Aims and Objectives: The detection of SARS-COV-2 in the oral cavity has generated endless claims about the efficacy of using oral mouthwashes to reduce viral load. This review aims to assess the current evidence on the use of oral antiseptics against SARS-CoV-2 and to assess the certainty of the evidence according to the GRADE system. The question this study focussed on was what is the efficacy of oral antiseptics against SARS-CoV-2?

Materials and Methods: A bibliographic search was performed in Medline databases through PubMed, Science Direct, and Google Scholar (until February 2022), using search terms related to COVID-19 and oral antiseptics. Two independent researchers extracted the information from the articles included in an excel form. The identification and selection of the studies was carried out from August 2021 to February 2022.

Results: It was found that oral antiseptics can have a potential beneficial effect on COVID-19, mainly in reducing viral load. However, these potential benefits are mainly based on in-vitro studies or clinical studies with various methodological limitations. At present, the certainty of the evidence is very low due to inconsistency (heterogeneity), moderate-to-high risk of bias, and imprecision of the results.

Conclusion: The certainty of the current evidence on the efficacy of oral antiseptics against SARS-CoV-2 is very low, mainly due to the methodological limitations of the studies. Therefore, for evidence-based decision-making about this intervention, clinical studies with greater methodological rigor are required. Oral antiseptics could present potential benefits in patients with COVID-19 mainly by reducing viral load. However, a careful and conscious evaluation of the evidence is required for decision-making in clinical practice.

KEYWORDS: COVID-19, GRADE approach, mouthwashes, SARS-CoV-2

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INTRODUCTION

The use of oral rinses in dentistry has been a practice that has developed as an adjunct to oral cleaning or as a standard measure before routine dental procedures.[1] This is because they play an important role in reducing microorganisms in the oral cavity.[2-4] Similarly, in this COVID-19 pandemic, oral rinses have been the subject of various studies due to their potential beneficial effect in reducing viral load and without apparent evidence of harm/adverse effects.[1,2,4,5]

Given the various variants of SARS-CoV-2 and the identification of ACE2 as the main protein that enters the host, studies of RNA sequencing profiles have reported a high density of ACE2 in epithelial cells of the oral mucosa.[1,3] Based on this, it was considered that the increase in viral particles in the mouth could favor the progression of the disease in patients infected with COVID-19. Furthermore, high levels of SARS-CoV-2 have been identified in the saliva of asymptomatic infected persons. For this reason, the profession of dentistry has been considered a high-risk activity.[1,3] Therefore,
identifying the role of oral antiseptics against SARS-CoV-2 is of importance and relevance in these times of the COVID-19 pandemic, since knowing if they have a protective role against this virus, could be developed: prevention strategies in the population to reduce cases and control strategies to reduce severe forms of this disease. There are currently in vitro and in vivo investigations that evaluate the use of mouthwashes on the reduction of the clinical manifestations of COVID-19. However, studies are required that can synthesize the information and evaluate the quality of the current evidence on the role of mouthwashes in reducing viral load and their possible preventive use in all health professionals.

This article aims to present a review of the current evidence on the use of conventional and unconventional oral antiseptics against SARS-CoV-2, considering assessing the certainty of the current evidence. The question that was considered in this review was what is the effect of oral antiseptics against SARS-CoV-2?

MATERIALS AND METHODS

SEARCH STRATEGY
A bibliographic search was carried out in the databases of Medline (through PubMed), Scopus, Science Direct, and Google Scholar. Search terms such as “SARS-CoV-2,” “COVID-19,” “Mouthwashes,” “Mouth Rinse,” and specific terms for each oral antiseptic are included. Studies published in Spanish or English were selected, and there was no restriction by date. To carry out the search strategy, it was considered to use the terms related to the population, the intervention, and the type of study. For the selection of the studies, preclinical and clinical studies on the effect of oral antiseptics against SARS-CoV-2 were considered as inclusion criteria. Two researchers performed the search, selection, and extraction of data independently. An Excel form was used to extract the data.

The available evidence for each oral antiseptic is presented in Table 1 with its potential benefits and harms are discussed.

RESULTS
From the initial evaluation, 1658 articles were found, of which 1562 studies were excluded according to the evaluation of the title and abstract. After that, 96 articles were evaluated in full text and 24 studies were finally included [Figure 1].

CHLORHEXIDINE
Chlorhexidine is a broad-spectrum antimicrobial antiseptic agent that acts against bacteria and fungi. In addition, in vitro, it has been shown to have a virucidal effect against influenza, parainfluenza, cytomegalovirus, and herpes virus type 1. Chlorhexidine can bind to the negative charges of bacteria and viruses to eliminate them. About in vitro studies, contradictory results have been reported regarding the reduction of viral load with the administration of this solution.

Concerning clinical studies in hospitalized patients for COVID-19, Yoon et al. found that when taking saliva samples before and after mouthwash with chlorhexidine 0.12% (15 mL for 30 s), the viral load in saliva was reduced below the detectable amount (3 log 10 viral copies/mL) for 2 h after using the mouthwash. Similarly, Eduardo et al. found that, when taking saliva samples before and after the 0.2% chlorhexidine gluconate mouth rinse (15 mL for 30 s), there was a significant reduction in viral load at 60 min (4.2 ± 2.4 times). Furthermore, Elzein et al. took saliva samples after 5 min of mouth rinse with 0.12% chlorhexidine (15 mL for 30 s), and a significant difference of delta cycle threshold [Ct] of the control group (0.52 ± 0.51), and chlorhexidine (6.37 ± 1.08) (P = 0.0024). Ct values are inversely proportional to viral load and are an indirect method to quantify viral load in a sample. On the contrary, Seneviratne et al. evaluated hospitalized patients with COVID-19 and that mouthwash with 0.12% chlorhexidine (15 mL for 30 s) did not reduce the viral load levels (during the first 6 h) when compared with the control group.

Huang and Huang conducted a study in 684 patients hospitalized for COVID-19 and reported that 86% of the associated patients who received the oropharyngeal aerosol mouthwash (chlorhexidine 0.12%) eliminated the SARS-CoV-2 viral load when compared with the group that only received chlorhexidine (62.1%) (P < 0.01). In contrast, Mukhtar et al. evaluated 89 hospitalized patients diagnosed with COVID-19; and they found that in the intervention group (standard treatment + mixed mouthwash [Chlorhexidine gluconate 0.2% + Hydrogen peroxide 6%]) they had less mortality, need for mechanical ventilation, and viral load. Moreover, there was an improvement in the resolution of symptoms, compared with the control group (standard treatment). Nonetheless, this study was at high risk of bias when assessing its certainty of the evidence.

CETYLPYRIDINIUM CHLORIDE (CPC)
It is a cationic quaternary ammonium compound with antibacterial and fungicidal activity and that possesses antiviral activity against some viruses that infect the respiratory tract, such as influenza. The mechanisms of action proposed against the SARS-CoV-2 lie in its lysosomotropic capacity and its disintegrating action on the viral capsid.
| Study                  | Study design | Study sample                                      | SARS-CoV-2 strain | Type of oral antiseptic | Solutions used and method of administration of the intervention | Results                                                                                                                                                                                                 | Conflict of interest |
|-----------------------|--------------|---------------------------------------------------|-------------------|------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Yoon et al. [10] 2020; Korea | Clinical trial | 2 COVID-19 patients Age: 46 and 65 years old      | Unspecified       | CHX                    | Oral rinse: CHX 0.12% (30 s)                                   | CHX 0.12% reduced the viral load in saliva below the detectable amount (3 log 10 viral copies/mL) for up to 2 h after Viral load at 4 days ($P<0.01$): CHX mouthwash reduced viral load by 62.1% and the control group reduced it by 5.5% CHX mouthwash + spray reduced viral load by 86% and the control group reduced it by 6.2% | Undeclared          |
| Huang and Huang [13] 2021; EEUU | RCT          | 684 COVID-19 patients Age: 23–89 years old         | Unspecified       | CHX                    | Intervention 1: CHX 0.12% mouthwash (30 s) bid for 4 days Intervention 2: CHX 0.12% mouthwash (30 s) + CHX oropharyngeal spray 0.12% (5 s) bid for 4 days Control: No use CHX | Viral load at 4 days ($P<0.01$): CHX mouthwash reduced viral load by 62.1% and the control group reduced it by 5.5% CHX mouthwash + spray reduced viral load by 86% and the control group reduced it by 6.2% | Undeclared          |
| Costa et al. [37] 2021 | RCT          | Patients with mild COVID-19 infection Age: 39 ± 12 Male: 50% Hypertension: 17% Diabetes: 4% Obesity: 25% | Unspecified       | CHX                    | Mouthwashes were used (60 s). Saliva samples were collected at baseline, 5 and 60 min later | Differences in Ct values between 5 min evaluation and baseline: GI: 2.19 ± 4.30 GC: -0.40 ± 3.87 Differences in Ct values between 60 min evaluation and baseline: GI: 2.45 ± 3.88 GC: 0.76 ± 4.41 | Undeclared          |
| Hassandarvish et al. [29] 2020; Malaysia | In vitro | Vero E6 cells SARS-CoV-2 (SARS-COV-2/ MY/UM/6-3; TIDREC) | PVP-I             | PVP-I (solution of gargle and mouthwash: 1% and 0.5%) | Both solutions reduced the SARS-CoV-2 virus to 99.9% at 15, 30, and 60 s | CHX reduced the salivary load of SARS-CoV-2 for at least 60 min The four solutions achieved antiviral effectiveness greater than 99.9% against the SARS-CoV-2 virus | Undeclared          |
| Anderson et al. [30] 2020; Singapore | In vitro | Vero E6 cells SARS-CoV-2 (hCoV-19/ Singapore/2/2020) | PVP-I             | 30 s 10% PVP-I (antiseptic solution) 7.5% PVP-I (skin cleanser) 1% PVP-I (gargle and mouthwash) 0.45% PVP-I (throat spray) | The four solutions achieved antiviral effectiveness greater than 99.9% against the SARS-CoV-2 virus | The four solutions achieved antiviral effectiveness greater than 99.9% against the SARS-CoV-2 virus The authors worked for the Mundipharma Laboratory | Undeclared          |
| Martínez-Lamas et al. [25] 2020; España | Case reports | 4 COVID-19 patients Age: 43–74 years old | Unspecified       | PVP-I                    | 1% PVP-I                                                      | Evaluation of viral load in saliva (5 min, 1 h, 2 h, and 3 h) 2/4 (50%) of patients had a significant reduction in viral load that lasted at least 3 h | Undeclared          |
| Study | Study design | Study sample | SARS-CoV-2 strain | Type of oral antiseptic | Solutions used and method of administration of the intervention | Results | Conflict of interest |
|-------|--------------|--------------|-------------------|------------------------|---------------------------------------------------------------|---------|---------------------|
| Khan and Parab, 2021; India | Observational | 6,692 patients from the Otorhinolaryngology Service / s symptoms of COVID-19 | Unspecified | PVP-I | 0.5% PVP-I (gargles, 15 min before + 3–4 nasal drops, tid, 8 d) | Gargling and nasal drops had no adverse effects | Undeclared |
| Guenezan et al., 2021; Francia | RCT | 24 high-risk patients for detection of COVID-19 | Age: 23 and 68 years old | PVP-I | Control: hospital treatment 1% PVP (4 successive rinses + intranasal spray) | The intervention did not influence viral load (changes in viral RNA quantification over time) at 24 and 48 h and 7 days | Undeclared |
| Mohamed et al., 2020; Malaysia | RCT | 20 asymptomatic patients with COVID-19 | Age: 22 and 56 years old | PVP-I | 1% PVP-I (Gargle, tid, 7 d) Essential oils Listerine® (Gargle, tid, 7 d) H2O (Gargle, tid, 7 d) Control: hospital protocol | After the evaluation at 6 d it was found (negative cases): PVP-I: 100% Essential oils: 80% H2O: 20% Control: 0% | Undeclared |
| Gottsauner et al., 2020; Alemanía | Clinical pilot study | 12 patients with COVID-19 (CRP-TR) | Age: 22–81 years old | H2O2 | Viral load count (PCR-TR) and virus culture of oropharyngeal samples. 6% H2O2 (gargle and mouthwash, 20 mL, 30 s) | No significant difference in median viral load was observed between baseline specimen and 30 min post-hydrogen peroxide mouth rinse specimen | Undeclared |
| Di Doménico et al., 2021; Brazil | RCT | 40 patients with COVID-19 (CRP-TR) | Age: <35: n = 4 36–59: n = 20 > 60: n = 11 | H2O2 | Placebo (gargle with mint solution rinses, tid, 30 s) + H2O (nasal wash, bid), 7 d 1% H2O2 (gargle, 30 s) + 0.5% H2O (nasal spray, bid), 7 d | Discharge time (days): P>0.05: H2O2: 3.86±1.60 Placebo: 4.15 ± 1.77 Clinical improvement; P>0.05: HR: 1.06 (95% CI: 0.42–2.68) | Undeclared |
| Giarratana et al., 2021 | In vitro | Vero 76 cells line | Strain: USA_WA1/2020 | HClO | The compound AOS2020 (90% hypochlorous acid) was applied in vitro to a viral solution 10% by: < 1 min 3 min | The AOS2020 90% solution showed a virucidal efficacy greater than 99.8% with < 1 and 3 min against SARS-CoV-2 | Some co-authors work for Applied Pharma Research SA and Eurofins Advinus Limited |
| Study | Study design | Study sample | SARS-CoV-2 strain | Type of oral antiseptic | Solutions used and method of administration of the intervention | Results | Conflict of interest |
|-------|--------------|--------------|-------------------|------------------------|---------------------------------------------------------------|---------|---------------------|
| Carrouel et al., 2021; Francia | RCT | 176 COVID-19 patients Age: 18–85 years old | Unspecified | β-cyclodextrin citrox | Oral rinse for 60 s every 8 h for 7 days: Intervention: β-cyclodextrin 0.1% + citrox 0.01% Control: distilled water | Viral load was reduced in the intervention group: Day 2 vs. 1: –0.38 (–1.39 to 0.00) log 10 Day 3 vs. 1: –0.24 (–1.55 to 0.06) log 10 Day 7 vs. 1: –2.07 (–4.03 to –0.50) log 10 | Partial support by Curaden AG and by the Laboratory “Systemic Health Care” |
| Jain et al., 2021; India | In vitro | Vero E6 cells line | Unspecified | CHX PVP-I | Virus supernatant solution mixed with rinses of: CHX 0.12% for 30 s (A) CHX 0.12% for 60 s (B) CHX 0.2% for 30 s (C) CHX 0.2% for 60 s (D) PVP-I 1% for 30 s (E) PVP-I 1% for 60 s (F) | All compounds showed antiviral efficacy against SARS-CoV-2 A, B: 99.9% C, D, F: > 99.9% E: > 99.8% However, no differences were reported between the solutions evaluated | Undeclared |
| Elzein et al., 2021; República Libanesa | RCT | 61 patients with COVID-19 (CRP-TR) Age: 45.3 ± 16.7 years old | Unspecified | CHX PVP-I | H2O (mouthwash 15 mL, 30 s) 0.2% CHX (mouthwash, 15 mL, 30 s) 1% PVP-I (gargle, 15 mL, 30 s) | Upon evaluation of the viral load, before and 5 min after oral rinse, the ∆Ct values are: CHX: 6.37 ± 0.18 PVP-I: 4.72 ± 0.89 H2O: 0.519 ± 0.519 | Undeclared |
| Mukhtar et al., 2021; Qatar | RCT | 101 positive patients with COVID-19 (PRCR-TR) Control: 49.4 years old Experimental: 49.7 years old | Unspecified | CHX H2O2 | Recovery rate (clinical symptoms and RT-PCR level), tested at 5 and 15 days of treatment Mouthwash + gargle (30 s) tid × 15 days: Intervention: CHX 2% (10 mL) + H2O2 6% (5 mL) Control: standard hospital treatment | Recovery: At 5 days, there was a difference between the conversion of the PCR from positive to negative between the intervention (13.3%) and the control (0%); P < 0.047 At 15 days no difference Mortality at 28 days: 4.4% (n = 2) died in the control and none in the intervention group | Undeclared |
Table 1: Continued

| Study                  | Study design | Study sample                                      | SARS-CoV-2 strain          | Type of oral antiseptic | Solutions used and method of administration of the intervention | Results                                                                 | Conflict of interest |
|------------------------|--------------|---------------------------------------------------|-----------------------------|-------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------|
| Pelletier et al.,[31] 2020; USA | *In vitro* | Vero E6 cells                                      | SARS-CoV-2, USA-WA1/2020    | PVP-I, Ethanol           | PVP-I (oral rinse antiseptic: 1%, 1.5%, 3%) PVP-I (nasal antiseptic: 1%, 2.5%, 5%) Ethanol | SARS-CoV-2 virus and LRV titers were effectively reduced by >4 log10 CCID50/mL of infectious virus (5.3 to 1) | Some authors (Veloce BioPharma) |
| Bidra et al.,[27] 2020; USA | *In vitro* | Vero E6 cells                                      | SARS-CoV-2, USA-WA1/2020    | PVP-I, H2O2, Ethanol     | PVP-I (oral rinse: 1%, 2.5%, 3%) H2O2 (3%, 6%) Ethanol            | At 15–30 s: All PVP-I solutions → virucidal effect. H2O2 solutions → minimal virucidal activity | Undeclared |
| Bidra et al.,[27] 2020; USA | *In vitro* | Vero E6 cells                                      | SARS-CoV-2 virus, strain USA-WA1/2020 | PVP-I, Ethanol           | PVP-I (oral rinse antiseptic: 0.5%, 1%, 1.5%) 70% Ethanol H2O2    | PVP-I (0.5%, 1%, 1.5%): reduced viral load within 15 s Ethanol: reduced viral load after 30 s | Undeclared |
| Seneviratne et al.,[4] 2021; Singapore | RCT         | 16 SARS-CoV-2-positive patients Age: 27 and 52 years old | Unspecified                 | PVP-I, CHX, CPC, Water | Mouthwash (30 s) 0.5% PVP-I 0.2% CHX 0.075% CPC Water Mouthwash: Placebo (60 s) 0.075% CPC + 0.28% Zn (30 s) 1.5 H2O2 (60 s) 0.12% CHX (30 s) 1.5% H2O2 (60 s) + 0.12% CHX (30 s) | There is no difference in viral load between the groups (basal, 5 min, 3 h, and 6 h) The viral load on CPC and PVP-I remained low for up to 6 h | Undeclared |
| Eduardo et al.,[11] 2021; Brazil | RCT         | 60 patients with COVID-19 (PRC-TR) Age: 34–88 years old | Unspecified                 | CPC, H2O2, CHX           | Mouthwash: Placebo (60 s) 0.075% CPC + 0.28% Zn (30 s) 1.5 H2O2 (60 s) 0.12% CHX (30 s) 1.5% H2O2 (60 s) + 0.12% CHX (30 s) | Viral load in saliva: baseline (T0), immediately (T1), 30 min (T2), and 60 min (T3) Viral load: CPC + Zn: reduction to 1 h (2.6 ± 0.1) H2O2: reduction to 30 min (6.5 ± 3.4) CHX: reduced viral load T1 (2.1 ± 1.5), T2 (6.2 ± 3.8), T3 (4.2 ± 2.4) H2O2 + CHX: did not reduce viral load T1 (2.1 ± 0.5), T2 (1.6 ± 0.2), T3 (3.9 ± 0.3) Viral load evaluation at 30, 60, and 120 min | Some co-authors work for Colgate-Palmolive Company |
| Ferrer et al.,[33] 2021 | RCT         | Patients with moderate-to-severe COVID-19 infection Age: 54.5 (19–87) years old | Unspecified                 | PVP-I, H2O2, CPC, CHX    | Mouthwashes (60 s) were performed and saliva samples were collected. PVP-I 2% (n=18) H2O2 1% (n=16) CPC 0.07% (n=17) CHX 0.12% (n=17) H2O2 13 (n=16) | Viral load evaluation at 30, 60, and 120 min There were no statistically significant changes in salivary viral load with the use of the different mouthrinses | Undeclared |
| Study                  | Study design | Study sample | SARS-CoV-2 strain | Type of oral antiseptic | Solutions used and method of administration of the intervention | Results                                                                 | Conflict of interest |
|-----------------------|--------------|--------------|-------------------|-------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------|---------------------|
| Meister et al.,[5] 2020; EEUU | In vitro     | 50,000 Vero E6 cells | Strain 1: UK Essen–Germany | H₂O₂, CHX, PVP-I, Ethanol, OCT, PHMB | Three virus strains were exposed *in vitro* (30 s) to H₂O₂ (A), dequalinium chloride/benzalkonium chloride (C), CHX (B and D), PVP-I (E), ethanol w/essential oils (F), OCT (G), and PHMB (H) | The rinses reduced viral infectivity (reduction of TCID50/mL) significantly compared to the control: C, E, and F are reduced by more than 3 logarithmic magnitudes A, B, D, and G reduced between 0.3 and 1.78 log magnitudes H reduced the log magnitudes by more than 0.61 (strain 1), 1.78 (strain 2), and 1.61 (strain 3) | Undeclared          |
| Davies et al.,[9] 2021; Inglaterra | In vitro     | Vero E6 cells line | SARS-CoV-2 strain England 2 | NaF/ZnF₂, K₂OX, HClO, PVP-I, CHX, H₂O₂ | A solution with virus supernatant mixed for 60 s with the rinses: NaF/ZnF₂ (A), K₂OX 1.4% (B), HClO 0.001–0.02% (C), PVP-I 0.58% (D), CHX 0.2% (E), H₂O₂ 1.5% (F) | It was determined that they only presented significant virucidal effects (95% CI): A: TCID50/mL = ≥4.1 (3.8–4.4) log 10 B: TCID50/mL = ≥3.5 (3.2–3.8) log 10 C: TCID50/mL = ≥5.5 (5.2–5.8) log 10 D: TCID50/mL = ≥4.1 (3.8–4.4) log 10 | Undeclared          |

H₂O = water, PVP-I = povidone-iodine, H₂O₂ = hydrogen peroxide, Zn = zinc, CHX = chlorhexidine, CPC = cetylpyridinium chloride, OCT = octeidine dihydrochloride, PHMB = polyaminopropyl biguanide, NaF = sodium fluoride, ZnF₂ = zinc fluoride, K₂OX = dipotassium oxalate, HClO = hypochlorous acid, LRV = log reduction value, HR = hazard ratio, tid = three times a day, bid = twice times a day
Eduardo et al.\textsuperscript{[11]} conducted a study in hospitalized patients with a diagnosis of SARS-CoV-2 and found that the combination of mouthwash with CPC 0.075% + Zinc lactate 0.28% (20 mL for 30 s) significantly reduced the viral load at 60 min after the rinse (2.6 ± 0.1 times).

Seneviratne et al.\textsuperscript{[14]} reported that mouthwash with CPC 0.075% (20 mL for 30 s) significantly reduced viral load levels [increase in the change of Ct times at 5 min (1) and 6 h (0.9)]; $P < 0.05$ compared with a control group.

**Hypochlorous Acid**

It is a disinfectant agent that has potent antiviral activity due to its ability to form chloramines and nitrogen-derived radicals, destroying the genetic material of the virus.\textsuperscript{[18]}

Davies et al.\textsuperscript{[9]} found that the two hypochlorous acid solutions, 0.01%, and 0.02%, significantly reduced (TCID\textsubscript{50}/mL≥5.5) the SARS-CoV-2 viral load. Similarly, Giarratana et al.\textsuperscript{[19]} evaluated the virucidal effect against SARS-CoV-2 of a solution, designed for disinfection of the upper airways, composed of 95% hypochlorous acid, and stabilized with a hypotonic solution. The said study found that this solution presented an efficacy greater than 99.8% of virucidal activity when it was subjected \textit{in vitro} to an exposure time of <1 min. In addition, it was found that there was no mucosal toxicity.

**Hydrogen Peroxide**

Hydrogen peroxide is a reactive and oxidizing antiseptic that destabilizes the lipid membranes of some viruses, by adding free radicals, when used in concentrations around 0.5%\textsuperscript{[30]}. Ortega et al.\textsuperscript{[21]} in their systematic review evaluated the virucidal effect of hydrogen peroxide, used as a mouthwash at any concentration. However, not sufficient evidence was found to demonstrate the virucidal effect of hydrogen peroxide on the SARS-CoV-2 virus. This could be due to the almost instantaneous disintegration of the peroxide, which would not prevent immediate recontamination. For this reason, it is important to have solutions with high substantivity, slow-release, and a longer duration of the potential virucidal effect.

Di Domênico et al.\textsuperscript{[20]} conducted a study in patients diagnosed with COVID-19 and found no differences in viral load between the experimental group (nasal wash with 0.5% hydrogen peroxide and gargle with 1% hydrogen peroxide for 30 s; 3 times/day for 7 days) and control group. Similarly, Gottsauner et al.\textsuperscript{[22]} conducted a study in patients hospitalized for COVID-19, who were administered 1% hydrogen peroxide (20 mL for 30 s) and the viral load was quantified in oropharyngeal samples (before and 30 minutes later) without finding significant differences. Nevertheless, Eduardo et al.\textsuperscript{[11]} reported that the administration of 10 mL of 1.5% hydrogen peroxide for 60 s reduced the viral load after 30 min (6.5 ± 3.4), but at 60 min no effect.

**Povidone-Iodine**

Povidone-iodine is a broad-spectrum antimicrobial widely used for disinfection of skin, mucosa, and surfaces. Furthermore, a potential effect on enveloped and non-enveloped viruses has been found.\textsuperscript{[12]}

\textit{In-vitro} studies have been carried out, in which povidone-iodine 0.23% has shown virucidal activity on the Ebola virus, SARS-CoV, and MERS-CoV.\textsuperscript{[17,23]} It has been reported that administration as a mouthwash, gargle, or nasal spray of povidone-iodine in concentrations between 0.5% and 2.5% can reduce the viral load (SARS-CoV-2) for up to 3 h in applications between 15 and 30 s.\textsuperscript{[12,24]}

Seneviratne et al.\textsuperscript{[4]} conducted a study in hospitalized patients with COVID-19, who were administered 0.5% povidone-iodine and distilled water as mouthwashes for 30 s. It was found that povidone-iodine at 6 h showed a decrease in viral load compared with distilled water (significant increase in the difference in Ct by 1). In addition, Elzein et al.\textsuperscript{[12]} found that the administration of 15 mL of 1% povidone-iodine as a mouthwash reduced viral load (change in Ct values: 4.72 ± 0.89) compared with the control group (distilled water). Likewise, Martinez-Lamas et al.\textsuperscript{[25]} followed four patients diagnosed with COVID-19, who were administered 1% povidone-iodine rinses for 1 min. Then a saliva sample was taken to assess viral load (before, 5 min, 1 h, 2 and 3 h later) and found a significant reduction in two patients for at least 3 h. Furthermore, Mohamed et al.\textsuperscript{[26]} evaluated the effect of gargling 10 mL of 1% povidone-iodine for 30 s in asymptomatic
patients diagnosed with COVID-19, reporting that the SARS-CoV-2 virus was not detected at 4, 6, and 12 days. However, Guenezan et al.\textsuperscript{[24]} conducted an randomized controlled trial (RCT) in adults diagnosed with COVID-19. Participants in the first group gargled with 0.5% povidone-iodine and rinse with 25 mL of 1% povidone-iodine, a nasal spray of the same solution was applied to the second group, and a topical application of 10 povidone-iodine was applied to the third group % (4 times/day for 5 days). Then, the viral load was quantified before starting and then repeated on days 3, 5, and 7. A reduction in viral loads was found, but there was no significant difference when compared with the control group.

Regarding the damage, it has been reported that the local administration of 0.5% povidone-iodine as gargles and nasal drops does not cause irritation or alterations to the thyroid or dental tissues.\textsuperscript{[23]}

**Discussion**

The use of mouthwashes prior to dental procedures is not something new. However, its use against SARS-CoV-2 has become a therapeutic and preventive alternative. Among the main findings of the effect of each mouthwash against SARS-CoV-2, it was found that chlorhexidine and cetylpyridinium chloride as a mouthwash present limited evidence on their potential benefits against SARS-CoV-2 by reducing viral load. Clinical studies show that it could reduce viral load within the first few hours of evaluation.

We found that the use of mouthwashes could reduce viral load, mainly with the use of cetylpyridine chloride, although the evidence is uncertain.

In the case of the use of hydrogen peroxide, it is attributed to an oxidative effect capable of reducing the viral load. However, this oxidative effect is immediate and is not sustained over time. Ortega et al.\textsuperscript{[21]} reported that this was caused by low substantivity, which is why a slow and sustained release solution is required over time.

Mild antiviral activity of hydrogen peroxide was seen in studies in which concentrations up to 6% over 60 s were needed to reduce viral load. This somehow evidences its low potency compared with other oral rinses that, with a lower concentration and shorter exposure time, managed to reduce the viral load.\textsuperscript{[27]}

In contrast, povidone-iodine demonstrated an antiviral effect in both in-vitro and in-vivo studies. The released iodine destabilizes the lipid envelope favoring the lysis of spike proteins as well as reducing free radicals.\textsuperscript{[28]} Although the evidence is uncertain, povidone-iodine has shown an effect in reducing SARS-CoV-2 predecessor viruses such as severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS).\textsuperscript{[29]} Against SARS-CoV-2, mainly in-vitro studies have been found in which there was a reduction in viral load even at low concentrations. Anderson et al.\textsuperscript{[30]} reported that 99.9% of viral load eradication was achieved even with 0.45% and 30 s of exposure. Similar results were reported by Jain et al.,\textsuperscript{[8]} Pelletier et al.,\textsuperscript{[31]} and Bidra et al.,\textsuperscript{[27,22]} who used solutions between 0.5% and 6%.

Clinical studies are very limited; case series such as those by Martinez-Lamas et al.\textsuperscript{[25]} and Mohamed et al.\textsuperscript{[32]} reported a potential beneficial effect of the use of oral mouthwashes. Elzein et al.\textsuperscript{[26]} designed an RCT and found a reduction in viral load after the use of 2% chlorhexidine and 1% povidone-iodine for 30 s. This coincides with that reported by Seneviratne et al.,\textsuperscript{[4]} who observed a reduction in viral load of up to 6 h with the use of 0.5% povidone-iodine. However, Guenezan et al.\textsuperscript{[24]} and Ferrer et al.\textsuperscript{[33]} found no statistical difference in viral load after the use of this oral mouthwash. These differences may be due to the clinical variability (different severity of the disease) of the patients included in these studies or to the variability in the methodology. Garcia-Sánchez et al.\textsuperscript{[34]} conducted a systematic review of RCTs and reported a significant virucidal capacity of povidone-iodine at 0.5% and 1%. However, they did not find a benefit in the reduction of SARS-CoV-2 viral load in saliva with the 2% concentration at 30 and 60 s. However, they state that the evidence is currently uncertain and that more RCTs are required.

In contrast, Verma et al.\textsuperscript{[35]} in their systematic review on mouthwashes against SARS-CoV-2 mention that povidone-iodine, chlorhexidine, and essential oils were effective in reducing viral load under in-vitro and in-vivo conditions. Currently, there is very little evidence to support its beneficial protective effect against COVID-19. Furthermore, on the contrary, Chen and Chang\textsuperscript{[36]} conducted a review of original and review articles on the effectiveness of oral mouthwashes in reducing the oropharyngeal viral load of SARS-CoV-2. They concluded that in-vitro studies, povidone-iodine, cetylpyridinium chloride, and essential oils with ethanol showed virucidal effects on SARS-CoV-2. In addition, they mentioned that based on clinical studies, povidone-iodine, cetylpyridinium chloride, hydrogen peroxide, and chlorhexidine reduced the oropharyngeal viral load of SARS-CoV-2. Likewise, Garcia-Sánchez et al.\textsuperscript{[34]} in a systematic review of RCTs reported that
povidone-iodine, chlorhexidine, and cetylpyridinium chloride have significant virucidal activity against SARS-CoV-2 in saliva, which could reduce the risk of cross-infection.

An important factor studied in the evaluation of the effectiveness of oral antiseptics against SARS-CoV-2 was the exposure time. In the RCTs evaluated for the present study, not only the comparison of multiple antiseptic solutions is made, but also the time of exposure to them, the time most frequently reported in the studies being 60 s, to then perform the final evaluation of the antiviral effect at 30, 60, and in some investigations up to 120 min after the intervention.\[31,37\] In addition, several in-vitro studies have been performed on Vero E6 cell lines, using different solutions; some were oral solutions (oral antiseptic solutions, gargle and rinse solutions, sprays); the studies showed a reduction of viral load after exposure for at least 15, 30, and 60 s, even at low concentrations.\[27,29,30,32\]

The assessment of the certainty of the evidence with the GRADE system consists of several domains such as study design, risk of bias, inconsistency, indirect evidence, imprecision, and other considerations such as publication bias.

When evaluating the studies, there are several limitations, first, about the study design, the preclinical studies (in vitro and in vivo) inherently have their limitations due to their design, since they are carried out in laboratory settings, it is not possible to simulate the physiological conditions in clinical settings. Regarding the risk of bias, we can mention that in the clinical studies some did not present a control group, they did not show baseline characteristics of the patients (sociodemographic, clinical such as the presence of comorbidities, use of previous medication, oral conditions, oral hygiene behaviors), which can alter the efficacy results of oral antiseptics. This can lead to unbalanced groups from the beginning, which does not allow an adequate comparison. Moreover, the studies have small sample sizes, which increase the imprecision of the results (evidenced by the wide confidence intervals) and limit the external validity of the reported results. In contrast, it is important to mention that the cytotoxic effects of antiseptics should be evaluated in advance to determine their inherent virucidal activity.

Two sources of heterogeneity were found: methodological and clinical. Regarding the methodological heterogeneity, the studies, although they performed molecular tests (real-time polymerase chain reaction) for the detection of SARS-CoV-2, used different ways of collecting samples such as a nasopharyngeal swab, pharyngeal swab, or salivary sample. This could affect the comparison of results between studies due to the detection of SARS-CoV-2 RNA and the consequent measurement of viral load. Similarly, there was variability in the way the intervention was administered by mouthwashes alone, gargles, or in combination with the application of nasal drops/nasal wash. On the contrary, about clinical heterogeneity, we find that the studies were carried out in different populations such as countries in America, Europe, and Asia.

PAHO\[38\] conducts a systematic review to evaluate the effect of oral rinses in patients with COVID-19. Outcomes prioritized are mortality, the need for invasive mechanical ventilation, resolution of symptoms, and adverse events. They found that there was very low certainty of the evidence mainly due to the risk of bias (blinding not specified, unclear with allocation concealment, etc.), imprecision, and heterogeneity of the results.

This review is limited by the study design itself. This is because, as it is not a systematic review, there is the possibility of not having found studies that answered the research question. However, a search with keywords and specific terms in the most relevant databases in oral health was considered. In contrast this review presents as strength that an evaluation of the certainty of the evidence was included in the analysis of the evidence, considering its components for informed decision-making in oral health.

**Conclusions**

Therefore, considering that the certainty of the evidence on the efficacy of oral mouthwashes against SARS-CoV-2 is very low (due to the high risk of bias of the studies, high methodological-clinical heterogeneity, and the small sample sizes that lead to the imprecision of the estimates), so far no decision could be made to implement this intervention as a public health measure. To evaluate the efficacy of these oral mouthwashes, RCTs are required that have an adequate methodological design that has controlled their main sources of bias and that allows them to be used as evidence for decision-making.

Misinformation or dissemination of inadequate information in the population can lead to the relaxation of protection measures against COVID-19 because it can induce a false sense of security, which would cause an increase in the number of infections. Evaluating the balance of benefits and harms considering the components assessed in the GRADE system (risk of bias, imprecision, heterogeneity, indirect evidence, and publication bias) will allow decision-makers to have
greater clarity when establishing strategies for public health measures.

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CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.

AUTHORS CONTRIBUTIONS
VCC and LCR participated in the conception and design of the article, writing, and review. ERR, CFQ and CEP have participated in the writing and critical review of the article. All authors read and approved the final version of the article.

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