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Antiseptics: An expeditious third force in the prevention and management of coronavirus diseases

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ABSTRACT

Notably, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and coronavirus disease 2019 (COVID-19) have all had significant negative impact on global health and economy. COVID-19 alone, has resulted to millions of deaths with new cases and mortality still being reported in its various waves. The development and use of vaccines have not stopped the transmission of SARS coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19, even among vaccinated individuals. The use of vaccines and curative drugs should be supplemented with adoption of simple hygiene preventive measures in the fight against the spread of the virus, especially for healthcare workers. Several virucidal topical antiseptics, such as povidone-iodine (PVP-I), citrox, cyclodextrins among others, have been demonstrated to be efficacious in the inactivation of SARS-CoV-2 and other coronaviruses in both *in vitro* and *in vivo* studies. The strategic application of these virucidal formulations could provide the additional impetus needed to effectively control the spread of the virus. We have here presented a simple dimension towards curtailing the dissemination of COVID-19, and other coronaviruses, through the application of effective oral, nasal and eye antiseptics among patients and medical personnel. We have further discussed the mechanism of action of some of these commonly available virucidal solutions while also highlighting some essential controversies in their use.

1. Introduction

The coronaviruses are the etiological agents responsible for deadly diseases in several birds and mammals (Fehr and Perlman, 2015; Alluwaimi et al., 2020; Wang et al., 2020). In humans, these viruses are usually disseminated through airborne droplets and fluid from infected persons (Wang et al., 2020; Jayaweera et al., 2020; Shereen et al., 2020). The virus got its first detailed description in the 1960s and its name was derived from the distinctive corona (*i.e.* crown) shape of the projecting glycosylated club-shaped spikes from the surrounding envelope of the particle (Li, 2016; Nova, 2021). Coronaviruses belong to the Orthocoronavirinae subfamily, in Coronaviridae family, Nidovirales order and realm Riboviria (Alluwaimi et al., 2020; Wang et al., 2020; Nova, 2021).

Four out of the 7 coronaviruses which are known to infect humans, do spread with seasonal regularity, resulting to symptoms similar to mild cold with flu-like discomforts. Since the onset of the 21st century, 3 of these coronaviruses have been established to cross species barrier leading to very serious pneumonia in infected persons (Carod-Artal, 2020; Dhama et al., 2020; Walls et al., 2020). The notable strains are SARS-CoV-2, the etiological agent of COVID-19, MERS-CoV and SARS-CoV which cause the Middle East respiratory syndrome (MERS) and the severe acute respiratory syndrome (SARS), respectively (Dhama et al., 2020; Swelum et al., 2020). The reported causes of death are complex, though it is mainly due to heightened immune response which leads to damages in several organ systems all over the body (Walls et al., 2020).

SARS was originally identified as a distinct strain of the coronavirus in 2003. Although the origin of the virus is not quite clear, the first reported human incident was however in 2002 in China's Guangdong province. The virus eventually became a pandemic, leading to 8098 infections in 26 countries in over five continents with 774 deaths (Walls et al., 2020; Cherry and Krogstad, 2004; Muller and McGeer, 2007). MERS was identified in 2012 among persons showing symptoms of fever, cough, shortness of breath and occasional gastrointestinal

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problems like diarrhoea in Saudi Arabia. Official animal hosts for the virus have not been confirmed yet, but evidence suggests dromedary camels as the potential reservoir. MERS-CoV disseminated to about 27 countries, infecting over 2494 people with 858 reported deaths (Zumla et al., 2015; de Wit et al., 2016; Chafekar and Fielding, 2018).

The new coronavirus, SARS-CoV-2, is responsible for the deadly COVID-19 disease. This virus was previously unknown before its discovery in December 2019 in the city of Wuhan in Hubei province of China. The virus was isolated and sequenced by January 2020 (Zhu et al., 2019; Safari et al., 2020). The virus was declared an epidemic of public health emergency, and as a pandemic on 30th of January and 11th of March 2020, respectively, by the World Health Organization (Cucinotta and Vanelli, 2020; WHO 2021). According to the WHO, as at June 2, 2024, there had been 775,583,309 confirmed cases of COVID-19, out of which 7,050,691 deaths had been reported to WHO (World Health Organization Data 2024). Morbidity and mortality attributable to SARS-CoV-2 has exceeded that reported for both MERS-CoV and SARS CoV.

In the current therapeutic approach for handling coronavirus respiratory diseases, most of the recent updates have been on the use of vaccines, drugs, antibodies, immune-suppressants, angiotensin-converting enzyme (ACE) inhibitors and blockers (South et al., 2020; Chung et al., 2021; Ita, 2021; Majumder and Minko, 2021; Tarighi et al., 2021). Among all these, the use of vaccination is the most widely adopted. It is generally agreed that vaccines and vaccination hold the best means of ending the COVID-19 pandemic (Keegan et al., 2021; Viana et al., 2021; Nnaemeka et al., 2023). Nevertheless, vaccination has a number of limitations, prominent among them being vaccine escape variants of the virus that can be transmitted to both vaccinated and non-vaccinated individuals (Riemersma et al., 2022; Singanayaman et al., 2022). Hence, there is the need to consider other means of controlling the viral spread to compliment the use of vaccination. There has been very little reference on the use of mouthwash or gargles, throat, nose and eye sprays in the prevention of infection establishment or in the hindrance of progression of the disease, particularly since its first port of call before entering the lungs or digestive tract is the throat.

When infectious diseases spread through aerosol or by direct contact, respiratory pathogens attach to and then colonize the mucus of the oropharynx, which leads to the development of upper respiratory tract infections (URTI) (Murphy et al., 2009; Bosch et al., 2013; Rosas-Salazar et al., 2021). Considering the infection complexity and/or disease progression, it is pertinent to contemplate "how a prophylactic mouth/-throat rinse and nose/eye spray with virucidal activities may hinder the progression of infection and establishment of disease" (Chopra et al., 2021; Pattanshetty et al., 2021; Gandhi et al., 2021). Both oral and oropharyngeal cavities are habitats for a wide variety of microbes with pathogenic potentials. This therefore should necessitate evaluation of antiseptic compounds with broad spectrum antimicrobial activity for inclusion in oral/nasal formulations to ensure oropharyngeal coverage (Chopra et al., 2021; Kanagalingam et al., 2015; Vieira Colombo et al., 2016; Kumpitsch et al., 2019).

Reports have shown that the viral load in human's oropharyngeal mucosa is high in both symptomatic and asymptomatic patients during SARS-CoV-2 infection (Zou et al., 2020). There is, therefore, the need to minimize this viral load in the oropharynx adopting adequate prophylactic measures (Chopra et al., 2021; Gandhi et al., 2021). For this purpose, considering the use of prophylactic mouthwash with anti-viral activity to remove/lower SARS-CoV-2 loads in the oropharyngeal mucosa is vital. Since SARS-CoV-2 is quite susceptible to oxidation (Suhail et al., 2020; Forcados et al., 2021; Tu et al., 2021), the use of 0.5% H_2O_2 or 0.2% povidone-iodine (PVP-I) as mouthwash/gargle may help minimize the risk of transmission of SARS-CoV-2 (Pattanshetty et al., 2021).

2. Applications of mouthwash, throat, nose and eye sprays in pandemics involving respiratory diseases

2.1. Povidone-Iodine (PVP-I)

PVP-I is made-up of iodine and polyvinylpyrrolidone, a water-soluble polymer, which is also known as polyvidone or povidone. It displays antimicrobial activity as it dissociates to release iodine. It is this iodine that penetrates the target microbe, oxidizing nucleic acids and disrupting proteins by attacking the sulfuryl and disulphide bonds of the protein (Zhao et al., 2016; Kurakula and Rao, 2020; Carrouel et al., 2021; Ghafoor et al., 2021). Thus, PVP-I kills microorganisms through the perturbation metabolic pathways and disorganization of microbial cell membrane (Carrouel et al., 2021). There are two potent antiseptic components of PVP-I, viz: hypoiodous acid (HIO) and molecular iodine (I_2). Both deliver the potent free iodine which can oxidize the cell membrane and amino acids of pathogens. Through cellular receptors oxidation, PVP-I inhibits attachment of viral pathogens to these receptors (Kanagalingam et al., 2015; Sriwilaijaroen et al., 2009).

For over six decades, PVP-I has been used as an effective topical antiseptic agent. It is attributed to having the broadest antimicrobial spectrum when compared to some other antiseptics such as polyhexanide, chlorhexidine, hexetidine and octenidine (Selvaggi et al., 2003; Lachapelle et al., 2013). It has activity against bacteria and bacterial spores, protozoa, fungi and some viruses (Lachapelle et al., 2013). The persistent effect of PVP-I was demonstrated in a research that used 1% PVP-I as a preprocedural antimicrobial agent in persons with different levels of oral hygiene. Reduction in microbial load was reported to be maintained for minimum of four hours (Domingo et al., 1996).

Several works have shown the efficacy of using different PVP-I antiseptics in deactivating SARS-CoV-2, SARS-CoV and MERS-CoV in *in vitro* assays both singly and in combination with other antiseptics (Table 1). The action of PVP-I oral/nasal rinses and sprays on SARS-CoV-2 could largely be due to the susceptibility of the virus to oxidation (Pattanshetty et al., 2021; Forcados et al., 2021; Tu et al., 2021). The application of these PVP-I products as topical oral/nasal antiseptic solutions has been reported to be safe (Chopra et al., 2021; Frank et al., 2020; Arefin, 2021). Therefore, in cases of COVID-19 outbreak, applications of PVP-I products have been proposed for use in mouthwash/gargle, nasal spray and in skin cleanser for both patients and healthcare workers (HCWs), as well as in disinfectants used for intubation, bronchoscopy and endoscopy instruments [(Arefin, 2021; Malaysian Health Technology Assessment Section (MaHTAS) 2020; Naqvi et al., 2020)]. The use of oral and intra-nasal PVP-I applications by infected persons and their attendant HCWs during this COVID-19 pandemic has been advocated to help reduce the viral load and transmission through aerosols and droplets (Cascella et al., 2022) (Fig. 1).

Considering the reported *in vitro* effectiveness of PVP-I antiseptics, gargling with PVP-I mouthwash/rinse may be quite an effective preventive measure against the dissemination of respiratory viruses (Chopra et al., 2021; Eggers et al., 2018; Ahmad, 2021). Furthermore, since the reported average time of viral shedding in COVID-19 patients was 20 days, and 37 days at the most in China (Zou et al., 2020), an effective gargle/mouthwash and nasal spray, especially one containing PVP-I, would be very useful in reducing transmission of the disease to medical personnel and care givers in isolation centers. It may also prevent patients who have recovered from the disease from infecting their loved ones through viral shedding (Chopra et al., 2021; Arefin, 2021). It could also prevent those who are vaccinated from spreading the virus and from being re-infected, since it is well established that infection and spread of the virus also occur in vaccinated persons (Keegan et al., 2021; Bergwerk et al., 2021; Franco-Paredes, 2022). The benefits of using PVP-I gargle was reported in Japanese clinical respiratory guidelines (Sriwilaijaroen et al., 2009; Japan Ministry of Health, Labour and Welfare (JMHLW) 2007; Eggers, 2019), which recommends the gargling

Table 1
The efficacy of topical antiseptics against coronaviruses.

Virucidal agent/Active ingredients	Tested concentrations	Corona Virus tested	Treatment time	Effect/Activity	Reference
PVP-I products such as: Isodine Nodo Fresh, Isodine Palm, Isodine Gargle, Isodine and Isodine Scrub[1]	0.23, 0.25, 0.47,1 and 1%[1]	SARS-CoV	2 mins	Infectivity of virus was reduced below detectable level from 1.17×10^6 $TCID_{50}$/mL by all the PVP-I products	(Kariwa et al., 2006)
PVP-I mouthwash/gargle	0.23%	SARS-CoV and MERS-CoV	15 s	Viruses were inactivated [titre value reduction of ≥ 4 log_{10} (99.99%) compared with control] in clean and dirty conditions	(Eggers et al., 2018)
PVP-I products: PVP-I mouthwash/gargle, skin cleanser and surgical scrub[1]	1, 4 and 7.5%[1]	MERS-CoV	15 s	Reduction of MERS-CoV titre value by ≥ 4 log_{10} (99.99%) in both clean and dirty conditions by all the PVP-I products	(Eggers et al., 2015a)
PVP-I products: throat spray, gargle/mouth wash, skin cleanser and antiseptic solution[1]	0.45, 1, 7.5 and 10%	SARS-CoV-2	30 s	Reduction of SARS-CoV-2 titre value by ≥ 4 log_{10} (99.99%), compared with control, by all the PVP-I products. Furthermore, 1:2 dilution of the mouth wash also lowered SARS-CoV-2 titre value by ≥ 4 log_{10}	(Anderson et al., 2020)
PVP-I oral rinses and hydrogen peroxide	PVP-I: 1, 2.5 and 3%; H_2O_2: 3 and 6%	SARS-CoV-2	15 and 30 s	SARS-CoV-2 was completely inactivated (*i.e.* $<$ 0.67 log_{10} CCID50/0.1 mL) by all the tested concentrations of PVP-I compared to control. While H_2O_2 was only minimally effective against SARS-CoV-2 (*i.e.* $\leq$ 3.67 and $\leq$ 3.33 log_{10} CCID50/0.1 mL for 3 %, then $\leq$ 4.0 and $\leq$ 2.5 log_{10} CCID50/0.1 mL for 6%) after 15 s and 30 s, respectively	(Bidra et al., 2020)
PVP-I nasal antiseptics	0.5, 1.25, and 2.5 %	SARS-CoV-2	15 and 30 s	SARS-CoV-2 was completely inactivated by all the tested concentrations of PVP-I (by > 3 log_{10} of 50 % cell culture infectious dose) within 15 s	(Frank et al., 2020)
PVP-I mouthwash and gargle	0.5 and 1%	SARS-CoV-2	15, 30 and 60 s	Greater than 5 log_{10} reduction of SARS-CoV-2 titre value by 1 % PVP-1 at $\geq$15 s treatment exposure under dirty and clean conditions. While the 0.5% PVP-I gave a > 5 log_{10} and > 5 log_{10} reductions by 15 and 30 s of treatment, respectively, in clean and dirty conditions, all compared to control	(Hassandarvish et al., 2020)
PVP-I nasal and oral rinse antiseptics	0.25 – 2.5%	SARS-CoV-2	60 s	The PVP-I products tested reduced SARS-CoV-2 to $\leq$ 1 log_{10} CCID50/0.1 mL from a viral load of 5.3 log_{10} CCID50/0.1 mL	(Pelletier et al., 2021)
Oral rinses with these active ingredients: PVP-I, H_2O_2, chlorhexidinebis, octenidine dihydrochloride, dequalinium chloride/ benzalkonium chloride, ethanol/essential oils and polyaminopropyl biguanide	–	SARS-CoV-2	30 s	PVP-I, dequalinium chloride and ethanol/ essential oils significantly reduced the infectivity of the tested 3 strains of SARS-COV-2 ($\geq$ 3.11 log_{10})	(Meister et al., 2020)
Stabilized hypochlorous acid; chlorhexidine (CHX) gluconate (both alcohol based and free); PVP-1; dipotassium oxalate; and H_2O_2[1]	0.01–0.02; 0.2; 0.58; 1.4; and 1.5%[1]	SARS-CoV-2	1 min	Reduction of viral titre value by $\geq$ 4.1 to $\geq$5.5 log_{10} after treatment with all the mouthwashes except for the 0.2 CHX gluconate and 1.5 H_2O_2 that did not give activity against SARS-CoV-2.	(Davies et al., 2021)

[1] Products and their concentrations in respective order of listing.

with PVP-I solution as a potent antiseptic agent against influenza pandemic and in the prevention of nosocomial pneumonia (Japan Ministry of Health, Labour and Welfare (JMHLW) 2007; Kariwa et al., 2004).

During lacrimal surgeries, the surgeon usually comes into contact with ocular surface, nasal tissues and tears. Hence, among ophthalmology healthcare personnel, the risk of transmitting SARS-CoV-2 may be higher in lacrimal surgeons (Ali et al., 2020). PVP-I may be used in all the frequently contacted areas in specific concentrations proven to be safe in the respective anatomical regions (Ali et al., 2020). The viral load on ocular surface could be adequately managed with PVP-I eye drops (1%) (Grzybowski et al., 2018; Koerner et al., 2018), while 0.4% reconstituted PVP-I solution could be used for both lacrimal and nasal drainage tissues, and 1% PVP-I gargles applied in the oral mucosa (Pattanshetty et al., 2021). *In vitro* studies have demonstrated that about 5 - 10% PVP-I could be ciliotoxic to epithelium of the respiratory system while 10% could lead to iodine toxicity (Kim et al., 2015). On the other hand, the use of 0.5% PVP-I nose drops and mouthwash/rinse have been confirmed to be safe, without allergic reactions, in both patients and HCWs (Lachapelle et al., 2013; Khan et al., 2020; Kirk-Bayley et al., 2020). However, PVP-I usage is contraindicated in pregnant women, and in patients having iodine allergy as well as in those with thyroid diseases, or persons undertaking treatments with radioactive iodine (Gray et al., 2013).

The dental authorities of some countries have recommended application of an effective antiviral mouth rinse/wash during oral treatment to help protect both personnel and patients. However, there is currently no such recommendations from the WHO or most national Ministries of Health to use mouth rinses/wash by COVID-19 patients or as a preventive and protective measure to the general population (Alharbi et al., 2020; Ather et al., 2020). Considering that mouth rinses and nasal sprays may act as agents that could help in the reduction of viral load of SARS-CoV-2 in both asymptomatic and symptomatic patients, the adoption of these antiseptics in the crusade against COVID-19 pandemic is quite an attractive concept (Carrouel et al., 2021) and ought to be evaluated for inclusion in health policy. Mouth rinses/washes which contain PVP-I or cetylpyridinium chloride (CPC) can decrease SARS-CoV-2 oral load and the consequent risk of transmitting the virus through generated droplets and aerosols in normal life and dental procedures, respectively (Castro-Ruiz and Vergara-Buenaventura, 2020; Dev Kumar et al., 2020; Herrera et al., 2020). Therefore, usage of pre-procedural mouth rinses (PPMRs) was recommended to prevent nosocomial SARS-CoV-2 transmission (Peng et al., 2020).

SARS-CoV-2 is found in secretions of both oropharynx and

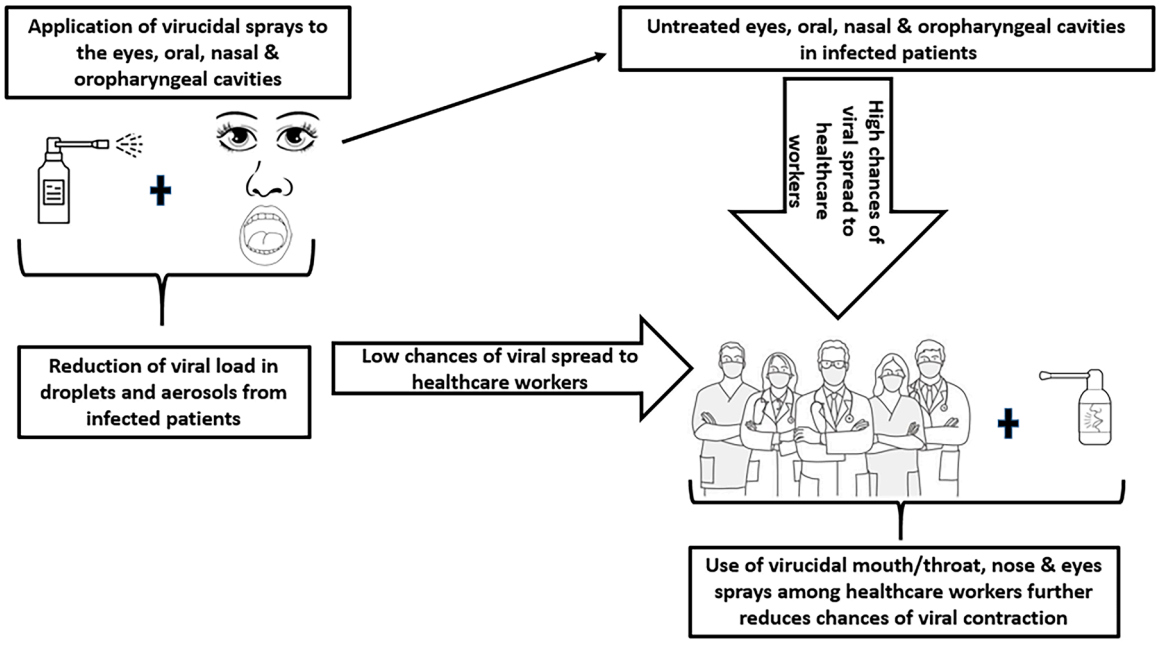

Fig. 1. Application of virucidal antiseptics reduces the spread/dissemination of respiratory viral diseases like COVID-19 to healthcare workers.

nasopharynx. Saliva is a crucial means of the viral transmission. There is usually a high load of SARS-CoV-2 in the saliva, especially in the early disease stage. The virus is detected in over 90% saliva samples obtained from patients with COVID-19. The number of viral infective copies/mL in these samples could amount to 1.2×10^8 (To et al., 2020; Yoon et al., 2020). When an individual coughs, sneezes, converses or breathes, such a one generates saliva droplets harbouring microorganisms. A cough or five minutes of conversation could produce about three thousand saliva droplets while a sneeze could produce about forty thousand droplets which can be transmitted several meters in the air (Baghizadeh, 2020). Over 60 μm of saliva droplets could lead to the spread of SARS-CoV-2 when there are close contacts among people (Carrouel et al., 2021). Droplets with SARS-CoV-2 could penetrate susceptible hosts through the eyes and/or mouth, or could be inhaled straight to the lungs through the nose. Thus, the infected host can become sick with COVID-19 disease (Carrouel et al., 2021; Dhand and Li, 2020; Lelieveld et al., 2020). However, the application of PVP-I mouth rinses reduces viral load in the saliva/salivary glands which could consequently help in the prevention of disease spread by decreasing the chances of contracting the virus.

The activated spike protein on SARS-CoV-2 virus, binds to its receptor, ACE2, making the virus to act like a pathogen (Duan et al., 2020; Hoffmann et al., 2020; Shang et al., 2020). ACE2 and the proprotein convertase furin, transmembrane serine protease 2 (TMPRSS2), are involved in the penetration of the virus into host cells and have high expression in the salivary glands (Hoffmann et al., 2020; Zupin et al., 2021). At the eye level, ACE2 and TMPRSS2 are both expressed on humans' ocular surfaces (Carrouel et al., 2021). Since ACE2 is expressed on the eye surface cells which produce TMPRSS2 also, this helps SARS-CoV-2 enter host cells (Ni et al., 2020; Salamanna et al., 2020; Zhou et al., 2020), which is why people are advised to avoid auto-infection through rubbing their eyes with unclean hands (Coroneoand Collignon, 2021; Dawood, 2021). Considering the fact that the virus can establish itself on ocular surfaces, it can therefore be transmitted via the tear duct which connects the eyes with the nasal cavity and thereafter infects the respiratory cells (Sun et al., 2020; Agrawal et al., 2021; Liu et al., 2021).

Conjunctivitis commonly known as pinkeye can be a symptom of COVID-19 and it is recommended that people with symptoms, characterized by redness, tearing, itchiness, gritty sensation and discharge in the eyes, should get tested for COVID-19 (Scalinci and Trovato Battagliola, 2020; Al-Namaeh, 2021; Ozturker, 2021). There have been reports of SARS-CoV-2 detection in the conjunctival and tears swab samples collected from COVID-19 patients (Kaya et al., 2020; Arora et al., 2021). Eye protection goggles or glasses are highly recommended for HCWs in order to avoid infection through droplet transmission (Chu et al., 2020; Byambasuren et al., 2021). As earlier stated, viral load on ocular surfaces can be effectively reduced with 1% PVP-I eye drops (Grzybowski et al., 2018; Koerner et al., 2018).

The few available *in vivo* clinical studies which utilized PVP-I treatments on COVID-19 patients have indicated the possibility of the antiseptic reducing SARS-CoV-2 viral load in the saliva/mouths of people and sustaining such reduced viral load for some hours (Table 2). Application of PVP-I products is therefore a prospective option in the reduction of COVID-19 transmission risk and a wonderful additional preventive/protective measure for HCWs (Chopra et al., 2021; Arefin, 2021; Cascella et al., 2022).

2.1.1. *Emphasis on oral hygiene in a respiratory pandemic era*

Respiratory and oral tract pathogens could cause serious threat to humans' health (Jain et al., 2001; Grief, 2013). The widespread of nosocomial infections greatly add to the increase of morbidity and mortality among patients, especially the vulnerable ones (Koch et al., 2015; Haque et al., 2018). The practice of appropriate hygiene is usually recommended among individuals and HCWs in an emerging infectious disease outbreak to help curtail the dissemination of such disease by interrupting its transmission. The observance of routine adequate oral hygiene can further increase the positive outcome of general hygiene practice, especially against respiratory pathogens (Chopra et al., 2021; Arefin, 2021; Cascella et al., 2022; Kirk-Bayley et al., 2020; Yimenu et al., 2020). In this regard, the application of PVP-I mouthwash/gargle presents a useful protection measure against the spread of respiratory and oral tract infections (Chopra et al., 2021; Ahmad, 2021).

Daily gargling was recommended by the Ministry of Health, Labour and Welfare in Japan as a protective and/or preventive hygiene protocol to limit spread of URTIs (Japan Ministry of Health, Labour and Welfare (JMHLW) 2007), and this was greatly promoted during the 2009 H1N1 swine flu outbreak (Kramar and Eggers, 2020). This practice has been confirmed by several studies investigating the functions of oral gargling in some healthy individuals and people suffering from persistent URTIs (Nagatake et al., 2002; Satomura et al., 2005; Kitamura et al., 2007).

Table 2
In vivo clinical studies of some topical antiseptics on SARS-CoV-2.

Virucidal Agent & concentration	Treatment time	Number of patients	Ages of patients (yr)	Kind of samples	Method of viral detection	Effect/Activity	Reference
0.12% Chlorhexidine mouthwash	30 s	02	46 and 65	Nasopharyngeal, oropharyngeal, sputum & urine	rRT-PCR	Saliva viral load decreased transiently for about 2 h after usage of mouthwash. However, there was an eventual increase in viral load by 2 to 4 h after mouthwash	(Yoon et al., 2020)
PVP-I (0.5%), cetylpyridinium chloride (CPC) (0.075%) & chlorhexidine gluconate (CHX) (0.2%)	30 s	16	35.7 ± 8.5 – 43.6 ± 8.6[1]	Saliva	RT-PCR	No significant difference in the cycle threshold (Ct) values of patients in the tested groups and water control at all the tested times. There was however a significant increase of Ct value fold changes of CPC (at 5 min & 6 h) and PVP-I (at 6 h) tested groups compared to the control group fold change. Therefore, PVP-I & CPC had a sustained reducing effect on SARS-CoV-2 load in the saliva of tested persons	(Seneviratne et al., 2021)
1% PVP-I	1 min	04	43, 54, 73 and 74	Nasopharyngeal & saliva	rRT-PCR	Significant drop in SARS-CoV-2 load in two patients after administration of PVP-I which was sustained for at least 3 h	(Martínez Lamas et al., 2020)
β-cyclodextrin-citrox mouthwash (CDCM)	1 min	176	18 - 85	Saliva	RT-PCR	CDCM gave significantly ($p = 0.036$) better effect than the placebo by 4 h after the first dose resulting in 12.58% viral median percentage decrease; the small median value for CDCM was further sustained by the second dose. There was also greater median decrease percentage in the viral load for CDCM group when compared to the placebo by day 7	(Carrouel et al., 2021)
0.12% chlorhexidine gluconate (CHX) oral rinse & oropharyngeal spray	30 s	294 COVID-19 patients + 15 healthcare workers	23 – 89 (median age: 62)	Oropharyngeal swab	rRT-PCR	SARS-CoV-2 was eliminated in the oropharynx of 61.1% patients who applied only CHX oral rinse as against 5.5% of control patients who did not. While there was 86% eradication of SARS-CoV-2 in patients who used both CHX oropharyngeal spray and oral rinse as against 6.3% control group who did not after 4 days of treatment. Furthermore, none of the healthcare personnel that used CHX developed COVID-19 as against 50% rate among their colleagues in other hospitals	(Huang and Huang, 2021)
0.2% CHX & 1% PVP-I gargle/mouth-wash	30 s	61	17 – 85 (45.3 ± 16.7)[1]	Saliva	rRT-PCR	There was significant difference in the delta Ct obtained from the control group (with distilled water) and that of the two treated groups – CHX ($P = 0.0024$) and PVP-I ($P = 0.012$). However, there was no significance between CHX and PVP-I treated groups. There was also significant difference ($P < 0.0001$) in delta Ct of the treated groups before and after treatments while such was not witnessed in the control group	(Elzein et al., 2021)
PVP-I (2%), H_2O_2 (1%), cetylpyridinium chloride (0.07%) & CHX (0.12%)	1 min	84		Saliva	rRT-PCR	There was no statistical difference in the SARS-CoV-2 load after use of all the tested mouthwashes	(Ferrer et al., 2021)
1% H_2O_2 mouthrinse	30 s	12	22 – 81 (median age: 55)	Oropharyngeal	RT-PCR	SARS-CoV-2 load was not reduced by 1% H_2O_2 in tested patients	(Gottsauner et al., 2020)

[1] Mean age ± SD.

Since clinical studies that applied PVP-I to decrease respiratory infections in different settings have validated its efficacy, its use in the current pandemic should hence be considered (Martínez Lamas et al., 2020; Elzein et al., 2021).

Oral hygiene with PVP-I could be of particular importance in specific groups of patients such as the immunocompromised who are at great risk of extended viral shedding that could facilitate the potential of antiviral drug resistance, nosocomial transmission and evolution of new variants (Eggers et al., 2018; Corey et al., 2021). There is currently a risk of prolonged viral shedding in COVID-19 patients even after recovery therefore the prospect of reducing this viral shedding by applying oral gargling with 1% PVP-1 should be explored (Chopra et al., 2021; Arefin,

2021). With its established safety profile, PVP-I might just be the added lifesaver and lifeguard, in addition to vaccination, to protect HCWs as they take care of COVID-19 patients who have active diseases or asymptomatic patients in isolation. Several *in vitro* and *in vivo* studies have confirmed the potency of PVP-I against coronaviruses, including SARS-CoV-2 (Tables 1 and 2).

2.2. Citrox

Citrox is a derivative of citrus fruits. It constituents include natural soluble bioflavonoids and hydroxylated phenolic compounds which are obtained from plants (Carrouel et al., 2021). Flavonoids are an essential class of natural products. These include several subgroups, such as flavonols, flavones, isoflavones and chalcones (Panche et al., 2016). Bioflavonoids that are produced from plants have been demonstrated to have antimicrobial activities against viruses, bacteria and fungi (Middleton et al., 2000; Nair et al., 2006; Russo et al., 2020). Flavonoids usually display a broad spectrum of activities because of their antioxidant properties as well as their potentials to modulate several cell receptors and/or enzymes (Panche et al., 2016). These activities include anti-inflammatory (Spagnuolo et al., 2018), anti-allergic (Park et al., 2020), antiangiogenic (Khater et al., 2020), cytostatic (Go et al., 2018), analgesic (Nesterova et al., 2017), apoptotic (Tavsan and Kayali, 2019), hepatoprotective (Ma et al., 2020), among others.

A number of flavonoids have been demonstrated to elicit efficacious activities against several human viruses. For example, two flavonoids (orbifolin and pedalitin) from *Pterogyne nitens* were shown to prevent the entrance of hepatitis C virus into the tested host cells at non-cytotoxic concentrations (Shimizu et al., 2017). Moreover, some other flavonoids, such as baicalin, herbacetin, isobavachalcone, helichrysetin, quercetin 3-β-D-glucoside, amentoflavone, etc., inhibited the activity of MERS-CoV protease (MERS-CoV/SARS-CoV-2 3CLpro), which performs vital roles in the replication of the MERS virus (Ryu et al., 2010; Jo et al., 2019), and that of SARS-CoV-2 3-chymotrypsin-like cysteine protease.

Since chymotrypsin-like and papain-like proteases are essential coronaviral encoded proteins responsible for both replications of the virus and inhibition of host immune response, targeting these proteases are therefore quite attractive measures in the treatment and prevention of coronaviral diseases (Zhang and Liu, 2020). Interestingly, some flavonoids have already been demonstrated to have inhibitory effects against these proteases (Park et al., 2020; Ryu et al., 2010; Jo et al., 2019; Mouffouk et al., 2021). Some other flavonoids, such as hesperidin, isorhamnetin, rutin etc., were reported to show potential good activity against SARS-CoV-2 through binding to the ACE2 and/or TMPRSS2 thereby preventing their expression and interaction with SARS-CoV-2 (Mouffouk et al., 2021; Hu et al., 2020; Muchtaridi et al., 2020; Cheng et al., 2021; Zhan et al., 2021). Furthermore, since SARS-CoV-2 is susceptible to oxidative reaction, it is therefore recommended to apply a mouth rinse/gargle with oxidizing agents like citrox to decrease the oral salivary microbiota which include potential SARS-CoV-2 carriage (Carrouel et al., 2021; Carrouel et al., 2020).

2.3. Cyclodextrins (CDs)

Cyclodextrins (CDs) are natural glucose derivatives which possess rigid cyclic structure that contain α (1–4)–linked gluco-pyranoside units (Jambhekar and Breen, 2016). α-, β- and γ-CDs contain 6-, 7- and 8-units of glucopyranoside, respectively. CDs are applied in the improvement of bioavailability and/or in water-solubility of medicines (Saokham et al., 2018). They can also be applied in preventing or reducing gastrointestinal and ocular irritations, decreasing or eliminating disagreeable smells or tastes, preventing interactions among drugs or drug additives in formulations. The advantages of CDs usage include: better biocompatibility compared to most oxides in oral products (*i.e.*, gold or silver); ease of use; lack resistance reactions, and are non-toxic (Adeoye and Cabral-Marques, 2017; Muankaew and Loftsson, 2018; Menezes et al., 2019). CDs applications are becoming very valuable in the prevention of viral infections of the mucosal membranes in the throat, mouth and nose (Garrido et al., 2020).

Sulfonated CDs have been reported to show antiviral activities against HIV, albeit, their activity was discovered to be virus specific and virustatic (Jones et al., 2020). The structure of CDs may be modified and applied in infection control or as virucidal agents (Braga, 2019). For example, methylated β-CD can inhibit some viruses, including coronavirus by sequestering the viral cholesterol or by removing it from the cell membranes of the host thereby deforming the viral envelope (Danthi and Chow, 2004; Pratelli and Colao, 2015; Palacios-Rápalo et al., 2021). Hydroxypropyl-β-CD has been applied as a vaccine adjuvant to provide immunity in the cynomolgus monkey model against H1N1 influenza virus (Carrouel et al., 2020).

The modified cyclodextrin (CD) with mercaptoundecane sulfonic acids has been reported to have promising antiviral activities. By inhibiting the outer membrane of a virus, this modified CD molecule can destroy virions simply by contact instead of inhibiting viral growth. And this antiviral mechanism appears to be similar technique used against all other viruses (Carrouel et al., 2020; Jones et al., 2020). These modified CDs are biocompatible with broad-spectrum activities even at micro-molar concentrations against a lot of viruses including respiratory syncytial virus (RSV), Zika virus, herpes simplex virus (HSV) and dengue virus in *vitro* assays. They are also effective against clinical and laboratory strains of HSV-2 and RSV in *ex vivo* vaginal and respiratory tissue culture models, respectively (Jones et al., 2020).

Application of CDs to mucous membrane of the oropharynx can help prevent infection and viral spread in the mouth, nose and throat. This can be potentially exploited in the reduction of SARS-CoV-2 load that may be transmitted via aerosols and droplets especially in this COVID-19 pandemic era. This will greatly reduce virus transmission and the chances of infecting HCWs and care givers by infected patients (Carrouel et al., 2020).

The combination of β-CD and citrox in one mouthwash solution has been demonstrated to produce efficacious effect against SARS-CoV-2. β-CD and citrox mouthwash (CDCM) were demonstrated to significantly reduced SARS-CoV-2 and sustained the low viral load by the seventh day (Carrouel et al., 2021; Carrouel et al., 2020) (Table 2). Therefore, this combination may really be beneficial in COVID-19 control and prevention.

2.4. Chlorhexidine and hydrogen peroxide

Chlorhexidine (CHX) is a known cationic bisbiguanide which is applied as a broad-spectrum antiseptic in general medical practice (Gilbert and Moore, 2005; Thangavelu et al., 2020). CHX has antiviral activities that are particularly potent against enveloped viruses (Huang and Huang, 2021; Elzein et al., 2021; Montefiori et al., 1990).

There seems to be a controversy in the recommendation/adoption of CHX as adequate mouthwash antiseptic against SARS-CoV-2 as some researchers have reported it to be ineffective against SARS-CoV-2 in both *in vitro* and *in vivo* clinical studies (Meister et al., 2020; Davies et al., 2021; Ferrer et al., 2021) (Tables 1 and 2). However, some other studies have demonstrated it to show adequate *in vivo* activities against SARS-CoV-2 (Yoon et al., 2020; Huang and Huang, 2021; Elzein et al., 2021) (Table 2). Further studies are therefore needed to authenticate both the *in vitro* and *in vivo* claims on CHX activities.

Hydrogen peroxide is a colourless chemical compound which is broadly used for its antimicrobial properties. The efficacy of H_2O_2 has been shown on some human viruses, of which influenza viruses and coronaviruses were the most sensitive (Dev Kumar et al., 2020; Gottsauner et al., 2020; Dembinski et al., 2014) (Table 1). H_2O_2 liberates oxygen-free radicals from the envelope of these viruses thereby disrupting the lipid membrane (Peng et al., 2020; O'Donnell et al., 2020). An important advantage of using H_2O_2 is that it is safe on the mucosal membranes whether used as mouth washes/rinse or as nasal sprays,

even when applied at 3% concentration for 6 months (Caruso et al., 2020).

Furthermore, the American Dental Association recommended the use of 1.5% H_2O_2 (or 0.2% PVP-1) as a preprocedural mouth rinse (PPMR) (American Dental Association (ADA) 2022), because of its efficacy against microbes. However, H_2O_2, just like CHX has got a number of controversial reports that cast doubts on its efficacy against SARS-CoV-2 in both *in vitro* (Meister et al., 2020; Davies et al., 2021) and *in* vivo (Ferrer et al., 2021) studies (Tables 1 and 2). This therefore may affect its adoption as a preferential antiseptic oral/nasal rinse in this COVID-19 pandemic.

3. Challenges associated with the use of mouth and throat washes

Perhaps, one of the biggest challenges of prolonged usage of some mouth/throat washes is the possibility of them affecting the oral/pharyngeal microbiota which might lead to dysbiosis (Carvalho et al., 2024; Brookes et al., 2023). The category of beneficial microorganisms disrupted ushers in the real consequent long-term effect of using such oral antiseptics. For example, the reduction/elimination of essential nitrate-reducing bacteria, such as some species of *Veillonella, Provotella, Haemophilus, Rothia, Actinomyces* and/or *Neisseria* from the oral cavity by mouth/throat washes, could lead to high blood pressure, obesity among other negative effects (Brookes et al., 2023; Bescos et al., 2020; Liu et al., 2023). This is because these nitrate-reducing bacteria are supposed to reduce the salivary nitrates in ingested food or from endogenous sources to give nitrite and nitric oxide which is essential in the modulation of cardiovascular vessels (Brookes et al., 2023; Bescos et al., 2020; Sitanaya et al., 2023). However, it is very important to state that several researches have either supported or negated this claim of dysbiosis which therefore requires further studies to substantiate (Brookes et al., 2023; Bescos et al., 2020; Fan et al., 2018; Brookes et al., 2021; Mitsui and Harasawa, 2017; Ren et al., 2023; Plummer et al., 2022). Ultimately, just like most other medications, the type and usage of mouth/throat washes should be based on medical prescriptions to avoid any possible side effects (Radzki et al., 2022).

Other challenges that might arise from the use of some types of antiseptic mouth and throat washes such as CHX, PVP-1, etc., include: malabsorption and increased risk of systemic diseases, change in saliva lactate and pH, diabetes mellitus, oral cancer and Alzheimer's disease (Carvalho et al., 2024; Bescos et al., 2020; Sitanaya et al., 2023; Brookes et al., 2021; Alrashdan et al., 2023). However, most of these side effects lack adequate scientific evidence at the moment.

4. Conclusion

So much emphases have been placed on vaccination and hand hygiene in this COVID-19 pandemic era. How about oral/nasal hygiene? The roles of oropharyngeal and nasopharyngeal mucosae in respiratory viral dissemination are critical in the control and management of the COVID-19 pandemic. Therefore, adopting and/or emphasising effective oral and other vital mucosal hygiene, through the use of antiseptics, might be an effective additional measure to reduce SARS-CoV-2 spread, especially among COVID-19 patients and their care givers. Reducing and/or eliminating these mucosal viral loads by the use of antiseptics practically decrease the chances of viral spread through aerosols and droplets which are essential channels of COVID-19 transmission.

CRediT authorship contribution statement

Kizito I. Okeke: Conceptualization, Writing – original draft. **Chukwuemeka Samson Ahamefule:** Writing – review & editing. **Obianuju O. Nnabuife:** Writing – review & editing. **Ibuchukwu N. Orabueze:** Writing – review & editing. **Christian U. Iroegbu:** Writing – review & editing. **Kingsley A. Egbe:** Writing – review & editing. **Anthony C. Ike:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Data availability

No data was used for the research described in the article.

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