European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 05, 2023

Mouthwashes as Adjuvant in the Treatment of COVID 19 Patients: Review of Literature and Updates

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ABSTRACT

Background: COVID-19 has wreaked havoc on the world, causing millions of deaths and even more permanent health issues. Studies have examined various adjuvant treatments for this virus, with existing literature indicating that the use of mouthwashes and oral rinses can reduce viral load as well as improve clinical symptoms. However, there are many different types of mouthwash products available, with both *in vivo* and *in vitro* studies having been conducted. The aim of this review of the literature is to examine the use of various mouthwashes as an adjuvant treatment against the COVID-19 virus.

Method: A database search of CINAHL, PubMed, Embase, and Web of Science databases was conducted using certain keywords and phrases, along with Boolean operators. The results were limited to those published between 2020 and 2023.

Results: A total of 16 articles were identified which examined five primary molecules in mouthwashes: hydrogen peroxide, povidone-iodine, chlorhexidine, chlorine dioxide, and phthalocyanine derivate.

Conclusion: There is good evidence to support the use of povidone-iodine, chlorhexidine, and phthalocyanine derivate as adjuvant treatments for COVID-19.

Keywords: COVID-19, SARS- CoV- 2, adjuvant treatment, mouthwashes, rinses

Introduction

COVID-19 is the 2019 novel coronavirus, also known as severe acute respiratory syndrome coronavirus- 2 (SARS- CoV- 2), is the fifth documented pandemic in the world [1]. The first symptoms were observed in Wuhan, China on December 1, 2019, with patients experiencing fever, dry cough, malaise, and dyspnea [1]. Whole-genome sequencing eventually determined that the causative agent was the novel coronavirus [1]. Since it was first discovered, the COVID-19 virus has rapidly spread to other countries throughout the world, with the World Health Organization declaring a pandemic on March 11, 2020 [1]. It has caused millions of deaths, leading to significant challenges in terms of not only health care, but also the economy [2].

While COVID-19 predominantly impacts the lungs, infecting people through their inhalation of aerosol particulates in the air, research has clearly shown that the oral cavity also represents a vital entry point for this virus [2]. In fact, the corona virus is able to invade the oral mucosa and salivary gland epithelium, as these sites contain an elevated expression of angiotensin converting enzyme 2 (ACE2) receptors [2]. This ultimately causes a higher viral load to exist in the oral cavity [2]. COVID-19's pathogenesis depends upon the virus's membrane having a 'spike protein' or S protein, as it interacts with the ACE2 receptors [2]. These receptors are distributed throughout the oral cavity, enabling the virus to infect people via this route [2]. For example, the mouth, salivary glands, and tongue all contain non-keratinized mucosa, expressing SARS-CoV-2 entry and variables of transmission [2, 3]. Cellular transmembrane serine protease 2 (TMPRSS2) helps to prime the virus S protein, which suggests that the oral tissues represent a reservoir for the SARS- CoV- 2 virus [2, 3]. Therefore, when people are infected with this virus, they can easily infect others not only through sneezing and coughing, but also just talking and breathing [2].

Due to the rapid spread of COVID-19, not to mention its subsequent associated morbidity and mortality rates, researchers have been examining other forms of preventing the transmission of this virus. Specifically, the use of mouthwashes as an adjuvant in treating COVID-19 represents a novel approach that has shown much promise. Mouthwashes have been applied both in the routine treatment of this infection as well as for prophylactic purposes, as they can potentially reduce viral load within the oral mucosa [3]. In doing so, not only can mouthwashes help to fight against COVID-19, but also prevent its spread to other people. There have been many *in vivo* studies, both randomized and non-randomized, investigating this adjuvant treatment, with various antiviral molecules in mouthwashes examined [3, 4]. These have included hydrogen peroxide, povidone-iodine, chlorhexidine, chlorine dioxide, and phthalocyanine derivate, as these molecules can potentially combat the COVID-19 virus [3, 4].

Therefore, this review of literature examines the most recent studies and articles published that have investigated the use of these mouthwashes as adjuvant treatment in COVID-19. It presents evidence from *in vivo* and *in vitro* studies on different types of antiviral molecules, exploring which of these molecules – and thus, mouthwashes – are effective in fighting against this virus.

Aims and objectives of the study: To examine the use of various mouthwashes as an adjuvant treatment against the COVID-19 virus.

Materials and Methods

A review of the literature was conducted, searching various nursing and medical databases such as CINAHL, PubMed, Embase, and Web of Science. Keywords and phrases were

used in this search, including "COVID-19" OR "SARS- CoV- 2" OR "coronavirus" AND "adjuvant treatment" OR "adjunct treatment" AND "mouthwash" OR "mouth rinse" OR "gargle" OR "mouth spray" using appropriate Boolean operators. To specifically search for the five identified compounds, other keywords were employed, such as "hydrogen peroxide", "povidone-iodine," "chlorhexidine," "chlorine dioxide," and "phthalocyanine derivate." The search was limited to only articles published since 2020 when the COVID-19 pandemic first arose, while all articles were written in the English language. The focus was on both *in vivo* and *in vitro* studies on the use of mouthwash as an adjuvant treatment for this virus.

Results and Discussion

A total of 16 articles were identified during the literature search. There were five primary molecules in mouthwashes that were focused on in this review of literature: hydrogen peroxide, povidone-iodine, chlorhexidine, chlorine dioxide, and phthalocyanine derivate.

Hydrogen Peroxide:

In the study by Gottsauner et al. (2020), the researchers conducted a prospective clinical pilot study, examining how 1% hydrogen peroxide mouth rinse affected COVID-19's intraoral viral load [5]. There were 12 participants who tested positive for COVID-19 included in the study [5]. The participants were told to gargle with 20 mL of 1% hydrogen peroxide for 30 seconds, with intraoral viral load measured both before and 30 minutes after gargling [5]. A virus culture was also conducted, looking for any specimens that had a viral load of 103 RNA copies/mL or higher at baseline [5]. The results of this study showed that hydrogen peroxide mouth rinse did not significantly decrease intraoral viral load [5]. Additionally, the virus culture did not show any evidence on infectivity in the detected RNA copies observed [5].

Similarly, the study by Capetti et al. (2020) did find that hydrogen peroxide was able to suppress COVID-19's viral shedding, although only for a limited amount of time [6]. In their study, they enrolled eight patients who were carriers of the virus, having them use hydrogen peroxide as a mouthwash [6]. Swabs were conducted both before and after they used the mouthwash, with the researchers continuing to swab their mouths until either the virus reappeared or 14 days passed, as this was the period of incubation [6]. The results showed that 111 days was the median time from exposure or onset of symptoms [6]. Three of the participants relapsed, while one had to be excluded due to a negative baseline swab [6]. However, two of the participants did suppress the virus for the full 14 days, while four participants were able to suppress the virus for three days and one participant suppressed it for two days [6]. Unfortunately, all of the participants did rebound [6]. This indicates that using this type of mouthwash can help to reduce circulating viral burden, at least temporarily [6].

On the other hand, in the article by da Mota Santana et al. (2020), the authors mention that using even a 0.5% hydrogen peroxide spray may be an effective alternative for controlling COVID-19 [7]. They cite several studies where hydrogen peroxide's oxidative properties against COVID-19 were supported [8, 9]. Specifically, in the article by Ortega et al. (2020), the researchers examined the existing evidence on the use of 0.5% hydrogen peroxide, specifically the virus's susceptibility to this disinfectant [9]. Unfortunately, there were no available studies on

this specific dosage of hydrogen peroxide [9]. Additionally, due to the potential corrosiveness of hydrogen peroxide, it is recommended that it not be used routinely as a mouthwash, but rather in dental care only to help reduce transmission risk, as it can reduce the rate of viral replication [7].

Povidone-iodine:

The study by Martínez Lamas et al. (2022) examined the use of povidone iodine mouthwash, investigating if it is effective against COVID-19 [10]. Four patients who tested positive for COVID-19 were included in the study [10]. All patients underwent both baseline saliva sampling and nasopharyngeal swabs, after which they were told to rinse with 15 ml of 1% povidone iodine for one minute [10]. The researchers then took serial saliva samples at various time intervals after they rinsed, including five minutes, one hour, two hours, and three hours [10]. While the saliva samples showed all four participants had the virus, the nasopharyngeal exudate found that two of them were actually negative [10]. Interestingly, it was one of these patients who tested negative that showed a reduced viral load after rinsing with povidone iodine, although one of the patients who did have COVID-19 also demonstrated this finding [10]. Nonetheless, with the small sample size, this study is not able to conclusively lend evidence in support of this particular mouthwash as an adjuvant treatment for COVID-19 [10]. In fact, the authors state that povidone iodine should only be used in patients who are symptomatic during the first week after symptoms begin, as this is when the saliva has the highest viral charges [10].

Another study by Pelletier et al. (2021) examined both oral and nasal antiseptic formulations of povidone iodine (1% to 5%), investigating its virucidal activity against COVID-19 [11]. The researchers utilized a control group, with some participants receiving the oral rinse formulation, others receiving the nasal formulation, and still others acting as a control – where they did not use either product [11]. Virucidal assays were performed to determine the compounds' ability to inactivate COVID-19 after 60 seconds of exposure [11]. The findings of this study showed that both oral rinse and nasal antiseptics were able to inactivate the virus, suggesting that these compounds are effective as an adjuvant treatment [11].

Similarly, Anderson et al. (2020) also investigated the *in vitro* virucidal activity of povidone-iodine products, both oral and topical, against COVID-19 [12]. Specifically, four different products were tested: 1) gargle and mouth wash, 2) throat spray, 3) antiseptic solution, and 4) skin cleanser [12]. Again, suspension assays were used to detect virucidal activity, with exposure time for only 30 seconds [12]. All four products were able to achieve 99.99% or more virucidal activity against this virus, providing evidence of povidone-iodine's effectiveness as an adjuvant treatment [12]. Frank et al. (2020) conducted a controlled *in vitro* laboratory research study on the use of povidone-iodine nasal formulation as a method for inactivating COVID-19, finding that as little as 15 seconds of exposure are needed, with doses as low as 0.5% showing efficacy [13]. Guenezan et al. (2021) performed a randomized clinical trial on this compound's ability to decrease COVID-19 viral loads, specifically with the use of a nasopharyngeal formulation [14]. Again, the findings corroborate the previous studies mentioned, showing that povidone iodine has high efficacy as a potential adjuvant treatment against this virus [14].

Chlorhexidine:

Chlorhexidine has also been studied as a potential mouthwash to reduce the viral load of COVID-19. In the study by Yoon et al. (2020), the researchers observed two patients who had contracted this virus and were hospitalized, taking body fluid specimens through both oropharyngeal and nasopharyngeal swabs as well as sputum, saliva, and urine [15]. They were then administered 0.12% chlorhexidine mouthwash, after which saliva samples were again taken at one hour, two hours, and four hours after [15]. The virus was detected in both patients' five specimens, with the nasopharynx swab showing the highest viral load, with saliva being the next highest [15]. However, after the patients used the chlorhexidine mouthwash, there was a notable decrease in viral load for two hours after, suggesting short-term benefits [15].

Huang and Huang (2021) also studied the use of chlorhexidine oral rinse and posterior oropharyngeal spray in patients with COVID-19 who were hospitalized [16]. They used a randomized, prospective cohort study, with the primary outcome measured being either the presence or absence of the virus in the oral and oropharyngeal cavities after four days of treatment [16]. The participants were randomly assigned to either an intervention group using chlorhexidine along with standard care or a control group with only standard care [15]. Additionally, the chlorhexidine group was further divided into those participants who used only the oral rinse and those who used both the oral rinse and oropharyngeal spray [16]. The results showed that in 62.1% of participants who used chlorhexidine mouth rinse, COVID-19 was eradicated from the oropharynx, which was statistically significant compared to only 5% in the control group [16]. Additionally, 86.0% of participants who combined chlorhexidine oral rinse with oropharyngeal spray showed the virus was eliminated, compared to only 6.3% of those participants in the control group [16].

Chlorine Dioxide:

Another study by Avhad et al. (2020) examined chlorhexidine mouthwash as an adjuvant treatment for COVID-19, although the researchers used a higher dose of 0.2% [17]. They also compared this product against 0.1% chlorine dioxide for reducing viral loads [17]. There was a total of 40 participants with COVID-19 who were randomly assigned to either a 0.2% chlorhexidine gluconate mouthwash group or a 0.1% chlorine dioxide mouthwash group [17]. Each group was asked to rinse and gargle three times a day for a week [17]. The findings of the study showed that symptoms such as sore throat and cough improved for both groups, although the group receiving chlorine dioxide mouthwash had lower viral loads [17]. Therefore, the researchers concluded that regularly using chlorine dioxide as a mouthwash is effective in decreasing both oral viral load and symptoms associated with COVID-19, helping to not only treat this virus, but also reduce transmission risk [17].

When considering the use of chlorine dioxide mouthwash and oral rinses alone in reducing COVID-19's viral load, Travis et al. (2022) conducted an *in vivo* test to examine this product's antiviral activity [18]. Chlorine dioxide oral rinse was preincubated with this virus, after which it was transduced to human embryonic kidney epithelial (HEK293T- ACE2) cells, as they express ACE- 2 receptors [18]. Luciferase activity was used to measure viral entry, while cell-to- cell fusion assay was performed as well [18]. Dosage- dependent cytotoxic effects of the

chlorine dioxide oral rinse were evaluated at two different time points, with the findings showing that there was an antiviral effect against COVID-19 cell entry [18]. Therefore, the researchers concluded that this oral rinse can be potentially effective for decreasing viral infectivity in those diagnosed with this infection [18].

Phthalocyanine derivate:

In the article by da Fonseca Orcina et al. (2021), the researchers examined the use of phthalocyanine derivate as a potential compound to reduce the viral load of COVID-19 [19]. The article reported a case series of eight patients who had this infection and gargled and rinsed with 5mL of phthalocyanine derivate mouthwash [19]. The study was over a 14-day period, with the participants asked to gargle and rinse with this product five times a day for one minute each time [19]. Clinical symptoms were measured using both the Visual Analogue Scale for Pain (VAS) to determine sore throat pain as well as the Performance Status (PS) to ascertain clinical conditions [19]. The researchers found that all patients had statistically significant decreases in clinical symptoms, suggesting that phthalocyanine derivate mouthwash may be an adjuvant treatment for COVID-19 [19].

In the study by da Silva Santos et al. (2021), a research group examined the use of an anionic phthalocyanine derivative in mouthwash as a protocol to improve patients' clinical condition when infected with COVID-19 [20]. In a two-arm *in vitro* study, phthalocyanine derivative's antiviral activity and cytotoxicity were investigated, while a triple-blind randomized controlled trial was also undertaken [20]. This controlled trial included 41 patients who had this virus and were also in the hospital, with 20 randomly assigned to an experimental group where they received the phthalocyanine derivative mouthwash [20]. The remaining 21 participants were in the control group, where they were given an inactive mouthwash to use as a placebo [20]. Both groups were told to gargle and rinse with the mouthwash five times daily for at least one minute [20]. Measures included length of hospital stay and symptom duration, with the findings showing that the phthalocyanine derivative mouthwash was effective in reducing the viral load, while it also did not have any cytotoxicity effects [20]. Furthermore, the group receiving this mouthwash also had a much shorter hospital length of stay, with a median reduction of four days in comparison to the control group [20]. Therefore, the researchers concluded that phthalocyanine derivative mouthwash can be used as an adjuvant treatment for hospitalized patients with COVID-19 [20].

Conclusion

When examining the results from this review of literature and the 16 articles analyzed, there is definitive evidence in support of the use of certain mouthwashes in reducing the viral load of COVID-19, which can subsequently help to prevent the virus's spread. Unfortunately, studies have found that hydrogen peroxide is not an effective agent against this virus, at least as a long-term adjuvant treatment approach. While some articles did show that its use as a mouthwash was able to temporarily reduce viral loads, the effects did not last long. Similarly, there is not enough evidence, especially *in vitro* studies, to support the use of chlorine dioxide mouthwash and oral rinses. While *in vivo* studies indicate that chlorine dioxide may be effective

in reducing the viral load of this infection, there is a noticeable lack of human research on its effects, including its potential toxicity. Therefore, neither hydrogen peroxide or chlorine dioxide can reasonably be recommended as adjuvant treatments for COVID-19, based on the findings from this review of existing literature.

However, this literature review did find several mouthwash products that were effective in reducing viral load for COVID-19. For example, the studies examined in this review all indicated the positive effects of povidone iodine mouthwash. However, one of the articles recommended that it be used only during the first week after symptoms present, as this is when the greatest viral loads can be found in saliva. Additionally, different dosages may have different effects, although most of the studies agreed that a dosage of povidone iodine between 1% to 5% seemed to prove most effective. Another product to show great potential as an adjuvant treatment for this infection is chlorhexidine. The articles showed that both the oral rinse and oropharyngeal spray can significantly reduce viral load when compared to control groups, presenting evidence to support the use of chlorhexidine against COVID-19. Finally, studies do indicate that an anionic phthalocyanine derivative can be applied as a mouthwash in patients testing positive for COVID-19, as it effectively reduces not only the duration of symptoms, but also the length of hospital stay.

Therefore, based on the results of this review of existing literature, there are three potential adjuvant mouthwash and rinse treatments that can be used for treating COVID-19: povidone iodine, chlorhexidine, and phthalocyanine derivatives. However, more research, both *in vivo* and *in vitro*, is recommended, particularly with human participants, examining both clinical symptom improvement as well as viral load. Nonetheless, updated research does clearly show the positive effects of these three mouthwash products, representing adjuvant treatments for this potentially deadly infection.

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