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## Antiviral mouthwashes: possible benefit for COVID-19 with evidence-based approach

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### ABSTRACT

**Background** The outbreak, and pandemic of COVID-19 causing widespread concerns in all health systems of countries. Virus-carrying aerosols can penetrate the healthy human body and lungs, resulting in rapid transmission. For the first time, in this evidence-based article, the effects of different types of mouthwashes to reduce the viral load were investigated. Also, another aim of this essay is a reduction in viral load in patients with COVID-19 and prevention developing ventilator-associated pneumonia in critically ill patients.

**Methods** Related databases were comprehensively searched for relevant studies. The present study was performed according to the preferred cases for standard systematic reviews (PRISMA).

**Results** Five original studies in which the subject matter was directly evaluated were included. Different types of mouthwashes and viruses were investigated in this study.

**Conclusions** The antiviral mouthwashes play a certainly important role in reducing the viral load of the salivary virus. In the present study, this importance could be proved in two different aspects, that is, the use of mouthwash before dental procedures to reduce the risk of transmission of the virus to the dental team and the use of this mouthwash in COVID-19 patients to help improve systemic problems associated with oral microbial flora.

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Mouthrinses; mouthwash; preprocedural; aerosols; chlorhexidine; C31G; PVP-I

### Introduction

The sudden onset, outbreak, and pandemic of COVID-19 began in late 2019, causing widespread problems and concerns [1].

COVID-19 belongs to the Coronavirus family. SARS-CoV and MERS-CoV viruses, which have spread in recent years but are less widespread and less contagious than COVID-19, also belong to this family. Only  $\alpha$  and  $\beta$  family coronaviruses can infect humans, and SARS-CoV, MERS-CoV, and COVID-19 belong to  $\beta$  family coronaviruses [2]. Previous researches also show that more than 80% of the COVID-19 genome resembles that of the SARS-CoV [3].

The very rapid spread of the COVID-19 virus in a very short time in more than 100 countries shows the very high transmission potential of this disease, which has caused concern in all health systems of countries [4,5]. Human-to-human transmission of COVID-19 occurs due to close contact with an infected person, exposure to coughing, sneezing, breathing drops, or airborne particles [6]. The COVID-19 crisis, with its rapid spread, has disrupted education, economic, and health care systems, resulting in severe damage to all countries

[7]. This virus has entered the human ecosystem and new considerations have been created for us given that humans can host the virus.

The angiotensin-converting enzyme 2 (ACE2) receptor of the epithelial cells of the salivary glands is the primary target of the COVID-19 virus. This receptor is abundant in the tongue, indicating a high probability of infection in the oral cavity [8].

According to research, there are  $1 \cdot 2 \times 10^8$  infective copies/mL of COVID-19 virus in the tested saliva of patients [9]. Studies also show that virus shedding is very high in the early stages of the disease in the upper respiratory system [10]. Considering the role of saliva and salivary glands in the entry of COVID-19 virus into the body, the process of infection and as a source of the presence of this virus should be considered even in asymptomatic carriers [11]. Recent reports declared that the coronavirus has the potential of transmission from the asymptomatic carriers. This can be due to the incubation period ranging from 0 to 24 days and false-negative RT-PCR results in asymptomatic carriers. Also, they mentioned if more than 30% of transmission occurred by the incubation period, more than 90% of the contacts could be followed

out [12,13]. Saliva plays an important role in transmitting the infection through the spread of virus-infected droplets [11]. Aerosols are liquid or solid particles (less than 5  $\mu\text{m}$ ) that remain suspended in the air for long periods and they evaporate faster and widespread in the air and fall out away. There are also larger droplets (more than 5  $\mu\text{m}$ ) that are heavier, fall out nearby faster than they evaporate, and unable to stay suspended for long periods [14,15]. Virus-carrying aerosols can penetrate the healthy human body and lungs through direct inhalation through the nose or mouth (COVID-19 can transport to 1 meter during normal breathing and the exhalation can diffuse COVID-19 beyond 2 meters), sneezing and coughing, or through contact with the mouth, nose, and eye mucosa, resulting in rapid transmission of the disease to people in the society [16,17].

Results of previous studies reveal that dentists and dental clinics pose the highest risk of COVID-19 transmission [7]. A large number of dental procedures, including the use of ultrasonic scalers slow-speed and high-speed handpieces, and other procedures have led to the production and release of aerosols and droplets [7,18]. These particles are pushed into the air for about 3 feet and then fall to the ground. Aerosols also stay in the air for a very long time and can spread infection and contamination of the entire clinic environment [19].

Providing a virus-free environment is considered as a dentist's duty, but clinics are unable to do so due to the easy and rapid spread of COVID-19, especially following dental procedures, leading to the closure of a large number of dental offices during this crisis; however, a high number of emergency patients in need of dental treatment is inevitable, and it is essential to find solutions to effectively reduce the viral load [19].

So far, there has been no specific study on reducing COVID-19 virus in aerosols produced following dental procedures or reducing its salivary load. One of the solutions suggested to reduce the viral load in the dental environment is to use effective mouthwashes before treatment [7,18,20]. One of the solutions to achieve the protocol of using effective mouthwashes is to collect information on similar topics regarding the effect of mouthwashes on viruses in the oral cavity, especially on those with a similar structure. The effect of antiviral agents is usually the same for viruses with the same structure; therefore, since COVID-19 is an enveloped virus, the results can be used in previous studies with a similar structure.

For the first time, attempts were made in the present study to carry out an evidence-based investigation on all available articles on the effect of different types of mouthwashes and effective

reduction of viral load in the oral environment. Disease transmission through aerosol, droplet and saliva transmission in the dental environment will be reduced by identifying the possibility of using an effective mouthwash and reducing the load of COVID-19 virus, leading to the reopening of dental offices and the support of patients in need of treatment, and effective reduction of the probable spread of the disease.

Another aspect of the importance of mouthwashes and the reduction of oral viral load is related to patients with COVID-19. A systematic review in 2016 of more than 38 RCTs found that increased oral hygiene by mouthwashes can prevent developing ventilator-associated pneumonia in critically ill patients [21]. Different studies have evaluated the antiviral effect of Povidone Iodine, 0.12%-chlorhexidine gluconate, Cetylpyridinium chloride, C31 G, chloroxylonol, benzalkonium chloride and cetrimide/Chlorhexidine [22–27].

As shown in the systematic review, the use of mouthwash alone has the same effect as mouth washing and brushing, and since it is easier for patients to use mouthwash, it is very important to investigate the use of mouthwashes in this regard.

## Materials and methods

The present study was performed according to the preferred cases for standard systematic reviews (PRISMA) [28].

### Search strategy and selection criteria

The resources required in this study were obtained by searching PubMed (MEDLINE) and Scopus electronic databases. Articles were searched using the keywords Mouthwash, Mouthrinse, Virus, and Viral. Accordingly, 219 articles were found in PubMed (MEDLINE) and Scopus until June 2020.

Considering that there were few relevant studies, no restrictions were placed on the language and date of publication of articles in the resources found. Details of the search strategy are given in the PRISMA diagram. All the results shown were carefully evaluated, and the articles that directly evaluated the subject matter were separated from the rest of the results (N = 5).

The studies found include the following:

1. Introducing mouthwash and expressing non-toxicity and its effectiveness range.
2. Mentioning the names of the studied viruses and the possibility of their presence in the mouth.
3. The effectiveness of the mouthwash the viral load and in vitro results.

Methodological quality assessment was not applicable due to a lack of reliable checklist for in vitro studies.

## Review questions

'Which mouthwashes (outcome) affect the viruses that present in saliva (participants)?' The review question was based on the PICO model.

To further analyze this question, the following criteria were extracted from the articles: author's name, year of publication, type of study, evaluated mouthwash, tested viruses, type of placebo, testing time, and reduction in viral load.

Through discussion, the authors sought to avoid disagreement over the choice of study, quality assessment, and data extraction.

## Results

### Study selection

A search of PubMed (MEDLINE) and Scopus electronic databases yielded 219 without applying language and time limits since there was an insufficient number of relevant studies.

Google Scholar was searched as a general web search engine to ensure complete results.

The titles and abstracts of all these articles were carefully reviewed, and a total of 199 studies were excluded after removing the duplicate items as well as excluding the studies in which the subject matter was directly evaluated. After reviewing the full text of the 20 articles and considering the importance of calculating the viral load changes, finally, four studies entered the evaluation process.

### Characteristics of studies

PICO question developed in the present study included 'Which mouthwashes affect salivary viruses?' Table 1 shows the characteristics of the reviewed studies in reducing the viral load. Table 2 shows the size of each sample in the study and explains the test procedure.

### Study results

There was a significant difference in the reduction of viral load between the mouthwash group and the control group in all the articles reviewed. Table 1 demonstrates the investigation of the tested cases, the effect of mouthwash on the evaluated viruses, as well as the results of each study.

## Discussion

Broad-spectrum antimicrobial mouthwashes are one of the most available solutions to reduce pathogens. The effectiveness of different types of mouthwashes has been widely questioned in patients with COVID-19.

The present study reviewed four in vitro studies on the effect of mouthwash on viral load reduction. These four studies were the only resources found in search engines and about statistical and numerical reports of the results of mouthwashes on reducing viral load.

We have classified the achievements of the present study regarding the prescription and effectiveness of mouthwashes in the COVID-19 crisis in three groups of mouthwashes evaluated as follows.

### Chlorhexidine (CHX)

Chlorhexidine (CHX) is used as a standard gold mouthwash worldwide [29].

This mouthwash has a wide range of antimicrobial effects. Previous studies have shown that CHX has the greatest effect on a variety of gram-positive and gram-negative, aerobic and non-aerobic bacteria, which is superior and more effective than other mouthwashes in this regard [23,30–32].

CHX side effects include tooth staining, supragingival calculus formation, and a change in taste sensation [31].

Prescribing CHX before dental procedures is a routine procedure that reduces the level of oral microorganisms in the aerosols generated during dental procedures [15,18,32,33].

### As a pre-procedural mouthwash in dental practice

In vitro studies on the effect of CHX on several viruses show the effectiveness of this mouthwash on reducing the viral load [26]. Furthermore, considering the effectiveness of CHX in reducing the load of the SARS virus from the coronavirus family, its use was recommended before dental procedures [19]. Results of other studies of other enveloped viruses have proved that varying concentrations of CHX kill the virus [24]. Essential oils mouthwashes have also been shown to have antiviral properties against enveloped viruses [24], although they are less effective than CHX and are more effective against bacteria [15].

Recent studies, however, suggest that CHX may be less effective than PVP-I in eliminating COVID-19 before dental procedures [7].

### As a mouthwash in COVID-19 patients

It is noteworthy that patients with respiratory infections have altered oral flora. When exposed to pathogenic microorganisms, these floras alter patients' systemic symptoms. Attempts to restore the normal flora in patients with respiratory infections reduce the systemic complications of the disease and accelerate the recovery process [34].

Table 1. Study details.

Article	First author	Kind of mouthrinse	Antiseptic/ Antibacterial	Placebo	Contaminate	Reduction in viral load	Testing time	Author's Conclusions
In vitro Virucidal Effectiveness of a 0.12%-Chlorhexidine Gluconate Mouthrinse 6 November 1989	D BERNSTEIN [1]	Peridex (Chlorhexidine Gluconate 0.12% Oral Rinse)	Antimicrobial	Excipients	Herpes Simplex Cytomegalovirus Influenza A Parainfluenza Hepatitis polio virus	Reductions in all virus concentration except the polio virus.	30	s-5 m-15 m
Virucidal effectiveness of 0.12%-Chlorhexidine Gluconate increased with time.								
In vitro effect of oral antiseptics on human immunodeficiency virus-1 and herpes simplex virus type1 Baqui Jul,2001	AAMA Baqui [2]	-ListerineA Antiseptic (LA) -Tartar control ListerineA -Antiseptic (TLA) -PeridexA (PX, 0.12% chlorhexidine digluconate) -Chlorhexidine digluconate (CHX, 20% w/v)	Antimicrobial	-	Human Immunodeficiency Virus (HIV-1) Herpes simplex virus (HSV-1)	Reduced viral load.	30 sec	Each of the mouthrinses tested possess in vitro anti-HIV and anti-HSV properties at their commercial concentrations and some demonstrated efficacy up to 1:16 dilutions.
In Vitro Virucidal Effect of Mouthrinse Containing C31 G on Seasonal Influenza Viruses Lee 1 April 2014	Dong-Hun Lee [3]	-3.0% solution of C31 G - mouthrinse containing 3.0% C31 G, SenseTime (ILDONG Pharmaceutical, Korea),	Antimicrobial	Phosphate buffered saline (PBS)	B/Brisbane/60/2008, virus A/Brisbane/59/2007 (H1N1) A/Brisbane/10/2007 (H3N2)	Reduced and inhibited the infection of seasonal influenza viruses.	30 min	C31 G and Sense-Time completely inactivated all of the tested viruses Although Sense-Time contained the same concentration of C31 G, the C31 G solution showed a higher virucidal.
Rapid and Effective Virucidal Activity of PovidoneIodine Products Against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Modified Vaccinia Virus Ankara (MVA) Eggers 28 September 2015	Maren Eggers [4]	1% PVP-I	Antiseptic	Double-distilled water	MERS-CoV	Reduction of viral load required 30 s of exposure at the 1:10 dilution	15s, 30s, 60 s	the excellent virucidal activity of PVP-I against enveloped viruses.
In Vitro Bactericidal and Virucidal Efficacy of Povidone-Iodine Gargle/Mouthwash Against Respiratory and Oral Tract Pathogens Eggers 9 April 2018	Maren Eggers [5]	7% PVP-I	Antiseptic	Distilled water	SARS-CoV MERS-CoV influenza virus A subtype H1N1 rotavirus	All viral titres were reduced by between 4.40 and 6.00 log <sub>10</sub> TCID <sub>50</sub> /ml.	Clean conditions: 15s- 30s- 60s- 120s Dirty conditions: 15s- 30s	All viral titres were reduced after 15 s of contact time with PVP-I gargle at a concentration of 0.7% and 0.23%

**Table 2.** Culture methods.

Article	Source	Virus concentration	Method
In vitro Virucidal Effectiveness of a 0.12%-Chlorhexidine Gluconate Mouthrinse [1]	Rabbit kidney (RK) cells Human foreskin fibroblast (HFF) Rhabdomyosarcoma (RD) African green monkey kidney (CV-1) Madin Darby canine kidney (MDCK)	0.1 mL of a virus suspension	Herpes simplex virus type 1 (McIntyre strain) were evaluated on RK cells, cytomegalovirus (strain AD169) on HFF cells, polio type 1 (Chat strain) on RD cells, influenza (strain A/Bethesda 1/85) on MDCK cells, and parainfluenza type 3 (strain HA-1) on CV-1 cells. since HBV does not grow in tissue culture, inactivation of the virus was tested by the assay of the virus-associated DNA polymerase activity during contact with active and placebo mouthrinses.
In vitro effect of oral antiseptics on human immunodeficiency virus-1 and herpes simplex virus type1 [2]	Primary African monkey kidney cell cultures (Vero) for HSV Transformed lymphoblastoid cell line (MT-2) for HIV	$2.5 \times 10^5$ virus/ml	suspensions
50 ml of the undiluted and diluted LA, TLA, PX and CHX were added onto the 50 ml of the $2.5 \times 10^5$ virus/ml suspensions of HSV-1 and HIV1 McIntyre strain. Each mixture was incubated for 30 sec at room temperature.			
In Vitro Virucidal Effect of Mouthrinse Containing C31 G on Seasonal Influenza Viruses [3]	Chicken embryonated eggs Madin-Darby Canine Kidney	2.5 ml of each virus	2.5 ml of undiluted and diluted C31 G and Sense-Time were added onto 2.5 ml of each virus.
Rapid and Effective Virucidal Activity of Povidone-Iodine Products Against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Modified Vaccinia Virus Ankara (MVA) [4]	Baby hamster kidney cells (BHK)-21 cells	100 $\mu$ L virus suspension	Aliquots of 100 $\mu$ L from each dilution were added to six 200 $\mu$ L samples of BHK-21 cells.
In Vitro Bactericidal and Virucidal Efficacy of Povidone-Iodine Gargle/Mouthwash Against Respiratory and Oral Tract Pathogens [5]	Vero E6 cells for SARS-CoV and MERSCoV Madin-Darby Canine Kidney (MDCK) cells for influenza virus A subtype H1N1 MA104 cells for human rotavirus strain Wa.	100 $\mu$ L virus suspension	The test assay comprised 100 $\mu$ L virus suspension, 100 $\mu$ L interfering substance and 800 $\mu$ L PVP-I product (at the defined dilutions).

Results of a study of hospitalized patients have also shown that pathogenic microorganisms are present in patients' mouths from day one and show an increasing trend during hospitalization [35]. Therefore, it seems that the use of CHX in COVID-19 patients who have altered oral flora, whether in a hospital or non-hospital setting is an important procedure to improve the symptoms in these patients [25,36].

Also, in critically ill patients, it has been shown that CHX mouthwash or gel can help reduce the incidence of ventilator-associated pneumonia from 24% to about 18% [21].

This is also an important procedure ensuring the greater safety of caregivers and staff in the healthcare system who are in direct contact with these patients [37].

### C31G

C31 G is a potent broad-spectrum antimicrobial. C31 G contains a buffered equimolar mixture of two amphoteric surface-active agents. This agent can adhere to the surface of microorganism via the polar head group of the amine oxide-betaine mixture

and subsequently disrupt the microbial membrane with the alkyl portion of the molecule [38]. Its antiviral activity against enveloped viruses has been shown in previous studies [39,40].

Studies have shown no significant difference in the use of C31 G mouthwash compared to CHX after dental surgery. The most important advantage of C31 G, as compared to CHX, is that it does not stain teeth, restorative materials, and oral mucosa [41].

### *As a pre-procedural mouthwash in dental practice*

An in vitro study showed that C31 G mouthwash was effective in reducing the viral load of seasonal flu viruses [42].

This suggests that this mouthwash may have a potential effect on eliminating the COVID-19 virus before dental procedures and thus reducing the risk of the disease spreading in the clinic.

### *As a mouthwash in COVID-19 patients*

Gargling the C31 G mouthwash increases oral hygiene and respiration. Previous studies indicate

that C31 G plays a role in reducing the transmission of the seasonal flu virus [42]. Concerning this evidence and mechanism of action, it is probable that C31 G be effective in reducing the oral microorganisms of patients with COVID-19. Further clinical studies are needed.

### **Povidone-iodine (iodine with the water-soluble polymer polyvinylpyrrolidone, PVP-I)**

PVP-I is one of the broad-spectrum antimicrobial mouthwashes [22]. PVP-I is a water-soluble complex with polyvinyl pyrrolidone. It has free iodine (usually 1 ppm), and it releases gradually. The most common formulation is a 10% solution. Oxidation of amino acids and nucleic acids is its basic action. It damages the microorganism by perturbation of various metabolic pathways and destabilization of the cell membrane [43]. Studies have reported that PVP-I has more antiviral properties than other mouthwashes [44,45].

In vitro studies have reported the effect of this mouthwash on reducing enveloped and non-enveloped viruses [44].

### ***As a pre-procedural mouthwash in dental practice***

The results of two in vitro studies reviewed in this paper and other studies showed that PVP-I mouthwash leads to a significant reduction in the viral load of SARS-CoV and MERS-CoV viruses from the coronavirus [44,46,47]. The use of this mouthwash is effective in reducing the presence of viruses in droplets and aerosols considering its strong antiviral properties [7,46–49]. Also, recent studies have recommended the use of this mouthwash in the COVID-19 crisis before dental procedures to prevent disease transmission [7].

### ***As a mouthwash in COVID-19 patients***

A hospital study on the COVID-19 crisis recommended the use of this mouthwash for patients and staff of the health department who are in direct contact with COVID-19 patients [49].

Gargling this mouthwash has also been suggested in several studies to reduce viral load and thus to control oral hygiene and respiratory tract [46,47,49].

This procedure reduces the risk of the virus spreading during coughing, sneezing, and even talking, and it may thus be effective in controlling the COVID-19 epidemic [46,47].

The use of this mouthwash has also been recommended in people with a high risk of respiratory infections to reduce other pathogens in the oral flora and thus to prevent the infection and accelerate recovery in these patients [47,50].

### **Conclusion**

There are at least three different pathways for COVID-19 to present in saliva: firstly, from COVID-19 in the lower and upper respiratory tract that enters the oral cavity together with the liquid droplets frequently exchanged by these organs. Secondly, COVID-19 present in the blood can access the mouth via crevicular fluid, an oral cavity-specific exudate that contains local proteins derived from extracellular matrix and serum-derived proteins. Finally, another way for COVID-19 to occur in the oral cavity is by major- and minor-salivary gland infection, with subsequent release of particles in saliva via salivary ducts [51].

Dentists need to focus the patient positioning, hand hygiene, all personal protective equipment (PPE), and safety measures in the production of aerosol production, as preventive measures to prevent COVID-19 infection [51]. As the present review study showed, antiviral mouthwashes play a certainly important role in reducing the viral load of the salivary virus.

In the present study, this importance could be proved in two different aspects, that is, the use of mouthwash before dental procedures to reduce the risk of transmission of the virus through the aerosol and saliva to the dental team and the use of this mouthwash in COVID-19 patients to help improve systemic problems associated with oral microbial flora.

Extensive searches showed no clinical study on the effectiveness of mouthwashes in reducing viral load. It was surprising to find a few such important studies to provide a guide ensuring the prescription of more effective mouthwashes, and it seems necessary to perform further studies in this regard. Also, the lack of an in vitro studies quality assessment checklist was another limitation of the present review study.

Therefore, there is a need for further clinical trials regarding two different aspects, that is the use of mouthwash in dental procedures as well as in the treatment of COVID-19 patients.

### **Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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