REVIEW ARTICLE

In Vivo Efficacy of Povidone-iodine Mouth Gargles in Reducing Salivary Viral Load in COVID-19 Patients: A Systematic Review

TS Vinodhini Sudhakar[1], Sudhakar Venkatachalapathy[2], Balaguhan Balasubramanian[3], Kirthika Natarajan[4], Mathan M Aiyathurai[5]

Abstract

Aim and objective: Based on the published research, this article aims to systematically review the *in vivo* effectiveness of povidone-iodine (PVP-I) mouth gargles in reducing salivary viral load in COVID-19 patients.

Materials and methods: The inhibitory potential of different variables such as PVP-I, chlorhexidine gluconate (CHX), cetylpyridinium chloride (CPC), saline, and hydrogen peroxide (H_2O_2) were tested against SARS-CoV-2 in recent clinical trials. In this systematic review, appropriate randomized controlled trials (RCTs) for the evidence-based question: "what is the efficacy of PVP-I mouth gargle in reducing salivary viral load in COVID-19 patients?" were searched in Medline/PubMed, Scopus, Science Direct, Embase, Google Scholar, and the Cochrane Library database from January 15, 2020, to June 15, 2021, based on defined inclusion and exclusion criteria. From the selected articles, their references and reviews relevant to our topic were also looked for any missed studies.

Results: After a pertinent search for appropriate studies, five *in vivo* RCTs were selected and others were excluded. All the trials used reverse transcription-polymerase chain reaction (RT-PCR) for mRNA detection and quantitation. Povidone-iodine mouth gargle (0.5–1%) used by COVID-19 patients 4th hourly effectively reduced salivary SARS-CoV-2 viral load, thereby reducing the carriage of infectious virion in adults. Statistically significant increase in Ct values, post 5, 15, and 45 minutes, 3 and 6 hours post-rinsing demonstrated the strong antiviral effect of PVP-I.

Conclusion: In this COVID-19 pandemic, based on the published evidence of a few *in vivo* RCTs, it can be concluded that 0.5 to 1% PVP-I mouth gargle has the potency to effectively reduce the salivary SARS-CoV-2 viral load. To reinforce the use of PVP-I mouth gargles against SARS-CoV-2, this systematic review emphasizes the necessity for future research that is highly focused, robust, and has consistent techniques and a large sample size.

Clinical significance: Research on the efficacy of PVP-I mouth gargle should be framed to focus on the most effective minimal concentration, exposure time, and volume of mouth gargle as well as the SARS-CoV-2 strain. The effect of PVP-I mouth gargles on viral infectivity and their cytotoxic effect on epithelial cells were not distinguished in the studies reviewed. Hence, viral cell culture technique should be employed to establish the potential virucidal activity of PVP-I against SARS-CoV-2. Host immunity against SARS-CoV-2 should also be considered in assessing the effectiveness of mouth gargles.

Keywords: COVID-19, Mouth Gargle, Povidone-iodine, SARS-CoV-2, Treatment.

World Journal of Dentistry (2021): 10.5005/jp-journals-10015-1868

Introduction

COVID-19 disease caused by SARS-CoV-2 is creating severe community and nosocomial outbreaks globally. The highly contagious nature and easy transmissibility of this Virion have made COVID-19 pandemic, alarmingly increasing the number of infections and death every day. The 2019 novel corona virus (SARS-CoV-2) is phylogenetically related to Bat SARS-like coronaviruses and belongs to the Betacoronavirus genus lineage B.[1,2] However, the spike proteins ORF8 and ORF3b differ significantly from other known SARS-like coronaviruses, which may confer differences in pathogenicity and transmissibility from SARS-CoV.[3]

The receptor-binding protein (RBP) domain of S-protein (SARS-CoV-2) supports strong interaction with human ACE2 molecules,[4] thus ACE2 plays a pivotal role in the cellular entry of this virus.[5] High ACE2 expressing cells in the human body, such as type II alveolar cells of lung,[5,6] absorptive enterocytes from ileum and colon,[7] goblet and ciliated epithelial cells of nasal mucosa,[8] epithelial cells of tongue (oral mucosa),[9] cholangiocytes,[10] myocardial cells, kidney proximal tubule cells, bladder urothelial cells,[5] and their organs are potential target site for SARS-CoV-2 and are at high risk of infection and injury.

[1]Department of Oral Medicine and Radiology, Karpaga Vinayaga Institute of Dental Sciences, Chengalpattu, Tamil Nadu, India

[2]Department of Orthodontics and Dentofacial Orthopedics, Adhiparashakthi Dental College and Hospital, Melmaruvathur, Chengalpattu, Tamil Nadu, India

[3,5]Department of Oral and Maxillofacial Surgery, Karpaga Vinayaga Institute of Dental Sciences, Chengalpattu, Tamil Nadu, India

[4]Department of Conservative Dentistry and Endodontics, Karpaga Vinayaga Institute of Dental Sciences, Chengalpattu, Tamil Nadu, India

Corresponding Author: TS Vinodhini Sudhakar, Department of Oral Medicine and Radiology, Karpaga Vinayaga Institute of Dental Sciences, Chinna Kolambakkam, Palayanoor, Madurantakam, Chengalpattu, Tamil Nadu, India, Phone: +91 9941760017, e-mail: vinodhinisudhakar@gmail.com

How to cite this article: Vinodhini Sudhakar TS, Venkatachalapathy S, Balasubramanian B, *et al*. *In Vivo* Efficacy of Povidone-iodine Mouth Gargles in Reducing Salivary Viral Load in COVID-19 Patients: A Systematic Review. World J Dent 2021;12(6):504–509.

Source of support: Nil

Conflict of interest: None

SARS-CoV-2 is transmitted via droplets and fomites during close unprotected contact between an infector and infectee.[11] Large salivary droplets with a diameter of >60 µm tend to settle fast, restricting transmission to individuals who are close to the source. Smaller droplets (diameter <60 µm), which evaporate, create droplet nuclei with a diameter <10 µm, have the potential to transmit aerosols over long distances.[12] Even before clinical symptoms appear, presymptomatic and asymptomatic carriers shed viral particles, making them more infectious. This could be due to the presence of ACE2 cellular receptors in tongue (oral mucosa)[9] epithelial cells with which the virus would bind to and begin multiplying at an uncontrollable rate before symptoms appear. These findings raise concerns that those who are in contact with unknown asymptomatic carriers may be at potential risk of contracting the disease. Reducing salivary viral titers could be a game-changer in terms of COVID-19 transmission control.

Effective measures should be implemented to reduce viral shedding. This can be achieved by following strict oral hygiene protocols that effectively reduce salivary viral load. Povidone-iodine (PVP-I) is a broad-spectrum antibiotic that has been used for over 60 years in infection control and prevention.[13] Povidone-iodine is effective against gram-positive, gram-negative, and some spore-forming bacteria (*Clostridia*, *Bacillus* spp), Mycobacteria, and a wide range of enveloped and non-enveloped viruses.[14–16]

While using a PVP-I mouth gargle, non-PVP-bound ("free") iodine is released into the solution.[17] The basic mechanism of action (oxidation of amino acids and nucleic acids in biological structures) is mediated by free iodine, which is impossible to counteract. Iodine exposure primarily degenerates coronavirus nucleoproteins, disrupts the surface protein, and destabilize structural cellular components, resulting in irreversible virus damage.[18]

Povidone-iodine can be safely administered in the oral cavity for up to 6 months.[19] An *in vivo* study confirmed that prolonged use of 1–1.25% PVP-I gargle did not irritate mucosa or result in any adverse effect up to 28 months. Povidone-iodine gargle did not stain teeth or cause a change in gustatory function.[20] However, in patients with hyperthyroidism, thyroid disease, pregnancy, or lactation, PVP-I should be avoided. Povidone-iodine allergy is likewise extremely uncommon, with an incidence rate of 0.4%.[17]

This systematic review aimed to check the efficacy of PVP-I mouth gargle in reducing salivary viral load as a primary outcome and to recommend an Adjunctive Clinical and Household Practice Guideline (ACHPG) that can be easily implemented with current preventive and control measures as a secondary outcome, based on the antiviral activity of PVP-I mouth gargle.

Materials and Methods

Protocol and Criteria for Eligibility

The protocol for this systematic review was designed using PICOS with an evidence-based question: "what is the efficacy of PVP-I mouth gargle in reducing salivary viral load in COVID-19 patients?" Only human-controlled *in vivo* randomized controlled trials (RCTs) published in English were considered in the review. *In vitro* studies, case series, literature reviews, and expert comments were excluded.

Search Strategy and Study Selection

The terms "COVID-19", "Mouth Gargle", "Povidone Iodine", "Randomized Controlled Trial", "SARS-CoV-2", and "Treatment" were used to search Medline/PubMed, Scopus, Science Direct, Embase, Google Scholar, and the Cochrane Library database for appropriate published studies in English from January 15, 2020, to June 15, 2021, based on defined inclusion and exclusion criteria.

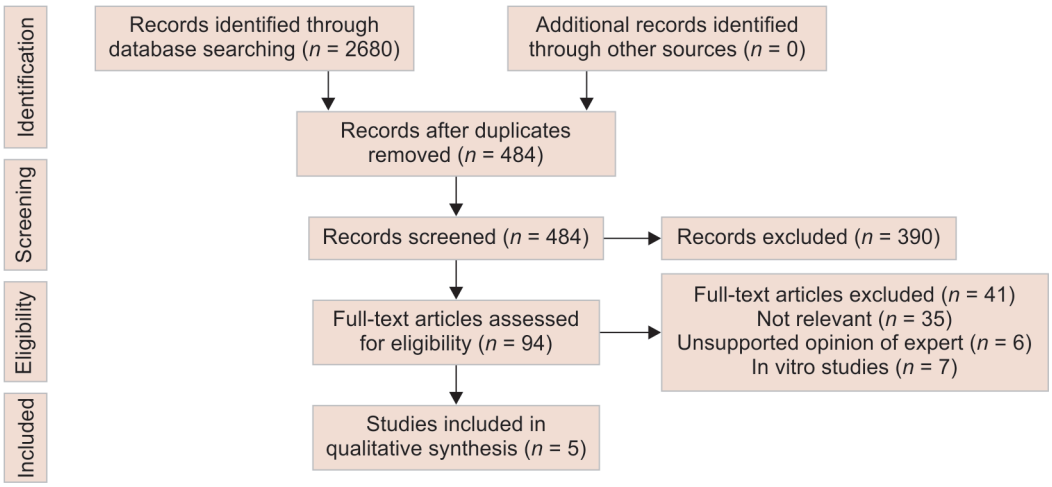
The systematic review was written using the PRISMA guidelines and recommendations after a systematic search for published articles (Flowchart 1). Reference list was checked manually. Papers that were pertinent to the study were found, and the list of references was reviewed for further appropriate publications. Clinical trials, cohort studies, and cross-sectional studies were selected for review and analysis. Case reports and duplicate publications were discarded.

The first searches yielded 2,680 papers. After two examiners (TS and VS) checked the titles and abstracts separately, 6 abstracts and 94 documents were recovered in complete form, with 5 being accepted for this report.

Data Management

Two authors (KN and BB) independently extracted the available data from the included studies using established data extraction forms. With the help of the third author, any conflicts were discussed and resolved (MA).

Flowchart 1: PRISMA flowchart showing the study selection process



Results

Study Selection

The initial electronic search yielded a total of 2,680 articles. After reading the titles and abstracts of these studies, 94 articles were selected. Only five articles remained after the removal of duplicates. No additional articles were found after the manual search in the references of those studies. In this systematic review, all five articles that met the inclusion criteria were analyzed. The search process is illustrated in the flowchart (Flowchart 1).

Study Characteristics

The characteristics of each included study are summarized in Table 1. The selected articles were published between 2020 and 2021 in medical and dental journals. Only RCTs were selected for the review. The sample sizes of the studies were quite variable. In all the trials, patients with known allergies to the variables (PVP-I, CHX, CPC, H_2O_2) were excluded from the study. Similarly, all forms of thyroid disease, radioactive iodine treatment, lithium therapy, known pregnancy malignancy, and renal failure were considered as exclusion criteria. The study group patients were confirmed COVID-19 positive by RT-PCR of a nasopharyngeal swab. The interval between detection and enrollment in the trial ranged from 0 to 2 days. In all the studies, salivary samples were subjected to SARS-CoV-2 RT-PCR assay.

Characteristics of the Interventions and Comparison

The effectiveness of PVP-I mouth gargle in lowering salivary SARS-CoV-2 virus load was assessed in all of the included studies. Seneviratne et al.[21] and Chaudhary et al.,[25] used 0.5% PVP-I mouth gargle and salivary samples were collected at baseline, 5 minutes, 3 hours, 6 hours, and at baseline, 15 minutes, 45 minutes after gargling, respectively. Elzein et al.[24] tested efficacy of 1% PVP-I by collecting salivary samples at baseline and 5 minutes after gargling. Choudhury et al.[22] used 1% PVP-I fourth hourly and collected samples at baseline, 3rd, 5th, and 7th day, whereas Guenezan et al.[23] used 1% PVP-I four times a day for 5 days, and samples were collected at baseline, first, 3rd, 5th, and 7th day and analyzed.

Except for Chaudhary et al.,[25] who used normal saline as a control, all of the research employed sterile/lukewarm/distilled water as a control. In the study by Guenezan et al.,[23] the control group did not receive any intervention like water or saline.

Characteristics of the Outcomes

All of the studies reported statistically significant higher Ct (Cycle threshold) values post rinsing, clearly indicating the virucidal effect of PVP-I. Ct values are thought to be inversely related to viral load, hence they can be used as an indirect technique of determining the viral load in a sample. At 15 and 45 minutes, median viral reductions of 61–89 and 70–97% were seen in both the experimental PVP-I and control saline groups, respectively.[25] In the PVP-I group, the mean relative difference in virus titers between baseline and day 1 was 75%, while in the control group, it was 32%.[23] On the third day, the fourth hourly administration of PVP-I mouth gargle reduced RT-PCR positivity to 11.55%, compared to 96.04% in the control group.[22]

Synthesis of the Results

Povidone-iodine mouth gargle (0.5–1%) used by COVID-19 patients 4th hourly effectively lowered salivary SARS-CoV-2 viral load, thereby reducing the carriage of infectious virion in adults. The strong antiviral impact of PVP-I is demonstrated by statistically significant increases in Ct values after 5, 15, and 45 minutes, as well as 3 and 6 hours after rinsing.[21] The use of PVP-I mouth gargles in conjunction with other nasal hygiene measures dramatically reduced COVID-19 patients' hospitalization, oxygen support, and mortality.[22]

Discussion

Summary of Evidence

The results of this systematic review are the first on this topic and as such there were no others for comparison. Instead of using (AND), the search method used keywords, MeSH terms, and (OR) Boolean operators, which resulted in a significant amount of literature and assured that all possibly acceptable literature was found. In this review, all of the studies were prospective RCTs with high-quality evidence.

The National Health Commission of the People's Republic of China's Guideline for the Diagnosis and Treatment of Novel Corona Virus Pneumonia (the 5th edition) recommended using a preprocedural mouth rinse containing oxidative agents such as 1% hydrogen peroxide or 0.2% PVP-I for dental procedures to reduce the salivary load of SARS-CoV-2.[11]

Australian Dental Association suggested preprocedural mouth-rinse for 20–30 seconds before commencing treatment using either 1% hydrogen peroxide, 0.2% PVP-I , 0.2% chlorhexidine, or essential oil mouth rinse for all dental patients.[26] Similarly, Indian Dental Association also recommends preprocedural mouth rinse with 1.5% hydrogen peroxide or 0.2% PVP-I for 1 minute.[27]

The aforementioned guideline was followed despite the lack of clinical evidence supporting the virucidal efficacy of such preprocedural mouth rinses on SARS-CoV-2. Our systematic review aims to summarize the results of five *in vivo* randomized controlled trials on this topic, that have been published so far. In these studies along with the selected variable of our research question (PVP-I), other variables such as CHX, CPC, saline, and H_2O_2 were also evaluated. Only analysis of PVP-I and control were considered to limit ourselves to the aim of the systemic review.

In their RCT, Seneviratne et al.[21] evaluated the effectiveness of 0.5% PVP-I with water as a control in SARS-CoV-2 patients. They concluded that the PVP-I group had a higher fold change in Ct values after 5 minutes, 3 hours, and 6 hours, indicating a considerable reduction in viral load. When compared to control, a statistically significant increase in fold change was seen 6 hours after rinsing. This finding is consistent with an *in vivo* investigation by Martínez Lamas et al.,[28] who found that 1% PVP-I reduced salivary viral load for at least 3 hours after rinsing.

In an RCT enrolling 606 COVID-19 patients, Choudhury et al.[22] compared 1% PVP-I to water as a control. Salivary samples were obtained on the 3rd, 5th, and 7th days, and RT-PCR was used to analyze them. On the third day, 11.55% of patients in the study group tested positive for RT-PCR, compared to 96.04% in the control group, and this number dropped to 2.64% in the study group and 70.30% in the control group. Furthermore, just 3.30% of the study group required oxygen assistance, compared to 20.79% in the control group. While comparing the study and control groups, the death rate was 0.66 and 5.61%, respectively. The use of 1% PVP-I for decreasing salivary viral load effectively lowered illness, mortality, and financial burden on persons in the COVID-19 pandemic, according to this study.

Table 1: Characteristics of included studies with outcome

S. no.	*Author/study name*	*Study type*	*Participants*	*Intervention parameter studied/ compared*	*Statistical analysis*	*Study outcome*
1	Seneviratne et al.,[21] 2020	Randomized controlled trial	6 patients. Saliva samples were collected at baseline, 5 min, 3, and 6 hours (RT-PCR analysis)	Povidone-iodine (0.5%) compared with sterile water as control	ANOVA and *post hoc* test, *t*-test	Povidone-iodine (PVP-I) group showed higher fold changes in Ct (cycle threshold) value post 5 min, 3, and 6 hours post rinsing
2	Choudhury et al.,[22] 2021	Randomized controlled trial	606 patients. Saliva samples were collected on the 3rd, 5th, and 7th days (RT-PCR analysis)	Povidone-iodine (1%) compared with lukewarm water as control	ANOVA, *t*-test	11.55% PVP-I patients were RT-PCR positive rather than 96.04% positive in the control group on the 3rd day. PVP-I mouth gargles significantly reduced hospitalization, oxygen support, and mortality rather than the control group.
3	Guenezan et al.,[23] 2021	Randomized controlled trial	24 patients. Saliva samples were collected at baseline, 1, 3, 5, and on the 7th day (RT-PCR analysis)	Aqueous povidone-iodine (1%) compared with control group with no intervention	ANOVA, *t*-test	Mean relative difference in viral titers between baseline and day 1 was a 75% decrease in the PVP-I group and 32% decrease in control group. PVP-I mouth gargle may reduce the carriage of infectious SARS-CoV-2 in adults.
4	Elzein et al.,[24] 2021	Randomized controlled trial	36 patients. Saliva samples were collected at baseline and 5 minutes after gargling (RT-PCR analysis)	Povidone-iodine (1%) compared with distilled water as control	Kolmogorov–Simonov test, Kruskal–Wallis test, and Student paired *t*-test	Povidone-iodine group showed statistically significant higher Ct (cycle threshold) values post 5 minutes than distilled water group.
5.	Chaudhary,[25] 2021	Randomized controlled trial	20 patients. Saliva samples were collected at baseline and 15 and 45 minutes after gargling (RT-PCR analysis)	Povidone-iodine (0.5%) compared with normal saline as control	Dunn's test and chi-square test	Median viral reduction of 61–89 and 70–97% were observed at 15 and 45 minutes in both groups. Simple and highly effective means of reducing salivary viral load and also a valuable tool in disease mitigation.

The study's strength is a large number of samples ($n = 606$), whereas its weaknesses include patient adherence to the study protocol and salivary sample collection schedule. To et al.[29] recommended collecting salivary samples early in the morning, because samples collected in the early morning before and after rinsing give more reliable results.

When viral titers were examined between baseline and one day after gargling 6th hourly, Guenezan et al.[23] found that in the PVP-I group, mean viral titer was reduced by 75%, but it was only 32% in the control group. Furthermore, the author stated that T3, T4, and creatinine levels did not change, while TSH levels increased on the 5th day, returning to baseline on the 7th to 12th day.[23] The authors of this study advocated for a larger clinical trial to demonstrate PVP-efficacy in decreasing SARS-CoV-2 secretion and transmission from human to human.

In their RCT, Elzein et al.[24] compared the efficiency of 1% PVP-I against SARS-CoV-2. Salivary samples were collected at baseline and 5 minutes after gargling. In the PVP-I group, the Ct value increased by 4.45. Seneviratne et al.[21] found that gargling with 0.5% PVP-I for 5 minutes increased the Ct value by 1.1. Ct values are inversely related to viral load and are used as an indirect technique of quantifying the viral load in a sample. A drop in viral titer is indicated by an increase in Ct value.

The effectiveness of 0.5% PVP-I and saline were evaluated in an RCT by Chaudhary et al.[25] Saliva samples were taken at three intervals: baseline, 15 minutes, and 45 minutes. At 15 and 45 minutes, both groups showed a reduction in median viral load of 61–89 and 70–97%, respectively. Guenezan et al.[23] stated that taking 1% PVP-I for one day reduced mean viral titer by 75%. Ramalingam et al.[30] demonstrated the virucidal effect of saline by demonstrating that phagocytes (myeloid cells) used the chloride ion given by saline to make hypochlorous acid, which destroys ingested microorganisms, using the enzyme myeloperoxidase.

As a primary outcome, all *in vivo* RCT studies demonstrated the efficacy of PVP-I mouth gargles in actively lowering viral load in COVID-19 patients. Based on the above-published evidence, an ACHPG is recommended as a secondary outcome, which

can be easily adopted with current prevention and treatment measures. Adjunctive Clinical and Household Practice Guideline recommends the use of 0.5–1% PVP-I mouth gargle (15–30 mL) for 60 seconds four times a day along with nasal hygiene routines. Because it is difficult to identify asymptomatic and presymptomatic patients, the ACHPG recommends using PVP-I mouth gargle in the general public as an effective technique of breaking the chain of transmission.

Limitations

The smaller sample size of the preceding research (except Choudhury et al.) is one of their limitations. The presence of salivary enzymes, organic matter, and serum proteins in the saliva can inflect the effectiveness of PVP-I mouth gargle.[31] The RT-PCR technique was utilized to detect SARS-CoV-2 in all of the investigations above, but the sample's infectivity was not investigated. As a result, doing viral cell culture to determine the infectivity of the salivary sample is critical.

Implications in Future Practice and Research

Future research with a sufficient sample size and a control group should be conducted to produce more reliable results with improved external validity. Further trials on the efficacy of PVP-I mouth gargle should concentrate on the most effective minimal concentration, exposure time, and mouth gargle volume, as well as the SARS-CoV-2 strain. Povidone-iodine mouth gargle's impact on viral infectivity and cytotoxicity on epithelial cells were not identified in the studies evaluated. Antiseptic-associated cell death can result in fewer target cells for viral infection, resulting in a reduction in viral infectivity that can be misinterpreted as a significant antiviral effect.[32] As a result, viral cell culture techniques should be used to determine the potential of PVP-I's virucidal activity against SARS-CoV-2. Host immune response against SARS-CoV-2 should also be considered in assessing the effectiveness of mouth gargles.

Conclusion

This article is timely and is of immense importance to medical practitioners, dentists, dental care workers, healthcare workers, and the general public as it emphasizes the role of PVP-I in controlling SAR-CoV-2 infection. Based on published results from *in vivo* RCTs, it can be concluded that 0.5–1% PVP-I mouth gargle can successfully reduce the salivary SARS-CoV-2 virus load. Iodine absorption is minimal at this dosage, which is below the total daily iodine intake of 150 µg recommended for a healthy adult.[33] This systematic review underlines the importance of future research that is well focused, robust, and uses standardized methodologies and a large sample size.

Contributors

Sudhakar Venkatachalapathy and Vinodhini Sudhakar contributed to Theme selection, literature search, validating the Evidence, Compilation, Analysis and Interpretation of data, Recommendations, Designing guidelines, and writing. Balaguhan Balasubramanian and Kirthika Natarajan contributed to literature search, Tracing Evidence, Article layout, Design, and Data Interpretation. Mathan Mohan A contributed to Data Analysis, Protocol Designing, Guideline finalizing, and writing. All authors reviewed and approved the final version of the article.

References

1. Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395(10223):514–523. DOI: 10.1016/S0140-6736(20)30154-9.
2. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–273. DOI: 10.1038/s41586-020-2012-7.
3. Chan JF-W, Kok K-H, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Micro Infect 2020;9(1):221–236. DOI: 10.1080/22221751.2020.1719902.
4. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63(3):457–460. DOI: 10.1007/s11427-020-1637-5.
5. Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020;14(2):185–192. DOI: 10.1007/s11684-020-0754-0.
6. Zhao Y, Zhao Z, Wang Y, et al. Single-Cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med 2020;202(5):756–759. DOI: 10.1164/rccm.202001-0179LE.
7. Zhang H, Kang Z, Gong H, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. Gut 2020;69(8):1010–1018. DOI: 10.1136/gutjnl-2020-320953.
8. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26(5):681–687. DOI: 10.1038/s41591-020-0868-6.
9. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12(1):8. DOI: 10.1038/s41368-020-0074-x.
10. Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Genomics 2020. DOI: 10.1101/2020.02.03.931766.
11. WHO Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19) Feb 28, 2020. https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19). n.d.
12. Xu R, Cui B, Duan X, et al. Saliva: potential diagnostic value and transmission of 2019-nCoV. Int J Oral Sci 2020;12(1):11. DOI: 10.1038/s41368-020-0080-z.
13. Sneader W. Drug discovery: a history. 1st ed., Wiley; 2005. DOI: 10.1002/0470015535.
14. Wutzler P, Sauerbrei A, Klöcking R, et al. Virucidal activity and cytotoxicity of the liposomal formulation of povidone-iodine. Antiv Res 2002;54(2):89–97. DOI: 10.1016/S0166-3542(01)00213-3.
15. Kawana R, Kitamura T, Nakagomi O, et al. Inactivation of human viruses by povidone-iodine in comparison with other antiseptics. Dermatology 1997;195(2):29–35. DOI: 10.1159/000246027.
16. Kariwa H, Fujii N, Takashima I. Inactivation of SARS coronavirus by means of povidone-iodine, physical conditions and chemical reagents. Dermatology 2006;212(4):119–123. DOI: 10.1159/000089211.
17. Kanagalingam J, Feliciano R, Hah JH, et al. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. Int J Clin Pract 2015;69(11):1247–1256. DOI: 10.1111/ijcp.12707.
18. Sriwilaijaroen N, Wilairat P, Hiramatsu H, et al. Mechanisms of the action of povidone-iodine against human and avian influenza A viruses: its effects on hemagglutination and sialidase activities. Virol J 2009;6(1):124. DOI: 10.1186/1743-422X-6-124.
19. Challacombe SJ, Kirk-Bayley J, Sunkaraneni VS, et al. Povidone iodine. Br Dent J 2020;228(9):656–657. DOI: 10.1038/s41415-020-1589-4.
20. Shankar S, Saha A, Jamir L, et al. Protection at portal of entry (PPE) with povidone iodine for COVID-19. Int J Med Pub Health 2020;10(4):166–168. DOI: 10.5530/ijmedph.2020.4.36n.d.

21. Seneviratne CJ, Balan P, Ko KKK, et al. Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: randomized control trial in Singapore. Infection 2021;49(2):305–311. DOI: 10.1007/s15010-020-01563-9.
22. Choudhury MIM, Shabnam N, Ahsan T, et al. Effect of 1% povidone iodine mouthwash/gargle, nasal and eye drop in COVID-19 patient. Bioresearch Communications 2021;7(1):919–923. DOI: 10.3329/brc.v7i1.54245n.d.
23. Guenezan J, Garcia M, Strasters D, et al. Povidone iodine mouthwash, gargle, and nasal spray to reduce nasopharyngeal viral load in patients with COVID-19: a randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2021;147(4):400. DOI: 10.1001/jamaoto.2020.5490.
24. Elzein R, Abdel-Sater F, Fakhreddine S, et al. In vivo evaluation of the virucidal efficacy of chlorhexidine and povidone-iodine mouthwashes against salivary SARS-CoV-2. A randomized-controlled clinical trial. J Evid Based Dent Pract 2021;21(3):101584. DOI: 10.1016/j.jebdp.2021.101584.
25. Chaudhary PP, Melkonyan A, Meethil A, et al. Estimating salivary carriage of SARS-CoV2 in non-symptomatic individuals and efficacy of mouthwash in reducing viral load: a randomized controlled trial. J Am Dent Assoc 2021. S000281772100355X 10.1016/j.adaj.2021.05.021.
26. Managing COVID-19 Guidelines. Available online at: https://www.ada.org.au/Campaign/COVID-19/Guide-to-Managing-COVID-19/ADA-Managing COVID-19-Guide-v-2.aspx (accessed June 19, 2021). n.d.
27. Indian Dental Association. Protocol–COVID-19. New Delhi: Indian Dental Association; 2020. p. 26.
28. Martínez Lamas L, Diz Dios P, Pérez Rodríguez MT, et al. Is povidone iodine mouthwash effective against SARS-CoV-2? First in vivo tests. Oral Dis 2020. DOI: 10.1111/odi.13526.
29. To KK-W, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020;20(5):565–574. DOI: 10.1016/S1473-3099(20)30196-1.
30. Ramalingam S, Cai B, Wong J, et al. Antiviral innate immune response in non-myeloid cells is augmented by chloride ions via an increase in intracellular hypochlorous acid levels. Sci Rep 2018;8(1):13630. DOI: 10.1038/s41598-018-31936-y.
31. Ross NM, Charles CH, Dills SS. Long-term effects of Listerine antiseptic on dental plaque and gingivitis. J Clin Dent 1989;1(4):92–95. n.d.
32. Xu C, Wang A, Hoskin ER, et al. Differential effects of antiseptic mouth rinses on SARS-CoV-2 infectivity in vitro. Pathogens 2021;10(3):272. DOI: 10.3390/pathogens10030272.
33. Frank S, Capriotti J, Brown SM, et al. Povidone-iodine use in sinonasal and oral cavities: a review of safety in the COVID-19 era. Ear Nose Throat J 2020;99(9):586–593. DOI: 10.1177/0145561320932318.