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Review Article

Could antiseptic gargling prevent COVID-19?

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Abstract. Coronavirus Disease 2019 (COVID-19) has infected more than 8 million people globally since its discovery in December 2019. For COVID-19 prevention, the World Health Organization recommended regular handwashing with soap, cough etiquette, mask wearing and social distancing. However, COVID-19 is rather difficult to contain because of its high transmissibility property. Gargling is effective for reducing infection in the respiratory tract. Most antiseptic gargles have antimicrobial properties against common respiratory pathogens. No published study on the effectiveness of antiseptic gargling among COVID-19 patients has been available to date. This article reviewed available literature on methods and solutions available for gargling and their effect on respiratory tract infections.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was first recognised in Wuhan, China, in December 2019. Until now, the disease has infected more than 40 million people worldwide and has caused more than a million deaths (World Health Organisation (WHO), 2020b). The disease caused by the Coronavirus 2 Severe Acute Respiratory Syndrome (SARS-CoV-2) is transmitted either through close contact with infected people, or indirectly through contaminated surfaces. There are currently no approved medicinal products or disease vaccines available. To avoid COVID-19, the World Health Organization recommended daily hand washing with soap, cough etiquette, wearing a mask and social distancing (World Health Organisation (WHO), 2020a). However, COVID-19 is rather difficult to contain because of its high transmissibility property (Liu *et al.*, 2020). The pathogenesis begins when SARS-CoV-2 attacks nose, throat and eye mucus membranes. It is thought that the virus replicates in the nose and throat, as evidenced by the high viral load at the early stage of infection in these areas (Wölfel *et al.*, 2020). Given the pathogenesis of the disease, gargling with an antiseptic that has virucidal activity against SARS-CoV-2 could aid in the treatment and prevention of COVID-19.

This article reviewed *in vitro* and *in vivo* studies with regard to gargling practices concerning respiratory tract infections, antimicrobial effects and mechanism of actions of antiseptic gargles.

GARGLING AND RESPIRATORY INFECTIONS

Gargling is an act of using liquid gargle or plain water to wash one's mouth and throat area. Technically, gargling loosens the mucus and rinses irritants in the mouth, oropharynx and nasopharynx, such as allergens and pathogens. Gargling was also hypothesized

to be able to remove oral/pharyngeal protease that helps viral replication (Kitamura *et al.*, 2007).

Water

A randomised controlled trial in community healthcare settings studied the effect of gargling with plain water for 15 seconds, three times per day for 60 days. The result showed that simple water gargling significantly reduced the incidence rate of upper respiratory tract infections (URTI) by 36%. This result was explained by two possibilities: whirling water wash out pathogens from the pharynx, and oral cavity and the presence of high chlorine in the tap water might deactivate viruses (Satomura *et al.*, 2005). Satomura 's study was opposed by another study evaluating the efficacy of gargling versus non-gargling in preventing viral URTI among university students. Participants had to gargle twice daily for 30 seconds, with roughly 30mL of tap water. Considering that the result showed that water gargling did not reduce the risk of URTI, gargling was advised to be done more often to achieve the beneficial effect (Goodall *et al.*, 2014).

Povidone-iodine

A study reported a 24 per cent reduction in the cumulative incidence of URTI and influenza among school children when gargling with diluted 7 per cent povidone-iodine (PVP-I) three times daily (Kitamura *et al.*, 2007). Besides, four times a day gargling with povidone-iodine decreased by about 50% of infections with *Pseudomonas aeruginosa*, *S. aureus* including MRSA, and *Haemophilus influenzae* among adults with chronic respiratory illnesses (Nagatake *et al.*, 2002).

PVP-I-containing gargle and throat spray demonstrated rapid virucidal activity against highly pathogenic and low pathogenic avian influenza A (Ito *et al.*, 2006). In a more recent study, after 15 seconds of treatment, 0.23 per cent of PVP-I gargle / mouthwash was found to be effective against *Klebsiella pneumoniae* and *Streptococcus pneumoniae* and rapidly inactivated SARS-CoV, MERS-CoV, influenza A (H1N1) and rotavirus (Eggers *et al.*, 2018).

Mechanisms of action of povidone-iodine

Hydrogen iodide, elemental iodine, and synthetic polymer polyvinylpyrrolidone (PVP) make up the povidone-iodine complex. PVP transports non-PVP-bound' free' iodine to enter the membranes of the cells. Free iodine mediates the oxidation of amino acids and nucleic acids in biological structures, causing metabolic disruption, destabilization of cell membranes that eventually lead to irreversible pathogen damage. PVP-I also inhibits the release of pathogenic factors such as endotoxins, exotoxins and harmful enzymes with direct bacterial killing (Kanagalingam *et al.*, 2015). In addition, iodine elicits anti-inflammatory properties which scavenge free species of radical oxygen (Nada *et al.*, 2018).

Chlorhexidine

Chlorhexidine is widely available in many forms such as sprays, gel, toothpaste and mouthwash at 0.12% and 0.2% concentrations. It is prescribed to patients as an antiplaque agent, anti-gingivitis, oral irrigations and oropharyngeal decontamination (Karpiński & Szkaradkiewicz, 2015). Chlorhexidine mouthwash is commonly used in the intensive care setting and has been shown to reduce the incidence of nosocomial pneumonia and ventilator-associated pneumonia (Tantipong *et al.*, 2008). A study in 1990 showed that chlorhexidine mouth rinse had a virucidal effect against herpes simplex virus, cytomegalovirus, influenza A, parainfluenza and hepatitis B virus (Bernstein *et al.*, 1990).

Mechanisms of action of Chlorhexidine

Chlorhexidine consists of two bisguaniade groups and two symmetric 4-chlorophenyl rings which connected by a hexamethylene chain. This cationic molecule could affect bacterial inner cell membrane, causes permeability and leakage of potassium ions on the cell membrane (Mathur *et al.*, 2011). The synergistic effect can be achieved by combining chlorhexidine with fluoride, thymol or calcium hydroxide (Sohi *et al.*, 2012).

Hydrogen Peroxide

Hydrogen peroxide is a high-level disinfectant that can also be used oral antiseptic at a concentration of 1.5%. Hydrogen peroxide mouthwash was found more effective than normal saline in the prevention of ventilator-associated pneumonia (Nobahar *et al.*, 2016). An analysis by Kampf *et al.* revealed that human coronaviruses such as Severe Acute Respiratory Syndrome (SARS) coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus and endemic human coronavirus (hCoV) were efficiently inactivated by 0.5% hydrogen peroxide (Kampf *et al.*, 2020).

Mechanism of hydrogen peroxide

Hydrogen peroxide is an oxidative biocide capable of oxidizing susceptible chemical group and become themselves reduced in the process (Finnegan *et al.*, 2010). The high biocidal concentration causes massive damage to the cells and apoptosis (Eryilmaz *et al.*, 2016).

Essential Oils

Essential oils mouthwash and gargle are quite popular and easily available in the market. A study showed that exposure to widely used essential oil formula, i.e. Listerine® for 30 seconds had an antiviral effect against herpes simplex type-1 and type-2 (96.3% and 100% reduction in infectious virus, respectively) and influenza A (100% reduction) (Dennison *et al.*, 1995). Thymol oil showed antibacterial activity against methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Ács *et al.*, 2016).

Mechanism of Actions of Essential Oils

Essential oils refer to over the counter mouthwash that contains four types of essential oils, namely thymol, eucalyptol, methyl salicylate and menthol. Thymol and eucalyptol are associated with phenol which destroys plasma membrane and denatures protein. Essential oils have been shown to penetrate dental plaque biofilm, and destroying pathogens even in interproximal spaces (Stoeken *et al.*, 2007).

Green Tea

A study reported that gargling with green tea reduce the incidence of influenza among elderly in the nursing home (Yamada *et al.*, 2006). In contrast; another study found no significant effects of gargling with tea catechin on prevention of influenza in healthy adult (Yamada *et al.*, 2007). The result was also similar to a study among school-aged children that found no significant difference between gargling with water and green tea (Ide *et al.*, 2014).

Mechanism of Actions of Green tea

Green tea contains 4000 bioactive components and a third of these are polyphenols. One of the important polyphenols is catechins. The catechins in green tea could reduce infections by binding to the bacterial lipid bilayer cell membrane. This binding inhibits and damages the cell membrane, as well as inhibits enzymes such as protein tyrosine kinase, cysteine proteinases, DNA gyrase, and ATP synth (Reygaert, 2014).

CONCLUSIONS

Given the disease progression of COVID-19, the positive effects of gargling, and the absence of specific treatment, prophylactic gargling to reduce SARS-C0V-2 viral load in the throat is worth considering. Povidone-iodine is a suitable component for the mouthwash due to the *in vitro* and *in vivo* evidences. Meanwhile, hydrogen peroxide, essential oils, chlorhexidine, green tea and tap water require more evidence to support their use during this pandemic. Randomised clinical trials and virucidal studies should be done to ascertain the effectiveness of gargling in the management of COVID-19.

Author Contributions

Azimah Zainol Hady and Nurul Azmawati Mohamed did the literature search and wrote the first draft of the manuscript, Azrul Hafiz Abdul Aziz made the amendment and added more literatures, Ilina Isahak gave ideas, and proofread the draft.

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