Antiviral effect of mouthwashes against SARS-COV-2: A systematic review

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Received 7 July 2021; revised 21 January 2022; accepted 25 January 2022
Available online 1 February 2022

Abstract Objective: This systematic review aimed to evaluate the antiviral effect of mouthwashes against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Material and methods: An electronic search was performed on PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ProQuest, and Google Scholar, and was complemented by a manual search. Both clinical and in vitro studies that focused on the antiviral effect of mouthwashes against SARS-CoV-2 were included. Risk of bias assessment was performed only on the clinical studies using the RoB-2 and ROBINS-I tools.

Results: A total of 907 records were found; after initial selection by title and abstract, 33 full-text articles were selected to be evaluated for eligibility. Finally, a total of 27 studies were included for the qualitative synthesis, including 16 in vitro studies and 11 clinical trials. Antiviral effects were evaluated separately for the in vitro and clinical studies. In vitro studies included mouthwashes containing hydrogen peroxide, chlorhexidine digluconate, povidone-iodine, essential oils, cetylpyridinium chloride, and other compounds; in vivo studies included mouthwashes containing hydrogen peroxide, chlorhexidine digluconate, povidone-iodine, cetylpyridinium chloride, essential oils, chlorine dioxide, β-cyclodextrin-citrox, and sorbitol with xylitol. Povidone-iodine, cetylpyridinium chloride, and essential oils were effective in vitro, while hydrogen peroxide, chlorhexidine digluconate, povidone-iodine, cetylpyridinium chloride, and sorbitol with xylitol were effective in vivo. Unclear or high risk of bias was found for almost all clinical studies,

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Peer review under responsibility of King Saud University.
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mainly transmitted by respiratory droplets expelled when speaking, breathing, coughing, and sneezing, and by contact between objects contaminated by these droplets and the mucosa (J. Xu et al., 2020; R. Xu et al., 2020). The virus accumulates and replicates in the upper respiratory tract, as high viral loads can be found in the oral cavity, nose, and oropharynx in patients affected with the 2019 coronavirus disease (COVID-19) (Wölfel et al., 2020; Zou et al., 2020). A prolonged viral load is found in the sputum of infected patients (Wölfel et al., 2020), as saliva is a viral reservoir in patients with asymptomatic to mild COVID-19 (R. Xu et al., 2020), a possible method to decrease the amount of SARS-CoV-2 in saliva could be through mouthwash use, as some reagents target the outer lipid membrane of the virus (F. Carrouel et al., 2021; Gottsauner et al., 2020).

Mouthwashes containing chlorhexidine digluconate (CHX), cetylpyridinium chloride (CPC), povidone-iodine (PVP-I), and essential oils have been shown to reduce the viral load of SARS-CoV-2 in vitro and clinically (Elzein et al., 2021; Meister et al., 2020; Mohamed et al., 2020; Seneviratne et al., 2021; Statkute et al., 2020), highlighting their potential for use against COVID-19. Although mouthwash use is practical and affordable, scientific evidence is urgently needed to support its use against COVID-19 spread. Hence, the present systematic review aimed to evaluate the antiviral effect of mouthwashes against SARS-CoV-2.

2. Materials & methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) guidelines (Page et al., 2021). The protocol was registered in PROSPERO after the preliminary search was performed (identification number: CRD42021236134). The following review question was addressed: Does the use of certain mouthwashes have an antiviral effect on SARS-CoV-2?

The PICO strategy was as follows:
- Population: Adult patients with or without COVID-19; samples of saliva, sputum, oral plaque, or oral tissue.
- Intervention: Use of any mouthwash, including hydrogen peroxide (H₂O₂), CHX, PVP-I, CPC, or another antiviral compound, at any concentration.
- Comparator: No intervention.
- Outcome: In vitro studies: SARS-CoV-2 strains.

Although povidone-iodine, cetylpyridinium chloride, and essential oils may be an alternative to reduce the viral load in vitro and in vivo, more studies are needed to determine the real antiviral effect of these different mouthwashes against SARS-CoV-2. This work was not funded. The protocol was registered in PROSPERO (identification number: CRD42021236134).
Mouthwashes antiviral effect against SARS-CoV-2

2.1. Search strategy

The following databases were assessed for the article search: PubMed, Scopus, Web of Science, Cochrane Library, and LILACS. ProQuest and Google Scholar were also searched. The electronic search was complemented by a manual search of the list of references of the items included. The final search was conducted until April 12th, 2021. A complementary update of the search was performed until September 30th, 2021. There were no limitations, publication date restrictions, or language restrictions.

Keywords used for the search comprised MeSH and free text terms: 'hydrogen peroxide', 'acetylpyridine', 'cetylpyridinium chloride', 'chlorhexidine digluconate', 'povidone iodine', 'mouthwash', 'mouth rinse', 'oral rinse', 'mouth bath', 'mouth wash', 'mouth washes', 'oral collutory', 'COVID-19', 'SARS-CoV-2', and 'coronavirus'.

The following search strategy was used in PubMed without any limit or filter, and then adapted for the other databases: (COVID-19 OR SARS-COV-2 OR coronavirus) AND ("hydrogen peroxide" OR "cetylpyridinium chloride" OR acetylpyridine OR "chlorhexidine digluconate" OR chlorhexidine OR "povidone iodine" OR iodopovidone OR "mouth rinse" OR rinse OR "oral rinse" OR "mouth bath" OR "mouth wash" OR mouthwash OR collutory).

Study selection was based on the predefined eligibility criteria, considering both published and unpublished studies. The web application Rayyan QCRI was used for the study selection process. Reviewer calibration was performed previously, obtaining a suitable inter-rater reliability value (K = 0.71).

Study selection by title and abstract was independently performed by two reviewers (GTSB and BPTU). In cases of disagreement, a third reviewer (JPIMM) would participate in the final decision when necessary. The final study selection by full-text article was performed by the initial two reviewers, based on the selection criteria. Disagreements were discussed with the same third reviewer and consensus was sought.

2.2. Selection criteria

Inclusion criteria:

- Randomized controlled trials (RCT); non-randomized controlled trials (non-RCT); and cohort, case-control, and cross-sectional studies evaluating the antiviral effect, virucidal effect, or decrease in viral load against SARS-CoV-2 after mouthwash use.
- Clinical studies that included adult patients with or without COVID-19; studies using saliva, sputum, oral plaque, or oral tissue samples.
- In vitro studies with a detailed protocol that studied the antiviral effect, virucidal effect, or decrease in viral load of SARS-CoV-2 after mouthwash use.
- In vitro studies that evaluated the action of mouthwashes against SARS-CoV-2 strains.

Exclusion criteria:

- Case report studies, experts’ opinions, animal studies, literature reviews.
- Studies only in children or adolescent patients.
- Studies with patients diagnosed with any systemic disease that could affect the results.
- Studies with disabled patients with difficulties in performing oral care.
- In vitro studies using microorganisms other than SARS-CoV-2.

2.3. Data extraction

Data extraction was performed independently by four reviewers (JPIMM, RPCP, PSGHL, and DAPR), considering the following parameters: author; year of publication; country; sample number; patient age; intervention and control group; virus strain; mouthwash concentration; mouthwash dosing; decrease in viral load, antiviral, or virucidal effect; decrease in viral count; and percentage of viral inactivation. Data extraction was analyzed separately for in vitro and clinical studies.

2.4. Risk of bias assessment

The tools for assessing the risk of bias in interventional studies (RoB-2 for RCT (Sterne et al., 2019) and ROBINS-I for non-RCT (Sterne et al., 2016)) were used. No risk of bias assessment was performed for in vitro studies.

The risk of bias assessment was performed independently by two reviewers (KHUK, JM), considering a high, unclear, or low risk of bias. In the case of insufficient or unclear data, the study author was contacted for clarification. Discrepancies were identified and resolved through a discussion by the reviewers. The RevMan (Review Manager Software version 5.4, Cochrane Collaboration, Copenhagen, Denmark) program was used to analyze the risk of bias figures.

2.5. Strategy for data synthesis

A narrative analysis of the included studies was conducted, dividing the studies by their design into in vitro and clinical studies. No quantitative analysis was performed.

Study outcomes, such as the decrease in viral load, antiviral effect, virus count, or virucidal effect against SARS-CoV-2 after mouthwash use were considered, and were expressed as cycle threshold (Ct) reduction, percentage of virus inactivation, plaque forming unit count, log reduction, or any other representative value to evaluate virus reduction before and after treatment.

3. Results

The total search resulted in 907 records, including the articles found upon searching the databases and in other resources. A total of 368 duplicates were removed, leaving 539 records for title and abstract assessment. Then, 33 articles were selected by title and abstract for their full text to be evaluated for
eligibility. Six articles were excluded, leading to a total of 27 titles included in the qualitative synthesis. The PRISMA flow-chart is shown in Fig. 1.

The final studies included 16 in vitro studies (Anderson et al., 2020; Bidra et al., 2020b, 2020a; Davies et al., 2021; Hassandarvish et al., 2020; Jain et al., 2021; Koch-Heier et al., 2021; Komine et al., 2021; Meister et al., 2020; Muñoz-Basagoiti et al., 2021; Pelletier et al., 2021; C. A. Santos et al., 2021; P. S. da S. Santos et al., 2021; Statkute et al., 2020; Steinhauser et al., 2021; Xu et al., 2021), and 11 clinical studies, including 9 RCTs (Avhad et al., 2020; Florence Carrouel et al., 2021a; Chaudhary et al., 2021; Choudhury et al., 2020; Eduardo et al., 2021; Elzein et al., 2021; Guenezan et al., 2021; Mohamed et al., 2020; Seneviratne et al., 2021) and two non-RCTs (Gottsauner et al., 2020; Schürmann et al., 2021). Due to the moderate to high risk of bias obtained in most clinical studies, no further quantitative analysis was performed.

3.1. Measurement of exposures and outcomes

Table 1 shows the summary of data from the in vitro studies. Mouthwashes with \( \text{H}_2\text{O}_2 \), CHX, PVP-I, essential oils, CPC, CPC + \( \text{H}_2\text{O}_2 \), CHX + CPC, octenidine dihydrochloride, anionic phthalocyanine derivate (APD), dequalinium chloride + benzalkonium chloride, polyaminopropyl biguanide (polyhexanide), ethanol + ethyl lauroyl arginate, delmopinol, dipotassium oxalate, and stabilized hypochlorous acid were studied. Results varied for mouthwashes of different concentrations.

Table 2 presents the summary of data from the clinical studies. Mouthwashes containing \( \text{H}_2\text{O}_2 \), CHX, PVP-I, CPC, CPC + zinc lactate, \( \text{H}_2\text{O}_2 \) + CHX, essential oils, chlorine dioxide, β-cyclodextrin-citrox (CDCM), and sorbitol + xylitol were used. Results varied for mouthwashes of different concentrations.
Table 1 Summary of data from *in vitro* studies.

| Study | SARS-CoV-2 strain | Sample | Mouthwash | Time | Measurement | Results | Study remarks |
|-------|------------------|--------|-----------|------|-------------|---------|---------------|
| Meister et al., 2020 (Meister et al., 2020) | Strain 1: UKEssen strain | n = 3 | Group A: H₂O₂ – Cavex Oral Pre Rinse | 30 sec | Quantitative suspension test: tissue culture infective dose (TCID₅₀/mL) | Significant reduction of strains 1–3 | Different strains of SARS-CoV-2 can be inactivated efficiently by commercial mouth rinses *in vitro*. |
|       | Strain 2: BetaCoV/ Germany/ Ulm/01/ 2020 |        | Group B: CHX – Chlorhexamed Forte |      |             |         |               |
|       | Strain 3: BetaCoV/ Germany/ Ulm/02/ 2020 (Germany) |        | Group C: Dequalinium chloride, benzalkonium chloride – Dequonal |      |             |         |               |
|       |       |        | Group D: CHX – Dynexidine Forte 0.2% |      |             |         |               |
|       |       |        | Group E: PVP-I – Iso-Betadine mouthwash 1.0% |      |             |         |               |
|       |       |        | Group F: Ethanol, essential oils – Listerine Cool Mint |      |             |         |               |
|       |       |        | Group G: Octenidine dihydrochloride – Octenident mouthwash |      |             |         |               |
|       |       |        | Group H: Polyaminopropyl biguanide (polyhexanide) – ProntOral mouthwash |      |             |         |               |
|       |       |        | Control: organic secretion |      |             |         |               |

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| Study | SARS-CoV-2 strain | Sample | Mouthwash | Time | Measurement | Results | Study remarks |
|-------|-------------------|--------|------------|------|-------------|---------|---------------|
| Bidra et al., 2020 *(Bidra et al., 2020a)* | USA-WA1/2020 strain (USA) | n = 3 | Group 1: PVP-I 0.5% oral rinse – Veloce BioPharma | 15 sec, 30 sec | Standard end-point dilution assay: 50% cell culture infectious dose (CCID50) of virus per 0.1 mL | Group 1: PVP-I 0.5% | PVP-I mouth rinse could reduce the SARS-CoV-2 viral load at all concentrations at 15 and 30 s. |
| | | | Group 2: PVP-I 1.25% oral rinse – Veloce BioPharma | | | Group 2: PVP-I 1.25% | |
| | | | Group 3: PVP-I 1.5% oral rinse – Veloce BioPharma | | | Group 3: PVP-I 1.5% | |
| | | | Group 4: $\text{H}_2\text{O}_2$ 1.5% – Sigma-Aldrich | | | Group 3: PVP-I 1.5% | |
| | | | Group 5: $\text{H}_2\text{O}_2$ 3.0% – Sigma-Aldrich | | | Group 4: $\text{H}_2\text{O}_2$ 1.5% | |
| | | | Positive control: Ethanol 70% | | | | |
| | | | Negative control: Water | | | | |
| | | | | | | | |
| Bidra et al., 2020 *(Bidra et al., 2020b)* | USA-WA1/2020 strain (USA) | n = 3 | Group 1: PVP-I 1.5% oral rinse – Veloce BioPharma | 15 sec, 30 sec | Standard end-point dilution assay: 50% cell culture infectious dose (CCID50) of virus per 0.1 mL | Group 1: PVP-I 1.5% | PVP-I mouth rinse could reduce the SARS-CoV-2 viral load at all concentrations after 15 and 30 s. |
| | | | Group 2: PVP-I 0.75% oral rinse – Veloce BioPharma | | | Group 2: PVP-I 0.75% | |
| | | | Group 3: PVP-I 0.5% oral rinse – Veloce BioPharma | | | Group 3: PVP-I 0.5% | |
| | | | Positive control: Ethanol 70% | | | | |
| | | | Negative control: Water | | | | |
| | | | | | | | |
### Table 1  (continued)

| Study | SARS-CoV-2 strain | Sample | Mouthwash | Time | Measurement | Results | Study remarks |
|-------|------------------|--------|-----------|------|-------------|---------|--------------|
| Anderson et al., 2020 (Anderson et al., 2020) | hCoV-19/ Singapore/ 2/2020 (Singapore) | n = 3 | Group 1: PVP-I 10% antiseptic solution – BETADINE Group 2: PVP-I 0.45% throat spray – BETADINE Group 3: PVP-I 7.5% antiseptic skin cleanser – BETADINE Group 4: PVP-I 1.0% gargle and mouth wash – BETADINE Group 5: PVP-I 1.0% (1:2 dilution) gargle and mouth wash – BETADINE Control: PBS | 30 sec | Viral kill time assay: median tissue culture infectious dose (TCID50/mL) | Group 1: PVP-I 10% Antiseptic solution log10 reduction: ≥4.00 Group 2: PVP-I 0.45% Throat spray log10 reduction: ≥4.00 Group 3: PVP-I 7.5% Antiseptic skin cleanser log10 reduction: ≥4.00 Group 4: PVP-I 1.0% Gargle and mouth wash log10 reduction: ≥4.00 Group 5: PVP-I 1.0% (1:2 dilution) Gargle and mouth wash log10 reduction: ≥4.00 | All PVP-I solutions showed great virucidal activity against SARS-CoV-2 after 30 s, corresponding to a ≥ 99.99% kill for all products. |
| Hassandarvish et al., 2020 (Hassandarvish et al., 2020) | SARS-CoV-2/ MY/UM/6-3; TIDREC (Malaysia) | Not mentioned | Group 1: PVP-I 1.0% gargle and mouth wash – BETADINE Group 2: PVP-I 0.5% gargle and mouth wash – BETADINE Control: Distilled water | 15 sec, 30 sec, 60 sec | Virus time-kill assay: Median tissue culture infectious dose (TCID50/mL). | Group 1: PVP-I 1.0% Gargle and mouth wash 15 sec: log10 reduction: > 5.00 30 sec: log10 reduction: > 5.00 60 sec: log10 reduction: > 5.00 Group 2: PVP-I 0.5% Gargle and mouth wash 15 sec: log10 reduction: > 4.00 30 sec: log10 reduction: > 5.00 60 sec: log10 reduction: > 5.00 | Both concentrations of PVP-I showed potent and rapid virucidal activity against SARS-CoV-2 at 15, 30 and 60 s. |

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| Study                        | SARS-CoV-2 strain | Sample                                                                 | Mouthwash                  | Time | Measurement                              | Results                                           | Study remarks                                                                 |
|------------------------------|-------------------|------------------------------------------------------------------------|----------------------------|------|------------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------|
| Statkute et al., 2020(UK)    | England2 strain   | Not mentioned                                                          | Group 1: Ethanol 7%, CHX 0.2% – Corsodyl | 30 sec | Plaque assay: visual inspection of monolayer integrity | Dirty condition (bovine serum albumin + human erythrocytes): Group 1: PVP-I 1.0% Gargle and mouth wash 15 sec: log10 reduction: >5.00 30 sec: log10 reduction: >5.00 60 sec: log10 reduction: >5.00 Group 2: PVP-I 0.5% Gargle and mouth wash 15 sec: log10 reduction: >4.00 30 sec: log10 reduction: >5.00 60 sec: log10 reduction: >5.00 Two CPC mouth rinses (Dentyl) and ethanol / ethyl lauroyl arginate (Listerine Advanced) showed high virus elimination. Moderate elimination was shown on ethanol/essential oils (Listerine Cool Mint), CPC with sodium citric acid (SCD Max), and PVP-I. CHX or ethanol alone showed little or no effect. |                                                                                  |
|                              |                   |                                                                        | Group 2: CPC 0.05%-0.1% – Denty Dual Action |      |                                          | Complete virus eradication: (log10 reduction: >5) Group 2: CPC 0.05%-0.1% – Denty Dual Action |                                                                                  |
|                              |                   |                                                                        | Group 3: CPC 0.05%-0.1% – Denty Fresh Protect |      |                                          | Group 3: CPC 0.05%-0.1% – Denty Fresh Protect |                                                                                  |
|                              |                   |                                                                        | Group 4: Ethanol 21%, essential oils – Listerine Cool Mint |      |                                          | Group 4: Ethanol 21%, essential oils – Listerine Cool Mint |                                                                                  |
|                              |                   |                                                                        | Group 5: Ethanol 23%, ethyl lauroyl arginate 0.147% – Listerine Advanced Gum Treatment |      |                                          | Group 5: Ethanol 23%, ethyl lauroyl arginate – Listerine Advanced Gum Treatment |                                                                                  |
|                              |                   |                                                                        | Group 6: CPC 0.07–0.1%, sodium citric acid 0.05% – SCD Max |      |                                          | Moderate effect: (log10 reduction: ~3) Group 4: Ethanol 21%, essential oils – Listerine Cool Mint |                                                                                  |
|                              |                   |                                                                        | Group 7: PVP-I 0.5% – Videne |      |                                          | Group 6: CPC 0.07–0.1%, sodium citric acid 0.05% – SCD Max |                                                                                  |
|                              |                   |                                                                        | Group 8: Ethanol 21% |      |                                          | Group 7: PVP-I 0.5% – Videne |                                                                                  |
|                              |                   |                                                                        | Group 9: 23% Control: |      |                                          | Low effect: (log10 reduction: <2) Group 1: Ethanol 7%, CHX 0.2% – Corsodyl |                                                                                  |
| Study | SARS-CoV-2 strain | Sample | Mouthwash | Time | Measurement | Results | Study remarks |
|-------|------------------|--------|------------|------|-------------|---------|---------------|
| Pelletier et al., 2021 (Pelletier et al., 2021) | USA-WA1/2020 strain (USA) | n = 3 | Group 1: PVP-I 2.5% nasal antiseptic – Veloce BioPharma | 60 sec | Standard end-point dilution assay: 50% cell culture infectious dose (CCID50) of virus per 0.1 mL | Group 1: PVP-I 2.5% nasal antiseptic log10 reduction: 4.63 | All PVP-I concentrations of nasal and oral rinse antiseptics completely inactivated the SARS-CoV-2 after 60 s. |
| Jain et al., 2021 (Jain et al., 2021) | Strain isolated from an Indian patient (India) | Not mentioned | Group 1:CHX 0.12% – Sigma-Aldrich | 30 sec, 60 sec | Ct values obtained from RT-qPCR | Relative Ct change (Percent SARS-CoV-2 inactivation): Group 1:CHX 0.12% 30 sec: Ct change: 10.5 ± 0.5 (99.9% inactivation) 60 sec: Ct change 11 ± 1.0 (99.9% inactivation) Group 2:CHX 0.2% 30 sec: Ct change: 12.5 ± 0.5 (>99.9% inactivation) 60 sec: Ct change 13 ± 0 (<99.9% inactivation) Group 3: PVP-I 1% 30 sec: Ct change: 9.5 ± 0.5 (99.8% inactivation) 60 sec: Ct change 11 ± 2 (>99.9% inactivation) | Both CHX and PVP-I showed high level of antiviral effect against SARS-CoV-2 at 30 and 60 s. |
| Study | SARS-CoV-2 strain | Sample | Mouthwash Time Measurement Results | Study remarks |
|-------|-------------------|--------|-------------------------------------|---------------|
| Koch-Heier et al., 2021 (Koch-Heier et al., 2021) | Isolate “FI-100” strain (Germany) | n = 2 Group 1: CPC 0.05%, H₂O₂ 1.5% – ViruProX® pro | 30seg Plaque assay: counting of plaque forming units per milliliter (pfu/mL) | Both ViruProX® and BacterX®, along with CPC + CHX combination, and CPC alone showed a significant reduction on the SARS-CoV-2. H₂O₂ and CHX alone had no virucidal effect against SARS-CoV-2. |
| Komine et al., 2021 (Komine et al., 2021) | JPN/TY/WK-521 strain (Japan) | n = 3 Group 1: CPC 0.0125% toothpaste – GUM® WELL PLUS Dental paste | 20sec, 30sec, 3 min Plaque assay: plaque forming units per milliliter (pfu/mL) Virus suspension dilution measured per 0.1 mL | All dental care products containing 0.0125 to 0.30% CPC, as well as the mouthwash containing 0.20% delmopinol hydrochloride inactivated the SARS-CoV-2 in vitro. The mouthwash containing only 0.12% CHX did not inactivate sufficiently the SARS-CoV-2 in vitro. |
Table 1  (continued)

| Study | SARS-CoV-2 strain | Sample | Mouthwash | Time | Measurement | Results | Study remarks |
|-------|-------------------|--------|-----------|------|-------------|---------|---------------|
|       |                   |        | CHX)      |      |             | 0.05% mouthwash | 30 sec: log10 pfu/mL reduction: | >4.3 (>99.995% reduction) |
|       |                   |        | Group 7: CPC | 0.075% mouthwash – GUM® Oral Rinse | | | |
|       |                   |        | Group 8: CHX | 0.12% mouthwash – GUM® PAROEX (0.12% CHX) | | | |
|       |                   |        | Group 9: Delmopinol 0.20% mouthwash – GUM® PerioShield | | | |
|       |                   |        | Group 10: CPC | 0.04% mouthwash – GUM® MOUTH-WASH HERB 2020 | | | |
|       |                   |        | Positive control: Ethanol 70% | | | |
|       |                   |        | Negative control: PBS | | | |
|       |                   |        | Group 6: CHX 0.12% + CPC 0.05% mouthwash | 30 sec: log10 pfu/mL reduction: | >4.3 (>99.995% reduction) |
|       |                   |        | Group 7: CPC 0.075% mouthwash | 30 sec: log10 pfu/mL reduction: | >4.3 (>99.995% reduction) |
|       |                   |        | Group 8: CHX 0.12% mouthwash | 30 sec: log10 pfu/mL reduction: | 0.2 (42.5% reduction) |
|       |                   |        | Group 9: Delmopinol 0.20% mouthwash – GUM® Octenisept 15 sec, 30 sec, 1 min, 5 min, 10 min | Quantitative suspension test: tissue culture infective dose (TCID50/mL) | Octenidine dihydrochloride mouthwash was effective within 15 sec against SARS-CoV-2. Both CHX mouthrinses had limited efficacy against SARS-CoV-2. |
|       |                   |        | Group 10: CPC 0.04% mouthwash – GUM® MOUTH-WASH HERB 2020 | 20 sec: log10 pfu/mL reduction: | >5.4 (>99.996% reduction) |
|       |                   |        | Ethanol 70% | | | |

Steinhauer et al., 2021
(Steinhauer et al., 2021) Not mentioned n = 2

Group A: CHX 0.1% – Chlorhexamed fluid 0.1%
Group B: CHX 0.2% – Chlorhexamed forte alkoholfrei 0.2%
Group C: Octenidine dihydrochloride 0.1%, phenoxyethanol 2% – Octenisept

15 sec, 30 sec, 1 min, 5 min, 10 min
Quantitative suspension test: tissue culture infective dose (TCID50/mL)

Group A: CHX 0.1% (80% v/v) 5 min, 10 min: log10 reduction: <1
Group B: CHX 0.2% (80% v/v) 1 min, 5 min: log10 reduction: <1
Group C: Octenidine dihydrochloride + phenoxyethanol (80% v/v) 15 sec, 30 sec, 1 min: log10 reduction: ≥4.38
| Study | SARS-CoV-2 strain | Sample | Mouthwash | Time | Measurement | Results | Study remarks |
|-------|------------------|--------|-----------|------|-------------|---------|---------------|
| Xu et al., 2021 (Xu et al., 2021) | USA_WA1/2020 strain (USA) | n = 2 | Group 1:20–30% ethanol, essential oils – Listerine Antiseptic original Group 2: CHX 0.12% – Chlorhexidine gluconate Xtrium Laboratories Group 3: H₂O₂ 1.5% – Colgate Peroxyl Group 4: PVP-I 10% (1% available iodine) – PVP-I CVS Pharmacy | 30 min | Plaque assay: measure of fluorescence intensity | Group 1:20–30% ethanol, essential oils 50% (v/v): complete inactivation (relative light units x10⁴) 5% (v/v): moderate antiviral effect (relative light units x10⁴) Group 2: CHX 0.12% 50% (v/v): complete inactivation (relative light units x10⁴) 5% (v/v): moderate antiviral effect (relative light units x10⁴) Group 3: H₂O₂ 1.5% 50% (v/v): complete inactivation (relative light units x10⁴) 5% (v/v): complete inactivation (relative light units x10⁴) Group 4: PVP-I 10% (1% available iodine) 5% (v/v): complete inactivation (relative light units x10⁴) 0.5% (v/v): no inactivation | All mouthwashes inactivated the SARS-CoV2 without prolonged incubation. |
| Davies et al., 2021 (Davies et al., 2021) | England 2 strain (UK) | n = 3 | Group 1: CHX 0.2% – Chlorhexidine Gluconate Antiseptic Mouthwash (with ethanol) Group 2: CHX 0.2% – Corsodyl (alcohol free) Group 3: dipotassium oxalate 1.4% – Listerine Advanced Defence Sensitive (alcohol free) Group 4: essential oils, sodium | 1 min | Quantitative suspension test: tissue culture infective dose (TCID₅₀/mL) | Tissue culture fluid unconcentrated Group 1: CHX 0.2% (with ethanol) log₁₀ reduction: 0.5 (0.1–0.9) Group 2: CHX 0.2% (alcohol free) log₁₀ reduction: 0.2 (0.2–0.7) Group 3: dipotassium oxalate 1.4% (alcohol free) log₁₀ reduction: ≥3.5 (3.2–3.8) Group 4: essential oils, sodium | Mouthwashes with 0.01–0.02% stabilized hypochlorous acid, 0.58% PVP-I, and both alcohol-based and non-alcohol-based products (both Listerine) were effective against the SARS-CoV-2 in vitro. H₂O₂ 1.5% and 0.2% CHX were ineffective against the SARS-CoV-2 in vitro. |
| Study | SARS-CoV-2 strain | Sample                                                                 | Mouthwash                                                                 | Time | Measurement  | Results | Study remarks |
|-------|-------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|------|--------------|---------|---------------|
| Munoz-Basagoiti et al., 2021 (Muñoz-Basagoiti et al., 2021) | B.1.1.7 variant and D614G variant (Spain) | Group 1: 1.47 mM CPC – Vitis Encias Intensive Care | 30 sec, 1 min, 2 min | ELISA, dynamic light scattering analysis, Tissue Culture Infectious Dose 50% (TCID50/mL) | ≥5.2 (4.9–5.4) | CPC inhibits the entrance of SARS-CoV-2. CPC mouthwashes decreased more than a thousand times the infectivity of SARS-CoV-2 in vitro. CPC is effective against SARS-CoV-2 variants, also in the presence of sterilized saliva. |
|       |                   | Group 2: 1.47 mM CPC + 1.33 mM CHX – Perio Aid Intensive Care          |                                                                           |      |              |         |               |
|       |                   | Group 3: 2.063 mM CPC – Vitis CPC Protect                              |                                                                           |      |              |         |               |
|       |                   | Group 4: essential oils, sodium fluoride, zinc fluoride                |                                                                           |      |              |         |               |
|       |                   | Group 5: stabilized hypochlorous acid 0.01–0.02% – OraWize +          |                                                                           |      |              |         |               |
|       |                   | Group 6: H₂O₂ 1.5% – Peroxyl                                           |                                                                           |      |              |         |               |
|       |                   | Group 7: PVP-I 0.58% – Povident                                       |                                                                           |      |              |         |               |

Munoz-Basagoiti et al., 2021 (Muñoz-Basagoiti et al., 2021)
| Study | SARS-CoV-2 strain | Sample | Mouthwash | Time | Measurement | Results | Study remarks |
|-------|------------------|--------|------------|------|-------------|---------|--------------|
| Santos et al., 2021, (C. A. Santos et al., 2021) | Not mentioned | n = 3 | Group 1: anionic phthalocyanine derivate (APD) dental gel | 30 sec, 1 min, 5 min | Plaque assay: Median tissue culture infection dose (TCID50) | Group 1: anionic phthalocyanine derivate (APD) dental gel 30 sec, 1 min, 5 min: 99.99% inactivation Group 2: anionic phthalocyanine derivate (APD) mouthwash 30 sec, 1 min, 5 min: 90% inactivation | Both anionic phthalocyanine derivate (APD) mouthwash and dental gel can reduce the viability of SARS-CoV-2 in vitro in 30 s. |
| Santos et al., 2021 (P. S. da S. Santos et al., 2021) | Not mentioned | n = 4 | Group 1: APD 1:2 dilution (1.0 mg/mL) | 30 min | Plaque assay, RT-PCR | Group 1: APD 1:2 dilution 99.96% reduction of viral load Group 2: APD 1:4 dilution 99.88% reduction of viral load Group 3: APD 1:8 dilution 99.84% reduction of viral load Group 4: APD 1:16 dilution 92.65% reduction of viral load Group 5: APD 1:32 dilution 77.42% reduction of viral load Group 6: APD 1:64 dilution 11.06% reduction of viral load Group 7: APD 1:128 dilution No viral neutralization | APD in the 1.0 mg/mL to 0.125 mg/mL range was highly effective for the reduction of SARS-CoV-2 viral load, without causing any cytotoxicity. |

1. H$_2$O$_2$: Hydrogen peroxide; CHX: Chlorhexidine digluconate; PVP-I: Povidone-iodine; CPC: Cetylpyridinium chloride; OCT: octenidine dihydrochloride; APD: Anionic phtalocyanine derivate; PBS: Phosphate-buffered saline.
| Study | Country | Study design | Sample | Age | Mouthwash | Dosage | Treatment length | Detection method | Results | Study remarks | Risk of bias |
|-------|---------|--------------|--------|-----|-----------|--------|-----------------|-----------------|---------|---------------|-------------|
| Gottsauner et al., 2020 (Gottsauner et al., 2020) | Germany | Non-randomized clinical trial | 12 hospitalized patients positive to Sars-CoV-2 | 55 years (22–81 years) | H₂O₂ 1% (gargling mouth and throat) | 20 mL for 30 sec | 1 time | RT-PCR | RT-PCR at baseline: 1.8 x 10⁷ (3.1 x 10⁵; 4.7 x 10⁶) copies/mL. RT-PCR after procedure 1.5 x 10³ (8.3 x 10²; 3.4 x 10³) copies/mL. No significant differences (p = 0.96). | A H₂O₂ 1% mouthrinse did not reduce the intraoral viral load of SARS-CoV-2. | Critical (high) |
| Avhad et al., 2020 (Avhad et al., 2020) | India | Randomized clinical trial | 40 patients positive to SARS-CoV-2 | 19–49 years | Control group (n = 20): CHX 0.2% (rinse and gargle) | 10 mL | 3 times a day for 7 days | RT-PCR | RT-PCR after one week: Control group: CHX 0.2% Positive cases: 12 Negative cases: 8 Study group: chlorine dioxide (0.1%) Positive cases: 8 Negative cases: 12 Chlorine dioxide mouthwash presented more cases with reduction of intensity of symptoms and negativity for COVID-19 in the patients. | Unclear risk |
| Choudhury et al., 2020 (Choudhury et al., 2020) | Bangladesh | Randomized clinical trial | 606 patients positive to SARS-CoV-2 | 11–90 years | Group A (n = 303): PVP-I 1% (mouthwash/gargle, nasal drops and eye drops) | 1 mL of PVP-I in 10 mL of sterile water/purified water | 4 hourly for 4 weeks | RT-PCR | RT-PCR positive: Group A: PVP-I 1% 3rd day: 11.55% 5th day: 7.92% 7th day: 2.64% Group B: lukewarm water 3rd day: 96.04% 5th day: 88.45% 7th day: 70.30% PVP-I 1% as mouthwash/gargle, nasal drop and eye drop, reduced mortality and morbidity by COVID-19, as well as reduce positivity cases at the 3rd, 5th and 7th day. | High risk |
| Mohamed et al., 2020 (Mohamed et al., 2020) | Malaysia | Randomized clinical trial | 20 patients positive to SARS-CoV-2 | 22–56 years | Group A (n = 5): PVP-I 1% – Betadine® (gargle) Group B (n = 5): essential oils, ethanol – Listerine Original (gargle) | Group A: 10 mL for 30 sec Group B: 20 mL for 30 sec | 3 times a day for 7 days | RT-PCR | RT-PCR results: Group A: PVP-I 1% 4th day: 100% negative 6th day: 100% negative 12th day: 100% PVP-I 1% PCR results were significantly reduced (p < 0.05) after the 4th, 6th and 12th day, when compared to the | High risk |

(continued on next page)
| Study | Country | Study design | Sample | Age | Mouthwash | Dosage | Treatment length | Detection method | Results | Study remarks | Risk of bias |
|-------|---------|--------------|--------|-----|-----------|--------|-----------------|-----------------|--------|---------------|-------------|
|       |         |              |        |     | Group C (n = 5): tap water (gargle) | | | | negative | High rate of viral reduction after 4 days of PVP-I 1% and essential oil mouthwashes was achieved. | Unclear risk |
|       |         |              |        |     | Group D (n = 5): no intervention | | | | | | |
| Study | Group A: 100 mL for 30 sec | | | | | | | | | |
|       | Group B: essential oils | | | | | | | | | |
|       | 4th day: 80% negative, 20% positive | | | | | | | | | |
|       | 6th day: 80% negative, 20% positive | | | | | | | | | |
|       | 12th day: 80% negative, 20% positive | | | | | | | | | |
|       | Group C: tap water | | | | | | | | | |
|       | 4th day: 40% negative, 60% positive | | | | | | | | | |
|       | 6th day: 40% negative, 60% positive | | | | | | | | | |
|       | 12th day: 60% negative, 40% positive, 20% indeterminate | | | | | | | | | |
|       | Group D: no intervention | | | | | | | | | |
|       | 4th day: 20% negative, 40% positive, 40% indeterminate | | | | | | | | | |
|       | 6th day: 60% positive, 40% indeterminate | | | | | | | | | |
|       | 12th day: 20% negative, 60% positive, 20% indeterminate | | | | | | | | | |
| Seneviratne et al., 2021 (Seneviratne et al., 2021) | Singapore | Randomized clinical trial | 16 patients positive to SARS-CoV-2 | | Group 1: 40.7 ± 11.5 | | | | | |
|       | Group 2: 43.6 ± 8.6 | | | | Group 3: 35.7 ± 8.5 | | | | | |
|       | Group 4: | | | | | | | | | |
|       | Group 1 (n = 4): PVP-I 0.5% – Betadine® (mouthwash) | | | | | | | | | |
|       | Group 2 (n = 6): CHX 0.2% (mouthwash) | | | | | | | | | |
|       | PVP-I: 5 mL for 30 sec | | | | | | | | | |
|       | CHX: 15 mL for 30 sec | | | | | | | | | |
|       | CPC: 20 mL for 30 sec | | | | | | | | | |
|       | Water: | | | | | | | | | |
|       | 1 time | | | | | | | | | |
|       | RT-PCR | | | | | | | | | |
|       | Relative fold change of cycle threshold: Group 1: PVP-I 5 min: fold change: 1.1 | | | | | | | | | |
|       | 3 h: fold change: 1.2 | | | | | | | | | |
|       | 6 h: fold change: 1 | | | | | | | | | |
|       | There were not significant differences within all 3 mouthwashes. When comparing the mouthwashes with the water | | | | | | | | | |
|       | control. | | | | | | | | | |
| Study | Country       | Study design           | Sample | Age     | Mouthwash                          | Dosage | Treatment length | Detection method | Results                                                   | Study remarks                                                                                       | Risk of bias |
|-------|---------------|------------------------|--------|---------|------------------------------------|--------|------------------|------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------|
|       |               |                        |        |         |                                    |        |                  |                  | (p < 0.01)                                               | Group 2: CHX 0.2% 5 min: 0.9 (varied effect)                                                        |              |
|       |               |                        |        |         |                                    |        |                  |                  | 3 h: fold change: 1                                      | Group 3: CPC 5 min: fold change: 1 (p < 0.05)                                                       |              |
|       |               |                        |        |         |                                    |        |                  |                  | 6 h: fold change: 0.9                                    | Group 3: CPC 5 min: fold change: 1 (p < 0.05)                                                       |              |
|       |               |                        |        |         |                                    |        |                  |                  | p < 0.05                                                 | Group 3: CPC 5 min: fold change: 1 (p < 0.05)                                                       |              |
|       |               |                        |        |         |                                    |        |                  |                  | Mean relative difference in viral titers:               | The decrease of salivary load was maintained after 6 h for CPC and PVP-I mouthwashes. The use of PVP-I had no influence on the changes of viral RNA quantification over time. |              |
|       |               |                        |        |         |                                    |        |                  |                  | Baseline – Day 1:                                        |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | Control: 32% (95% CI, 10%-65%)                           |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | Intervention: 75%                                       |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | (95% CI, 43%-95%)                                        |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | No statistical differences between groups over time.  | Both CHX 0.2% and PVP-I 1% are effective against salivary SARS-CoV-2.                                |              |
|       |               |                        |        |         |                                    |        |                  |                  | A significant difference of Ct values between water     |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | group and CHX: (p = 0.0024)                              |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | PVP-I: (p = 0.012)                                       |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | No significant difference between: CHX and PVP-I:     |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | p = 0.24                                                 |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | Differences before and after mouthwash:                |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | CHX                                                      |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | Ct difference: 5.69 increase                           |                                                                                                   |              |
|       |               |                        |        |         |                                    |        |                  |                  | (p < 0.0001)                                             |                                                                                                   |              |

(continued on next page)
| Study                        | Country | Study design                   | Sample | Age                   | Mouthwash                  | Dosage | Treatment length | Detection method | Results                          | Study remarks                                                                 | Risk of bias |
|-----------------------------|---------|--------------------------------|--------|-----------------------|----------------------------|--------|------------------|------------------|----------------------------------|-----------------------------------------------------------------------------|--------------|
| Carrouel et al., 2021       | France  | Randomized clinical trial      | 176 ambulatory patients positive to SARS-CoV-2 | Control: 44.08 ± 16.16 years | Control group (n = 88): Placebo (mouthwash) | 30 mL for 1 min | 3 times a day (at 09.00, 14.00 and 19.00), for 7 days | RT-PCR | Ct difference: 4.45 increase (p < 0.0001) No difference for water group (p = 0.566) | CDCM had a significant beneficial effect on reducing SARS-CoV-2 salivary viral load in adults with asymptomatic or mild COVID-19, 4 h after the initial dose. | Low risk    |
| (Florence Carrouel et al., 2021a) |         |                                |        |                       | Intervention group (n = 88): CDCM (β-cyclodextrin-citroxi) (mouthwash) |        |                  |                  | % decrease T1-T2 (log10 copies/mL): Control group: −6.74% (-21.16% to 10.44%) Intervention group: −12.58% (-29.55% to −0.16%) |                                                          |              |
| Eduardo et al., 2021        | Brazil  | Randomized clinical trial      | 60 patients positive to SARS-CoV-2 | Group A (n = 9): Placebo (distilled water rinse) Group B (n = 7): CPC 0.075% + Zinc lactate 0.28% (Colgate Total 12® rinse) | Group A: 20 mL for 1 min Group B: 20 mL for 30 s Group C: 10 mL for 1 time |        |                  | RT-PCR | Group A (placebo): minor changes Group B (CPC + Zinc): 20.4 ± 3.7-fold reduction Group C (H₂O₂): 15.8 ± 0.08-fold reduction | CPC + Zinc and CHX mouthwashes reduced significantly SARS-CoV-2 viral load in saliva up to 60 min after rinsing H₂O₂ reduced | Unclear risk |
| (Eduardo et al., 2021)      |         |                                |        |                       |                            |        |                  |                  | Only statistical difference at T1-T2 difference |                                                          |              |
| Study                  | Country | Study design                  | Sample                  | Age              | Mouthwash                      | Dosage | Treatment length | Detection method | Results                                                                 | Study remarks                                                                 | Risk of bias |
|-----------------------|---------|--------------------------------|-------------------------|------------------|-------------------------------|--------|------------------|------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------|
| Chaudhary et al., 2021 (Chaudhary et al., 2021) | US      | Randomized clinical trial     | 40 patients positive to SARS-CoV-2 | 21-80 years-old  | Group C (n = 7): H₂O₂ 1.5% (Peroxyl® rinse) | 1 min  | Group D: 15 mL for 30 sec | Group D: 15 mL for 30 sec | Group D (CHX): ≥ 2-fold reduction Group E (H₂O₂ + CHX): ≥ 2-fold reduction | significantly the viral load up to 30 min after rinsing. H₂O₂ + CHX presented minimal reduction in the salivary viral load. | Critical (high) risk |
|                       |         |                               |                         |                  | Group D (n = 8): CHX 0.12% (PerioGard® rinse) |        |                  |                  |                                                                           |                                                                           |               |
|                       |         |                               |                         |                  | Group E (n = 12): H₂O₂1.5% + CHX 0.12% (Peroxyl® + PerioGard® rinse) |        |                  |                  |                                                                           |                                                                           |               |
|                       |         |                               |                         |                  | Group D (CHX): 15 mL for 30 sec |        |                  |                  |                                                                           |                                                                           |               |
|                       |         |                               |                         |                  | Group E (H₂O₂ + CHX): ≥ 2-fold reduction |        |                  |                  |                                                                           |                                                                           |               |
|                       |         |                               |                         |                  | Study remarks: Mouthwashes antiviral effect against SARS-CoV-2 |        |                  |                  |                                                                           |                                                                           |               |

1 H₂O₂: Hydrogen peroxide; CHX: Chlorhexidine digluconate; PVP-I: Povidone-iodine; CPC: Cetylpyridinium chloride.
3.2. Risk of bias of clinical studies

The risk of bias summary of clinical studies is shown in Fig. 2. Both non-RCTs showed a high risk of bias. For the RCTs, one study showed a low risk, five studies showed unclear bias, and three studies showed a high risk of bias.

The combined risk of bias graph of the clinical trials is shown in Fig. 3. The non-RCTs presented a high risk of bias. The RCTs presented approximately 10% low risk, 60% unclear risk, and 30% high risk of bias.

3.3. Antiviral effect of mouthwashes

Table 3 shows the summary of all mouthwashes in vitro and clinically. H$_2$O$_2$ showed low to no effect in vitro, but a varied effect clinically. CHX showed a varied effect or no effect in vitro, and a varied effect clinically. H$_2$O$_2$ + CHX had minimal effect clinically. PVP-I showed a moderate to high effect in vitro and was mostly effective in patients. The essential oils and CPC were effective clinically, with a moderate to high effect in vitro. CPC + zinc lactate was effective clinically; CPC + H$_2$O$_2$ and CPC + CHX were highly effective in vitro. Chlorine dioxide was clinically more effective than CHX. CDCM and sorbitol + xylitol were also clinically effective. In vitro, octenidine dihydrochloride and polyaminopropyl biguanide showed a moderate to high effect; APD, dequalinium chloride, ethanol + ethyl lauroyl arginate, delmopinol, and dipotassium oxalate showed a high effect; and stabilized hypochlorous acid had a varied effect.

4. Discussion

The transmission of COVID-19 is mainly by contact with respiratory droplets, as the virus can be found in the sputum and saliva of infected people (Florence Carrouel et al., 2021b; Wolff et al., 2020; J. Xu et al., 2020; R. Xu et al., 2020). SARS-CoV-2 is a single-stranded enveloped RNA virus that binds to angiotensin-converting enzyme 2 (ACE-2) receptors to enter the host cell (Shang et al., 2020). The oral cavity acts as an entry point and reservoir for this virus, as ACE-2 receptors are spread in the salivary glands, tongue, and oral mucosa; thus, good oral hygiene could be effective against COVID-19 (Gottsauner et al., 2020; Sampson et al., 2020).

Mouthwash use has been suggested to decrease the salivary viral load (F. Carrouel et al., 2021), as both clinical and in vitro
studies have demonstrated their antiviral effect (Bidra et al., 2020b; Elzein et al., 2021; Komine et al., 2021; Meister et al., 2020; Mohamed et al., 2020; Seneviratne et al., 2021). Because prevention methods to help reduce the spread of COVID-19 are urgently needed, it is important to evaluate the current literature regarding the role of mouthwashes to reduce the viral load of SARS-CoV-2 (Carrouel et al., 2020; Moosavi et al., 2020). Therefore, this systematic review aimed to evaluate the antiviral effect of different mouthwashes against SARS-CoV-2.

Regarding the in vitro studies, H_2O_2 showed mostly minimal to no effect (Bidra et al., 2020a; Davies et al., 2021; Koch-Heier et al., 2021), suggesting it might not be that effective against SARS-CoV-2. CHX showed inconsistent results, with some studies finding a strong (Jain et al., 2021; Xu et al., 2021), weak (Komine et al., 2021; Statkute et al., 2020; Steinhauer et al., 2021), or even no (Davies et al., 2021; Koch-Heier et al., 2021) effect against different strains of SARS-CoV-2. It is possible that both H_2O_2 and CHX alone are not that effective as mouthwashes, as these in vitro results were mostly negative.

PVP-I showed positive results in vitro, as most studies reported a strong antiviral effect against various SARS-CoV-2 strains at different doses (Anderson et al., 2020; Bidra et al., 2020a, 2020b; Hassandarvish et al., 2020; Jain et al., 2021; Meister et al., 2020; Pelletier et al., 2021). CPC alone (Koch-Heier et al., 2021; Komine et al., 2021; Muñoz-Basagüí et al., 2021; Statkute et al., 2020) and in combination with other reagents (Koch-Heier et al., 2021) also showed high viral reduction in vitro at different doses. Both PVP-I, and CPC alone and in combination (CPC + H_2O_2 and CPC + CHX) could help to reduce the spread of SARS-CoV-2.

The essential oils (eucalyptol, menthol, methyl salicylate, and thymol) combined with ethanol showed a moderate to high effect in all in vitro studies (Davies et al., 2021; Meister et al., 2020; Statkute et al., 2020; Xu et al., 2021), suggesting that they could be effective against SARS-CoV-2. Mouthwashes with octenidine dihydrochloride also showed a moderate to high effect in vitro (Meister et al., 2020; Steinhauer et al., 2021). APD (C. A. Santos et al., 2021; P. S. da S. Santos et al., 2021), dequalinium chloride (Meister et al., 2020), polyaminopropyl biguanide (Meister et al., 2020), ethyl lauroyl arginate

Fig. 3 Risk of bias graph of clinical studies: A) Risk of bias of non-randomized clinical studies assessed with the ROBINS-I tool, (B) Risk of bias of randomized clinical studies assessed with the RoB-2 tool. The green color represents a low risk of bias, yellow represents an unclear risk of bias, and red represents a high risk of bias.
| Mouthwash | Study type | N° of studies | Concentration | Dosage | Antiviral effect against SARS-CoV-2 | Overall effect |
|-----------|------------|---------------|---------------|--------|-----------------------------------|---------------|
| H₂O₂ | Clinical study | 2 (Chaudhary et al., 2021; Gottsauner et al., 2020) (High risk) | H₂O₂ 1% | 20 mL for 30 sec / 15 mL for 1 min | Varied effect | Varied effect |
| | | 1 (Eduardo et al., 2021) (Unclear risk) | H₂O₂ 1.5% | 10 mL for 1 min | Effective | |
| | In vitro study | 5 (Bidra et al., 2020a; Davies et al., 2021; Koch-Heier et al., 2021; Meister et al., 2020; Xu et al., 2021) | H₂O₂ 1.5% | 15 sec, 30 sec | Low effect to no effect | Low to no effect |
| | | 1 (Bidra et al., 2020a) | H₂O₂ 3.0% | 15 sec to 30 sec | Low effect | |
| CHX | Clinical study | 2 (Chaudhary et al., 2021; Eduardo et al., 2021) (Unclear and high risk) | CHX 0.12% | 15 mL for 30 sec | Effective | Varied effect, to effective in patients |
| | | 3 (Avhad et al., 2020; Elzein et al., 2021; Seneviratne et al., 2021) (unclear risk) | CHX 0.2% | 15 mL for 30 sec | Varied effect, to effective | No effect |
| | In vitro study | 2 (Koch-Heier et al., 2021; Steinhauser et al., 2021) | CHX 0.1% | 30 sec | Variable effect | Variable to no effect |
| | | 3 (Jain et al., 2021; Komine et al., 2021; Xu et al., 2021) | CHX 0.12% | 30 sec to 60 sec | Variable effect | |
| | | 4 (Davies et al., 2021; Jain et al., 2021; Meister et al., 2020; Steinhauser et al., 2021) | CHX 0.2% | 30 sec to 60 sec | Low to no effect | |
| | | 2 (Davies et al., 2021; Statkute et al., 2020) | CHX 0.2% + Ethanol | 30 sec to 60 sec | Minimal effect | |
| H₂O₂ + CHX | Clinical study | 1 (Eduardo et al., 2021) (Unclear risk) | H₂O₂ 1.5% + CHX 0.12% | 10 mL of H₂O₂ for 1 min, followed by 15 mL of CHX for 30 sec | Minimal effect | Minimal effect |
| PVP-I | Clinical study | 2 (Chaudhary et al., 2021; Seneviratne et al., 2021) (Unclear and high risk) | PVP-I 0.5% | 5 mL for 30 sec / 15 mL for 1 min | Effective | Varied effect, mostly effective in patients |
| | | 4 (Choudhary et al., 2020; Elzein et al., 2021; Guenezan et al., 2021; Mohamed et al., 2020) (Unclear and high risk) | PVP-I 1% | 10–15 mL for 30 sec, 3–4 times a day | Varied effect, mostly effective | Moderate to high effect |
| | In vitro study | 7 (Anderson et al., 2020; Bidra et al., 2020a, 2020b; Davies et al., 2021; Hassandarvish et al., 2020; Pelletier et al., 2021; Statkute et al., 2020) | PVP-I 0.5% | 15 sec to 60 sec | Moderate to high effect | Moderate to high effect |
| | | 2 (Bidra et al., 2020b; Pelletier et al., 2021) | PVP-I 0.75% | 15 sec to 60 sec | High effect | |
| | | 5 (Anderson et al., 2020; Hassandarvish et al., 2020; Jain et al., 2021; Meister et al., 2020, 2021; Xu et al., 2021) | PVP-I 1.0% | 15 sec to 60 sec | Mostly high effect | |
| | | 1 (Bidra et al., 2020a) | PVP-I 1.25% | 15 sec to 30 sec | High effect | |
| | | 3 (Bidra et al., 2020a, 2020b; Pelletier et al., 2021) | PVP-I 1.5% | 15 sec to 60 sec | High effect | |
| Essential oils | Clinical study | 1 (Mohamed et al., 2020) (High risk) | Ethanol + essential oils (Eucalyptol, Menthol, Methyl salicylate, Thymol) | 20 mL for 30 sec, 3 times a day | Effective | Effective in patients |
| | | | Ethanol + essential oils (Eucalyptol, Menthol, Methyl salicylate, Thymol) | 30 sec to 60 sec | Moderate to high effect | Moderate to high effect |
| | In vitro study | 4 (Davies et al., 2021; Meister et al., 2020; Statkute et al., 2020; Xu et al., 2021) | Ethanol + essential oils (Eucalyptol, Menthol, Methyl salicylate, Thymol) | 30 sec to 60 sec | Moderate to high effect | Moderate to high effect |

Table 3: Antiviral effect against SARS-CoV-2 in *in vitro* and clinical studies.
| Mouthwash | Study type | ° of studies | Concentration | Dosage | Antiviral effect against SARS-CoV-2 | Overall effect |
|------------|------------|--------------|---------------|--------|-------------------------------------|---------------|
| CPC        | Clinical study | 1 (Seneviratne et al., 2021) (Unclear risk) | CPC 0.075% | 20 mL for 30 sec | Effective | Effective in patients |
|            | In vitro study | 1 (Komine et al., 2021) | CPC 0.04% mouthwash | 20 sec | High effect | Moderate to high effect in vitro |
|            |            | 1 (Komine et al., 2021) | CPC 0.05% (alcoholic type) | 20 sec to 30 sec | High effect | Moderate to high effect in vitro |
|            |            | 4 (Koch-Heier et al., 2021; Komine et al., 2021; Muñoz-Basagoiti et al., 2021; Statkute et al., 2020) | CPC 0.05% (non-alcoholic type) | 20 sec to 2 min | High effect | Moderate effect |
|            |            | 2 (Komine et al., 2021; Muñoz-Basagoiti et al., 2021) | CPC 0.075% | 30 sec to 1 min | High effect | Moderate effect |
|            |            | 1 (Statkute et al., 2020) | CPC 0.07-0.1% + sodium citric acid 0.05% | 30 sec | High effect | Moderate effect |
| CPC + Zinc | Clinical study | 1 (Eduardo et al., 2021) (Unclear risk) | CPC 0.075% + Zinc lactate 0.28% | 20 mL for 30 sec | Effective | Effective in patients |
| CPC + H₂O₂ | In vitro study | 1 (Koch-Heier et al., 2021) | CPC 0.05%, H₂O₂ 1.5% | 30 sec | High effect | Moderate effect |
| CHX + CPC  | In vitro study | 1 (Komine et al., 2021) | CHX 0.06% + CPC 0.05% | 30 sec | High effect | Moderate effect in vitro |
|            |            | 1 (Koch-Heier et al., 2021) | CHX 0.1% + CPC 0.05% | 30 sec | High effect | Moderate effect in vitro |
|            |            | 2 (Komine et al., 2021; Muñoz-Basagoiti et al., 2021) | CHX 0.12% + CPC 0.05% | 30 sec to 2 min | High effect | Moderate to high effect |
| Octenidine dihydrochloride | In vitro study | 2 (Meister et al., 2020; Steinhauer et al., 2021) | Octenidine dihydrochloride 0.1%, phenoxyethanol 2% | 15 sec, 30 sec, 1 min | Moderate to high effect | Moderate to high effect |
| APD        | In vitro study | 2 (C. A. Santos et al., 2021; P. S. da S. Santos et al., 2021) | APD | 30 sec, 1 min, 5 min, 30 min | High effect | High effect in vitro |
| Chlorine dioxide | Clinical study | 1 (Avhad et al., 2020) (Unclear risk) | Chlorine dioxide 0.1% | 10 mL 3 times a day | More effective than CHX | Variable effect in patients |
| Dequalinium chloride | In vitro study | 1 (Meister et al., 2020) | Dequalinium chloride 1.5 mg, benzalkonium chloride 3.5 mg | 30 sec | High effect | Moderate effect in vitro |
| Polyaminopropyl biguanide | In vitro study | 1 (Meister et al., 2020) | Polyaminopropyl biguanide (polyhexanide) 0.1 - 0.25% | 30 sec | More effective than CHX | High effect |
| Ethanol + ethyl lauroyl arginate | In vitro study | 1 (Statkute et al., 2020) | Ethanol 23%, ethyl lauroyl arginate 0.147% | 30 sec | High effect | Moderate to high effect in vitro |
| Delmopinol | In vitro study | 1 (Komine et al., 2021) | Delmopinol 0.20% mouthwash | 30 sec | High effect | Moderate to high effect in vitro |
| Dipotassium oxalate | In vitro study | 1 (Davies et al., 2021) | Dipotassium oxalate 1.4% | 30 sec | High effect | Moderate to high effect in vitro |
| Stabilized hypochlorous acid | In vitro study | 1 (Davies et al., 2021) | Stabilized hypochlorous acid 0.01-0.02% | 30 sec | High effect | Moderate to high effect in vitro |
| CDCM (β-cyclodextrin-citrox) | Clinical study | 1 (Florence Carrouel et al., 2021a) (Low risk) | CDCM (β-cyclodextrin-citrox) | 30 mL for 1 min, 3 times a day 1 min | Effective | Effective in patients |
| Sorbitol and xylitol | Clinical study | 1 (Schürmann et al., 2021) (High risk) | Sorbitol and xylitol | 30 mL for 1 min, 3 times a day 1 min | Effective | Effective in patients |

1 H₂O₂: Hydrogen peroxide; CHX: Chlorhexidine digluconate; PVP-I: Povidone-iodine; CPC: Cetylpyridinium chloride; APD: Anionic phthalocyanine derivate.
with ethanol (Statkute et al., 2020), delmopinol (Komine et al., 2021), and dipotassium oxalate (Davies et al., 2021) showed a moderate to high effect in vitro; however, few studies supported these results.

Regarding the clinical studies, both H₂O₂ and CHX showed a varied effect in patients with COVID-19; some studies reported an antiviral effect for H₂O₂ (Chaudhary et al., 2021; Eduardo et al., 2021) and CHX (Chaudhary et al., 2021; Eduardo et al., 2021; Elzein et al., 2021), but their combination had minimal effect clinically. PVP-I was mostly effective against SARS-CoV-2 clinically (Choudhury et al., 2020; Elzein et al., 2021; Mohamed et al., 2020; Seneviratne et al., 2021). The essential oils (Mohamed et al., 2020), CPC (Seneviratne et al., 2021), CDCM (Florence Carrouel et al., 2021a), and sorbitol + xylitol (Schürmann et al., 2021) were effective in reducing the viral load in patients with COVID-19. In one study, mouthwash with chlorine dioxide showed a greater effect than CHX clinically (Avhad et al., 2020), but these results were limited by a lack of negative control.

In patients with COVID-19, H₂O₂, CHX, PVP-I, CPC (alone and combined), CDCM, sorbitol + xylitol, and essential oils were found to be effective; however, these studies presented an unclear or high risk of bias, except for the study of CDCM (Florence Carrouel et al., 2021a), which was assessed to have a low risk. More clinical studies of higher quality and less bias are still needed.

Regarding previous systematic reviews, Burton (Burton et al., 2020) could not include any clinical trials, so no further conclusion was achieved. Ortega (Ortega et al., 2020) focused on H₂O₂ and also lacked clinical studies. Pérez-Errázuriz (Pérez-Errázuriz et al., 2021) focused only on CPC, and concluded that more research was needed. Finally, Statthis (Statthis et al., 2021) found that oral and nasal antiseptics, including PVP-I, CHX, Listerine, and iota-carrageenan, showed an in vitro effect against SARS-CoV-2, while no completed clinical trials were found. Cavalcante-Leão (Cavalcante-Leão et al., 2021) included two in vitro studies of Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle-East Respiratory Syndrome Coronavirus (MERS-CoV), suggesting that PVP-I at 1–7% could be the most effective against SARS-CoV-2. Ultimately, as COVID-19 is still a new disease, there is limited evidence to suggest any final standardized clinical protocol regarding the use of mouthwashes against SARS-CoV-2.

The SARS-CoV-2 is comprised of a lipid envelope with spike glycoproteins that help bind the virus to its host cell (O’Donnell et al., 2020; Shang et al., 2020). A known virucidal strategy against many coronavirus species is to disrupt this envelope, which may be the mechanism of action of many of the mouthwash reagents. Viral envelopes are composed of host cell proteins, and for the coronaviruses, the composition of this structure may be related to the endoplasmic reticulum membrane (O’Donnell et al., 2020).

PVP-I is a common antiseptic used safely as mouthwash with in vitro antiviral effects to SARS-CoV-1 and MERS-CoV (Eggers et al., 2018). PVP-I is composed of iodine and polyvinylpyrrolidone; when converted to free iodine, it penetrates microorganisms by oxidizing nucleic acids and disrupting proteins. This may provoke viral destruction by disorganization of the cell membrane, thus altering their metabolic pathway and causing irreversible damage (Bidra et al., 2020b; F. Carrouel et al., 2021; Choudhury et al., 2020). Our findings suggest that PVP-I may be effective against SARS-CoV-2 both in vitro and clinically.

CPC is a quaternary ammonium compound that may interact with the viral envelope, making it effective against SARS-CoV-2 (Gottsauner et al., 2020; Seneviratne et al., 2021). CPC affects proteins and lipids on the bacterial surface, and has antiviral effects against other viruses like influenza in vivo and in vitro (O’Donnell et al., 2020; Popkin et al., 2017). CPC, alone and in combination with other reagents, could be effective against SARS-CoV-2.

The essential oils are usually combined with 21–26% ethanol, although low concentrations of ethanol may impact the viral envelope. Moreover, both thymol and eucalyptol have been shown to interfere with the lipid envelope of the herpesvirus, suggesting a possible effect in this viral structure of SARS-CoV-2 (Astani et al., 2010; O’Donnell et al., 2020). Essential oils with ethanol may be an option to reduce viral spread, as found in our results.

CHX is a cationic bisguanide antiseptic with broad antimicrobial activity and antiviral effects against enveloped viruses, though its role against SARS-CoV-2 is still controversial (Bernstein et al., 1990; Bidra et al., 2020b; F. Carrouel et al., 2021; Sampson et al., 2020). Its mechanism of action is mainly due to its positive charge, which allows entry into the cell by interacting with the negative charge of the microbial surface, thus causing leakage (O’Donnell et al., 2020). As CHX is usually combined with low concentrations of ethanol, this would help achieve its antiviral effect (O’Donnell et al., 2020). Based on the mixed results found in vitro and clinically, CHX alone may not be sufficiently effective against SARS-CoV-2, so combinations with ethanol or CPC may present better results.

While H₂O₂ is not widely used due to its possible adverse effects, it is a good disinfectant (Gottsauner et al., 2020; Seneviratne et al., 2021). H₂O₂ disrupts the viral envelope by liberating oxygen-free radicals (Peng et al., 2020). Although the clinical studies showed that H₂O₂ had some antiviral effect, the in vitro studies did not.

COVID-19 can be transmitted through small droplets of expelled saliva; after inhalation of these droplets, host cells can be infected and symptoms of the disease can appear (J. Xu et al., 2020; R. Xu et al., 2020). SARS-CoV-2 can be found not only in saliva, but also in dental plaque (Gomes et al., 2021; To et al., 2020). As the saliva and oral cavity are considered reservoirs of the virus, the use of mouthwashes could help in the decrease of COVID-19 transmission.

PVP-I, CPC (alone and combined), and essential oil mouthwashes were the most effective against SARS-CoV-2 both in vitro and clinically. Based on these results, PVP-I at 0.5–1.0% for 30 sec, CPC at 0.04–0.075% for 20–30 sec, and essential oils with ethanol for 30 sec may be effective in decreasing the viral load in infected patients. These compounds may be useful in reducing the spread of COVID-19, as mouthwashes are cheap and simple to use, though these results are not conclusive.

This review highlighted several in vitro and clinical studies found in the literature. Nevertheless, the different reagents, concentrations, doses, and outcome analysis methods used, along with the unclear and high risk of bias present, high-
lighted that more studies—especially clinical research studies—are needed to clearly define the antiviral effect of mouthwashes against the different SARS-CoV-2 strains.

5. Limitations

In vitro studies are limited as their results cannot be extrapolated to humans. Most of the clinical studies presented an unclear or high risk of bias, and data from these studies was considered too limited to inform clinical recommendations. Finally, a meta-analysis of these findings would not be possible due to the different reagents, different outcome analyses, and the bias of the clinical studies.

6. Conclusion

The in vitro studies showed that mouthwashes containing PVP-I, CPC, and essential oils may have an antiviral effect against different strains of SARS-CoV-2.

The evidence from clinical studies found that mouthwashes with H₂O₂, CHX, PVP-I, CPC, CDCM, sorbitol + xylitol, or essential oils had an antiviral effect against SARS-CoV-2; however, because most studies were assessed to have an unclear to high risk of bias, these results should not be a determinant for clinical recommendations.

Based on both clinical and in vitro studies, PVP-I, CPC, and essential oils with ethanol may present the best results against SARS-CoV-2. Therefore, more studies with these products may be beneficial.

As the COVID-19 pandemic is still a major health problem worldwide, more high-quality clinical studies investigating the real antiviral effect of different mouthwash compounds against SARS-CoV-2 are urgently needed.

CRediT author Contribution Statement

Jhon Paul Iakov Mezarina Mendoza: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. Brigitte Patricia Trelles Ubillús: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Gabriela Tazziana Salcedo Bolivar – Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Rosa Del Pilar Castañeda Palacios: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Paulo Sergio Gilmar Herrera Lopez: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. David Alex Padilla Rodriguez: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Karin Harumi Uchina-Koecklin: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Ethics Information

The present study is a systematic review, which utilized data from previous existing studies. The authors did not perform any experiments for this studies that involved human or animal beings. This study presents an original work analyzed in a truthful manner that does not require any further ethical consideration.

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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