Lesson Learned from Antiseptic Mouthwash in COVID-19 Pandemic Then, Now and Future: A Systematic Review

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Abstract

A new virus has been discovered, SARS-CoV-2 (severe acute respiratory syndrome coronavirus). SARS-CoV-2 is transmitted through aerosols or salivary droplets. Therefore, this may be a potential high-risk for viral infection and transmission in a dental clinic. After the pandemic we know that an oral viral load reduction could reduce the risk of transmission via saliva. Oral antiseptics seem to be one of useful methods in preventing viral transmission.

The aim of this review was to evaluate the available evidence on the effectiveness of mouthwashes in dental care facilities. Methods: An electronic search was conducted using MEDLINE, Pubmed and Scopus databases, using systematic review method and review final information. After those we summarized results, discussed, and recommended for using proper mouthwash in dental field.

A total of 308 articles were found. Six in vitro and six in vivo articles were selected, assessing the effectiveness of oral antiseptic mouthwashes. Conclusion: All documents clear evidence to support the use of antiseptics to potentially reduce the viral load of SARS-CoV-2. It is highly recommended that dental practitioners use oral antiseptics before dental procedures to protect against the transmission of Coronavirus virus and routine using in the future.

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Introduction

Coronavirus disease 2019 (COVID-19) was first discovered in December 2019, emerging from the Wuhan, Hubei province, China[1] and quickly spread throughout the world, resulting in a global pandemic.[2] More than 410 million people worldwide have contracted the disease, which has also killed more than 6 million people.[3,4] The COVID-19 virus has been around nearly three years now; with deestating effects on global economies, education, impacted for transportation, and public health systems.[5] Especially the health care workers and students. The survey reported that dental students have stress, anxiety, worry, and direct mental health care implementation.[6] COVID-19 belongs to the Coronavirus family (Betacoronavirus genus), which includes coronaviruses discovered in humans, bats, and other wild animals.[7] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new virus that has been recently discovered.[2,5] The virus is ellipsoidal in shape and has a characteristic crown-shaped appearance.[8] RNA viruses are enveloped, single-stranded RNA viruses that infect wild animals and humans. SARS-CoV-2 appears to have greater infectivity when compared with SARS-CoV and MERS-CoV. The nucleoprotein (N), membrane glycoprotein (M), small envelope glycoprotein (E), and spike protein (S) are the four structural proteins that are encoded by the SARS-CoV-2 genome (Fig.1). Coronaviruses' spike protein (S) aids viral entrance into target cells. Entry is required on the spike protein's surface units, each composed of two subunits, S1 and S2. The S1 attaches to ACE2 receptors to enable viral attachment to target cells' surfaces, while S2 is essential for the fusion of the viral and host membranes, but it is not fully exposed until after receptor binding.[9] The primary

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target cell receptor for the SAR-CoV-2 virus is the angiotensin converting enzyme II (ACE2) receptor on the epithelial cells of the oral mucosa. The invasion and propagation of viruses are determined by the ACE2 receptor. Therefore, ACE2-expressing cells can act as susceptible target cells to SARS-CoV-2 adhesion and infection. The expression of ACE2 was higher in the tongue than in other oral tissues.[10] As a result, it has been proposed that SARS-CoV-2 is present in saliva.

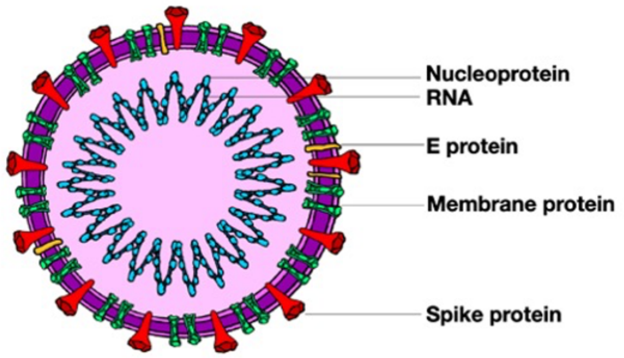

Figure 1. Typical scheme of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virion structure.

COVID-19 patients have reported a wide variety of symptoms, ranging from mild to severe pneumonia with acute respiratory distress syndrome and death. Symptoms may appear two–fourteen days after exposure to the virus. Oral manifestations related to undergoing COVID-19 include symptoms such as taste disorders in the majority of patients and painful oral ulcers.[11] A report on more than 370,000 confirmed COVID-19 cases with documented symptoms in the United States found that 36% of patients had muscle aches, 34% had headaches, and 70% of patients had fever, cough, or shortness of breath. Other symptoms that have been described include, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.[12] Symptomatic patients are predominantly responsible for transmission, while asymptomatic patients are also thought to be potential carriers.[13]

SARS-CoV-2 is mainly transmitted from human to human through airborne or salivary droplets. Viruses are transmitted through the air, contact, and contaminated surfaces. For example, when coughing, sneezing, breathing drops, or speaking.[5,8] An event of sneezing with droplets travelled for six meters at a speed of 50 m/s within 0.12 seconds, an event of coughing with droplets travelled two meters at a speed of 10 m/s within 0.2 seconds, and an event of exhaling with droplets travelled for one meter at a speed of 1 m/s within 1 second.[8] Within seconds of the spatter being produced, particles larger than 50 microns can deposit on a surface next to the patient's mouth. Particles smaller than 5 microns or droplets can float in the air for a long time as aerosol and spread from a few feet (one meter) to several meters.[14] However, aerosol is a composition of solid or liquid particles containing bacteria or viruses, suspended (for at least a few seconds) in a gas. The smaller particles of an aerosol have the potential to penetrate through the lungs and may be carry particle that can transfer infections.[15] The oral cavity has many bacteria and viruses that can come from the respiratory tract, dental plaque, and oral fluids. Therefore, dental treatment that has a potential to aerosolize saliva will cause airborne contamination with organisms.

People of all ages are susceptible to COVID-19, while healthcare workers are most at risk because of their close contact with patients.[16] The qualitative study in Indonesia reported that many of the informants perceived that they were at high risk of exposure to COVID-19 because their work involved frequent exposure to patients' saliva and blood during dental treatment.[17] In some areas mortality among dentists increased by 185% in 2020.[18] Due to the fact that the oral cavity acts as a pool for bacterial and viral strains, there is a significant danger of cross-infection, especially when viruses are the etiological agent. As a result, dental practice has substantially decreased throughout the COVID-19 era.[19] These brings to the reason why it is critical to reduce the risk of virus transmission in dental clinics prior to procedures. Oral viral load reduction could reduce the risk of transmission via salivary droplets.[14] The cross contamination between dental operatory and transmission of infectious agents from patients to dental professional can occurs because of the aerosolization of oral microorganism during operation.

Therefore, dental patients and professionals can be exposed to pathogenic microorganisms. Due to the specificity of procedures, dental care settings invariably carry the risk of virus infection. The results from previous studies reveal the high risk associated with dental procedures, such as the use of high-speed hand pieces, ultrasonic scalers, and triple syringes, which produce aerosols and dispersed droplets. These particles are spread into the air and contaminated with dental office objects (Fig.2). Furthermore, it persists for an extended period of time and is easily infected.[14,20] The contamination may occur by direct contact with patient secretions or indirectly from contact with surfaces and equipment that have become contaminated with scattered droplets.[21]

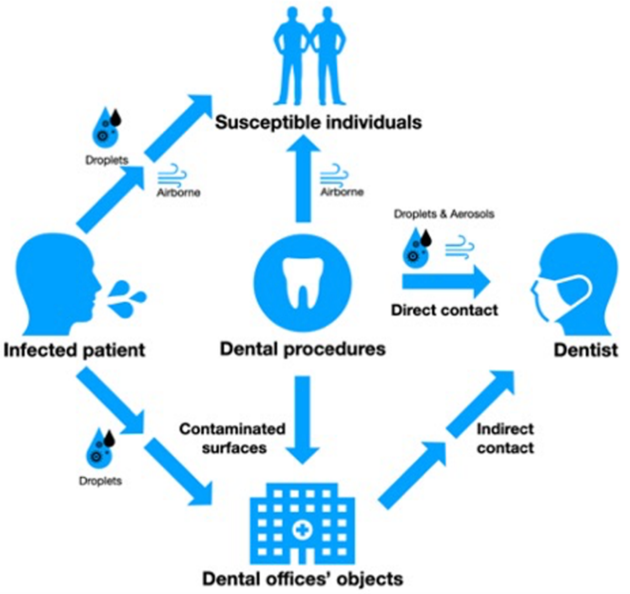

Figure 2. Illustration of transmission routes of 2019-nCoV.

Antiseptic mouthwashes are regularly used before oral surgery due to their ability to reduce the number of microorganisms in the oral cavity.[22,23] There are many studies related to mouthwash used for depressing oral malodor and anti-microbial mechanism of action by reduce the viable microbial content of aerosols initiated from dental procedures.[24,25] Many kinds of mouthwashes often contain properties that effected to kill microbial or fungicidal for example ethanol, chlorhexidine (CHX), cetylpyridinium chloride (CPC), povidone iodine (PI) and hydrogen peroxide (H2O2).

Moreover, herbal mouth rinse was found to be effective in reducing the aerosol contamination produced by ultrasonic scaling, though less potent than 0.2% CHX. Also due to its natural ingredients, it does not cause any side effects and can serve as a good alternative to patients who wish to avoid alcohol (e.g., those with xerostomia), sugar (e.g., those with diabetes), and any artificial preservatives and colors in their mouth rinses.[26,27] From previous studies above showed mouthwashes have been used in dental practices due to their affordable price. Thus, some dental professionals recommend using antiseptic mouthwashes that may be useful in preventing viral transmission.[28]

The goal of this review is to assess the present state of knowledge on the efficacy of many types of mouthwashes that should be used in dental care sections to protect against the Covid-19 Pandemic. The effectiveness of antiseptic mouthwashes is determined by its concentration and contact time in oral cavity during Pandemic period. Summarized the study about oral antiseptic mouthwashes to be the recommendation uses for COVID-19 preventive measures and routine practice in the future. In order to reinforce the research showing a strong correlation between dental treatment and fear. The patient's level of worry decreases with increasing information about oral health and dental therapy.[29]

Materials and methods

Search strategy

The literature search was conducted across two databases, including PubMed and Scopus, using the combination of following Medical Subject Headings (MeSH) terms: "mouthwash" OR "mouth rinse" OR “oral rinse" OR "povidone iodine" OR "hydrogen peroxide” OR "chlorhexidine" OR "cetylpyridinium chloride" AND "COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "SARS" OR “MERS" AND "dental" OR “dentistry" OR "dentist". The last search was conducted on December 31, 2021 and focus about Pandemic period.

The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines. The objective of this systematic review was to answer the following ‘PICO ’(P, patient/problem/population; I, intervention; C, comparison; O, outcome) question: Are antiseptic mouthwashes used in dental practice to protect against COVID-19 transmission? (Table1).

PICO question breakdown	
Component	**Description**
Problem	SAR-CoV-2 virus transmission via saliva and airborne.
Intervention	Antiseptic mouthwash
Comparison	Comparison of types and concentrations of mouthwashes and contact time in oral.
Outcome	Preventing the spread of COVID-19 in dental settings.
PICO question	Are antiseptic mouthwashes used in dental practice to protect against COVID-19 transmission?

Table 1. Showed detail about PICO question component in this study.

Inclusion criteria

To be included, the study must fulfill all the following inclusion criteria: (a) clinical trials with humans; (b) experimental laboratory studies; and (c) articles publish in English.

Exclusion criteria

Excluded studies were those which fulfilled the following criteria: (a) Studies in which the main topic was not the content of the effect of antiseptic mouthwashes on the SARS-CoV-2 virus; (b) systematic reviews; (c) reviews; (d) duplicate articles; (e) books or book chapters; (f) letters to the editor; and (g) author comments.

Bias risk assessment

Bias risk assessment was assessed independently by one reviewer.

PRISMA flow diagram reported various studies assessed for further evaluation and include in the review (Fig. 3).

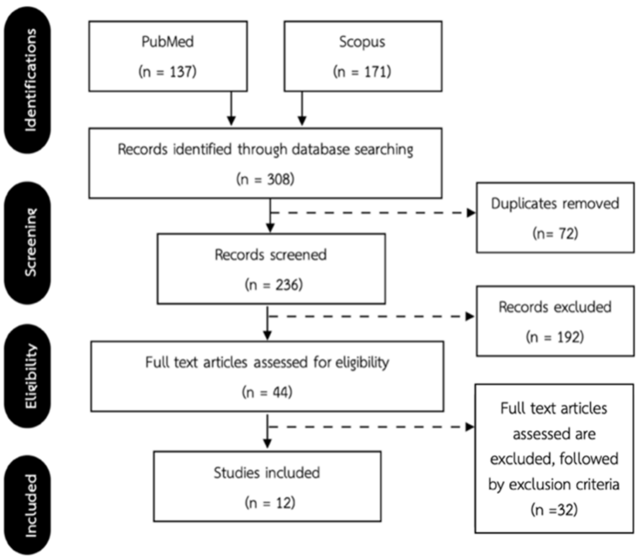

Figure 3. strategy of selection method for inclusion articles.

Results

The initial PubMed search yielded 137 articles, and the Scopus search yielded 171 of which 72 were eliminated as duplicates. The titles and abstracts of the 236 remaining articles were carefully reviewed, and 192 of them were excluded due to not being associated with the objective of the study. After reviewing the full text of 44 articles, 32 were excluded as they did not comply with the inclusion criteria established. Finally, twelve articles entered the review process. Six in vivo and six in vitro studies in serious situation pandemic time were found and showed in table 2. From the result table (table 2), that summarized the details one by one for showing important information.

All the studies included articles between 2020-2021 in Pandemic period to received information involved COVID-19 and mouthwash from patients at that time. Antiseptic mouthwashes are recommended by the World Health Organization (WHO), the American Dental Association (ADA), and the Centers for Disease Control and Prevention (CDC) before oral procedures to reduce SARS-CoV-2 viral load in patient saliva as a control measure to reduce risk of infection. The mechanism of action from mouthwashes effected to viral load that all mouth rinses tested could inactivated replication competent SAR-CoV-2 viruses and pseudo typed viruses expressing spike protein. It's likely that these disinfectant treatments reduce the number of viruses in oral cavity in a short period of time. From the related evidence, risk of infection in dental offices could be lowered. Available mouthwashes in the market are chlorhexidine, hydrogen peroxide, providone iodine, and essential oils. The main findings from all articles could described and summarized each type of mouthwashes below.

Chlorhexidine (CHX)

Chlorhexidine gluconate (1,1'-hexamethylene bi [5-(p-chlorophenyl) biguanide] di-D-gluconate) (CHX) has been around since the 1950s for clinical use. CHX is a bisbiguanide that has cationic properties. Two chlorophenyle rings and two bigunide groups are joined by a central hexamethylene chain in this symmetric molecule. CHX has a strong base. It exists as a variety of salts, including acetate, gluconate, and hydrochloride. CHX is a broad-spectrum antiseptic that acts against gram positive and negative bacteria and certain types of enveloped viruses, including hepatitis virus, herpes simplex, HIV, cytomegalovirus, influenza, and respiratory syncytial viruses. It works by increasing permeability of bacterial cell wall, causing it to lyse.[30,31] CHX is slowly released, leading to prolonged activity, which can be called substantivity. As a result, it is currently used as a disinfectant agent to clean catheters and non-living clinical surfaces, and dental professionals use it orally as an antiseptic mouthwash because it is generally biocompatible and helps to prevent the buildup of plaque and bacterial biofilm.

Costa et al., 2021 suggested 0.12% CHX mouthwash had effective in reducing salivary SARS-CoV-2 load for at least 60 mins from randomized control trial experiment. They also recommended that CHX 0.12% reduced the salivary viral load in healthcare service.[32]

Therefore, it has been widely proven as an effective antiplaque and antigingivitis solution.[33] In addition, it can reduce bacterial concentration in aerosol at concentration between 0.12% and 0.20% at both 30- and 60-seconds contact times.18 However, prolonged use of CHX is also reported to be associated with several disadvantages, such as brownish discoloration of teeth, restoration, and tongue, taste sensation disturbance, increased calculus formation, and burning sensation.[34]

Hydrogen peroxide (HP)

Hydrogen peroxide (H_2O_2) has been utilized in dentistry for more than 70 years, either in conjunction with salts or on its own. HP has several benefits, including simplicity of use, and affordability. It has effective effect against several viruses for example adenovirus, rhinovirus, myxovirus and influenza A. There was study found that rinsing HP could reduce of salivary viral load up to 30 min after rinsing, but 60 min was not significant.[25] Similarly, Eduardo et al., 2021 studied comparison CHX, CPC and HP mouth rinse at different concentration and contact time. From the results showed that for HP could reduce in significant viral load level up to 30 mins after rinsing. However, its disadvantages include the possibility of toxicity.[35] HP is an unstable compound in the presence of a base or catalyst. It is generally stored with a stabilizer in a weakly acidic solution. When HP encounters an enzyme (catalase) found in bacteria in the mouth, it breaks down into oxygen and water.[24] HP acts as a broad spectrum of antimicrobial activity because it can kill bacteria, yeasts, fungus, viruses, and spores. Moreover, hydrogen peroxide is an oxidizer that has been employed in plaque control and treating acute ulcerative gingivitis.

Povidone-iodine (PI)

PI formulations first has become available since 1995 that is a water-soluble iodine complex. Commercial formulations typically consist of a 10% PI solution containing 1% available iodine. For repeated mouthwash and gargle are recommend used in lower PI concentration. PI has the broadest spectrum of action acting against several of viruses and antibiotic resistant bacterial strains with the minimum contraindications, including allergy to iodine, thyroid disease, and pregnancy.[36,37] From Bidra et al., 2021 showed comparison between HP and PI mouthwashes and found that diluted PI in the range of 0.5% to 1.5% may be preferred over HP.[38]

The two most potent antiseptic metabolites of PI are molecular I2 and hypoiodous acid, which deliver free iodine. These free iodine molecules oxidize amino acids, nucleic acids and cell membranes. Through oxidation of cell surface receptors, PI prevents the attachment of viruses to cellular receptors.[39] From Garcia-Sanchez et al. 2022 showed that efficacy in reducing the salivary loading virus transmission than other solutions and no complications after oral PI using at different concentrations. However, they concluded potentially PI preprocedural mouthwash using related both symptomatic and asymptomatic COVID-19 positive patients. In clinical treatment, the recommendation for rinsing of 0.50/1% PI could be using 30-60 seconds before dental procedure.[40]

Cetylpyridinium chloride (CPC)

CPC is a quaternary ammonium compound. It has been used as antimicrobials and antiseptics for decades. CPC 0.05% products, available in mouthwashes and dentifrices, over-the-counter, advertised for reducing plaque formation and gingival inflammation.37,38 Additionally, CPC has bactericidal and antiviral properties that make it effective against coronaviruses and the influenza virus. It inactivates the virus by destroying the capsid.[41,42] However, from Seneviratne et al., 2020 recommended that CPC and PI can use both because from randomized control trial studied in Singapore found that they have a sustained effect on reducing salivary SAR-CoV-2 level in COVID-19 patients especially asymptomatic group.[43]

CPC is a cationic biocide that interferes with bacteria's membrane function, resulting in leakage of cytoplasmic components, interference with cell metabolism, cell growth inhibition, and cell death. The CPC molecules have both hydrophilic and hydrophobic groups. The positive charged hydrophilic region of the molecules binds with the negative charged bacterial cell. CPC is tasteless, odorless, and thus suitable for applications in oral care products. For individuals who have mucosal irritation and discoloration as a result of CHX, this mouthwash is an option. Regular use of the quaternary ammonium compound could lead to antibiotic resistance in bacteria.

Discussion

From dental and patients contact between procedure, there are cross contamination of patient's saliva and aerosols. Saliva is the main components for viral spread especially SAR-CoV-2, therefore dental professional should find protection method to prevent transmission in dental clinic. Since then, many cases of variation from SAR-CoV-2 virus are still reported and have been increasing all over the world. COVID-19 is still concerned communicable disease especially older people and who has underlying diseases. Although the symptoms are less severe now, moreover there should concern the high transmissibility, virulence, and risk of infection by airborne transmission. Strict infection control methods are important in clinical setting, pre-procedural mouthwashes could potentially be advantageous to decrease the risk of cross-infection between patients and personnel. Therefore, preoperative rinse is the one of beneficial way to reduce the number of microorganisms in patients' oral cavity before dental treatment.[44]

To date, there is some scientific proof and highly recommend mouthwashes with antiviral effects against SARS-CoV-2 to reduce viral load in the oral cavity and until today it is not known which mouth rinsing solutions or which components are effective and have properties against this novel coronavirus. Therefore, official recommendations for dental practice have given little guidance about specific compounds for preprocedural mouth rinses.

Several studies discussed about antiseptic mouthwashes for efficacy against SAR-CoV-2 viral load, including providone-iodine (PI), chlorhexidine (CHX), hydrogen peroxide (HP), and other antibacterial mouthwashes that contain cetylpyridinium chloride (CPC), alcohol, or essential oils. Two trials were conducted in the laboratory through virus culture and in patients with COVID-19. Six studies identify four mouthwashes that were used to treat COVID-19 patients: CHX, PI, CPC, and HP. PI and CPC mouthwashes had the greatest effect on viral load reductions, lasting up to two hours[45] and three-six hours[46] after rinsing. The efficacy of the CPC formulation was able to rapidly reduce the viral load after rinsing[47] but PI solution was able to significantly inactivate SAR-CoV-2 after five minutes.[48] Prolonged use of PI gargle can affect the thyroid's function. It is suggested to use in a lower concentration in order to minimize adverse effects.[49] The CHX mouthwash was similarly efficient in lowering the viral load after 30 minutes of rinsing.[48,50] CHX had an antibacterial effect and was effective for up to one hour.[41,43,51] The CHX solution that combined the oral rinse with the posterior oropharyngeal spray was more effective than the oral rinse alone.[46-50] The HP efficiency had an immediate effect on the coronavirus. However, the efficacy was maintained for only 30 minutes[43] and one hour[41] after rinsing.

Finally, Ferrer et. al, 2021 found that using mouthwashes had no influence on viral load reduction over time when compared to distilled water. As a result, the amount of SAR-CoV-2 was reduced accordingly with the treatment. And there were differences in the response to mouthwashes depending on the person. Many of the articles also had a limit on the number of subjects.[46]

Six papers, in vitro experiments, showed that the PI solution was able to completely inactivate the SAR-CoV-2 virus at all concentrations. The lowest concentration was 0.5% PI for at least 15 seconds.[52,53] Moreover, the concentration can be reduced to 0.23% povidone-iodine, which is still effective against SAR-CoV, MER-CoV, H1N1, and rotaviruses.[54] When the PI solution was compared to other mouthwashes, it was discovered that the hydrogen peroxide had minimal virucidal effect, whereas the PI mouth rinse was completely inactive.[55] This was consistent with the study by Davies et. al,2021 which found HP formulation had no effect on SAR-CoV-2 viral load.[54] The CHX mouthwash was also ineffective against SAR-CoV-2. Available mouthwashes that consist of alcohol, essential oils, or CPC were effective in decreasing SAR-CoV-2 level.[55,56]

The cytotoxic effect of the solution on cells was highest with HP, followed by PI, CHX, and mouthwash such as Listerine, respectively.[54] Therefore, using a higher concentration mouthwash to reduce more viral load should be considered a side effect of cytotoxic on cells. Using antiseptic mouthwashes can prevent the spread of viral infections through aerosols and saliva droplets. Antiseptics should be used before any dental procedure. The concentration and adverse effects of the solution are recognized. The 0.5% providone iodine and 0.12% chlorhexidine gargle for at least 15 seconds can provide a virucidal effect and still have an effect for a long time after rinsing. PI and CHX solutions should be used with caution. The ability of diluted PI with water may change the efficacy of antiseptics. CPC mouthwash inactivates SAR-CoV-2 immediately and is effective for up to 6 hours after rinse. There is no evidence of side effects when used continuously. Using HP mouthwash to reduce viral loads has a variety of outcomes. There are other commercial solutions with a potential virucidal effect on SARS-CoV-2 in saliva for example products containing essential oils (i.e., Listerine®) and CDCM® is composed of Beta-cyclodextrin and Citrox® that had a significant effect on reducing viral load 4 h after the initial dose. Moreover, CPC solutions are also commonly found in general oral products. Therefore, it can be used on a regular basis. From recently study had testing about individual components from commercial products ViruProX® and BacterX® pro, that had 0.05% CPC was able to strongly reduce infectious SARS-CoV-2 particles within 30 second incubation. It can be hypothesized that CPC is the effective component, and we would recommend the use of mouth rinses containing CPC, like commercial brands in preprocedural use in dental practice to reduce this viral during dental treatments.[57]

From all the above results obtained from the previous studies showed strong evidence base for mouth rinsing benefit before any dental procedures, yet very few clinicians follow this protocol. The implication of this procedure depends on the professional understanding and realizing the protective benefits in reducing the spread of microorganisms from their patients' mouths.

Conclusions

From review many articles related in COVID-19 pandemic period and review about using antiseptic mouthwashes that can prevent the spread of viral infections through aerosols and saliva droplets. It has ability to reduce viral loads in the oral cavity for a period between treatment. In dental practice, using antiseptics before dental procedures to protect against COVID-19 is recommended. In conclusion, mouthwash containing CPC can be used in routine prevention. This study is a narrative review related to all types of pre-procedural mouth rinses from COVID-19 pandemic periods and follow selected articles from systematic criteria and electronic searching strategy. However, COVID-19 is a disease that is continuously being spread and still observe in many countries. Lesson learned from SAR-CoV-2 virus cross contamination between dental procedure and our review represented that using CPC in clinical practice for prevention in routine procedures in the future. Further in vitro and randomize control trials are needed to demonstrate the concentration, safety, and efficacy of future mouthwashes routine in dental clinic.

Declaration of Interest

The authors report no conflict of interest.

Study	Study type and Author (year)	Concentration& Formulation of Mouthwashes	Contact time	Method of assessment	Outcome	Conclusion
In vivo Evaluation of the virucidal efficacy of chlorhexidine and providone-iodine mouthwashes against salivary SARS-CoV-2. A Randomized-Controlled clinical trial	*In Vivo*, Elzein et al. (2021)	1.Chlorhexidine gluconate 0.2%, 15ml. 2.Providone iodine 1%, 15ml. 3.Distilled water 15ml.	30 sec	Saliva samples were collected before and 5 min. after mouthwash. Evaluation of the efficacy was based on difference in cycle threshold (Ct) values of salivary SAR-CoV-2 (Ct delta) RCT, n=61 (CHX=,PI=,control=)	1.A significant difference; between the delta Ct between distilled water and 2 solutions 2.No significant difference; between 0.12%CHX (P=0.0024) and 1%PI (P=0.012) 3.A significant mean Ct value difference between before and after mouthwash P<0.0001; CHX (higher sig. diff.) and PI 4.No significant difference; before and after the experiment in the control gr.	Chlorhexidine gluconate 0.2% and 1% Providone iodine oral solutions are effective preprocedual mouthwashes against salivary SAR-CoV-2 in dental treatments. Their use as a preventive strategy to reduce the spread of COVID-19 during dental practice should be considered.
Efficacy of commercial mouth-rinses on SAR-CoV-2 viral load in saliva Randomized control trial in Singapore	*In Vivo*, C. J. Seneviratne et al. (2020)	1.0.5% w/v Providone iodine 10ml. 2.0.2% w/v Chlorhexidine gluconate 15ml. 3.0.075% Cetylpyridinium chloride 20ml. 4.Sterile water 20ml.	30 sec	Saliva samples were collected at baseline and at 5 min, 3h, and 6h after mouthwash. Cycle threshold values, Fold change of Ct values at baseline, 5 min, 3h, 6h time points. RCT, n=16 (PI=4, CHX=6, CPC=4, control=2)	1.No significant difference; Ct values of each group of PI, CHX, CPC, and water at 5min, 3h, 6h time point. 2.A significant increase in fold change of Ct values of CPC at 5min, 6h and PI at 6h compared with water. 3.CHX demonstrated a varied effect among saliva Ct value after 5min rinsing. 4.CPC decreased the salivary SAR-CoV-2 levels within 5min of use, compared to water. 5.PI and CPC sustained at 3h, 6h time points compared with control gr.	CPC and PI formulation have a sustained effect on reducing salivary SAR-CoV-2 level in COVID-19 patients. These mouth-rinses could be a useful pre-procedural transmutation reduction strategy in clinical dental setting. Asymptomatic COVID-19 patients, the routine use of antiseptic mouth-rinsing could be a cost-effective approach in reducing viral out spread.

Study	Study type and Author (year)	Concentration& Formulation of Mouthwashes	Contact time	Method of assessment	Outcome	Conclusion
Cholhexidine mouthwash reduces the salivary viral load of SAR-CoV-2	*In vivo,* D. D. Costa et al. (2021)	0.12% Chlorhexidine gluconate 15ml.	1 min	Salivary samples were obtained before (baseline), and 5min, and 60min after using the solution. qRT-PCR were carried out and the cycle threshold was computed. RCT, n=100 (intervention=50, control=50)	The difference Ct values between the 5min evaluation and baseline (test group=2.19±4.3; control group=-0.4±3.87) and between 60min and baseline (test group=2.45±3.88; control group=0.76±4.41) were significantly greater in the test group, revealing a reduction of viral load. Furthermore, there was a reduction in the load of SAR-CoV-2 in 72% of the volunteers using CHX VS 30% in the control group.	Chlorhexidine gluconate (0.12%) was effective in reducing salivary SARS-CoV-2 load for at least 60min. It can therefore be recommended to reduce the salivary load of this virus in healthcare serviced where salivary expose is expected, as well as in situations involving close contact between people in domestic and public places.
Salivary SAR-CoV-2 load reduction with mouthwash use	*In vivo,* F. P. Eduardo et al. (2021)	1.0.075% Cetylpyridinium chloride + 0.28% Zinc lactate 20ml. 2.1.5% Hydrogen peroxide 10ml. 3.0.12% Chlorhexidine gluconate 15ml. 4.1.5% Hydrogen peroxide 10ml. followed by 0.12% Chlorhexidine gluconate 15ml. (HP+CHX) 5.Distilled water 20ml. (Control)	1.CPC+Zn 30sec 2.HP 1min 3.CHX 30sec 4.HP 1min + CHX 30sec 5.Control 1min	Cycle threshold values in saliva of COVID-19 patient treated with mouth-rinses in accordance with T0 (Baseline), T1(immediately after rinsing), T2(30min after rinsing), T3(60min after rinsing) RCT, n=43 (CPC+Zn=7, HP=7, CHX=8, HP followed by CHX=12, Control=9)	The mean Ct value for each experiment was compared to the baseline value; A significant different was observed for CPC+Zn at T1 HP at T1, T2, T3 CHX at T2, T3 HP+CHX at T1 HP and CPC+Zn resulted better reduction in viral load, with 15.8±0.08 and 20.4±3.7 fold reduction at T1, respectively CPC+Zn maintained 2.6±0.1 fold reduction at T3 HP maintained 6.5±3.4 fold reduction at T2 CHX significant reduction reduce the viral load at T1(2.1±1.5 fold reduction), T2(6.2±3.8 fold reduction), T3(4.2±2.4 fold reduction)	Mouthwash with CPC+Zn and CHX resulted in significant reduction of SAR-CoV-2 viral load in saliva up to 60min after rinsing, while mouthwash with HP up to 30min after rinsing

Study	Study type and Author (year)	Concentration& Formulation of Mouthwashes	Contact time	Method of assessment	Outcome	Conclusion
Use of Chlorhexidine to eradicate oropharyngeal SAR-CoV-2 in COVID-19 patients	*In vivo,* Huang and Huang (2021)	0.12% Chlorhexidine gluconate 15ml.	Oral rinse; 30sec Spray; 5sec	CHX oral rinse only: twice a day (4 days) Using CHX as an oral rinse and posterior oropharyngeal spray: twice a day (4 days) After 4 days, the oropharynx was swabbed and tested for the presence of SAR-CoV-2 by rRT-PCR RCT, n=294 (oral rinse only; CHX=66, control=55 Both; CHX=93, control=80)	CHX as an oral rinse: SAR-CoV-2 was eliminated from oropharynx 62.1% VS control gr. 5.5% CHX as an oral rinse and oropharyngeal spray: SAR-CoV-2 was eliminated from oropharynx 86% VS control gr. 6.3%	CHX show a significant elimination of SAR-CoV-2 especially the posterior oropharyngeal spray more effectively
Clinical evaluation of antiseptic mouth rinses to reduce salivary load of SAR-CoV-2	*In vivo,* M. D. Ferrer et al. (2021)	1.2% Povidone-iodine (3ml 10%PI dilute with 12ml distilled water) 2.1% Hydrogen peroxide (5ml 3%HP dilute with 10ml distilled water) 3.0.07% Cetylpyridium chloride 4.0.12% Chlorhexidine 5.Distilled water (control)	1 min	Salivary samples were taken in the morning; baseline, 30min, 60min, 120min after mouthwash. RCT, n=84 (PI=9, HP=14, CPC=11, CHX=12, control=12)	None of the tested mouthwashes significantly reduce viral load at any time point compared with baseline The relative changes compared to the value before the mouthwash; the maximum effects on viral load were observed 2hr after treatment in PI and CPC (Mean viral load reduction~30%) HP; the largest effect was seen 1hr after treatment CHX; effect was seen already at 30min and was maintained with time	Salivary viral load in COVID-19 patients was not affected by the tested treatments. This could reflect that those mouthwashes are not effect in vivo, or that viral particles are not infective but viral RNA is still detected by PCR

Study	Study type and Author (year)	Concentration& Formulation of Mouthwashes	Contact time	Method of assessment	Outcome	Conclusion
Differential effect of antiseptic mouth rinses on SAR-CoV-2 infectivity in vitro	*In Vitro,* Chuan Xu et al. (2021)	1.Essential oil and Alcohol (20-30% ethanol) 2.0.12% Chlorhexidine 3.1.5% w/v Hydrogen peroxide 4.10% solution (1% available iodine)	after 2 hours and 24 hours	Cell culture: HEK293T, hACE2 expressing HeLa cells. Viruses expressing mNeoGreen were propagated in Vero E6 cell. SAR-CoV-2 Cells were cultured overnight. Virus were incubated with or without mouth rinse for 30min at 37°C before being added to HeLa-hACE2	All mouthrinses tested had cytotoxic effect on cells. The cytotoxicity of Colgate peroxyl>PI>CHX>Listerine can significantly reduce virus infectivity	All mouth rinses tested inactivated replication competent SAR-CoV-2 viruses and pseudo typed viruses expressing spike protein. The cytotoxic effects of mouthwashes should be considered when assessing their antiviral activities. Since diluted Listerine and CHX exhibited no cytotoxic effects, these product may be good candidates to reduce virus spread.

Study	Study type and Author (year)	Concentration& Formulation of Mouthwashes	Contact time	Method of assessment	Outcome	Conclusion
Comparison of in vitro inactivation of SAR-CoV-2 with hydrogen peroxide and providine iodine oral antiseptic rinses	*In Vitro,* A. S. Bidra et al. (2021)	1.3% Hydrogen peroxide 2.1.5% Hydrogen peroxide 3.0.5% Providone iodine 4.1.25% Providone iodine 5.1.5% Providone iodine 6.Ethanol (Positive control) 7.Water (Negative control)	15 sec and 30 sec	Laboratory procedures 5 tests compounds were then incubated in a 1:1 ratio with virus solution so that the final concentration of each individual test compound was 50% of the starting concentration Virus titres; CCID50	PI at all concentration completely inactive SAR-CoV-2 1.5,3% Hydrogen peroxide was minimally virucidal activity after 15sec, 30sec.	PI at the lowest concentration of 0.5% at the lowest contact time of 15 sec 1.5, 3% Hydrogen peroxide was minimally effective as a viricidal agent after contact time 30 sec. Therefore, pre-procedural rinsing with diluted PI in the range of 0.5% to 1.5% may be preferred over HP

Study	Study type and Author (year)	Concentration& Formulation of Mouthwashes	Contact time	Method of assessment	Outcome	Conclusion
Effective in vitro inactivation of SARS-CoV-2 by commercially available mouthwashes	*In Vitro,* K. Davies et al. (2021)	1. 0.2% Chlorhexidine gluconate (contains ethanol) 2. 0.2% Chlorhexidine gluconate (Alc. free) 3. 1.4% Dipotassium oxalate (Alc. free) 4. Eucalyptol 5. 0.01-0.02% Hypochlorous acid 6. 1.5% Hydrogen peroxide 7. 0.58% Providine iodine	1 min	Virus titre (TCID50)	1. not effective 2. not effective 3. effective 4. effective 5. effective 6. not effective 7. effective	Listerine advanced defense sensitive, Listerine total care, OraWize+, Provident Inactive SAR-CoV-2
Rapid in vitro inactivation of SAR-CoV-2 using Providine iodine oral antiseptic rinse	*In Vitro,* S. Bidra et al. (2020)	1. 0.5% Providine iodine 2. 1% Providine iodine 3. 1.5% Providine iodine 4. 70% Ethanol (Positive control) 5. water (Negativ control)	15 sec and 30 sec	Virus titre (CCID50)	0.5, 1, 1.5% PI completely Inactive virus within 15 sec 70% ethanol 15sec not completely inactive virus but completely active virus at 30 sec of contact	The viricidal activity was present at the lowest concentration of 0.5% PI and at the lowest contact time of 15 sec.
In vitro efficacy of a providine iodine nasal antiseptic for rapid inactivation of SAR-CoV-2	*In Vitro,* S. Frank et al. (2020)	1. 0.5% Providine iodine 2. 1.25% Providine iodine 3. 2.5% Providine iodine 4. 70% Ethanol (Positive control) 5. water (Negative control)	15 sec and 30 sec	Virus titre (CCID50)	0.5, 1.25, 2.5% PI completely Inactive virus within 15 sec 70% ethanol 15sec not completely inactive virus	PI at concentration as low as 0.5% rapidly inactive SAR-CoV-2 at contact time as short as 15 sec

Study	Study type and Author (year)	Concentration& Formulation of Mouthwashes	Contact time	Method of assessment	Outcome	Conclusion
Virucidal activity of oral care products against SAR-CoV-2 in vitro	*In Vitro,* Komine et al. (2021)	1.0.05% CPC mouthwash 2.0.05% CPC toothpaste + 0.03% CPC spray 3.0.06% CHX + 0.05 CPC mouthwash 4.0.12% CHX + 0.05 CPC mouthwash 5.0.075% CPC mouthwash 6.0.12% CHX 7.0.2%delmopinol hydrochloride 8.0.04% CPC mouthwash	manufacturer's instructions.	The mouthwashes were assessed for their virucidal activity with ASTEM E1052	The virus was inactivated in vitro by the contact time in directions for use of all oral care products containing CPC or delmopinol hydrochloride as antiseptics. The mouthwash containing only 0.12 % CHX as antiseptic did not show a sufficient inactivation effect against SARS-CoV-2 in this study	Oral care products containing CPC or delmopinol hydrochloride have antiviral activity against SARS-CoV-2. This supports the recommendation for a pre procedural use of CPC containing mouthwash for SARS-CoV-2 reduction in aerosol

Table 2. Summary of the included results.

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