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Special Covid-19

Mouthwashes in the Era of COVID-19: an Overview of Current Evidence

Enxaguatórios Bucais na Era de COVID-19: uma Visão Geral das Evidências Atuais
Enjuagatorios Bucales en la Era COVID-19: una Visión de las Evidencias Actuales

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Abstract
The COVID-19 pandemic is evolving with additional studies on the pathogenicity of SARS-CoV-2 and its mechanism of spread, while current knowledge about the antiviral activity of available mouthwashes is largely based on the characteristics of similar coronaviruses. Since SARS-CoV-2 is spread through respiratory droplets, saliva, or direct contact, it is prudent to reduce the viral load in saliva and respiratory secretions. Thus, the viable and cost-effective measures that can be adopted and applied by the public and healthcare professionals to mitigate cross-contamination and transmission in the community are oral and throat hygiene. In this article, we bring together the evidence and mechanisms of all available mouthwashes against SARS-CoV-2. In addition, dental aerosols, transmission route and viral load were explored in the light of the literature. Different mouthwashes with specific activity against SARS-CoV-2 were investigated; however, the role of hydrogen peroxide and chlorhexidine gluconate as a pre-procedural mouthwash was ruled out. Nonetheless, the role of povidone iodine and, to some extent, cetylpyridinium chloride against SARS-CoV-2 was supported. We encourage researchers to consider involving different populations to verify the short- and long-term effectiveness of mouthwashes before using them as a community arsenal against the spread of COVID-19 infection.

Descriptors: COVID-19; Dental Care; Mouthwash; Saliva; SARS-CoV-2.

Resumo
A pandemia de COVID-19 está evoluindo com estudos adicionais sobre a patogenicidade do SARS-CoV-2 e seu mecanismo de disseminação, enquanto o conhecimento atual sobre a atividade antiviral de enxaguatórios bucais disponíveis é amplamente baseado nas características de coronavírus semelhantes. Como o SARS-CoV-2 se dissemina através de gotículas respiratórias, saliva ou contato direto, é prudente reduzir a carga viral na saliva e nas secreções respiratórias. Assim, as medidas viáveis e econômicas que podem ser adotadas e aplicadas pelo público e pelos profissionais de saúde para mitigar a contaminação cruzada e a transmissão na comunidade são a higiene bucal e da garganta. Neste artigo, sumarizamos as evidências e os mecanismos de todos os enxaguatórios bucais disponíveis contra a SARS-CoV-2. Além disso, aerossóis odontológicos, via de transmissão e carga viral foram explorados à luz da literatura. Diferentes enxaguatórios com atividade específica contra SARS-CoV-2 foram investigados; no entanto, o papel do peróxido de hidrogênio e do gluconato de clorexidina como enxaguatório bucal pré-procedimento foi descartado. No entanto, o papel do iodopovidona e, em certa medida, do cloreto de cetilpiridínio contra a SARS-CoV-2 foi apoiado. Nós encorajamos os pesquisadores a considerar o envolvimento de diferentes populações para verificar a eficácia de curto e longo prazo dos enxaguatórios bucais antes de usá-los como um arsenal comunitário contra a disseminação da infecção por COVID-19.

Descritores: COVID-19; Saúde Bucal; Enxaguatório Bucal; Saliva; SARS-CoV-2.

Resumen
El conocimiento sobre la pandemia de COVID-19 está evolucionando positivamente con estudos adicionales sobre la patogenicidad del SARS-CoV-2 y su mecanismo de diseminación, mientras que el entendimiento actual sobre la actividad antiviral de los enjuagatorios bucales disponibles se basa principalmente en las características de coronavirus semejantes. Dado que el SARS-CoV-2 se transmite a través de las gotitas respiratorias, saliva o por contacto directo, es prudente reducir la carga viral en la saliva y las secreciones respiratorias. De esa manera, medidas viables y rentables pueden ser adoptadas y aplicadas por el público y los profesionales de la salud para disminuir la contaminación cruzada y la transmisión en la comunidad; y ellas son la higiene bucal y de garganta. En este artículo, resumimos las evidencias y los mecanismos de todos los enjuagatorios bucales disponibles contra el SARS-CoV-2. Además, se profundizaron aspectos sobre los aerosoles dentales, vía de transmisión y la carga viral según la literatura. Se investigaron diferentes enjuagatorios bucales con actividad específica contra el SARS-CoV-2; sin embargo, se descartó el papel del peróxido de hidrógeno y el gluconato de clorhexidina como enjuagatorio bucal previo al procedimiento. En cambio, se apoyó el papel de la povidona yodada y, hasta cierto punto, el cloruro de cetilpiridinio contra el SARS-CoV-2. Nosotros alentamos a los investigadores a involucrar la participación de diferentes poblaciones para verificar la efectividad a corto y largo plazo de los enjuagatorios bucales antes de usarlos como una alternativa comunitaria contra la propagación de infección por COVID-19.

Descriptores: COVID-19; Salud Bucal; Enjuagatorio Bucal; Saliva; SARS-CoV-2.

INTRODUCTION

With the SARS-CoV-2 pandemic underway, the need to strengthen oral decontamination, hand hygiene, and the adoption of strict aseptic protocols to prevent and reduce the outbreak by interrupting the virus transmission chain are timely. Since the emergence of multidrug-resistant organisms, the importance of using antiseptics as an infection prevention strategy is even more emphasized. According to the analysis of the World Economic Forum, dental hygienists, dental assistants, and dentists are among the professionals at high risk for infection with COVID-19[1].

Antiseptics have a broader spectrum of action against microbes, unlike antibiotics that specifically target only bacteria. Bacteria and viruses are important entities in the microbial spectrum. Their biological nature, morphological characteristics and pathogenicity differ remarkably[2]. For instance, bacterial species larger than the virus have a glycoprotein cell wall layer followed by a lipid polysaccharide or teichoic acid-based membrane, whereas most viruses have a nucleic core surrounded by a capsid with or without a lipid layer envelope[2]. Unlike bacteria, viruses need a host cell to replicate.

Due to the inherent structural differences between bacteria and viruses, the antimicrobial effectiveness of various chemical agents varies. Most biocides act on the cell wall layer of bacteria, followed by protein denaturation. In this context, it is important to understand that the virucidal activity differs among disinfectants due to physical, biological, and environmental factors. There are three main types of viruses with different structures. They are classified according to their increasing difficulty in being inactivated by chemical disinfection, namely enveloped viruses, large non-enveloped viruses, and small non-enveloped viruses[3].

It is known that the disruption of the lipid layer of enveloped viruses by lipophilic chemical agents inactivates them. However, not all disinfectants can inactivate the viral capsid proteins of non-enveloped viruses. Consequently, the association of virus particles with debris, aerosols or soil reduces their antimicrobial penetration effect, with the need for higher concentrations compared to bacteria or other enveloped viruses[4]. This clinical difference can be demonstrated, for example, by the need for 0.8% to 0.9% povidone-iodine for antimicrobial activity with maximum exposure times of 5 minutes for bacteria and 60 minutes for viruses. Likewise, satisfactory bactericidal effects of ethanol are exhibited at concentrations of 60% to 80%, with exposure times between ≤0.5 and ≥5 minutes. Indeed, application of 80% to 90% ethanol for 5 minutes is needed to exert virucidal/low-level activity against enveloped viruses plus adeno-, noro-, and rotaviruses[5].

A recent study detected the presence of SARS-CoV-2 in the saliva of 91.7% of patients with COVID-19, with a median viral load of 3.3 × 10^6 copies/mL and stable at 4°C, room temperature (~19°C), and 30°C for prolonged periods[6]. While the COVID-19 pandemic is evolving with additional studies on the pathogenicity of SARS-CoV-2 and its mechanism of spread, current knowledge of the antiviral activity of available mouthwashes is largely based on the characteristics of similar coronaviruses. In this article, we explore the most effective mouthwashes with a sustained effect against SARS-CoV-2 that may be useful additions to the oral treatment arsenal. In addition, we shed light on dental aerosols, transmission routes and viral load to help dentists, dental hygienists and healthcare professionals who are on the forefront against COVID-19.

LITERATURE REVIEW AND DISCUSSION

○ *Dental aerobiology*

Since the outbreak of the COVID-19 pandemic, the public has been instructed to practice a “hands-off” distanced approach to others, while dental professionals must continue to provide “hands-on” oral health services. The closed setting in a dental office is a viable source of aerosols generated from the dental handpiece, ultrasonic scalers, air polishing devices, and air abrasion units. These devices produce airborne particles by the collective action of water sprays, compressed air, organic particles (tissue), dental particle debris, and body fluids (blood and saliva)[7].

The study of airborne particles in the dental office has gained momentum since the outbreak of COVID-19. Aerosols are loaded with microbes and are potential sources of acute or chronic respiratory illness transmitted by air. Depending on the particle size of the aerosols, they float in the air or descend rapidly and splatter on objects in their trajectory. Of specific interest are aerosol particle sizes of 0.5 to 10 μm that can be easily inhaled and lodged in the terminal bronchioles and alveoli of the human lung[8]. Airborne particles >50 to 100 μm in diameter have inertial forces greater than the frictional forces of air and are ballistic. In fact, true aerosol particles are ≤50 μm in diameter, are invisible and remain airborne for long periods, while spatters composed of airborne particles ≥50 μm in diameter are too heavy to remain suspended in the air and, therefore, can settle on surfaces that become fomites[8].

The yardstick of 2 meters for physical distancing is not effective in an aerosolized environment that can capture the infectious virus up to 3 meters from its source[9,10]. Several factors influence the survival of these virus particles in closed spaces, such as dental operatories. These factors include particle size, atmospheric temperature, relative humidity, room ventilation, nature and composition of the aerosol, atmospheric gases, and irradiation[11]. Since rotary instruments such as ultrasonic scalers and air-driven high-speed handpieces emit high loads of aerosols[12], there has been an emerging quest to minimize aerosols during the COVID-19 pandemic. A study demonstrated complete suppression of aerosolization through the use of aqueous solutions of a Food and Drug Administration (FDA)-approved high molecular weight polymer (polyacrylic acid, xanthan gum). Its viscoelasticity modifies the physicochemical properties of the irrigation solution and suppresses the generation of droplets without modifying the flow pattern of dental water lines[9].

The virulence of aerosol generating procedures depends on the type of procedure. For instance, aerosol-generating medical procedures, such as endotracheal intubation, agitate the airway and force the patient to cough heavily. This aerosol is released with a high viral load titer. Less risky aerosol-generating medical procedures include nebulization and ventilation. On the other hand, dental aerosol generating procedures delivered by rotary instruments can be expelled by high volume evacuation. Dental procedures release low titers of the virus because patients do not scream or speak during the treatment[13]. However, salivary droplets (>60 µm) have been shown to allow transmission of SARS-CoV-2 when individuals are in close contact or even at up to 7 to 8 meters[14].

○ *Mouthwashes targeting the viral lipid envelope*

SARS-CoV-2 is surrounded by a layer of fat called the lipid envelope, in which the spikes of glycoproteins necessary for the infection are implanted. The lipid envelope is similar to the host membrane, comprising phospholipids, sphingolipids, and some amount of cholesterol. Considering that the throat is the main replication site in the early stages of COVID-19 infection, before symptoms appear, the mouthwash can act by damaging or destroying the lipid envelope, as it has the potential to reduce the viral load and eliminate it from the oropharynx. Indeed, membrane disrupting agents used in oral antiseptics can be lethal to the enveloped virus, as they promote their virucidal action by denaturation **(Figure 1)**. The other side of the effectiveness of mouthwashes is that their influence is only on a virus that is extracellular or actively budding[15].

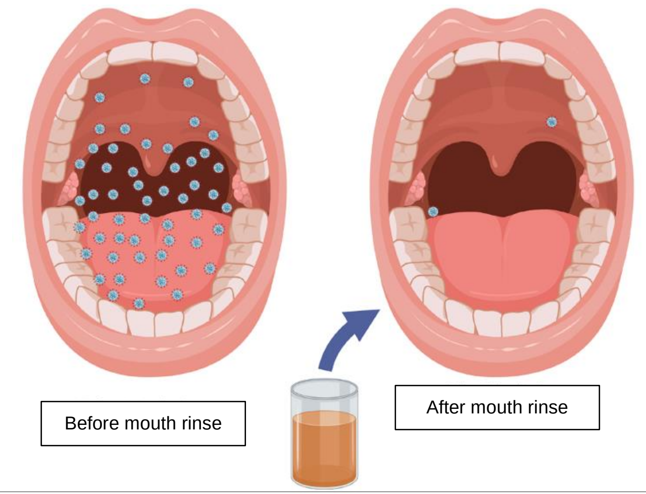

Figure 1: Reduction of oral microbial load by a pre-procedural mouthwash.

○ *Emerging evidence of mouthwashes against SARS-CoV-2*

The use of an antimicrobial pre-rinse may play an important auxiliary role in reducing bacterial and viral loads before starting dental hygiene procedures[16-56]. Several *in vitro* and *in vivo* studies[57-68] (Table 1) have hypothesized the potential of different mouthwashes and their formulations to be used in individuals with COVID-19 or as prophylactics in high-risk individuals to reduce transmission, cross-infection, and pathogenicity in affected individuals.

The years 2020 and 2021 witnessed an increase in literature reports on the usefulness of various products such as mouthwashes against COVID-19. Based on literature findings, povidone-iodine is more effective in clinical settings than chlorhexidine or hydrogen peroxide, which were recommended early in the pandemic. Nonetheless, more recent studies have shown a limited or ineffective *in vivo* action against COVID-19 for these two mouthwashes[13,44]. In addition, the use of quaternary ammonium compounds such as CPC, with proven antiviral efficacy as a mouthwash, was also supported by several reviews and *in vitro* and *in vivo* studies that established their role in reducing significant viral loads in the oral cavity[22,53]. Herein, the antiviral (against SARS-CoV-2) efficacies of common mouthwashes are discussed individually below.

○ *Chlorhexidine against COVID-19*

Chlorhexidine (1:6-di-4'-chlorophenyldiguanidohexane) is a synthetic biguanide broad-spectrum antiseptic and disinfectant with *in vivo* substantivity (slow prolonged release from multiple sites). Evidence does exist in the literature on the *in vitro* effect of chlorhexidine against lipid-enveloped viruses such as influenza A, parainfluenza, herpesvirus 1, cytomegalovirus, and hepatitis B. However, a recent study pointed out that chlorhexidine could only feebly incapacitate the COVID-19 strain[14]. Emerging data suggest that COVID-19, despite being an enveloped single-stranded RNA virus, may sustain the effects of 0.12% chlorhexidine mouthwashes compared to other mouthwashes[35,58]. Conversely, other studies have reported that chlorhexidine has no effective antiviral activity against COVID-19, while suggesting that the use of ethanol can improve its efficacy[14,36].

Table 1. Summary of research articles addressing mouthwashes in the era of COVID-19

Reference	Research type	Main aim of the study
Buenaventura et al.[16]	Review	To provide a comprehensive review of the current recommendations about the use of mouthwashes against the COVID-19 pandemic
Kelly[17]	Review	To describe the existing body of evidence supporting the potential role of oral rinses in preventing the transmission of SARS-CoV-2
Carrouel et al.[18]	Review	To describe the existing body of evidence supporting the potential therapeutic effects of mouthwash ingredients in preventing the transmission of SARS-CoV-2
Moosavi et al.[19]	Review	To study the effects of different types of mouthwashes on the rudection of viral load in COVID-19
Burton et al.[20]	Systematic review	To assess the benefits and harms of antimicrobial mouthwashes and nasal sprays administered to patients with suspected or confirmed COVID-19 infection for both the patients and the healthcare workers caring for them
Testori[21]	Review	To provide a narrative review of the preprocedural mouthwash protocols suggested for oral surgery in order to contrast the presence of SARS-CoV-2 in aerosol
Burton et al.[22]	Systematic review	To assess the benefits and harms of antimicrobial mouthwashes and nasal sprays used by healthcare workers to protect themselves when treating patients with suspected or confirmed COVID-19 infection
Stathis et al.[23]	Review	To review common and/or promising antiseptic techniques and some of the ongoing clinical trials that are investigating the use of these antiseptic compounds as potential treatments and preventive measures
Sette-de-Souza et al.[24]	Review	To review and report the current evidence supporting the use of mouthwashes as a pre-procedural protocol in dental offices
Burton et al.[25]	Review	To assess the benefits and harms of antimicrobial mouthwashes and nasal sprays administered to healthcare workers and/or patients when undertaking aerosol generating procedures on patients without suspected or confirmed COVID-19 infection
Mateos-Moreno[26]	Review	To evaluate the available evidence testing the *in vitro* and *in vivo* effects of oral antiseptics for the inactivation or eradication of coronaviruses
Cavalcante-Leão[27]	Review	To verify whether there is evidence in the literature regarding the decrease in viral load present in saliva after using three types of mouthwashes
Xu et al.[28]	Review	To determine the effect of commercially available mouthwashes and antiseptic povidone-iodine on the infectivity of SARS-CoV-2 virus
Davies et al.[29]	*In vitro* study	To evaluate *in vitro* the efficacy of SARS-CoV-2 inactivation by seven commercially available mouthwashes with a range of active ingredients
Koch-Heier[30]	*In vitro* study	To evaluate *in vitro* the virucidal effect of the mouth rinsing solutions ViruProX® with 0.05% cetylpyridinium chloride and 1.5% H_2O_2 (hydrogen peroxide) and BacterX® pro containing 0.1% chlorhexidine, 0.05% cetylpyridinium chloride, and 0.005% sodium fluoride (F-)
Meister[31]	*In vitro* study	To evaluate the virucidal activity of different available mouthwashes against SARS-CoV-2 under conditions mimicking nasopharyngeal secretions
Schurmann[32]	Clinical study	To determine the applicability of over-the-counter mouthwash solutions in reducing the viral load in the saliva of COVID-19 patients

Table 1 (continuation). Summary of research articles addressing mouthwashes in the era of COVID-19

Reference	Research type	Main aim of the study
Imran[33]	Descriptive cross sectional study	To evaluate the knowledge, attitude and practices among dental practitioners regarding the use of mouthwashes and to emphasize pre-procedural utilization of mouthwashes
Kampf et al.[35]	Review	To review the literature on all available information about the persistence of human and veterinary coronaviruses on inanimate surfaces as well as inactivation strategies with biocidal agents used for chemical disinfection (e.g., in healthcare facilities)
Seneviratne et al.[36]	Randomized control trial	To evaluate the efficacy of three commercial mouth-rinses, povidone-iodine, chlorhexidine gluconate and cetylpyridinium chloride, in reducing the salivary SARS-CoV-2 viral load in COVID-19 patients compared with water
Koletsi et al.[37]	Meta-analysis study	To identify and rank the effectiveness of different interventions used in dental practice to reduce the microbial load in aerosolized compounds
Jain[38]	*In vitro* study	Comparative evaluation of the effectiveness of the current 'gold standard' chlorhexidine and povidone iodine as a control agent, through an *in vitro* analysis against SARS-CoV-2
Assis[39]	Review	To compare the different disinfectants used for disinfection of several surfaces against coronavirus in a review of worldwide studies
Komine et al.[40]	*In vitro* study	To review of inactivation of SARS-CoV-2 by oral care products in several countries *in vitro*
Choudhury et al.[41]	*In silico* study	To study the efficacy of thirty known or repurposed compounds in inhibiting the RdRp (RNA-dependent RNA polymerase) of coronavirus
Mohamed[42]	Review	To review available literature on methods and solutions available for gargling and their effect on respiratory tract infections
Steinhauer[43]	*In vitro* study	To investigate commercially available antiseptic mouthwashes based on active ingredients such as chlorhexidine dicluconate and octenidine dihydrochloride regarding their efficacy against SARS-CoV-2 using the European Standard 14476
Xu et al.[44]	*In vitro* study	To evaluate the effect of commercially available mouth rinses and antiseptic povidone-iodine on the infectivity of SARS-CoV-2 virus
Bidra et al.[45]	*In vitro*	To investigate the optimal contact time and concentration for the viricidal activity of an oral preparation of povidone-iodine (PVP-I) against SARS-CoV-2 to mitigate the risk and transmission of the virus in dental practice
Kronbichler et al.[46]	Review	Recommendations for the management of patients with COVID-19, which should help reducing morbidity and mortality
Khan et al.[47]	Clinical study	To propose the use of 0.5% povidone-iodine (PVP-I) gargles and nasal drops as prerequisites for office-based nose and throat examination and procedures during the COVID 19 pandemic. To assess the tolerability of 0.5% PVP-I in patients and healthcare workers
Bajaj et al.[48]	Review	To provide a perspective on the potential use of salivary specimens for the detection and serial monitoring of SARS-CoV-2
Pelletier et al.[49]	*In vitro*	To evaluate nasal and oral antiseptic formulations of povidone-iodine for virucidal activity against SARS-CoV-2
Castro-Ruiz et al.[50]	Review	To provide a comprehensive review of the published evidence about the use of povidone-iodine (PVP-I) against SARS-CoV-2 and to propose a prophylactic protocol for dental care using PVP-I during the COVID-19 pandemic
Caruso et al.[51]	Review	To review the literature about the role of hydrogen peroxide concerning the innate response of nasal and oral epithelial cells
Ortega et al.[52]	Systematic review	To perform a systematic review to answer the following question: does a hydrogen peroxide mouthwash (at any concentration) have a virucidal effect?
Baker et al.[53]	Review	Bibliometric analysis of the antiviral efficacy of quaternary ammonium compounds
Carrouel et al.[54]	Review	To examine the effect of mouthrinses with β-cyclodextrin combined with citrox on preventing infection and progression of COVID-19
Gendrot et al.[55]	*In vitro*	To evaluate the *in vitro* activity of methylene blue against SARS-CoV-2
Yadalam[56]	*In silico* study	To study the antiviral efficacy of essential oil components specifically against SARS-CoV-2 by the molecular docking and conceptual DFT (density functional theory) approach
Eggers[57]	*In vitro* study	To investigate the *in vitro* bactericidal and virucidal efficacy of 7% povidone-iodine gargle/mouthwash at defined dilution against oral and respiratory tract pathogens
Peng[58]	Review	To recommend infection control measures during dental practice to block the person-to-person transmission routes in dental clinics and hospitals

Table 1 (continuation). Summary of research articles addressing mouthwashes in the era of COVID-19

Reference	Research type	Main aim of the study
Ather[59]	Review	Specific recommendations for dental practice in the era of COVID-19 for patient screening, infection control strategies, and patient management protocols
Mady et al.[60]	Opinion	To recommend the use of povidone-iodine to attenuate nosocomial transmission of COVID-19 surrounding head and neck and skull base oncology care
Challacombe et al.[61]	Opinion	Summary of evidence of the potential role of povidone-iodine in the reduction of the risk of cross infection and protection of dentists and other healthcare workers from COVID-19
Martínez Lamas[62]	Clinical study	To analyze the impact of a mouthwash with povidone-iodine on the salivary viral load of SARS-CoV-2 in patients with COVID-19
Popkin[64]	*In vitro* and *in vivo* study	To evaluate *in vitro* and *in vivo* the ability of CPC (Cetylpyridinium chloride) to disrupt influenza viruses
Arakeri et al.[68]	Opinion	To suggest methylene blue as a potential oral rinse to reduce the viral load in aerosols and drops during oropharyngeal procedures
Chopra[73]	Review	To discuss current evidence that supports the virucidal properties of PVI-P (Povidone Iodine) on the novel SAR-CoV-2 and its role in preventing the spread of infection during the COVID-19 pandemic

Interestingly, a small sample study by Yoon et al.[34] found suppression of SARS-CoV-2 for 2 hours after using 15 mL of 0.12% chlorhexidine, although there was an increase in viral load 2 to 4 hours later[34]. Hence, the time-dependent virucidal activity of chlorhexidine and its variable action against individual viruses may be partly explained by the subtle chemical or physical differences in the membranes of the enveloped viruses[69]. The evaluation of the ineffectiveness of chlorhexidine against the new coronavirus appears premature, with the reasons still not fully clarified due to the paucity of evidence.

o *Povidone-iodine against COVID-19*

Povidone-iodine is an iodophor consisting of a complex of iodide and a solubilizing polyvinylpyrrolidone carrier, which acts as a reservoir of "free" iodine (the active component). The most common formulations classically consist of a 10% PVP-I solution containing 1% available iodine.

It is known that povidone-iodine penetrates the cell membrane, destroys the walls of microbial cells inducing pore formation, leading to cytosol leakage. It inactivates cytosolic (cytoplasmic matrix) proteins, fatty acids, and nucleotides **(Figure 2)**. Povidone-iodine is effective even at minimal concentrations of 0.1% against *Neisseria gonorrhoeae* and of 0.5% against *Chlamydia trachomatis*, HIV, and HSV[70]. The remarkable action of this broad-spectrum solution is the rapid killing of bacteria, fungi, protozoa, chlamydia, and viruses at low concentrations, without the risk of antimicrobial resistance, and with good tolerance when applied topically to the most sensitive epithelium of the upper respiratory tract, effectively inhibiting the release of pathogenic factors such as exotoxins, endotoxins, and tissue-destroying enzymes. In contrast to povidone-iodine, bacterial resistance to chlorhexidine, quaternary ammonium salts, silver, and triclosan has been reported in the literature. Povidone-iodine also inhibits N1, N2, N3 neuraminidase, and hemagglutinin which blocks viral binding to its cellular receptors and thus halts viral release and spread from infected cells[71].

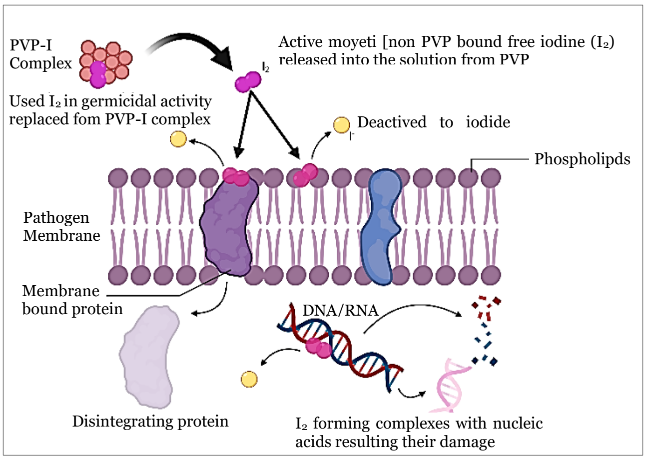

Figure 2: Iodide-mediated cellular inactivation and damage to COVID-19 nucleic acid.

After using the povidone-iodine solution, the released iodine can exist in various forms in the aqueous solution. Amongst the several forms, molecular I2 and hypoiodous acid (HOI) have potent antimicrobial activity. Moreover, iodine molecules oxidize critical targets such as amino acids, nucleic acids, and membrane components. An equilibrium is reached with more PVP-bound iodine released into the solution to replace the consumed iodine lost due to its germicidal activity. The preservation of this balance ensures long-lasting efficacy during bouts of microorganism replication, as well as better admissibility for patients due to lower levels of irritation[72].

The evidence for the efficacy of povidone-iodine as a mouthwash against COVID-19 has been overwhelmingly favorable. It has been time-tested in the past with established *in vitro* efficacy against SARS-CoV and Middle East respiratory syndrome at concentrations as low as 0.23%[73]. In addition, recent *in vitro* studies on oral povidone-iodine solution have validated its efficacy explicitly against SARS-CoV-2 at concentrations as low as 0.5% with a contact time of only 15 seconds. A concentration of 0.23% is equivalent to 70% ethanol in inactivating SARS-CoV *in vitro*[23]. According to the American Dental Association guidelines, pre-procedural rinsing with 0.2% povidone-iodine is recommended for all

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procedures to decrease the risk of COVID-19 transmission[63]. Likewise, *in vitro* studies have validated a 99.99% reduction in coronavirus titers, influenza virus, and rotavirus after a brief exposure to 0.25% povidone-iodine solution[57].

The few randomized controlled trials that tested the efficacy of various mouthwashes against SARS-CoV-2 and clinical systematic reviews have suggested superior activity of povidone-iodine compared to chlorhexidine and hydrogen peroxide[58,74]. This certainly can be attributed to its manifold action against the vulnerable targets, causing instantaneous cell wall damage, cytosol leakage, and inhibition of essential viral enzymes without the risk of cross/acquired resistance[57].

○ *CPC against COVID-19*

CPC or N-hexadecyl pyridinium chloride is a cationic quaternary ammonium compound with proven antimicrobial properties. The lysosomotropic action of CPC results in the disruption of the viral lipid envelope and prevents entry into the host cell. The antiviral effect of CPC has been demonstrated in patients with influenza, significantly reducing the duration and severity of cough and sore throat. In the context of COVID-19, a randomized controlled clinical trial tested the efficacy of three separate mouthwashes (chlorhexidine, povidone-iodine, and CPC) compared to a water control. Both CPC and povidone-iodine reduced the viral load of SARS-CoV-2 after 5 minutes and 6 minutes of use, respectively[36]. In addition to the safety profile of CPC, its established clinical efficacy in upper respiratory tract viral infections has resulted in its use as a mouthwash for COVID-19 due to its sustained favorable results in both *in vitro* and *in vivo* studies[36,53,64].

○ *Hydrogen peroxide against COVID-19*

Hydrogen peroxide is a potent broad-spectrum antimicrobial disinfectant and has a broad safety profile. It has been used routinely in dentistry as a mouthwash alone or in combination with other salts and active pharmacological agents for nearly a century[75]. Several randomized clinical trials attest to its safety as a daily rinse at concentrations of 1% to 1.5% with the absence of any adverse mucosal reactions during comprehensive long-term follow-up[76]. An *in vitro* study found that 3% hydrogen peroxide effectively inactivated adenovirus types 3 and 6, adeno-associated virus type 4, rhinoviruses 1A, 1B, and type 7, myxoviruses, influenza A and B, respiratory syncytial virus, long strain, and coronavirus strain 229E within 1 to 30 minutes[77].

Since SARS-CoV-2 is vulnerable to oxidation, pre-procedural mouthwashes containing oxidative agents have been suggested to reduce the salivary viral load **(Figure 3)**. Nevertheless, its use as a pre-procedural mouthwash against COVID-19 should be approached with caution despite its proven antimicrobial efficacy. A recent systematic review conducted by Ortega et al.[52] reported that there is no current scientific evidence to support the indication of a hydrogen peroxide mouthwash for viral load control regarding SARS-CoV-2 or any other viruses in saliva. Similarly, in a prospective controlled study by Gottsauner et al.[78], albeit with a small sample size, a 1% hydrogen peroxide mouthwash did not reduce the intraoral viral load in SARS-CoV-2-positive individuals[78]. Additionally, the virus culture did not yield any indication of the effects of the mouthwash on the infectivity of the detected RNA samples. At higher concentrations (>5%), hydrogen peroxide can damage the hard and soft intraoral tissues but, at much lower concentrations, it is rapidly inactivated by catalase activity in saliva. Therefore, the authors concluded that a pre-procedural mouthwash with hydrogen peroxide prior to intraoral procedures is questionable and thus should no longer be supported.

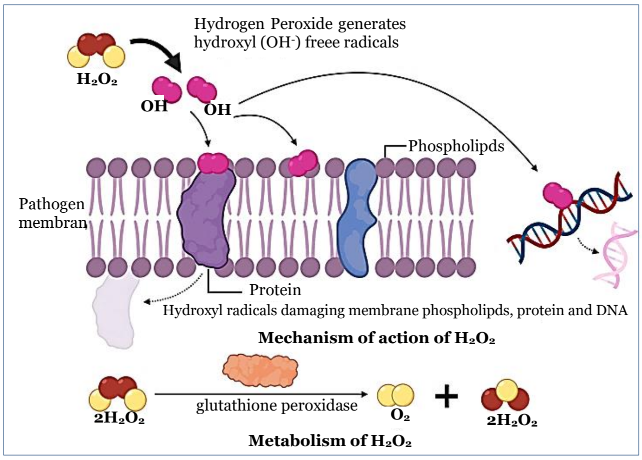

Figure 3: Action of hydrogen peroxide through free radical hydroxyl injury against cellular components.

○ *Other mouthwashes being investigated against COVID-19*

Methylene blue is a blue cationic thiazine dye initially synthesized in 1876 with a wide range of antimicrobial applications. There has been a focus on the use of a reduced form of methylene blue as a mouthwash against COVID-19, considering its distinct intrinsic properties. It may decrease the cytopathic effect and dissemination of COVID-19 by its redox property, contributing to a strong antiviral, anti-inflammatory action and with competitive inhibition of the cellular sites essential for virus attachment, penetration, and/or multiplication. Arakeri & Rao[68], in a letter to the editor, proposed the use of methylene blue as a mouthwash in COVID-19 settings to reduce disease transmission[68]. Yet, there are no published randomized controlled trials to provide the high level of evidence required to recommend its routine use against COVID-19.

Chloride/halide salts have historically been considered foes of the viral family. In cell culture models, it was detected that DNA, RNA, enveloped and non-enveloped viruses are all inhibited in the presence of NaCl. A hypertonic saline solution mouthwash, 6 times daily for 2 to 5 days, minimized the novel coronavirus shedding by >99% and common cold transmission by about one-third[79]. Of note, a post hoc secondary analysis of data from the recent Edinburgh and Lothias Viral Intervention study (ELVIS) pilot randomized controlled trial indicated that nasal irrigation and gargling with hypertonic saline reduces the duration of coronavirus upper respiratory tract infection by an average of two and half days. The inference from this trial is that a saline rinse may offer a potentially safe, effective, and scalable intervention for COVID-19 patients[80].

Flavonoids are hydroxylated phenolic structures synthesized from plants with antiviral, antibacterial, anti-inflammatory, cytostatic, apoptotic, and hepatoprotective properties[81]. A previous study highlighted the antiviral activity of flavonoids due to their inhibitory effect on 3C protease[82]. Flavonoids act as chymotrypsin-like protease inhibitors stalling coronaviral replication, prevent virus binding to ACE2 and suppress host innate hyperimmune responses[83]. The Citrox™ mouth rinse, which is a combination of natural bioflavonoids and other essential ingredients such as hyaluronic acid, chlorhexidine or phenoxetol, has been recommended as a mouthwash for reducing the salivary viral load also in potential asymptomatic carriers and for restraining the pro-inflammatory overreaction of the system[66]. Nevertheless, prospective randomized controlled trials comprehensively evaluating flavonoids against COVID-19 are warranted to provide a substantial level of evidence.

Cyclodextrins are natural glucose derivatives with a rigid cyclic structure composed of α(1-4)–linked gluco-pyranoside units. Their action against COVID-19 has been documented in the literature, although further clinical trials are required for more conclusive recommendations[84]. Methylated beta-cyclodextrin may be harmful to influenza A virus and COVID-19 via sequestration or depletion of lipids from the viral bio-structure. In combination with mercaptoundecane sulfonic acids, cyclodextrins can destroy viral particles by simple contact. Based on these findings, amphiphilic β-cyclodextrin nanoparticles have been added to commercial mouthwashes as valuable adjuncts[18,54].

Essential oils are volatile, odorous plant-based products, synthesized through the mevalonic acid, malonic acid, and methyl-d-erythritol-4-phosphate pathways in the cytoplasm and plastids of eukaryotes. Essential oils interfere with the phospholipid bilayer of coronaviruses and prevent the critical interaction between the SARS-CoV-2 spike protein and its ACE2 receptor[85]. Silva et al.[86] highlighted the affinity of essential oils for the viral spike protein and the docking scores obtained revealed that eugenol, menthol, and carvacrol are significantly relevant in their binding action onto the receptors[86]. Effective essential oil combinations with ethanol as mouthwashes have been used as adjuncts to inactivate COVID-19 through lipid damage[41,67]. Despite this, to date, there are no conclusive studies on the efficacy of essential oil mouthwashes against COVID-19.

Statins exhibit a lipid destabilizing action which interferes with ACE2 signaling. The use of 1% simvastatin mouthwash for over 15 to 20 seconds has been proposed to diminish viral loads in the oropharyngeal cavity[65]. However, further studies are required before endorsing any recommendations.

Finally, drawing conclusions from the review studies, povidone-iodine is more effective in a clinical setting than chlorhexidine or hydrogen peroxide recommended at the onset of the pandemic. Recent studies regarding chlorhexidine and hydrogen peroxide have shown limited or ineffective action *in vivo* against COVID-19[58,74]. The use of quaternary ammonium compounds such as CPC with proven antiviral efficacy as a mouthwash, has also been recommended to reduce significant viral loads in the oral cavity[53,64].

○ *Professional and regulatory council recommendations for the use of mouthwashes against COVID-19*

Professional organizations and regulatory councils have published guidelines for the use of pre-procedural mouthwashes against COVID-19 for dental professionals. For instance, the Canadian Dental Hygienists Association and Canadian Dental Association[87,88] currently recommend the use of a pre-procedural 0.2% povidone-iodine rinse and no longer recommend the use of hydrogen peroxide based on a December 2020 systematic review by Ortega et al.[52]. Noteworthy, the American Dental Association still continues to recommend the use of 1.5% hydrogen peroxide (commercially available in the US) or of 0.2% povidone as a pre-procedural mouthwash[63].

CONCLUSION

This review provides much-needed evidence on the efficacy of commercial mouthwashes for the reduction of salivary SARS-CoV-2 viral load. COVID-19 appears to be more virulent than earlier viruses that have threatened mankind. This explains the high transmission rate of COVID-19, which differentiates it from the flu, the common cold, and SARS-1. Oral and nasal decontamination using topical antiseptic solutions can mitigate the viral load and transmission via droplets and aerosols. Pre-procedural and intermittent rinsing of the mouth during dental procedures may minimize the viral load of freshly secreted saliva and must be espoused as a preventive practice to counter this potentially deadly virus. It is assumed that the naso-oropharyngeal gateway determines the viral load and the severity of symptoms based on the viral load, and may explain the dissimilarities in the detection, the tenacity of viral load, and the transmission dynamics between the previous SARS-CoV outbreaks and the ongoing COVID-19 pandemic[89].

The main findings of this literature overview provide the best evidence to date for the use of povidone-iodine as a pre-procedural rinse, with CPC following as a close second. Hydrogen peroxide and chlorhexidine have been recently removed from most professional and regulatory guidelines based on the latest research findings. Other agents such as essential oils and methylene blue need further *in vitro* testing. The current review has not yet addressed the optimum duration or the volume of mouthwashes that is effective before viral load recovers in the oral cavity. Studies have yet to determine the most effective combination of virucidal prophylaxis, if any. There is also a need for larger-scale prospective randomized controlled clinical trials testing the currently recommended mouthwashes against COVID-19, with emphasis on any adverse effects, long-term clinical efficacy in different settings, quantitative reduction of viral loads, and oral transmission in view of the fact that current studies, both *in vitro* and *in vivo*, are of low level evidence. Currently, there does not appear to be universal agreement on the use of these products; thus, it is recommended that clinicians follow the guidelines of their regional professional associations and regulatory authorities who keep abreast with the evolving evidence. Finally, studies involving different populations to verify the effectiveness of mouthwashes before using them as a community arsenal against the spread of COVID-19 infection are encouraged.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

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