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REVIEW ARTICLE

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Efficacy of Cetylpyridinium Chloride mouthwash against SARS-CoV-2: A systematic review of randomized controlled trials

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Abstract

Introduction: COVID-19 is a transmissible respiratory and multisystem disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Viral transmission occurs mainly through the spread of salivary droplets or aerosol from an infected subject. Studies suggest that salivary viral load is correlated with disease severity and probability of transmission. Cetylpyridinium chloride mouthwash has been found to be effective in reducing salivary viral load. The aim of this systematic review of randomized controlled trials is to evaluate the efficacy of the mouthwash ingredient cetylpyridinium chloride on salivary viral load in SARS-CoV-2 infection.

Methods: Randomized controlled trials comparing cetylpyridinium chloride mouthwash with placebo and other mouthwash ingredients in SARS-CoV-2 positive individuals were identified and evaluated.

Results: Six studies with a total of 301 patients that met the inclusion criteria were included. The studies reported the efficacy of cetylpyridinium chloride mouthwashes in reduction on SARS-CoV-2 salivary viral load compared to placebo and other mouthwash ingredients.

Conclusion: Mouthwashes containing cetylpyridinium chloride are effective against salivary viral load of SARS-CoV-2 in vivo. There is also the possibility that the use of mouthwash containing cetylpyridinium chloride in SARS-CoV-2 positive subjects could reduce transmissibility and severity of COVID-19.

KEYWORDS
COVID-19, cetylpyridinium chloride, CPC, mouthwash, salivary viral load, SARS-CoV-2

Abbreviations: CPC, cetylpyridinium chloride; CHX, chlorhexidine; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HP, hydrogen peroxide; IPM, isopropyl myristate; PI, povidone-iodine; RoB 2, Risk of bias for randomized included trials; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1 | BACKGROUND

COVID-19 is a highly transmissible infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zou et al., 2020). Viral spread can occur via direct or indirect contact with infected subjects. Direct transmission may occur when coughing, sneezing, breathing, or talking, and droplets and secretions of an infected person manage to reach the oral or nasal mucosa of a susceptible host (World Health Organization, 2020). SARS-Cov2 can be transmitted by droplets or aerosol (Ong et al., 2020; Rabaan et al., 2022; World Health Organization, 2020). Larger droplets settle down on nearby surfaces, medium droplets are responsible of medium-distance transmission, and smaller droplets evaporate to become aerosols (Van Der Valk & In 'T Veen, 2021). Respiratory droplets are particles >5 μm in diameter that mostly deposit on the ground and settle on surfaces spreading over short distances. Studies show that virus transmission may occur through the spread of smaller aerosolized droplet nuclei (particles ≤5 μm in diameter) that can be suspended in the air for a longer period and travel greater distances (McCarthy et al., 2022). Then, the upper respiratory tract (nasal passage) is the initial site of SARS-CoV-2 infection, rather than the airways of the lungs (Chen et al., 2021). Multiple epithelial cell types in the mouth are also highly susceptible to infection, and the virus is directly transferrable in saliva (Huang et al., 2021), the inference being that kissing is a route of infection.

Long-lasting viral load is found in the saliva of infected patients (Carrouel et al., 2021; Huang et al., 2021). Indeed, saliva acts as a viral reservoir and source of infection, including in asymptomatic patients and those with mild COVID-19 symptoms (Baghizadeh Fini, 2020). Both the major and minor salivary glands are a site of viral replication (Huang et al., 2021; Matuck et al., 2021) with viral load reaching as high as 10^8 copies per mL of saliva during the first week of infection (Zhu et al., 2020). Saliva sampling is more sensitive in detection of SARS-CoV-2 compared with nasopharyngeal sampling (Teo et al., 2021; Wyllie et al., 2020). Saliva remains positive in some individuals post infection for a much longer period than is widely appreciated—up to 3.5 weeks if asymptomatic and for greater than 2 months in some patients who are symptomatic (Huang et al., 2021). Salivary viral load is also reported to correlate with the severity of COVID-19 and is a better predictor of death than the patient's age, independent of nasopharyngeal viral load (J. Silva et al., 2021).

Certain mouthwashes contain ingredients that target the outer lipid membrane of the virus (Mendoza et al., 2022; Saud et al., 2022). Considering saliva as a route of disease transmission (Huang et al., 2021; Xu et al., 2020), it would be intuitive to consider mouthwashes as a potential method to decrease the viral load of SARS-CoV-2 in saliva, and thus reduce transmission between individuals. Studies suggest that mouthwashes with antiviral ingredients could play a role in reducing the risk of SARS-CoV-2 transmission, or preventing it (Garcia-Sanchez et al., 2022; Saud et al., 2022). In addition, the use of mouthwash that reduces viral load in the mouth is reported to be effective in reducing disease severity in terms of length of hospital stay, admission to intensive care, and death (Da Silva Santos et al., 2021).

In this context, cetylpyridinium chloride (CPC) emerged as a molecule with considerable potential. CPC is a quaternary ammonium salt which is a common mouthwash ingredient. It is well established for such use and has an excellent safety record with no adverse reactions reported (Scientific Committee on Consumer Safety, 2015).

This agent can disrupt viral lipid envelopes, thus facilitating activity against a wide spectrum of enveloped viruses (Popkin et al., 2017). In vitro studies demonstrated a virucidal effect of CPC-containing mouthwash against SARS-CoV-2, inactivating the virus (Komine et al., 2021; Meyers et al., 2021). Viral fusion with target cells is suppressed (Munoz-Basagoiti et al., 2021), and interactions between S-protein and ACE2 receptors are inhibited (Okamoto et al., 2022). Analysis of the antiviral effects of CPC on SARS-CoV-2 by Saud et al. showed that it destroys the viral envelope by a phospholipid-disrupting surfactant action. In this way, the virus is completely eradicated in vitro and rendered undetectable in saliva in vivo for a prolonged period (at least 1 h) (Saud et al., 2022). This study also suggested that CPC may be useful in infection prevention and control strategies for other enveloped respiratory viruses such as influenza and other coronaviruses.

On the basis that CPC mouthwash is active against SARS-CoV-2, the aim of this systematic review is to demonstrate that CPC mouthwash is effective in vivo by reducing viral load in saliva.

2 | METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page et al., 2021). The review question was developed using the Population, Intervention or exposure, Comparison, Outcome framework: Among patients with SARS-CoV-2 infection (P), is CPC mouthwash (I), compared with placebo (C), effective against SARS-CoV-2 in vivo (O)? The protocol of this review was registered in PROSPERO (CRD 42023362430)

2.1 | Eligibility criteria

Randomized controlled trials published in peer-reviewed journals that recruited SARS-CoV-2 positive individuals were included. We excluded animal studies, non-randomized trials, observational studies, systematic and narrative reviews, and editorials.

2.2 | Search strategy

We performed a systematic search on PubMed Embase, MEDLINE, Web of Science Core Collection, and Google Scholar up to September 1, 2022. Keywords and other free terms were used with Boolean operators (OR, AND) to combine searches:

((mouthwash [tiab]) or (mouthrinses [tiab]) or (mouth rinses [tiab]) or (mouth wash [tiab]) or (1-hexadecylpyridin-1-ium [tiab]) or (sprol tn [tiab]) or (cetylpyridinii chloridum [tiab]) or (d9om4sk49p [tiab]) or (pyridinium [tiab]) or (1-hexadecyl-chloride[tiab]) or

(unii-d9om4sk49p [tiab]) or (hexadecylpyridinium chloride monohydrate [tiab]) or (cetylpyridinium [tiab]) or (1-hexadecylpyridinium chloride monohydrate [tiab]) or (1-hexadecylpyridin-1-ium chloride hydrate [tiab]) or (cetylpyridinium chloride monohydrate [tiab]) or ((1-Hexadecyl)pyridinium chloride [tiab]) or (CPC [tiab])) and ((COVID-19 [tiab]) or (SARS-CoV-2 [tiab]) or (coronavirus[tiab]) or (covid [tiab])) and ((randomized controlled trial [publication type]) or ((randomized [tiab]) and (controlled [tiab]) and (trial [tiab])) or (randomized [tiab]) or (controlled trial [tiab]) or (placebo [tiab]))).

We also examined bibliographic references of included articles and selected those we considered relevant.

2.3 | Study selection

With the aid of a reference management system, two authors independently screened study eligibility at the title/abstract level using a standardized form. After the elimination of duplicates, disagreements resolved by consensus and by involving a third investigator if required. The final selection of included articles was based on complete manuscripts with disagreements resolved by consensus.

2.4 | Data collection

We extracted all available data as outlined in the protocol. We extracted study characteristics (first author, year of publication, country), population characteristics (demographic data, illness severity), sample size, details of studied mouthwashes (quantity, concentration, duration), and outcomes.

2.5 | Outcomes

The primary outcome was the efficacy of CPC mouthwash against SARS-CoV-2 in saliva in vivo (yes/no). Secondary outcome was the reduction of viral load in vivo in saliva at least one time point compared to placebo and mouthwashes containing other active ingredients.

2.6 | Risk of bias assessment

Two investigators independently assessed the risk of bias for each of the included trials using the revised Cochrane risk of bias tool for randomized trials (RoB 2) (Sterne et al., 2019). We resolved disagreement during the review process by discussion with a third reviewer and by consensus. We considered a trial as low risk of bias only if all domains were assessed as low risk of bias.

2.7 | Grading the quality of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall quality of evidence for the primary outcome (Guyatt et al., 2008).

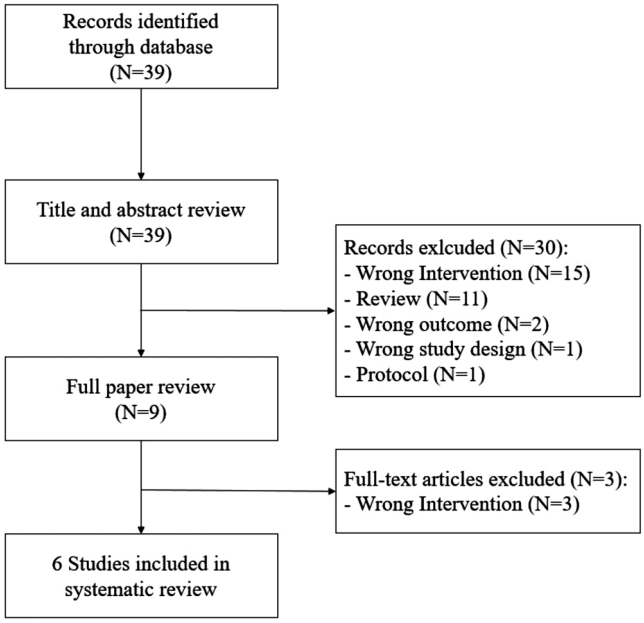

FIGURE 1 PRISMA flow diagram showing literature search results. Six trials were included in the analysis.

3 | RESULTS

3.1 | Characteristics of the studies

The research strategy of electronic databases detected 38 potentially relevant articles. Six studies with a total of 301 patients met the inclusion criteria and were included (Figure 1). All studies were conducted between June 2020 and July 2021. Four studies were conducted in Europe (Alemany et al., 2022; Barrueco et al., 2022; Ferrer et al., 2021; Saud et al., 2022), one in Brazil (Eduardo et al., 2021), and one in Singapore (Seneviratne et al., 2021). All were randomized controlled trials. Three studies were multicentric (Alemany et al., 2022; Barrueco et al., 2022; Saud et al., 2022). One study used a seven-parallel-group analysis to assess three different formulae of CPC and four other mouthwash formulae (chlorhexidine, povidone-iodine, ethanol, and ethanol with ethyl lauroyl arginate) (Saud et al., 2022). Three studies used five-parallel-group analysis (Barrueco et al., 2022; Eduardo et al., 2021; Ferrer et al., 2021). One study used four-parallel-group analysis (Seneviratne et al., 2021). One study used two-group analysis (Alemany et al., 2022). All studies included a placebo as a comparator. Different molecular components of mouthwashes were studied in parallel groups: povidone-iodine in four studies (N = 66%) (Barrueco et al., 2022; Ferrer et al., 2021; Saud et al., 2022; Seneviratne et al., 2021), chlorhexidine in four studies (N = 66%) (Barrueco et al., 2022; Eduardo et al., 2021; Ferrer et al., 2021; Seneviratne et al., 2021), and hydrogen peroxide in three studies (N = 50%) (Barrueco et al., 2022; Eduardo et al., 2021; Ferrer et al., 2021). CPC was tested at concentrations between 0.05% and 0.1%. Mouthwashes were performed for 30 s to 1 min with a volume between 10 and 20 mL. Five studies use reverse-transcription polymerase chain reaction (RT-PCR)

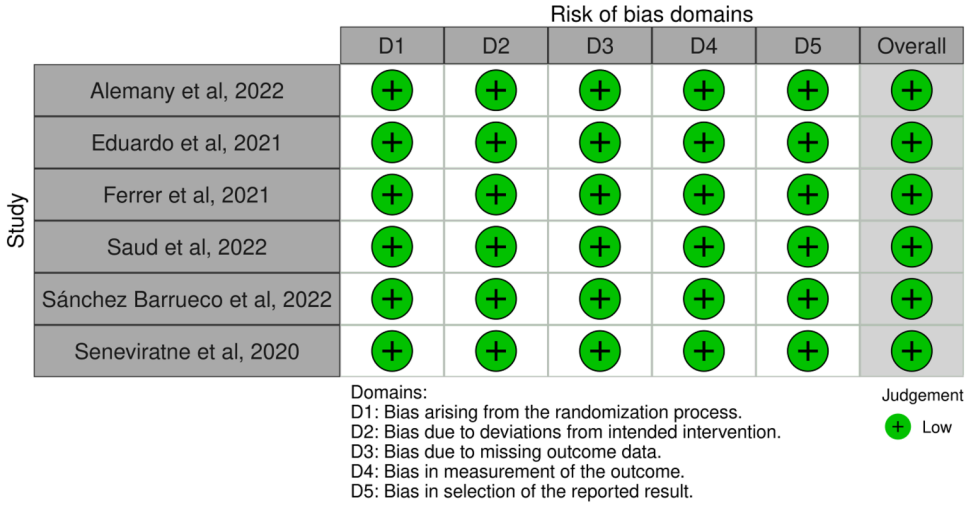

FIGURE 2 Risk of bias for randomized included trials (RoB 2).

to quantify viral load. One of these studies—Alemany et al. (2022)—also quantified SARS-CoV-2 nuceolcapsid protein level. One of these studies—Barrueco et al. (2022)—also quantified viral load by incubating saliva in cell cultures. One study—Saud et al. (2022)—quantified viral load by live virus titration. The characteristics of included studies are shown in Table 1.

Application of RoB 2 tool suggested that all trials had low risk of bias (Figure 2).

3.2 | Outcomes

All trials included in this systematic review showed efficacy of CPC mouthwashes against SARS-CoV-2 in vivo (Table 2).

Saud et al. investigated the effect of an oral rinse for 30 s on the salivary viral load in vivo at different time points in patients hospitalized for SARS-CoV-2 infection. Three products in which CPC was the main active ingredient were evaluated. The highest reduction in SARS-CoV-2 salivary viral load in vivo was observed after 1 min, at which time SARS-CoV-2 was undetectable in six out of seven patients. The product containing CPC and isopropyl myristate (IPM) was the only product to have a prolonged effect with a significant reduction of viral load at time points up to 1 h. Interestingly, the use of the aqueous portion of this product, which contains CPC, showed the same antiviral effect without the oil-based portion containing IPM. The study concluded that CPC alone can eradicate SARS-CoV-2 in this product and IPM is not required. Notably, not all commercially available CPC-containing tested mouthwashes had the same effect, indicating that some substances, such as benzoate, possibly blunt the CPC effects. Products containing essential oils, povidone-iodine, or chlorhexidine were shown to be ineffective against SARS-CoV-2. Products containing ethanol were also evaluated. Only one, which contained an additional ingredient—Ethyl Lauroyl Arginate—was shown to be effective, indicating it was responsible for the antiviral activity in this product rather than ethanol. This was the only study to quantify the antiviral efficacy of mouthwashes on salivary viral load directly using live virus titration (Saud et al., 2022).

Seneviratne et al. (2021) reported a significant decrease of salivary viral load at any time point when CPC was compared to placebo, while chlorhexidine showed no reduction and povidone iodine was better than placebo only at the 6-h time point.

Ferrer et al. reported that 59% of participants had a 50% decrease in salivary viral load after CPC mouthwash after 2 h. Although a downward trend occurred for both CPC and povidone iodine, the reduction in viral load was not statistically significant compared to placebo for any of the mouthwashes used in this study (Ferrer et al., 2021).

Eduardo et al. reported a more marked decrease of salivary viral load after the use of CPC-containing mouthwash when compared to hydrogen peroxide, chlorhexidine, or the combination of the two. A product containing CPC and Zinc was used. The study observed a 20-fold reduction in salivary viral load in vivo immediately after rinsing, and a sustained 2.6-fold reduction of SARS-CoV-2 in saliva at 1 h. Hydrogen peroxide showed a 15-fold reduction in salivary viral load immediately after rinsing, but this was not sustained beyond 30 min. The use of chlorhexidine showed only a twofold reduction in salivary viral load immediately after rinsing and, interestingly, when used in combination with hydrogen peroxide (chlorhexidine followed immediately by hydrogen peroxide), it did not show efficacy in reducing viral load, presumably, as the study concludes, because the chlorhexidine washed out the more active hydrogen peroxide (Eduardo et al., 2021).

Alemany et al. reported a significant increase of nucleocapsid protein levels (a sign of SARS-CoV-2 destruction) in saliva in non-hospitalized patients with asymptomatic or mild symptomatic SARS-CoV-2 infection following the use of CPC mouthwash and speculated about a possible reduction of viral spread (Alemany et al., 2022).

Sánchez Barrueco et al. observed, through viral culture, a 97% reduction of viral infectivity after CPC mouthwash, but only at 1 h after rinsing rather than at the 30-min time point, suggesting a delayed action. In the same trial, no significant differences were found for hydrogen peroxide, chlorhexidine, and povidone iodine, indicating

TABLE 1 Trial characteristics.

Study	Country	Study design	Groups of study	Overall patients included	CPC patients vs. placebo	Method of viral quantification	Mouthwash characteristics	Timeline protocol for collecting sample
Alemany et al. (2022)	Spain	Multicentric, case-control placebo-controlled trial	• CPC • Placebo	118	60 vs. 58	• Viral RNA load by RT-PCR • Nucleocapsid protein by high-sensitivity quantitative ELISA	15 mL of CPC 0.07% for 1 min	T0: before mouthwash T1: 1 h T2: 3 h
Eduardo et al. (2021)	Brazil	Single center, five-parallel group	• CPC + Zn • HP • CHX • HP + CHX • Placebo	41	7 vs. 9	• Viral RNA load by RT-PCR	20 mL of CPC 0.075% for 30 s	T0: after mouthwash T1: 30 min T2: 1 h
Ferrer et al. (2021)	Spain	Multicentric, five-parallel group	• PI • CHX • CPC • Placebo	58	11 vs. 12	• Viral RNA load by RT-PCR	CPC 0.07% for 1 min	T0: before mouthwash T1: 1 min T2: 30 min T3: 1 h T4: 2 h
Saud et al. (2022)	United Kingdom	Multicentric, four-parallel group	• CPC/IPM • PI • CPC/Benzoate • Placebo	28	15 vs. 6	• Live viral titration	10 mL of CPC 0.05%–0.1% for 30 s	T0: before mouthwash T1: 1 min T2: 15 min T3: 30 min T4: 1 h
Barrueco et al. (2022)	Spain	Single center, five-parallel group	• PI • HP • CPC • CHX • Placebo	40	10 vs. 10	• Viral RNA load by RT-PCR • SARS-CoV-2 infectivity by virus culture in Vero-E6 cells	15 mL of CPC 0.07% for 1 min	T0: before mouthwash T1: 30 min T2: 1 h
Seneviratne et al. (2021)	Singapore	Single center, four-parallel group	• PI • CHX • CPC • Placebo	16	4 vs. 2	• Viral RNA load by RT-PCR	20 mL of CPC 0.075% for 30 s	T0: before mouthwash T1: 5 min T2: 3 h T3: 6 h

Abbreviations: CHX, chlorhexidine; CPC, cetylpyridinium chloride; HP, hydrogen peroxide; IPM, isopropyl myristate; PI, povidone-iodine.

TABLE 2 Efficacy of cetylpyridinium chloride mouthwashes against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Study	Effective against SARS-CoV-2 (yes/no)	Results
Alemany et al. (2022)	Yes	• CPC mouthwash, compared to placebo, was associated with a statistically significant increase of nucleocapsid protein levels in saliva, indicating an increased disruption of viral particles
Eduardo et al. (2021)	Yes	• CPC mouthwash was associated with a 20-fold reduction in salivary viral load in vivo immediately after rinsing, and a maintained reduction 2.6-fold less of SARS-CoV-2 in saliva at 1 h
Ferrer et al. (2021)	Yes	• The maximum effects on viral load were observed 2 h after treatment in CPC and povidone-iodine groups, with mean viral load reductions around 30% • Fifty-nine percent of participants underwent a 50% decrease in viral load after CPC mouthwash • Similar pattern was observed for individuals undergoing a 90% decrease in viral load
Saud et al. (2022)	Yes	• Six of seven patients recorded no live virus 1 minute after CPC/IPM mouthwash • CPC/IPM was the only product to demonstrate a persistent effect, with a significant reduction evident throughout at 1, 15, 30, and 60 min • Three-eighths of patients treated with no live virus recovered at any time point after CPC/IPM mouthwash
Barrueco et al. (2022)	Yes	• A significant decrease of 1.5 log genome copies/mL of culture supernatant was observed in the mean number of infectious viruses 1 h after rinsing corresponding to a reduction in viral infectivity of 97.16%.
Seneviratne et al. (2021)	Yes	• CPC mouthwash was associated with significant decrease of *salivary* viral load in vivo at any time point compared to placebo

Abbreviations: CPC, cetylpyridinium chloride; IPM, isopropyl myristate.

enhanced disruption of viral particles by CPC mouthwash. A significant reduction in salivary viral copy number was only observed for CPC (Barrueco et al., 2022).

The quality of evidence assessed by the GRADE criteria for primary and secondary outcomes was considered high.

4 | DISCUSSION

We found that in all the six identified randomized trials, mouthwashes containing CPC were effective against SARS-CoV-2 in vivo. One study, which did not demonstrate statistically significant changes for any of the mouthwashes compared to placebo, suggested favorable results for both povidone-iodine and CPC compared with other mouthwash ingredients. In the other five randomized control trials, CPC was more effective in reducing viral load than the other common molecular components of mouthwashes (hydrogen peroxide, chlorhexidine, and povidone iodine). One study demonstrated a significant reduction in salivary viral load for CPC.

CPC destroys the SARS-CoV-2 lipid envelope, and the reduction in viral load is appreciated up to 6 h following rinsing with 10–20 mL of 0.05%–0.1% CPC mouthwashes for 30 s or up to 1 min. Notably, these properties might be blunted when adding other ingredients to commercially available products, suggesting the formulation in which CPC is delivered influences efficacy (Saud et al., 2022). Interestingly, the studies also demonstrated differing rapidity of action, one showing immediate effect (Eduardo et al., 2021) and one showing delayed effect (Barrueco et al., 2022).

The topic of mouthwashes against COVID-19 has been debated in the public domain since the beginning of the pandemic. Indeed, it is intuitive that reducing the viral load in the oral cavity could be beneficial in the context of an orally transmitted disease. It has been known for several years that mouthwashes are effective against certain viruses (Meiller et al., 2005). CPC has been found to be effective against several viruses. For example, CPC inhibits the formation of hepatitis B capsid structures, repressing its biogenesis by inhibition of its capsid assembly (Seo et al., 2019). CPC also blocks the herpes simplex (human herpesviruses types 1 and 2) viral replication cycle (Alvarez et al., 2020) and exhibits potent rapid activity against influenza viruses in vitro and in vivo (Popkin et al., 2017). However, before the COVID-19 pandemic era, the numbers of studies and interest in this field were so limited that any conclusions were impossible.

With the advent of COVID-19, laboratory studies were performed showing the virucidal effect of CPC-containing mouthwash against SARS-CoV-2. CPC (at 0.07%) was shown to inactivate ≥99.9% of SARS-CoV-2 within 30 s to 2 min incubation in tissue culture (Komine et al., 2021; Meyers et al., 2021; A. Silva et al., 2022). The same result was found in the presence of sterilized saliva (Munoz-Basagoiti et al., 2021). Proposed mechanisms were (i) viral envelope disruption and (ii) inhibition of the interaction between S-protein and ACE2 (Okamoto et al., 2022; Saud et al., 2022). Several studies and meta-analyses focus on mouthwashes, but they do not focus on CPC, and their evidence on

CPC mouthwash was limited to only one or two studies (Gandhi et al., 2022; Garcia-Sanchez et al., 2022; Mateos-Moreno et al., 2021; Mezarina Mendoza et al., 2022; J. Silva et al., 2022). In addition, comparative studies are few and with unclear results.

To the best of our knowledge, this is the first systematic review that focuses on CPC-containing mouthwash in the context of COVID-19. We observed that CPC mouthwash is effective against SARS-CoV-2, reducing viral load in saliva. All studies evaluated analyzed saliva harvested in vivo, not only in vitro. Moreover, when compared with other mouthwash ingredients, CPC was found to be the most effective in reducing viral load in vivo. It has been suggested elsewhere that salivary viral load is related to the transmissibility of SARS-CoV-2 (Carrouel et al., 2022, Marchesan et al., 2021). Therefore, it is plausible that the reduction of viral load results in a reduction of transmissibility between individuals. In addition, several studies demonstrated a correlation between COVID-19 severity and salivary viral load (Aydin et al., 2021; Chua et al., 2021; J. Silva et al., 2021), and it is possible, therefore, to hypothesize that a reduction in salivary viral load by using CPC-containing mouthwash could have clinical implications for community and hospitalized patients.

The findings of this review also suggest that there could be important implications in the management of COVID-19 in the prevention of transmission. Assuming that the reduction of viral load in the mouth reduces the transmissibility of the virus for hours after mouthwash, mouthwash could be routinely used to reduce the risk of virus transmission during events, especially in indoor places. In a prevention perspective, mouthwash could potentially be used in crowded places, before meetings in enclosed places, or in all clinical settings to decrease inter-individual transmission. Conceivably, mouthwash could also be used to reduce inter-individual transmission in the workplace, schools, or the family home setting. In this way, the use of mouthwash could become part of routine measures to reduce SARS-CoV-2 transmissibility as an adjunct to other measures, such as social distancing and the use of face masks. In asymptomatic patients, reduction of viral load could result in decreased spread among close contacts, non-progression to clinically symptomatic disease, and shortening duration of positivity.

The findings of this review suggest that there could be important implications for the use of CPC-containing mouthwashes in the management of COVID-19 in the prevention of transmission and treatment. The correlation between disease severity and salivary load suggests that reducing salivary load may have effects on the duration and severity of the disease. It is conceivable that in patients with mild, moderate, and severe disease, the use of a mouthwash that reduces salivary viral load, such as one containing CPC, could decrease the severity and duration of the disease. Clinical studies have shown that the use of mouthwash that reduces viral load in the mouth reduces the mortality and duration of COVID-19 (Choudhury et al., 2021; Da Silva Santos et al., 2021). A study by Da Silva Santos et al. demonstrates a reduction in hospital length of stay (from an average of 7 days to an average of 4 days), and a reduction of both ITU admission and death on the use of a mouthwash that reduces viral load in the mouth as a single addition to standard care. This study used an ingredient which, to our knowledge, is currently not available commercially outside Brazil. Considering these clinical results, in which it was concluded that—*protocol involving mouthwash containing a compound with antiviral effects against SARS-CoV-2 may reduce the symptoms of the patients and the spread of infection*—a strong rationale for the use of mouthwashes containing antiviral agents such as CPC emerges. Indeed, in all comparative studies on mouthwash against SARS-CoV-2, CPC was the most effective ingredient in reducing viral load in saliva.

This means that mouthwashes with antiviral activity may become an adjunct treatment for COVID-19. Although this measure is not yet included in clinical recommendations, we believe that it could represent an effective therapeutic strategy for COVID-19 in addition to standard care. Further larger studies will be required.

Furthermore, mouthwashes containing CPC are readily available and inexpensive. From an extensive analysis of commercial mouthwash, we report that CPC is contained in about 300 products worldwide. In at least 200 of these products, CPC is the only active ingredient. In the other 100 products, there is more than one active ingredient. Further analysis of the best formulation is required as one of the studies reviewed suggests that some other mouthwash ingredients can inhibit the action of CPC (Saud et al., 2022). In addition, commercial products containing CPC are non-pharmacological; thus, the presence of CPC can be hidden in the labeling, and products with very similar names have different contents. There are more than 10 synonyms or nomenclature of CPC (e.g., 1-hexadecylpyridin-1-iumor, d9om4sk49p, 1-hexadecyl-chloride, hexadecylpyridinium chloride monohydrate).

To our knowledge, our review provides the most up-to-date evidence for the effect of CPC-containing mouthwash in the context of COVID-19. The present review includes substantial new data, and it is the only systematic review specifically focused on CPC mouthwash. The methodologic strengths of this review include a focused research question with a defined population, intervention, comparator, and outcome. This systematic review is the first on this topic that includes only randomized controlled trials. In addition, all the studies analyzed are independent and received no funding. Two investigators independently assessed the risk of bias for each of the included trials using the RoB 2. We considered all the included trials as having a low risk of bias. The quality of evidence was high when assessed using GRADE.

Limitations of this review are mainly related to characteristics of the included trials, which reported outcomes at different time points and did not report outcomes which allowed a meta-analysis. The studies were conducted using a variety of methods for quantifying viral load and did not use standardized formulae of products containing CPC or other ingredients. So far, there are only a few studies available on this topic and with small samples. None of these studies report patient-centered or clinical outcomes. The studies do not discriminate SARS-CoV-2 variants.

One possible objection to the use of mouthwashes, especially using for long term, has been the effect on the nitrous oxide pathway, which plays a role in mediating blood pressure. Currently, evidence regarding this concern relates mainly to products containing chlorhexidine (Lila & Klompas, 2018). In view of this concern, it is not possible to provide a strong recommendation for the use of any mouthwash. The use of a

CPC mouthwash should be evaluated in the context of each specific clinical setting.

The safety of the ingredient benzoate/benzoic acid, found in some of the CPC formulae assessed, has been questioned, but is considered safe (Wilbur et al., 2017). This ingredient is found in some mouthwash formulations containing CPC (Saud et al., 2022). As the other ingredients of CPC products differ, and the safety of formulae should not be assumed, it is perhaps better to provide guidelines which suggest the use of CPC mouthwash only during a period of active COVID-19 infection, rather than for long-term use or sporadic use to prevent transmission without further evaluation.

Our review provides insight into the effect of CPC mouthwash on salivary viral load in vivo. These findings are not sufficient to demonstrate a potential clinical effect. Better understanding of such effects could be gained from randomized controlled trial on clinical outcomes. In addition, further studies are needed to understand whether mouthwashes can be used to prevent transmission or modulate the clinical course. Nevertheless, given the excellent safety record of CPC, and the wide availability and low cost of products containing this ingredient, we consider it reasonable to provide populations with information regarding its antiviral actions and to offer patients the choice to use CPC mouthwash, especially in the context of active COVID-19, or in specific social or clinical settings in which a potential additional method of transmission reduction is required, for example, care homes and dental surgeries.

5 | CONCLUSIONS

Our systematic review of currently existing data indicates that mouthwashes containing CPC are effective in reducing salivary viral load of SARS-CoV-2 in vivo and provides a rationale for larger studies to evaluate the efficacy of CPC mouthwashes in reducing transmissibility and clinical severity of COVID-19.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The author has provided the required Data Availability Statement, and if applicable, included functional and accurate links to said data therein.

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