



# Efficacy of Mouth Rinses Against SARS-CoV-2: A Scoping Review

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## OPEN ACCESS

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### Specialty section:

This article was submitted to  
Endodontics,  
a section of the journal  
Frontiers in Dental Medicine

Received: 31 December 2020

Accepted: 05 February 2021

Published: 09 March 2021

### Citation:

Ather A, Parolia A and Ruparel NB  
(2021) Efficacy of Mouth Rinses  
Against SARS-CoV-2: A Scoping  
Review. *Front. Dent. Med.* 2:648547.  
doi: 10.3389/fdmed.2021.648547

**Introduction:** The presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in saliva and nasopharyngeal secretions has challenged the routine practice of dentistry. Use of preprocedural mouth rinses has been recommended by several organizations to potentially reduce the transmission of SARS-CoV-2. This scoping review aimed at evaluating the available evidence on the efficacy of mouth rinses against SARS-CoV-2.

**Methods:** A thorough literature search on electronic databases (PubMed, Scopus, and Google Scholar) was performed by two independent reviewers and data from articles addressing the aim of this article were extracted.

**Results:** After exclusion of articles not addressing the end point in question, 12 articles were included in this scoping review. Of the 12 articles, seven were *in vitro* studies and five were *in vivo* human clinical studies. The *in vitro* studies used a standardized methodology (endpoint dilution assay) to evaluate the efficacy of antimicrobial mouth rinses against SARS-CoV-2. The *in vivo* studies were done utilizing polymerase chain reaction assay of samples obtained from saliva or nasopharyngeal swab or a combination of both nasopharyngeal and oropharyngeal swab. The reagents tested in these studies included povidone-iodine, chlorhexidine, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), essential oils, and quaternary ammonium compounds and demonstrated varied efficacy against SARS-CoV-2.

**Conclusion:** Based on the available evidence from *in vitro* studies, it can be concluded that mouth rinses have a potential to reduce SARS-CoV-2 viral load; however, effectiveness in *in vivo* conditions is still inconclusive. Owing to the substantial heterogeneity in reporting of the anti-SARS-CoV-2 efficacy of mouth rinses, this review highlights the need to conduct future research with robust and standardized methodologies to confirm effectiveness of mouth rinses.

**Keywords:** SARS-CoV-2, oral, mouth rinse, COVID-19, aerosols

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) and its rapid spread have drastically affected the dental community worldwide. This has led to a diverse set of recommendations in which some regions had a complete lockdown of dental practices, in contrast to certain areas where dentists continued to provide care for emergency patients. However, there has been a shift toward reopening of practices and provision of routine dental care, which has led to an increase in aerosol-generating procedures. Aerosols are air-borne suspended particles with a potential to contain salivary components and

microorganisms (1). This is a cause for concern as saliva and nasopharyngeal secretions can carry high viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in COVID-19 affected individuals (2). Although the main mode of transmission of SARS-CoV-2 is through respiratory droplets or close contact, transmission *via* aerosols is possible and has not been ruled out (3). *In vitro* studies have confirmed the potential of SARS-CoV-2 to be aerosolized for up to 3–16 h (4, 5). Therefore, various dental organizations responded by specifying guidelines for provision of dental care during the pandemic (6–8).

In addition to recommendations such as strict infection control practices, patient screening, and wearing appropriate personal protective equipment, use of preprocedural mouth rinse or gargle has also been suggested by numerous organizations across the world such as Centers for Disease Control and Prevention, American Dental Association, and Australian Dental Association (7–9). Use of preprocedural mouth rinse is based on the principle of reducing oral microbial load and hence mitigating the potential transmission of microbes *via* aerosol, splatter, or close contact. One of the most commonly used preprocedural mouth rinses in dentistry is chlorhexidine gluconate, which has been shown to be a highly effective antimicrobial agent (10). Several alternative mouth rinses such as iodine-based [povidone-iodine (PVP-I)] or essential oils-based (Listerine) or oxygenating agents [hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>)] have also demonstrated comparable antimicrobial efficacy (10).

The promising results of mouth rinses against coronaviruses made the basis for recommendations supporting the use of preprocedural mouth rinses during COVID-19 pandemic (10); however, most of these guidelines were not based on efficacy of mouth rinses against SARS-CoV-2 specifically (7–9). In the past few months, reports on efficacy of topical antimicrobials against SARS-CoV-2 have been published in the literature (11–22). The aim of this scoping review is to present and critically appraise the most updated evidence on the efficacy of mouth rinses against SARS-CoV-2.

## MATERIALS AND METHODS

### Focused Question

This scoping review was conducted according to PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews) statement (23), and the review focused on the following evidence-based question: “What is the efficacy of mouth rinses against SARS-CoV-2?”

### Search Strategy

To address the aforementioned question, an exhaustive search of literature on electronic databases (PubMed, Scopus, and Google Scholar) was conducted by two independent reviewers (AA, AP) on December 8, 2020. A search strategy on PubMed was built through combination of MeSH terms using Boolean operators “AND,” “OR:” (((Coronavirus)) OR (SARS-CoV-2 virus[MeSH terms])) OR (2019-nCoV[MeSH terms])) AND (((((((mouth rinse[MeSH terms]) OR (mouth wash[MeSH terms])) OR (oral sprays[MeSH terms])) OR (chlorhexidine[MeSH terms])) OR (povidone iodine[MeSH terms])) OR (cetylpyridinium

chloride[MeSH terms])) OR (essential oils[MeSH terms])) OR (benzalkonium compounds[MeSH terms])) OR (hydrogen peroxide[MeSH terms])) filters: from 2019 to 2020. The search strategy was then adapted for other databases. Articles published onward from December 2019 were included in the screening process. In addition, reference lists of extracted articles were further screened, and gray literature search was performed to find any missing studies. The articles were then imported into reference manager software (Mendeley Desktop, version 1.17.11; Mendeley Ltd., George Mason University, Fairfax, VA) to remove duplicates.

## Study Selection Process

### Inclusion Criteria

1. Original studies with *in vitro* or *in vivo* experimental design reporting on the anti-SARS-CoV-2 efficacy of mouth rinses or gargle.
2. No language restrictions were applied. Applicable articles were included regardless of languages used, as long as translation was available.

### Exclusion Criteria

- 1) Studies reporting on topical antiseptic formulations but intended for either only nasal application or as a surface disinfectant.
- 2) Studies in preprint stage that have not been peer reviewed and were not intended to be utilized to make clinical recommendations.
- 3) Opinions, commentaries, and review articles.
- 4) Studies reporting on efficacy of topical antiseptic formulations against related coronaviruses but not specifically against SARS-CoV-2.

## Study Selection

After removal of duplicate studies, two independent reviewers (AA, AP) screened the titles and abstract of all extracted articles and subjected them to the inclusion and exclusion criteria to perform preliminary elimination of ineligible studies. Further, full text of the articles was retrieved and evaluated for inclusion in the scoping review. Any duplication of data presented in studies was noted. Any disagreements in the process were resolved by consulting another reviewer (NBR).

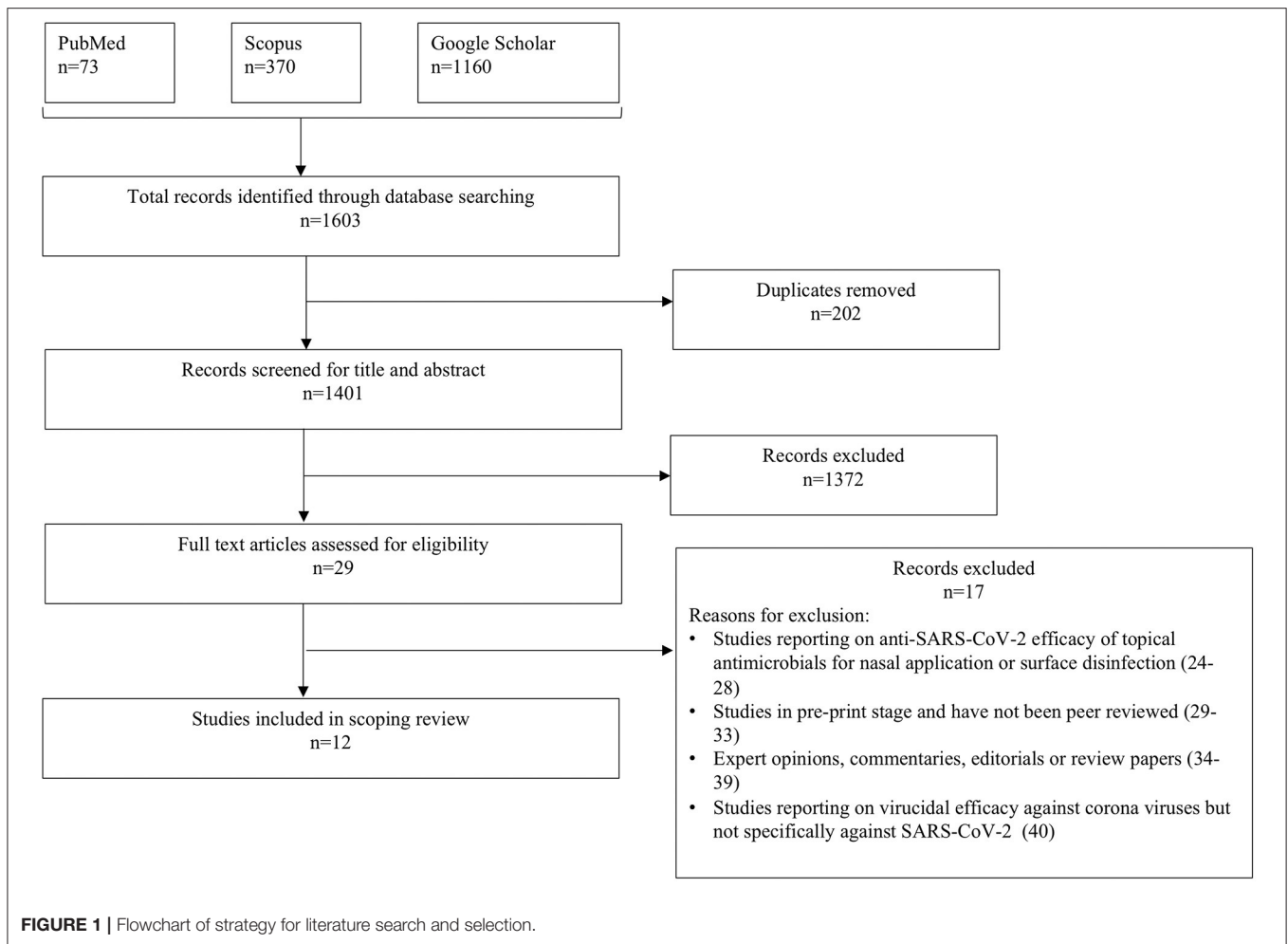
### Data Extraction

Two independent reviewers (AA, AP) performed data extraction using customized data retrieval forms. Extracted data included author, year, study design, type of SARS-CoV-2 strain, technique employed for detecting antiviral efficacy, test products or intervention, duration, key findings, details of funding (funding source), and conflict of interest.

## RESULTS

### Study Selection

The flowchart for study selection in this review is shown in **Figure 1**. A total of 1,603 potentially relevant records were identified through electronic database search and gray literature search. After removing duplicates, 1,401 records were screened



by reviewers (AA, AP) for title and abstract content, of which 1,372 records were excluded. Full texts of 29 articles were reviewed for eligibility assessment, and eventually 12 records (11–22) were included in the review based on the inclusion/exclusion criteria. The reasons for excluding 17 articles (24–40) are presented in **Figure 1**.

## Study Characteristics

The study characteristics of the included studies are presented in **Table 1**. Of the 12 included articles in this review, seven were *in vitro* studies (11–16, 19) and five were *in vivo* human clinical studies (17, 18, 20–22). Among the *in vivo* studies, one was a randomized controlled trial (22). All *in vitro* studies (11–16, 19) used a standardized methodology (endpoint dilution assay) to evaluate the efficacy of antimicrobial formulations against SARS-CoV-2. Briefly, endpoint dilution assay determines the amount of virus required to kill 50% of infected hosts or to produce a cytopathic effect in 50% of inoculated tissue culture cells (TCID<sub>50</sub>) (41). Data for virucidal activity are typically reported as log<sub>10</sub> reduction value (LRV), which denotes reduction in viral titers with experimental test group compared to virus control group (41). A log<sub>10</sub> reduction value of >4 indicates high virucidal

activity and represents 99.99% kill efficacy (42, 43). The *in vivo* studies were done utilizing real-time reverse transcription–polymerase chain reaction (rRT-PCR) assay of samples obtained from saliva or oropharyngeal gargle or nasopharyngeal swab or a combination of both nasopharyngeal and oropharyngeal swab (17, 18, 20–22).

The key results from the included studies are presented under the following subcategories based on the commonly used antimicrobial reagents present in mouth rinses.

## Povidone-Iodine

The search strategy yielded a total of nine studies reporting on the efficacy of PVP-I against SARS-CoV-2 (11–17, 19, 22). With the exception of two *in vivo* studies (17, 22), remaining of them had an *in vitro* study design (11–16, 19). The *in vitro* studies used a concentration of PVP-I ranging from 0.33 to 1.5% and a contact time varying from 15 to 60 s (11–16, 19). The collective results of these *in vitro* studies demonstrate that PVP-I causes a significant reduction in viral titers of SARS-CoV-2 with LRV values ranging from 2.61 to 5 (11–16, 19).

The *in vivo* study by Lamas et al. (17) evaluated the efficacy of 1% PVP-I mouth rinse for 1 min on the salivary viral load

**TABLE 1** | Study characteristics of included studies in the scoping review.

References	Study design	SARS-CoV-2 strain	Technique	Test products or intervention	Duration (s)	Findings	Funding	Conflict of interest
1. Hassandarvish et al. (11)	<i>In vitro</i>	Not mentioned	Standard end-point dilution assay	<ul style="list-style-type: none"> <li>PVP-I–1%</li> <li>PVP-I–0.5%</li> </ul>	<ul style="list-style-type: none"> <li>15</li> <li>30</li> <li>60</li> </ul>	<ul style="list-style-type: none"> <li>All tested concentrations demonstrated LRV ranging between 4 and 5</li> </ul>	ND	ND
2. Anderson et al. (12)	<i>In vitro</i>	SARSCoV2 (hCoV–19/Singapore/2/2020)	Suspension assays	<ul style="list-style-type: none"> <li>PVP-I–10% (Antiseptic solution)</li> <li>PVP-I–7.5% (Skin cleanser)</li> <li>PVP-I–1% (Gargle and mouth wash)</li> <li>PVP-I–0.45% (Throat spray)</li> </ul>	<ul style="list-style-type: none"> <li>30</li> </ul>	<ul style="list-style-type: none"> <li>Tested products indicated for oral use produced a &gt;4 log<sub>10</sub> reduction in viral titers</li> </ul>	Yes*	Yes
3. Bidra et al. (13)	<i>In vitro</i>	(SARS-CoV-2) USA-WA1/2020 strain	Standard end-point dilution assay	<ul style="list-style-type: none"> <li>PVP-I–0.5%</li> <li>PVP-I–1%</li> <li>PVP-I–1.5%</li> </ul>	<ul style="list-style-type: none"> <li>15</li> <li>30</li> </ul>	<ul style="list-style-type: none"> <li>Tested concentrations demonstrated a LRV of 3 and 3.33 after 15 and 30 s of exposure, respectively</li> </ul>	Yes*	None
4. Bidra et al. (14)	<i>In vitro</i>	(SARS-CoV-2) USA-WA1/2020 strain	Standard end-point dilution assay	<ul style="list-style-type: none"> <li>PVP-I–1%</li> <li>PVP-I–2.5%</li> <li>PVP-I–3%</li> <li>H<sub>2</sub>O<sub>2</sub>–3%</li> <li>H<sub>2</sub>O<sub>2</sub>–6%</li> <li>Ethanol–70% (Positive control)</li> <li>Water–(Negative control)</li> </ul>	<ul style="list-style-type: none"> <li>15</li> <li>30</li> </ul>	<ul style="list-style-type: none"> <li>All tested concentrations of PVP-I demonstrated a LRV of &gt;4.33 after 15 and 30 s</li> <li>Tested concentrations of H<sub>2</sub>O<sub>2</sub> i.e., 1.5 and 3% demonstrated inadequate virucidal activity with a LRV of 1–1.8</li> </ul>	Yes*	None
5. Pelletier et al. (15)	<i>In vitro</i>	(SARS-CoV-2) USA-WA1/2020 strain	Standard end-point dilution assay	<ul style="list-style-type: none"> <li>PVP-I–1, 2.5, 5% (Nasal Antiseptic)</li> <li>PVP-I–1, 1.5, 3% (Oral Rinse Antiseptic)</li> </ul>	<ul style="list-style-type: none"> <li>60</li> </ul>	<ul style="list-style-type: none"> <li>All tested products demonstrated a LRV of 4.63</li> </ul>	Yes*	None
6. Shin et al. (16)	<i>In vitro</i>	SARS-CoV-2 virus (nCoV/Korea/KUMC-01/2020)	Standard end-point dilution assay	<ul style="list-style-type: none"> <li>PVP-I–0.45% (Throat spray)</li> </ul>	<ul style="list-style-type: none"> <li>60</li> </ul>	<ul style="list-style-type: none"> <li>Under both clean and dirty conditions, test product produced a &gt;4 log<sub>10</sub> reduction in viral titers</li> </ul>	ND	None
7. Martínez Lamas et al. (17)	<i>In vivo</i> (N = 4)	N/A	RT-PCR of serial saliva samples in four patients with COVID-19	<ul style="list-style-type: none"> <li>PVP-I–1%</li> </ul>	<ul style="list-style-type: none"> <li>60</li> </ul>	<ul style="list-style-type: none"> <li>In 2 out of the 4 participants, there was a significant reduction in viral load which lasted for at least 3 h</li> </ul>	ND	None

(Continued)

TABLE 1 | Continued

References	Study design	SARS-CoV-2 strain	Technique	Test products or intervention	Duration (s)	Findings	Funding	Conflict of interest
8. Capetti et al. (18)	<i>In vivo</i> (N = 8)	N/A	PCR of nasopharyngeal swabs in persistent COVID-19 carriers. A baseline swab was taken followed by intervention and then swabs taken at 24, 48, 72 h	<ul style="list-style-type: none"> <li>H<sub>2</sub>O<sub>2</sub>–3% (nasopharyngeal washing and gargling) and hypertonic saline (nasopharyngeal washing)</li> </ul>	N/A	<ul style="list-style-type: none"> <li>All the patients (n = 8) had negative swabs till 72 h after which 4 patients became weak positive results with PCR</li> </ul>	Yes	None
9. Meister et al. (19)	<i>In vitro</i>	<ul style="list-style-type: none"> <li>BetaCoV/Germany/Ulm/01/2020</li> <li>BetaCoV/Germany/Ulm/02/2020</li> <li>UKEssen strain</li> </ul>	Quantitative suspension test	<ul style="list-style-type: none"> <li>H<sub>2</sub>O<sub>2</sub> (Cavex Oral Pre Rinse)</li> <li>Chlorhexidine (D-gluconate) (Chlorhexamed Forte Dequonal)</li> <li>Chlorhexidine (D-gluconate) (Dynexidine Forte)–0.2%</li> <li>PVP-I (Iso-betadine mouthwash) 1%</li> <li>Ethanol, essential oils (Listerine Cool Mint)</li> <li>Octenidine dihydrochloride (Octenident mouthwash)</li> <li>Polyaminopropyl biguanide (Prontoral mouthwash)</li> </ul>	<ul style="list-style-type: none"> <li>30</li> </ul>	<ul style="list-style-type: none"> <li>Only Listerine Cool Mint, Iso-Betadine, and Dequonal demonstrated a LRV approximating 3 (<math>\geq 2.61</math>–<math>\geq 3.11</math>)</li> <li>Cavex Oral Pre Rinse and DynexidineForte 0.2% demonstrated the least reduction in viral titers (LRV &lt;1)</li> </ul>	Yes	None
10. Gottsauner et al. (20)	<i>In vivo</i> (N = 10)	N/A	RT-PCR of oropharyngeal gargle specimens. Baseline specimen was taken followed by intervention and then repeat specimen was taken 30 min after mouthrinse	H <sub>2</sub> O <sub>2</sub> –1%	<ul style="list-style-type: none"> <li>30</li> </ul>	<ul style="list-style-type: none"> <li>With a sample size of 10 patients, no significant difference in median viral load was observed between baseline specimen and 30 min post hydrogen peroxide mouth rinse specimen</li> </ul>	Yes	None

(Continued)

TABLE 1 | Continued

References	Study design	SARS-CoV-2 strain	Technique	Test products or intervention	Duration (s)	Findings	Funding	Conflict of interest
11. Yoon et al. (21)	<i>In vivo</i> (N = 2)	N/A	rRT-PCR of serial saliva samples in two patients with COVID-19. This procedure was done twice i.e., on day 3 and day 6 of hospital admission. Baseline sample was taken followed by intervention and then repeat samples obtained at 1, 2 and 4 h	<ul style="list-style-type: none"> <li>Chlorhexidine—0.12%</li> </ul>	• 15	<ul style="list-style-type: none"> <li>The first part of the study on day 3 led to transient decrease (2 h) in viral load to an undetectable level; however, on day 6, this effect was not observed</li> </ul>	Yes	None
12. Seneviratne et al. (22)	<i>In vivo</i> (N = 16)	N/A	RT-PCR of serial saliva samples in 16 COVID-19 positive patients. Saliva samples were collected from all patients at baseline and at 5 min, 3 and 6 h post-application of mouth-rinses/water.	<ul style="list-style-type: none"> <li>PVP-I (Betadine)—0.5% (n = 4)</li> <li>Chlorhexidine (Pearly White Chlor-Rinse)—0.2% (n = 6)</li> <li>Cetyl Pyridinium Chloride (Colgate Plax)—0.075% (n = 4)</li> <li>Sterile water (n = 2)</li> </ul>	• 30	<ul style="list-style-type: none"> <li>CetylPyridinium Chloride significantly decreased the salivary SARS-CoV-2 levels within 5 min of use, compared to the control group patients and the effect of decreasing salivary viral load was observed to be sustained at 6-h time point interval</li> <li>PVP-I also caused a decrease in viral load; however, it was only significantly better than control group at 6-h time point interval</li> <li>Chlorhexidine mouth rinse demonstrated highly inconsistent results</li> </ul>	Yes	None

N/A, not applicable; ND, not disclosed. \*Funding from external pharmaceutical company.



of SARS-CoV-2 in four patients with COVID-19. Baseline saliva samples were obtained followed by mouth rinse use for 1 min, and then serial saliva samples were collected at different time intervals to determine presence of SARS-CoV-2 using rRT-PCR assay. All the baseline samples confirmed presence of SARS-CoV-2, and post-mouth rinse saliva samples showed a significant reduction in viral load for 3 h in two patients. Interestingly, PVP-I was only effective in patients who presented with high viral loads in baseline samples.

A randomized controlled trial (22) compared anti-SARS-CoV-2 efficacy of 0.5% PVP-I (Betadine gargle and mouthwash), 0.2% chlorhexidine mouthwash (Pearly White Chlor-Rinse), 0.075% cetylpyridinium chloride (CPC) (Colgate Plax mouthwash), and sterile water (control group) in confirmed COVID-19 patients. Viral load was detected by performing RT-PCR of saliva samples obtained by passive drooling technique in 16 patients. Samples were obtained at four time point intervals: baseline, 5 min, 3 and 6 h. PVP-I rinsing caused an increase in cycle threshold value, which is an indirect inverse measure of viral load. However, when compared to control group, statistically significant difference was only observed at 6-h time point interval.

## Chlorhexidine

A total of three studies were found that reported on the efficacy of chlorhexidine against SARS-CoV-2 (19–22). With the exception of one *in vitro* study (19), the remainder of them had an *in vivo* study design (21, 22). Meister et al. (19) using the *in vitro* TCID50 assay evaluated virucidal efficacy of two commercial preparations of chlorhexidine (Chlorhexamed Forte and Dynexidine Forte 0.2%) against three different strains of SARS-CoV-2 and demonstrated minimal benefit (LRV = 0.50–1.17).

Regarding the *in vivo* efficacy, Yoon et al. (21) evaluated the effectiveness of 0.12% chlorhexidine gluconate mouth rinse for 30 s on salivary viral load in two patients with confirmed COVID-19. The rRT-PCR analysis demonstrated presence of SARS-CoV-2 in baseline saliva samples of both patients and a transient (2 h) decrease in SARS-CoV-2 salivary load after chlorhexidine rinse. However, conflicting results were obtained in a randomized controlled trial that demonstrated no statistically significant difference between 0.2% chlorhexidine mouthwash (30 s) and sterile water in reducing viral load in COVID-19 patients (22).

## Hydrogen Peroxide

Literature search yielded four studies reporting on anti-SARS-CoV-2 efficacy of hydrogen peroxide, with an equal distribution of *in vitro* and *in vivo* study designs (14, 18–20). Bidra et al. (14) demonstrated limited virucidal activity of 1.5 and 3% hydrogen peroxide when tested for either 15- or 30-s duration, with LRVs ranging from 1 to 1.8. This LRV for H<sub>2</sub>O<sub>2</sub> was three times lower than the LRV obtained with any of the concentrations of PVP-I tested in their study (14). These findings were later corroborated by Meister et al. demonstrating LRV of <1 with commercial hydrogen peroxide-based mouth rinse (Cavex pre oral rinse) (19).

There are conflicting reports on the *in vivo* efficacy of hydrogen peroxide against SARS-CoV-2. Gottsauner et al. (20) demonstrated no significant difference in median viral load between the baseline oropharyngeal samples and the samples obtained 30 min after rinsing with 1% hydrogen peroxide for 30 s. On the contrary, Capetti et al. (18) reported excellent efficacy of 3% hydrogen peroxide usage by demonstrating negative PCR results in eight persistent COVID-19 carrier patients. This effect lasted for 72 h, following which four patients became weakly positive for COVID-19.

## Essential Oils

Only one *in vitro* study was found reporting on anti-SARS-CoV-2 efficacy of essential oil-based mouth rinse (Listerine Cool Mint) (19). The study utilizing the TCID50 assay demonstrated a viral titer reduction of three orders in magnitude with Listerine in comparison to the control group (19).

## Quaternary Ammonium Compounds

Literature search yielded two studies reporting on anti-SARS-CoV-2 efficacy of quaternary ammonium compounds (19, 22). An *in vitro* study by Meister et al. (19) evaluated a commercial preparation of benzalkonium chloride (Dequonal) for oral use and demonstrated its potent SARS-CoV-2 virucidal activity (LRV~3). A randomized controlled trial evaluated another quaternary ammonium compound, i.e., CPC, and demonstrated a statistically significant increase in fold change of cycle threshold value at 5 min and 6 h after rinsing with CPC mouth rinse compared to the sterile water group.

## DISCUSSION

Oral healthcare providers and patients are routinely exposed to aerosolized pathogens during dental treatment (44). One of the suggested measures to reduce the microbial load in aerosols is to use pre procedural mouth rinse (38). Use of preprocedural mouth rinses is not new to dentistry; however, its efficacy in reducing the transmission of infections has been a subject of debate (44). According to a survey, dentists' perceived benefits of preprocedural rinsing are to minimize microbial load and to decrease aerosolization of bacteria (44).

Dental profession has been categorized by the Occupational Safety and Health Administration to be "very high risk," especially if it involves aerosol-generating procedures (45). Therefore, in addition to use of personal protective equipment, high-volume suction, and rubber dam, several organizations have also recommended the use of preprocedural mouth rinse as a layer of defense against aerosol microbial transmission (7–9). However, the recommendations early on during the pandemic were based on antimicrobial activity of mouth rinses that were not specific to SARS-CoV-2 (6–9). Evidence on efficacy of mouth rinses or gargles against SARS-CoV-2 has recently been published in the literature (11–22). Thus, the present scoping review provided a critical appraisal of the available evidence on anti-SARS-CoV-2 efficacy of mouth rinses. The included studies mostly focused on evaluating PVP-I, chlorhexidine, hydrogen peroxide, essential oil-based, and

quaternary ammonium compounds-based mouth rinses (11–22).

PVP-I is a broad-spectrum antimicrobial typically used as a presurgical antiseptic or as a mouth rinse (46, 47). It acts by releasing free iodine, which disrupts microbial metabolic pathways and destabilizes structural components of cell membranes of pathogens (10). There have been some concerns about staining of teeth and tissues owing to the iodine content in PVP-I; however, a clinical trial has demonstrated that PVP-I causes less staining of teeth when compared to chlorhexidine-gluconate (48). The concentration of PVP-I tested in most of the studies included in this review (11, 13–17, 19, 22) is well below the recommended safe concentration of 5% for oral use (34). Ready-to-use PVP-I mouth rinse/gargle/throat spray are available in some countries; however, in the United States, PVP-I is available only as 10% topical solution (Betadine antiseptic solution, Betadine, Avrio Health L.P., USA) and 5% spray (Betadine antiseptic spray, Betadine, Avrio Health L.P., USA). Therefore, diluting them to an appropriate concentration will be needed prior to oral use (34).

The *in vitro* studies on PVP-I included in this review demonstrate adequate virucidal activity against SARS-CoV-2 (11–16, 19) and validate the previous recommendations made by various organizations (6–9), which were mostly based on indirect evidence. Majority of the *in vitro* studies on PVP-I efficacy suggest a  $\log_{10}$  reduction value of  $>4$  (11, 12, 14–16), which is in accordance with the European standard (EN 14776) (42) and the Robert Koch Institute guidelines for effective virucidal activity and represents 99.99% kill efficacy (43). However, data from *in vivo* research are currently limited to only two studies (17, 22), both with a small sample size of four patients per intervention. In the study by Lamas et al., PVP-I mouth rinse reduced viral load in 50% of the patients at 3-h time point interval; however, saliva sample obtained at 5-min time point interval did not show any significant reduction in viral load compared to baseline saliva sample (17). A similar finding was demonstrated by Seneviratne et al. wherein PVP-I was not significantly better than sterile water in reducing viral load at 5-min time point interval but fared significantly better after 6 h after rinse (22). The low viral titers obtained after 3 h (17) or 6 h (22) after rinsing in both these studies raise few questions. Is this finding a potential result of technical issues in methodology or whether PVP-I truly has a sustained virucidal effect? Substantivity with use of PVP-I has been a controversial topic; von Ohle et al. in a subgingival irrigation study demonstrated sustained antimicrobial effect of PVP-I for 31 days (49). Contrasting results were published by Macias et al., wherein PVP-I exhibited no substantivity (50). As far as anti-SARS-CoV-2 efficacy of PVP-I is concerned, data from *in vitro* studies look extremely promising, but clinical research still needs to corroborate these findings to draw any definitive conclusions and make clinical recommendations.

Chlorhexidine, a broad-spectrum biocide, has been used in dentistry for several years to treat gingivitis and also as a preprocedural mouth rinse (51, 52). The cationic chlorhexidine molecule interacts with the anionic phosphate residue of the lipid molecules in the cell membrane of pathogen and causes cell membrane disruption (52). Chlorhexidine has a tendency to bind

to tissues and release over an extended period of time, a beneficial antimicrobial property known as substantivity (52). Commercial preparations of chlorhexidine such as Peridex (Proctor and Gamble, Cincinnati, Ohio) usually combine 0.12% chlorhexidine with alcohol (11.6%), which can partly contribute to its microbicidal activity (53). Chlorhexidine has been demonstrated to be effective against lipid-enveloped viruses (54); however, an *in vitro* study reported limited to no efficacy (LRV  $<1$ ) against human coronavirus, even after 10 min of exposure (55).

As far as efficacy of chlorhexidine against SARS-CoV-2 is concerned, the available evidence in literature is limited. *In vitro* data on two commercial preparations of chlorhexidine have shown minimal virucidal activity against SARS-CoV-2 (LRV  $<1$ ) (19). The data from *in vivo* studies have conflicting results on anti-SARS-CoV-2 efficacy of chlorhexidine (21, 22). Yoon et al. demonstrated favorable results with use of 0.12% chlorhexidine rinse to reduce salivary SARS-CoV-2 load; however, the study was restricted to two patients and did not have a control group (21). On the other hand, the randomized controlled trial by Seneviratne et al. had inconsistent results with chlorhexidine use, which were not significantly better than sterile water group, and the authors refrained from making any firm conclusions on its virucidal efficacy (22).

Hydrogen peroxide, a widely used antiseptic in healthcare, exerts its microbicidal action by producing hydroxyl free radicals that can attack membrane lipids and other essential cell components of pathogens (10). In terms of its virucidal activity against human coronavirus, an accelerated hydrogen peroxide-based disinfectant was demonstrated to be highly effective within 1 min of contact (56). Based on these findings, use of hydrogen peroxide mouth rinse had been advocated during COVID-19 pandemic (57); however, the available *in vitro* studies evaluating activity of  $H_2O_2$  against SARS-CoV-2 fail to demonstrate effective virucidal activity (LRV  $<1.8$ ) (14, 19). The *in vivo* efficacy of hydrogen peroxide against SARS-CoV-2 is still inconclusive as results obtained from the two *in vivo* reports are contrasting. Gottsauner et al. (20) demonstrated no significant decrease in viral load after rinsing with 1% hydrogen peroxide. This indicates weak virucidal activity of hydrogen peroxide in *in vivo* conditions, which can also be partly attributed to the inactivation of hydrogen peroxide by catalase group of enzymes present in oral cavity (10). However, Capetti et al. (18) reported excellent efficacy of 3% hydrogen peroxide by demonstrating negative PCR results in eight persistent COVID-19 carrier patients. It is noteworthy that both the *in vivo* studies differ from each other in few aspects. First, the technique and concentration of hydrogen peroxide use in the study of Gottsauner et al. (20) were gargling with 1% hydrogen peroxide in contrast to the more aggressive approach in the study of Capetti et al. (18), wherein 3%  $H_2O_2$  gargle and hypertonic saline nasopharyngeal wash were used. This is important as it has been shown that hypertonic saline does possess antiviral properties (58) and might have contributed to the superior efficacy of  $H_2O_2$  as seen in the study of Capetti et al. (18). Second, the type of specimens obtained for PCR analysis differed between the two studies: oropharyngeal gargle (20) vs. nasopharyngeal swab (18). This can also potentially impact detection of viral RNA as it has



been shown that saliva or oropharyngeal rinse can contribute to dilution of samples and lead to suboptimal detection (59). On the other hand, it has also been demonstrated that in few cases SARS-CoV-2 RNA has been detected in saliva/oropharyngeal rinse samples but was missing in the corresponding nasopharyngeal swab sample, which could be attributed to errors in obtaining the swab (60). The available evidence from *in vitro* and *in vivo* studies does not provide encouraging outcomes with use of hydrogen peroxide mouth rinse against SARS-CoV-2, and more studies are needed to evaluate its virucidal efficacy against SARS-CoV-2, especially in *in vivo* conditions.

Data on anti-SARS-CoV-2 efficacy of essential oil-based mouth rinse (Listerine) and quaternary ammonium compounds (benzalkonium chloride and CPC) show promising results; however, these are based on few studies (19, 22) and will need further validation.

## LIMITATIONS

First, one of the limitations is that most of the evidence is based on *in vitro* studies wherein the viral titer reduction was evaluated in laboratory settings, which may significantly differ from a clinical scenario (61). Multiple factors such as presence of organic matter, serum proteins, and enzymes in the oral cavity can modulate effectiveness of topical antimicrobials (62). In addition, it is important to understand that virucidal activity of mouth rinses reported in *in vitro* studies can be a combination of their inherent virucidal efficacy along with cytotoxic effects induced by the antimicrobial agent (63). Therefore, cytotoxic effects of an antimicrobial should be evaluated separately in advance in order to establish the inherent virucidal activity of the compound being tested. Although a rigorous and standardized methodology has been used in all the *in vitro* studies included in this review, some of the studies have reported conflict of interest and funding from pharmaceutical companies (12–15), which can potentially bias the study outcome.

Second, most of the included *in vivo* studies have inherent limitations such as small sample size (17, 21, 22) and lack of control groups (17, 20, 21). In addition, heterogeneity among the *in vivo* studies in terms of methodology for sample collection (oropharyngeal swab, nasopharyngeal swab, or saliva) could have affected SARS-CoV-2 RNA detection, which makes it difficult to compare the results. The studies have employed RT-PCR assay, which is currently the gold standard for SARS-CoV-2 detection (64). RT-PCR tests yield cycle threshold (Ct) values, which are a surrogate measure and are inversely proportional to the amount of target nucleic acid in the sample (65). It is worth noting that the mere presence of nucleic acid in a sample does not translate to infectivity. Therefore, it is important to conduct virus culture studies to establish the infectivity of a sample. This phenomenon

was demonstrated in the study by Gottsauner et al., wherein five samples with a load of  $10^3$  SARS-CoV-2 RNA copies per milliliter were used for virus culture study, but only one sample was found to be actively replicating and infectious (20).

Lastly, several preprints could not be included in this review (29–33). Preprints are manuscripts that have not been peer reviewed, and data from the study should not be used for clinical guidance. These preprints, when peer reviewed and accepted for publication, will add to the existing literature on efficacy of mouth rinses against SARS-CoV-2.

## FUTURE RECOMMENDATIONS

Research on efficacy of oral mouth rinses should focus on reporting factors such as exposure time, strength, volume of mouth rinse, and SARS-CoV-2 strain, so that results can be extrapolated to clinical setting. Studies should have adequate sample size and control groups to yield more reliable conclusions and have better external validity. Factors in *in vivo* studies such as baseline viral titer load, patient demographics, and symptomatology should also be reported to match patient data and to provide a better understanding of the study. Viral culture technique should be employed in future *in vivo* research so as to establish the true potential of viral infectivity. In addition, guidelines to conduct *in vitro* studies, e.g., Preferred Reporting Items for Laboratory studies in Endodontology (PRILE), and clinical trials, e.g., Preferred Reporting Items for Randomized Trials in Endodontics (PRIRATE) or Consolidated Standards of Reporting Trials (CONSORT), should be followed (66–68).

## CONCLUSION

Based on the limited evidence from *in vitro* studies, it can be concluded that mouth rinses have a potential to reduce SARS-CoV-2 viral load; however, the emerging evidence from *in vivo* studies is still inconclusive to recommend one mouth rise over another. Owing to the substantial heterogeneity in reporting of the anti-SARS-CoV-2 efficacy of mouth rinses, this review highlights the need to conduct future research with robust and standardized methodologies to confirm effectiveness of mouth rinses.

## AUTHOR CONTRIBUTIONS

AA was responsible for conceptualization, data collection, writing, editing, and finalizing the manuscript. AP and NR were responsible for data collection, editing, and finalizing the manuscript. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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