Rinse was not effective against the tree strain virus under the conditions tested.
Meyers et al., 2020	*in vitro*	Peroxide Sore Mouth Cleanser (H2O2 - 1.5%); H2O2 diluted in 1.5% PBS (H2O2 - 1.5%); Orajel Antiseptic Rinse (H2O2 - 1.5%, Menthol 0.1%)	HCoV-229E	*	After the 30 s, 1 min and 2 min of exposure, the three products with H2O2 as their active ingredient all demonstrated similar abilities to inactivate HCoV, replicate assays showed some variability but overall the reduction of infectious virus ranged from lower than a 1 log10 reduction to a 2 log10 reduction or <90% to 99%.
Gottsauner et al., 2020	*in vivo*	H2O2 solution - 1%	SARS-CoV-2	10 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), were tested with hydrogen peroxide mouthwash (1%) for 30 s. Saliva samples collected at baseline and at 30 min post-application of mouth rinses. Samples subjected to SARS-CoV-2 RT-PCR analysis.	There was no statistically significant difference between baseline viral load and viral load after 30 min 1% hydrogen peroxide rinsing.
de Paula Eduardo, 2021	*in vivo*	Peroxyl (H2O2 - 1.5%), Peroxyl + PerioGard (H2O2 - 1.5% + CHX - 0.12%)	SARS-CoV-2	*	Mouthwash with CPC + Zinc and CHX resulted in significant reductions of the SARSCoV-2 viral load in saliva up to 60 mins after rinsing, while HP mouthwash resulted in a significant reduction up to 30 mins after rinsing.

Other studies verify some virucidal activity within after 30 s of treatment, but with only the elimination of 2–3log10 (99,9%) viral titres [35,8,11,17]. Potent antiviral activities with diluted povidone-iodine solutions were also verified, but only after 30-min contact time with the virus [12].

Five selected studies evaluated antiviral activity PVP-I solutions *in vivo* against SARS-CoV-2 with different approaches and results. Mohamed et al. [39] and Guenezan et al. [38] followed positive SARS-CoV-2 patients using the PVP-I solution and compared the *Ct value* (cycle threshold) of RT PCR with positive patients who rinsed with water (control). They showed 100% viral clearance after 6 days in 5 confirmed stage 1 COVID-19 patients using 1% PVP-I, 30 s, 3 times/day [39]. The other study followed positive patients (n = 12) for up to 7 days who used 1% aqueous PVP-I solution (4 successive mouthwashes and also nasal spray of the same solution - 4 times a day for 5 days) and did not find changes in viral RNA quantification over time of PVP-I [38].

Two studies *in vivo* analyzed the antiviral effectiveness and the duration of the effect after one mouthwash. Compared *Ct value* of RT-PCR salivary sample from 16 SARS-CoV-2 positive patients that rinsed PVP-I ($n = 4$) for 30 s before application (baseline) and 5 min, 3 h and 6 h post-application of mouthrinses (including PVP-I group) with control (water). It was only observed a reduction of viral load increase (*Ct value*) after 6 h [40]. Elzein et al. [41] found that SARS-CoV-2 positive patients rinsing with 1% PVP-I solution ($n = 25$) for 30 s was effective in reducing viral load in salivary samples after 5 min of mouthwash compared with control/water ($n = 9$). This result indicates that 1% povidone-iodine oral solutions are effective pre-procedure mouthwashes against salivary SARS-CoV-2 in dental treatments. In a clinical case with one positive COVID-19 patient who inhaled an aqueous solution of PVP-I at 1%, followed by gargling with the same solution for 60 s, twice a day, SARS-CoV-2 target gene was detected only 7 days later [42].

Another coronavirus has also demonstrated susceptibility to PVP-I. Reductions in viral titer ≥ 4log10 (99.99%) were found after only 15 s of exposure to both viruses MERS-CoV, HCoV-EMC/2012 and SARS-CoV-2 [43,33]. The other strain HCoV-229e was eliminated after 2 min of treatment [44].

Table 9
General characteristics of included studies that verified the effect of Others substances in different viruses. *When various substances were tested in the same work and the substance in question did not achieve the best result, the methods were exposed in the solution that achieved this.

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Steinhauer et al., 2021	*in vitro*	Octenidine dihydrochloride (OCT) - 0.1%	SARS-CoV-2	*	Octenidine dihydrochloride, due to cytotoxicity, was performed in large volume plating (LVP) experiments, and results showed a reduction of viral titres by 4.38 log10 after 15 s, being effective against SARS-CoV-2.
Davies et al., 2020	*in vitro*	OralWise (stabilized hypochlorous acid) - 0.01–0.02%	SARS-CoV-2	*	After the 1 min contact time, OraWize+, a product containing 0.01–0.02% hypochlorous acid (HOCl) as its active ingredient, reduced virus titre in unconcentrated TCF by ≥5.5 log10 TCID50 ml–1, to below the limit of detection for the assay.
Almanza-Reyes et al., 2021	*in vitro and in vivo*	Silver nanoparticles - 1% (0.6 mg/mL metallic silver)	SARS-CoV-2	To determine the efficacy of AgNPs against SARS-CoV-2 *in vitro*, they first analyzed its cytotoxicity on cultured Vero E6 cells. To analyze the effect of AgNPs on virus infectivity Vero E6 cells were infected with a fixed amount of virus and different concentrations of AgNPs, starting at 0.03%, were added to cells. At 72 h post-infection supernatants were collected and titrated in order to determine virus yields normalized to those reached in medium alone. Prospective randomized study of 231 participants that was carried out for 9 weeks. They were instructed to mix 4 to 6 spray shots of this solution with 20 mL of water and to gargle with the obtained solution for 15 to 30 s at least 3 times a day, also nasal lavages with the same solution using a cotton swab twice a day. As a second option, they were instructed to cover evenly the oral cavity with the spray shots of solution without its previous dilution in water. Participants of the control group were instructed to do mouthwash and nose rinse with a conventional mouthwash the way they normally did before the study.	AgNPs is effective against SARS-CoV-2, but didn't totally abolish viral production, infection was clearly controlled to some extent with a reduction of about 80% at a concentration of 0.03%. The incidence of SARS-CoV-2 infection ($p = .000$), was significantly lower in the experimental group *vs* the control group, where 1.8% (2 participants out of 114) and 28.2% (33 participants out of 117) were infected respectively. No adverse reactions were reported.
Ohgitani, 2021	*in vitro*	Black and green tea (TFDG and TSA) - 500 μM	SARS-CoV-2 (Japan/AI/I-004/2020)	Virus suspension (SARS-CoV-2) in saliva was treated with black tea or distilled water for 10 s. Reductions in titres were measured by using the tissue culture infectious dose 50 (TCID50) assay in VeroE6 cells.	After the 10 s contact time, it was clearly shown that both black and green tea significantly declined the titer of the virus in saliva. Virus titers in culture supernatants were either not detected or significantly lower compared with the titer of secondary virus released from the cells infected with intact virus.
Komine et al., 2021	*in vitro*	Delmopinol hydrochloride - 0.2%	SARS-CoV-2	*	After the 30 s contact time, mouthwash containing 0.20% delmopinol hydrochloride inactivated SARS-CoV-2 with a >5.4 Log10 PFU/mL reduction.
Meister et al., 2020	*in vitro*	Dequonal (Dequalinium chloride, benzalkonium chloride) - (BKC); Octenident mouthwash (Octenidine dihydrochloride) - (OCT); ProntOral mouthwash (Polyaminopropyl biguanide polyhexanide) - (PBP) - concentration not informed	SARS-CoV-2	*	The different SARS-CoV-2 strains (1–3) were susceptible to BKC with ≥2,5log reduction factor after 30 s exposure, but not to OCT and PBP.
Ebrahimi et al., 2014	*in vitro*	Irsha - diluted solution: 0.05%, 0.5%, 0.2%, 0.1%, 2.0%, 1.0%, 5.0%, 10%, 20%, 50% and 100%	HSV-1	Virus (HSV-1) and different concentrations of product were mixed thoroughly at RTa. Reductions in titres were measured by using the colorimetric test MTT in Vero cells.	CC50 for Irsha was 0.38%. All concentrations had inhibitory effects. The maximum and minimum logarithms of virus titer were observed at concentrations of 0.1% and 0.5% respectively. The highest virus titer was found with 0.1% Irsha. There was no significant difference between 0.1 and 0.2 Irsha concentrations ($p = .918$). There was a statistically significant difference between the 0.5% Irsha concentration with each of the 0.2% and 0.1% concentrations of this. mouthwash ($p = .002$).

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Table 9 (*continued*)

STUDY	STUDY TYPE	CONCENTRATION	VIRUS	METHODS	RESULTS
Lee et al., 2014	*in vitro*	C31G and mouthrinse containing C31G (Sense-Time) - 3%	H1N1 and H3N2	Virus (H1N1 and H3N2) and product were mixed thoroughly and incubated for 30 min at 4 °C. Infectious viral titers within the diluted mixtures were calculated from three replicates using the method of Spearman-Karber	After the 30 min contact time, the C31G solution showed a higher virucidal activity. C31G completely inactivated all of the tested viruses at their commercial concentration.
Avhad et al., 2020	*in vivo*	Freshclor (Chlorine dioxide 0.1%)	SARS-CoV-2	40 patients were provided with Chlorhexidine gluconate (0.2%) mouthwash and Chlorine dioxide (0.1%) mouthwash to rinse and gargle thrice a day for one week. The qualitative COVID antigen test confirmed by Qualitative PCR on an oropharyngeal swab collected from the patients was compared for both the groups at baseline and post-intervention levels.	After 20 patients in each group gargling thrice a day for one week, 12 remain positive for SARS-CoV-2 antigen from CHX group compared to 8 from Chlorine group.
Kumar et al., 2021	*in vivo*	Sodium Bicarbonate - 7.5%	SARS-CoV-2	10 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), patients received 7.5% sodium bicarbonate gargle and were instructed to gargle for 7 days by taking 20 mL of solution and perform gargle for at least 30 s. The clinical condition and laboratory evaluation were monitored using inflammatory markers like ferritin, lactate dehydrogenase (LDH), procalcitonin, and D-dimer from day 0 up to day 7. On the 5th day and 7th day after the study, nasopharyngeal and oropharyngeal swab samples for doing RT-PCR were obtained.	7.5% sodium bicarbonate 25 mL gargle statistically showed nonsignificant p-value for all of the studied variables. However, the PCR results were negative on 24 h, on day 5 and day 7.
Schürmann et al., 2021	*in vivo*	Biorepair® Zahnmilch (aqua, sorbitol, xylitol, zinc hydroxyapatite, cellulose gum, zinc pca, 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) - concentration not informed	SARS-CoV-2	34 SARS-CoV-2 positive hospitalized patients were recruited for an observational study. The patients gargled the mouthwash for 1 min. Directly before and 5 min after gargling pharyngeal swabs using a standardized protocol were taken and sent for SARS-CoV-2 analysis. To investigate the time course of viral load development after gargling, additional pharyngeal swabs were taken from five patients after 2 h, 4 h and 6 h. Real-time polymerase chain reaction (RT-qPCR) for SARSCoV-2 was performed. The viral loads of the patients obtained in this way (before and after rinsing and over the following hours) are used to calculate the reduction in viral load and the relative reduction of viral load for each patient.	The clinical pilot study demonstrated that the mouth rinsing solution was able to reduce the viral load by about 90% in the saliva of most patients [the mean values show an increase of the Ct-values of 3.1 (standard deviation 3.6)]. This reduction was determined to persist for about 6 h. In the experimental solutions, the ingredients dexpanthenol and zinc were able to reduce the expression of proinflammatory cytokines in the cell culture model, while the antiviral response was not altered significantly.
Carrouel et al., 2021	*in vivo*	CDCM: B-cyclodextrin (0.1%) and Citrox (0.01%)	SARS-CoV-2	176 patients positive for SARS-CoV-2 (nasopharyngeal virus detection by PCR), randomly assigned to two groups: CDCM or placebo. Saliva sampling was performed on day 1 at 09.00 (T1), 13.00 (T2) and 18.00 (T3). In the following 6 days, one sample was taken at 15.00. Quantitative RT-PCR was used to detect SARS-CoV-2.	The results demonstrated that, over the course of 1 day, CDCM was significantly more effective than placebo 4 h after the first dose, with a median percentage (log10 copies/mL) decrease T1-T2 of −12.58%. The second dose maintained the low median value for the CDCM (3.08 log10 copies/mL; IQR 0–4.19), compared with placebo (3.31 log10 copies/mL; IQR 1.18–4.75). At day 7, there was still a greater median percentage (log10 copies/mL) decrease in salivary viral load over time in the CDCM group compared with the placebo group.

The virucidal activity of povidone-iodine was analyzed and tested in other viruses only *in vitro* and the potential use with positive results was considered for HIV, Influenza and Herpes viruses that showed susceptibility with low concentration solutions (0,5–1%) and short exposure time (30 s-1 min). The virucidal activity of povidone-iodine was analyzed and tested in other viruses only *in vitro* and the potential use with positive results was considered for HIV, Influenza and Herpes viruses that showed susceptibility with low concentration solutions (0,5–1%) and short exposure time (30s-1 min). Study that analyzed PVP-I at different concentrations and exposure times *versus* enveloped and non-enveloped viruses (HIV, Herpes, Influenza, Adenovirus, Mumps virus, Measles, Rotavirus, Rhinovirus, Rubella) found effective virucidal action with an application of 0.5% concentration for Influenza, Herpes and HIV viruses, with viral load reduction or complete inactivation after 30 s of treatment [26]. These results are corroborated for Influenza virus, which verified > 99.99% reduction in viral load after 30 s of incubation by [27–28] and the HIV virus that was completely inactivated with the use of the 0.5% solution [23].

Based on the evidence obtained, PVP-I has an excellent antiviral effect when used as a mouthwash for 30 s to 1 min at a concentration of 1% against SARS-CoV-2 and similar viruses *in vitro*. Most of the *in vivo* studies corroborate the *in vitro* results, with a positive effect of PVP-I, indicating potential for pre-procedure clinical use and duration of the antiviral effect for a few hours. For other viruses, despite few studies, *in vitro* evidence was found indicating a great antiviral effect of PVP-I against HIV, Influenza and Herpes viruses with the same form of use.

Essential oils

Essential oils are typically used in a combination of natural essential oils such as phenol, thymol, eucalyptol, menthol and methyl salicylate. They have a substantivity compared to Chlorhexidine and an action against bacteria and yeast, in addition to being studied for their antiviral effect [45–47].

The essential oils were investigated in 10 articles, 2 *in vivo* and 8 *in vitro*. Most of the studies tested Listerine products that have similar compositions, based on ethanol, thymol, eucalyptol, menthol, methyl salicylate, sodium fluoride and/or zinc fluoride. For SARS-CoV-2, *in vitro* studies, tested the rinses by mixing the product with the virus for a short period of time. All studies achieved a decrease in viral load, indicating significant antiviral potential of essential oils against this virus. Three of these studies exposed SARS-CoV-2 for 30 s [8,17] with good results. While Davies et al. [13] who obtained the best result, used 1 min of exposure, being the longer contact time an explanation of the better antiviral activity. In another study, despite the long and unfeasible contact time, an excellent antiviral effect of EO against SARS-CoV-2 was demonstrated [12]. In the only *in vivo* study, essential oils were tested with collections from SARS-CoV-2 positive patients on days 4, 6, and 12 of the intervention. An early viral clearance of 80% was obtained for essential oils, showing the potential use of essential oils for 30 s, without side effects [39].

HCoV-229e have been used as a substitute for SARS-CoV-2 [44]. Although there are differences in these viruses, they are in the same virus family, with many similar structures and are both human respiratory pathogens. The products (Listerine Antiseptic, Listerine Ultra, Equate and Antiseptic Mouthwash) were tested by exposure to the virus with time periods of 30 s, 1 min and 2 min. The three formulations showed a decrease in viral load of more than 99%, where after 1 and 2 min it was not possible to detect the virus, especially for Listerine Antiseptic. These data show again the ability of essential oils to almost completely eliminate human respiratory pathogens viruses in 1 min.

HIV virus was tested in 2 *in vitro* studies with Listerine products. The first study used the HTLV-IIIB strain for 30 s of exposure and obtained a 60% reduction in both formulations: Listerine and Cool Mint Listerine [48]. The second used Listerine Antiseptic and Tartar control Listerine Antiseptic with HIV-1 for 30 s, which resulted in complete inactivation of the virus by the two products in a similar way [22]. This shows that essential oils also has an antiviral potential against HIV, which despite being shown in the literature as a virus that is not transmitted through saliva due to salivary proteins that have the ability to inhibit the virus [48,49], evidence also suggests its inactivation by mouthwash with Listerine products.

The antiviral activity of essential oils has been investigated with other viruses. HSV-I was tested with Listerine Antiseptic and Tartar Control Listerine Antiseptic for 30 s with complete inhibition by both rinses [22]. HSV-I and HSV-II, were tested with Listerine Antiseptic. For HSV-I there was a 96.3% reduction in viral load in 30 s and 100% in 2 min. For exposure of HSV-II with Listerine, all time periods evaluated (30 s, 2 min, and 5 min) inactivated 100% of the virus. These two *in vitro* studies showed the antiviral potential of Listerine products in a relatively short and applicable contact time [50]. An *in vivo* study with HSV-I and HSV-II tested the persistence of viral inhibition over time, after 30 and 60 min recoverable infectious virions were reduced to zero after 30 s and a continued significant reduction 30 min after rinsing when compared to baseline, showing a residual effect of Listerine Antiseptic Cool Mint and its components [51]. Rotavirus, Influenza A, and Adenovirus type 5 were also exposed to essential oils for 30 s, 2 and 5 min. The number of plaques formed by Rotavirus was reduced by 12.2% in 30 s and only 5.7% in 2 min. In the group treated with mouthwash, after 5 min virus infectivity was higher (21,5%) for the experimental group when compared with the virus group not treated. Influenza infectivity was eliminated in all periods of exposure to Listerine.

Adenovirus infection in vero cells when exposed to Listerine for 5 min resulted in a 49.9% +- 14.8% of the monolayer remaining. After 3 days, Adenovirus infection reduced the confluent vero monolayer of cells from 99.4% -+0,9% coverage to 25.1% -+ 15,5% [51]. Listerine Cool Mint tested in a quantitative suspension test with 3 different SARS-CoV-2 isolates and mixed with an interfering substance mimicking a respiratory secretion, significantly reduced viral infectivity to up to 3 orders of magnitude to background levels [17].

These results show the antiviral potential of essential oils, mainly Listerine, against different viruses present in the oral cavity. A greater effect can be observed against SARS-CoV-2 (and its similar HCoV-229E), HIV-I, HSV-I and HSV-II. The use of essential oils mouthwash for 30 s to reduce the viral load against SARS-CoV-2 and HSV can be recommended, since similar results were observed in different studies, including *in vivo*. For the other viruses tested, more studies should be carried out for better conclusions, but the EO have already presented results that favor their use.

Cetylpyridinium chloride

Cetylpyridinium Chloride is the most common quaternary ammonium salt and corresponds to a cationic molecule with substantivity, like Chlorhexidine, but with a much faster release (3 to 5 h). It acts on a wide spectrum of oral bacteria and its antiviral action has been observed and based on the disruption of the lipid envelope of viral organisms [53–56].

Cetylpyridinium chloride was investigated in 9 articles, including 7 studies *in vitro* and 2 *in vivo*. Of all the *in vitro* studies, 5 used the mouthwash against the SARS-CoV-2 virus or its similar. Statkute et al. [8] obtained excellent results in inactivating SARS-CoV-2 with 2 products containing 0.07%–0.1% CPC in 30 s of exposure, which were Dentyl Dual Action and Dentyl Fresh Protect. Another study used 0.0125 to 0.30% CPC formulations at contact times of 20–30 s and obtained excellent results, with all products containing 0.0125%–0.30% CPC inactivating SARS-CoV-2 (3.3 to > 4.4log10 PFU/mL) regardless of dosage form [16]. The antiviral activity of cetylpyridinium chloride (Vitis CPC Protect-2063 mM) tested for 2 min of exposure to SARS-CoV-2 (B.1.1.7/D614G), resulting in a competent antiviral activity against the virus, with an ability to reduce infectivity by 1000 times of a viral stock when treated at least at a 1:1 vol ratio for 2 min. When used in sterile saliva for 30 s it decreased the TCID50/ml of variant B.1.1.7 by 10 times compared to the untreated virus and there was no difference between the presence or absence of saliva [57]. Another 2 studies tested CPC at concentrations of 0.07% against the HCoV-229E virus [44,58], in which the first with a contact time of 30 s to 1 min obtained a reduction in viral load (≥99.9%) and the second similar with Crest Pro-Health decreasing viral load by at least 3log10 to greater than 4log10, or more than 99.99% after the contacts time (30 s, 1 and 2 min).

The CPC was studied *in vivo* against the SARS-CoV-2 virus in two works [40] using Colgate Plax mouthwash (0.075% CPC) in 16 SARS-CoV-2 positive patients for 30 s with salivary collections at baseline, 5 min, 3 h, and 6 h after mouthwash. When compared to the control group (mouthwash with water) it can be postulated that CPC mouthwash decreased the salivary SARS-CoV-2 levels within 5 min of use, and sustained this effect at 3-h and 6-h. The other study used Colgate total 12 (0.075% CPC and 28% Zinc lactate) in 60 patients with salivary collections at baseline, 30 min and 60 min after application. The use of a mouthwash containing the combination of CPC+Zinc resulted in a significant reduction in the viral load in saliva up to 60 min after appli-

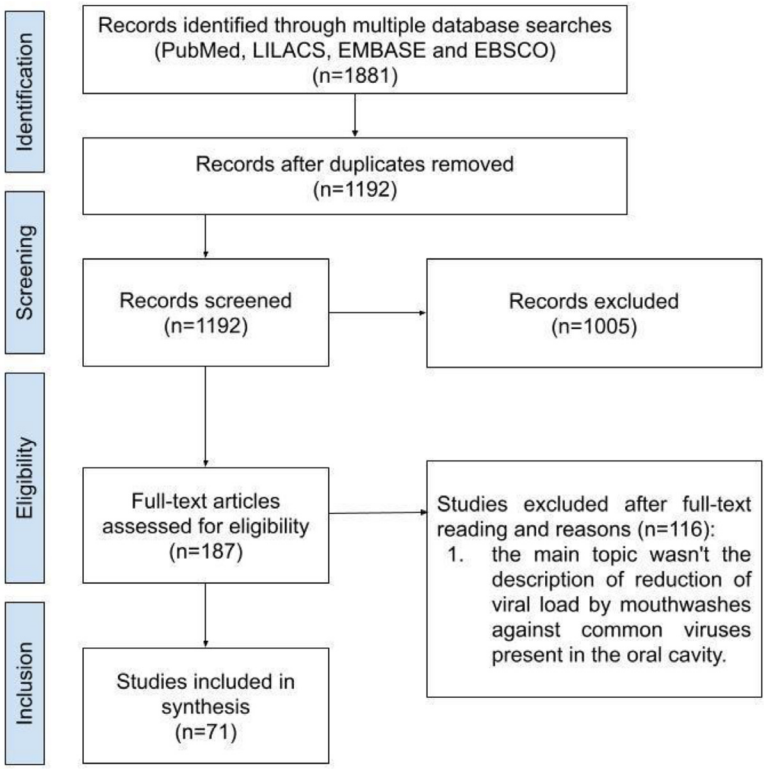

Fig. 1. Flowchart showing the follow-up to the selection of studies.

cation, reinforcing the effect of this product against this type of virus, both *in vitro* and *in vivo,* and its possible use in dental routine [20].

The HSV-1 and HSV-2 viruses were also tested with CPC (200 μg/mL) in vitro by exposing infected cells to cetylpyridinium chloride solution for 10 min. When compared to untreated cells, cells infected with the viruses (HSV-1 and HSV-2) showed lower PFU (plaque-forming unit) formation and lower viral titers after treatment with the product. CPC has an antiviral effect against this type of virus, however, the contact time required to obtain this effect makes its use difficult. These results demonstrate the possible *in vivo* effect of CPC and guide further studies' performance to obtain more consolidated results.

Hydrogen peroxide

The hydrogen peroxide action basically occurs through the release of oxygen, a potent free radical. The H2O2 solutions at concentrations of 1.5% and 3.0% showed minimal virucidal activity after 15 s and 30 s of contact time, when tested *in vitro* against SARS-CoV-2 [13,17,35]. Other results are conflictants with the same product, Peroxyl (containing 1.5% hydrogen peroxide), showed that mouth rinses inactivated the virus replication of SARS-CoV-2 and of pseudotyped SARS-CoV-2 viruses [12], but this result is closely related to the severe cytotoxicity of the product reported by the study and in another study was ineffective [13]. When tested *in vivo* against SARS-CoV-2 in a concentration of 1%, the viral load is similar in the baseline and 30 min after rinsing [59]. Hydrogen peroxide has little or no effect on viruses present in the oral cavity, and its use is not indicated as a mouthwash to reduce the viral load.

Others substances

Other substances have been tested and some of them show good results when used *in vivo* like Chlorine dioxide [21] and Silver nanoparticles [60]. Natural products have been used in some dental products, but their effect on viruses is not well established [61,62]. Other products like Biorepair® Zahnmilch [63], Delmopinol [16], C31G [64], ProntOral mouthwash (Polyaminopropyl biguanide polyhexanide); Dequonal (Dequalinium chloride, benzalkonium chloride); Octenident mouthwash (Octenidine dihydrochloride) [17], IRSHA [14], products containing different active compounds, virucidal activities could be observed, but more studies are necessary to check if in the oral cavity the effect will be the same.

Hypochlorous acid stabilized [13] and CDCM: B-cyclodextrin (0.1%) and Citrox (0.01%) [65,66], have demonstrated antiviral activity against some viruses, with inconsistent results in different situations showing the necessity of more studies.

Regarding the other substances, although some of them have demonstrated some antiviral effect, further studies are needed to demonstrate their antiviral potential and adverse effects (Fig. 1, Tables 4–9).

Conclusion

There are few products with an effect on reducing the viral load of viruses present in the oral cavity for use as a pre-procedural mouthwash. Essential oils, Cetylpyridinium Chloride, and Povidone-iodine solutions showed antiviral potential against common viruses present in the oral cavity, without significant side effects in short-term use, and are viable options for use as a pre-procedure in clinical routine against SARS-CoV-2 and other types of viruses. The other solutions, despite having some effect in reducing viral load, need further randomized clinical studies with a larger number of patients and with more controlled situations to determine the potential of various mouthrinses agents in reducing intraoral viral load.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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