Brazilian Dental Science
unesp
UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Instituto de Ciência e Tecnologia
Campus de São José dos Campos

LITERATURE REVIEW
DOI: https://doi.org/10.4322/bds.2023.e3721

Silver nanoparticles in mouthwashes against infection caused by SARS-CoV-2: a scoping review

Nanopartículas de prata em enxaguatórios bucais para uso em infecções por SARS-CoV-2: uma revisão de escopo

Kelly Fernanda MOLENA[1], Camila Raíssa Oliveira Gontijo MARTINS[1], Carolina Alves Freiria de OLIVEIRA[2], Murilo Fernando Neuppmann FERES[3], Alexandra Mussolino de QUEIROZ[3]

1 - Pós Graduanda do Programa de Odontopediatria, Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil
2 - Pós Graduanda do Programa de Reabilitação Oral Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil.
3 - Departamento de Clínica Infantil, Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil

How to cite: Molena KF, Martins CROG, Oliveira CAF, Feres MFN, Queiroz AM. Silver nanoparticles in mouthwashes against infection caused by SARS-CoV-2: a scoping review. Braz Dent Sci. 2023;26(2):e3721. https://doi.org/10.4322/bds.2023.e3721

ABSTRACT

The Silver nanoparticle (AgNPs) have received attention for their antiviral potential against SARS-CoV-2. The objective is to conduct a scope review and map the scientific evidence on the use of AgNPs in mouthwashes as an adjunct in decreasing the viral load in the oral cavity of patients with SARS-CoV-2. A search was performed in the PubMed, Medline, Scielo databases, and a manual search in the reference lists, following the standards of the Joanna Briggs Institute for Scoping Review without restriction of year, language or sample size. Thus, 14 articles were included, where they researched the use of AgNPs with antiviral effect against SARS-CoV-2, mouthwashes for SARS-CoV-2 and AgNPs as mouthwashes. We can suggest that AgNPs are likely antiviral therapies for SARS-CoV-2 and its use in mouthwashes associated with other therapies are promising strands for decreasing viral load and infection by the virus.

KEYWORDS

Nanoparticles; Silver; Mouthwashes; COVID-19; SARS-CoV-2.

RESUMO

As nanopartículas de prata (AgNPs) têm recebido atenção por seu potencial antiviral no SARS-CoV-2. O objetivo deste trabalho é realizar uma revisão de escopo e mapear as evidências científicas sobre o uso de AgNPs em bochechos como adjuvante na diminuição da carga viral na cavidade oral de pacientes com SARS-CoV-2. Foi realizada busca nas bases de dados PubMed, Medline, Scielo e busca manual nas listas de referências, seguindo os padrões do Joanna Briggs Institute for Scoping Review sem restrição de ano, idioma ou tamanho da amostra. Assim, foram incluídos 14 artigos, onde pesquisaram o uso de AgNPs com efeito antiviral contra SARS-CoV-2, enxaguatórios bucais para SARS-CoV-2 e AgNPs como enxaguatórios bucais, vertentes promissoras para diminuição da carga viral e infecção pelo vírus.

PALAVRAS-CHAVE

Nanopartículas; Prata; Enxaguatórios bucais; COVID-19; SARS-CoV-2.

Abbreviations

Silver nanoparticles (AgNPs), Severe acute respiratory syndrome (Sars-CoV-2), Center for Disease control and prevention (CDC), Respiratory syncytial virus (RSV), Hepatitis B virus (HBV), Human immunodeficiency virus (HIV), PRISMA (Preferred Report on Systematic Reviews and Meta-Analysis), Angiotensin-converting enzyme receptor 2 (ACE2)

INTRODUCTION

At the end of 2019, a virus emerged in Wuhan, China, which would later be called severe acute respiratory syndrome coronavirus 2, and spread rapidly around the world causing a global health emergency [1]. According to the Centers for Disease Control and Prevention (CDC) in the United States [2], the transmission of the virus is carried out mainly through direct contact or respiratory droplets [3] in a close and time-dependent manner, in addition to air transmission in certain circumstances, as most recently demonstrated [4,5], including prolonged exposure in an enclosed space without proper air handling [6,7,8]. Despite advances, the complexity of transmission and presentation of the disease has increased this, added to new variants brings the need to develop new preventive approaches [9].

The oral cavity is an important reservoir of SARS-CoV-2 [10,11,12], the use of an antiviral mouthwash is an interesting strategy, especially in the initial stage of the disease [13], where its viral load is extremely high in saliva [7,14]. In addition, saliva is an important source of transmission during the COVID-19 pandemic [10]. When a person coughs, sneezes, breathes or talks, drops of saliva are produced and can dissipate the virus [10,15]. Considering mouthwash as agents that can reduce the viral load of SARS-CoV-2 in the fight against the COVID-19 [10,16] pandemic is an extremely important concept to be taken into account [10,17].

In this way, nanomaterials can be described as single structures [18], free or in a compound, with a size within the nanometer range, generally less than 100 nm in at least one of its three dimensions [18,19]. There is a growing interest in nanomaterials, precisely because of their new or improved physico-chemical properties, such as durability, chemical reactivity, biocompatibility, conductivity or reduced toxicity [18,20]. Thus, they can be used in disinfectants, diagnostics, imaging tools, dressings, clothing, anti-cancer therapies, pharmaceuticals, drug administration, vaccines, diagnostic techniques and implants, among others [21,22,23]. Also, development of antiviral and antimicrobial drugs [24,25]. Antiviral nanomaterials are typically smaller than most viral particles, such as the SARS-CoV-2 viral particle, which has an average size of 120 nm [19,26], so they can interact with the entire viral particle or with surface proteins and other components structural, leading to virus inactivation [10].

Silver is an elemental metal and has a broad spectrum antimicrobial action against bacteria, fungi and viruses [27]. Silver nanoparticles (AgNPs) are highly versatile and are already present in microbicides for biological surfaces in various forms, such as medical devices, wound dressings, sprays and tissues [28]. In dentistry, AgNPs have drawn special attention because of their broad spectrum of antimicrobial activity, where their efficacy has already been demonstrated, however, the toxicity of AgNPs for use in oral infections is still being discussed [29]. AgNPs also attract the attention of dental researchers due to their potential for anticarious use [30], as they can inhibit the growth and adhesion of cariogenic bacteria especially *Streptococcus mutans* [30,31,32]. Studies investigate the addition of AgNPs in adhesives, toothpaste and restorative materials, studying the association between AgNPs and fluoride to stop caries, potentiating an antibacterial and remineralizing agent [33,34]. In addition, studies have demonstrated the potent antiviral action of AgNPs against various human pathogenic viruses, such as respiratory syncytial virus (RSV), influenza virus, norovirus, hepatitis B virus (HBV), human immunodeficiency virus (HIV) [26,35,36], and more currently, as a possibility for SARS-CoV-2 [28,35,36].

Recent studies have demonstrated the effectiveness of different mouthwashes to reduce salivary load and consequently to help reduce the transmission of SARS-CoV-2 [37,38]. However, there are still no studies in the literature evaluating the effectiveness of mouthwashes with AgNPs in reducing salivary viral load in patients with COVID-19 [39].

Therefore, the objective of this scope review is to map the scientific evidence and any gaps in knowledge about the use of mouthrinses with AgNPs as a potent antiviral agent or adjunct in decreasing the viral load in the oral cavity of patients infected with SARS-CoV-2.

MATERIAL AND METHODS

The methodology was defined following the Joanna Briggs Institute for Scoping reviews [40] and the PRISMA-ScR guidelines (Preferred Report on Systematic Reviews and Meta-Analysis for Scoping Reviews – Figure 1) [41]. The bibliographic research was conducted in 3 databases and in the gray literature, whose question was to map evidence on the use of AgNPs as an antiviral agent against SARS-CoV-2, and its use in mouthwashes with the potential to reduce viral load in the oral cavity, from patients affected by SARS-CoV-2, and with the guiding question: Mouthwashes with AgNPs, can be effective in reducing the viral load in oral cavity, of patients affected by SARS-CoV-2?

Scope of the search

A search was performed in the PubMed, Medline, Scielo databases, as well as a manual search in the reference lists of the studies that were included [42], without restriction of year, language or sample size. The first phase established an investigation to define the terms MeSH (Medical Subject Headings) to ensure high sensitivity and accuracy, and the researchers tracked titles and publications of abstracts. The MeSH terms used in searches in all databases were "COVID-19" or "SARS-CoV-2" or "Coronavirus Infections" or "Coronavirus" and "Mouthwashes" or "Mouth-rinses" and "Silver nanoparticles" and "Antiviral", and crossed elements ("silver nanoparticle" and "oral rinses"), ("silver nanoparticles"and "COVID-19"), ("silver nanoparticle"and COVID-19 and mouthwashe) and ("oral rinse" and " COVID-19").

Inclusion and exclusion criteria

This review included studies reporting the use of AgNPs in mouthwashes, as a therapeutic approach to reduce viral load in patients infected with SARS-CoV-2, to solve the hypothesis that it would be possible to use mouthwashes with AgNPs to reduce viral load in patients infected with SARS-CoV-2. At first, the original articles, without language or year restriction, with an abstract available in the database, were evaluated and validated within the inclusion criteria, by reading the title and abstract, by two authors [43]. Inclusion criteria were defined

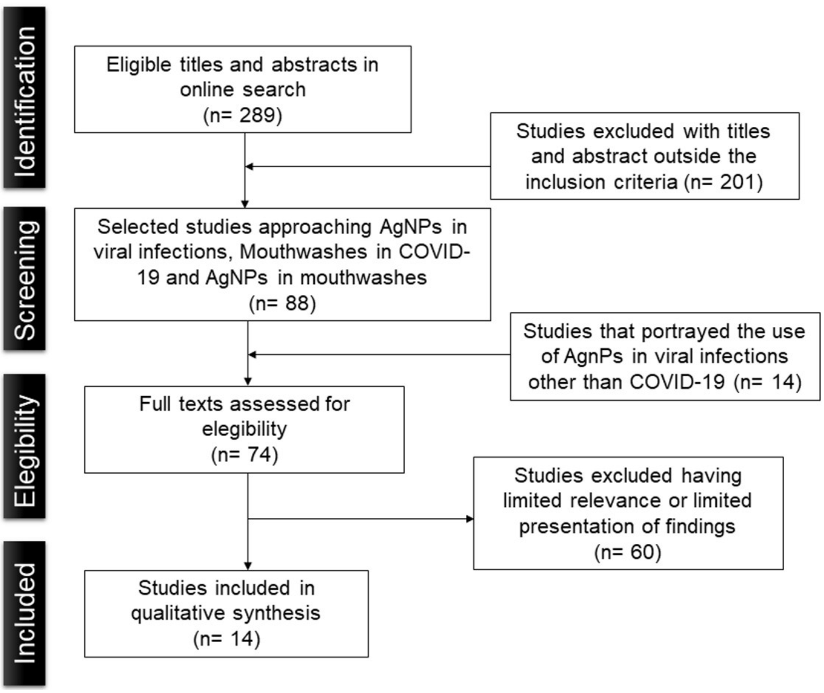

Figure 1 - PRISMA diagram. Process of identification and inclusion of studies - Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) diagram flow.

using the PCC strategy (Population, Concept, Context - Table I) and consisted of primary research studies in full, "*in vivo*", "*in vitro*" or animal research, and excluded opinion articles, letters to editor and literature reviews.

Selection and quality assessment of relevant studies

The articles selected according to the election criteria were retrieved in PDF format, numbered and randomly distributed among two researchers [43]. To increase the sensitivity and quality of review, the references list was manually checked. To discuss divergences, a consensus meeting was held [43] and an third experienced researcher was consulted

Extraction and processing

The articles included in the study were randomly distributed among the researchers for the collection of relevant data [43]. The articles were then organized into 03 tables, namely: studies that portray the use of AgNPs against SARS-CoV-2 with antiviral potential (Table II); studies that portray the use of mouthwashes for patients with COVID-19 (Table III) and studies that bring AgNPs in mouthwashes (Table IV).

RESULTS

After the process of evaluation and selection of articles, 14 articles were included in the scoping review, 03 of which portray AgNPs as antiviral

Table I - PCC estrategy and the criteria included in the search for articles

PCC Estrategy	
Population	People infected by SARS-CoV-2
Concept	Administration of mouthwashes with AgNPs to control / reduce the viral load of SARS-CoV-2
Context	Global health, in view of the current SARS-CoV-2 pandemic, and its high infectivity, mainly via the oral cavity through the formation of aerosol in the dental office, as well as droplets produced in speaking, coughing, and sneezing, for example.

Table II - Studies that portray the use of AgNPs with antiviral potential for SARS-CoV-2

Autor and Year	Title	Estrategy of use AgNPs	Outcomes
Chang et al., 2021 [44]	Nanoparticle composite TPNT1 is effective against SARS-CoV-2 and influenza viruses	A composite of metal nanoparticles, namely TPNT1, containing Au-NP (1 ppm), Ag-NP (5 ppm), ZnO-NP (60 ppm) and ClO 2 (42.5 ppm) in aqueous solution was prepared and characterized by spectroscopy, transmission electron microscopy, dynamic light scattering analysis and potentiometric titration	TPNT1 inhibited six major subtypes of SARS-CoV-2, and interfered with the formation of syncytium. It also effectively reduced the cytopathic effects induced by human (H1N1) and avian (H5N1) viruses, including those isolated from wild-type and resistant to oseltamivir viruses.
Jeremiah et al., 2020 [28]	Potent antiviral effect of silver nanoparticles on SARS-CoV-2.	PVP-AgNP 10 in stock concentration of 20 ppm and cAg were obtained from Sigma. AgNPs of different sizes; AgNP 2 (Cat No: US7150), AgNP 15 (Cat No: US7091), AgNP 50, AgNP 80 and AgNP 100 (US1038W), all silver formulations were dispersed in water and the desired concentration was prepared by diluting in sterile distilled water.	Particles in diameter around 10 nm were effective in extracellular inhibition of SARS-CoV-2 at concentrations ranging from 1 to 10 ppm, while the cytotoxic effect was observed at concentrations of 20 ppm and above. The luciferase-based pseudovirus entry assay revealed that AgNPs potently inhibited the viral entry step by disrupting viral integrity.
Valdez-Salas et al., 2021 [45]	Promotion of Surgical Masks Antimicrobial Activity by Disinfection and Impregnation with Disinfectant Silver Nanoparticles.	Developed a new alcohol disinfectant formulation combining special surfactants and AgNPs	The nano-disinfectant provides a valuable strategy for effective decontamination, reuse and even promotion of antimicrobials for surgical masks for frontline clinical personnel.

Table III - Studies that portray the use of mouthwashes in SARS-CoV-2 virus

Author and Year	Title	Mouthwashes studied against SARS-CoV-2	Outcome
Seneviratne et al., 2021 [37]	Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: randomized control trial.	Iodine-povidone (PVPI) 0.5%, chlorhexidine 0.2%, cetylpyridine chloride (CPC) 0.075%	The use of CPC and PI formulated that commercial mouthwashes can be useful as a pre-procedure rinse to help reduce the transmission of SARS-CoV-2.
Steinhauer et al., 2021 [43]	Comparison of the *in vitro* efficacy of different mouthwash solutions targeting SARS-CoV-2 based on the European Standard EN 14476.	Chlorhexidine digluconate 0.2% and octenidine dihydrochloride (OCT)	Based on these *in vitro* data, the OCT rinse is an interesting candidate for future clinical studies to prove its effectiveness in a potential prevention of the transmission of SARS-CoV-2 by aerosols.
Xu et al., 2020 [46]	Differential effects of antiseptic mouth rinses on SARS-CoV-2 infectivity *in vitro*.	Essential oils with ethanol (20-30% Ethanol Thymol 0.064% Methyl salicylate 0.06% Menthol (Racementol) 0.042% 0.092% Eucalyptol); 1% povidone-iodine; Hydrogen peroxide 1.5% and chlorhexidine gluconate 0.12%	All mouthwashes tested against inactivated SARS-CoV-2 virus. Listerine and CHG were less cytotoxic than Colgate Peroxyl or povidone-iodine and were active against the virus. When mouthwash was present in the cell culture during infection, the potent antiviral effect of mouthwash was in part due to the cytotoxicity associated with mouthwash.
Pelletier et al., 2021 [47]	Efficacy of Povidone-Iodine Nasal and Oral Antiseptic Preparations against SARS-CoV-2	PVPI 1% to 5%	The nasal and oral antiseptic solutions of PVPI are effective in inactivating SARS-CoV-2 in a variety of concentrations (nasal, oral and surface decontamination) after exposure times of 60 seconds.
Bidra et al., 2020 [48]	Rapid *in vitro* inactivation of SARS-CoV-2 using povidone-iodine oral antiseptic rinse (PVPI).	PVPI 0,5%, 1% and 1,5%	PVPI preparations rapidly inactivated the SARS-CoV-2 *in vitro*. The virucidal activity was present at the lowest concentration of 0.5% PVPI and the lowest contact time of 15 seconds.
Bidra et al., 2020 [49]	Comparison of *in vitro* inactivation of SARS-CoV-2 with hydrogen peroxide and povidone-iodine oral antiseptic rinses (PVPI).	PVPI 0.5%, 1.25% and 1.5%, and hydrogen peroxide (H2O2) was tested at 3% and 1.5%	SARS-CoV-2 was completely inactivated by the oral antiseptic rinse of PVPI *in vitro*, in the lowest concentration of 0.5% and in the shortest contact time of 15 seconds. H2O2 at the recommended oral rinse concentrations of 1.5% and 3.0% was minimally effective as a virucidal agent after contact times of up to 30 seconds. Therefore, the pre-procedure rinse with PVPI diluted in the range of 0.5% to 1.5% may be preferable to hydrogen peroxide during the COVID-19 pandemic.
Gottsauner et al., 2020 [50]	A prospective clinical pilot study on the effects of a hydrogen peroxide mouthrinse on the intraoral viral load of SARS-CoV-2.	Hydrogen peroxide 1%	A 1% hydrogen peroxide mouthwash does not reduce the intraoral viral load in individuals positive for SARS-CoV-2. However, the culture of the virus gave no indication of the effects of the mouthwash on the infectivity of the detected RNA copies.
Koch-Heier et al., 2021[51]	Inactivation of SARS-CoV-2 through treatment with the mouth rinsing Solutions ViruProX® and BacterX® Pro. Microorganisms.	ViruProX® with 0.05% cetilpiridinium (CPC) and 1.5% hydrogen peroxide (H2O2); BacterX® pro containing 0.1% chlorhexidine (CHX), 0.05% CPC and 0.005% sodium fluoride (F-); and some of their individual components as 0.05% CPC solution, 0.1% CHX solution, a combination of 0.05% CPC with 0.1% CHX solution, and 1.5% H2O2 solution	While a combination of CPC and CHX, as well as CPC alone led to a significant reduction in infectious viral particles, H2O2 and CHX alone had no virucidal effect against SARS-CoV-2. It can be assumed that pre-procedure mouth rinsing with ViruProX ® or BacterX ® pro will reduce the viral load in the oral cavity and, thus, decrease the transmission of SARS-CoV-2 in dental practice.

Table IV - Studies that portray AgNPs in mouthwashes

Author and Year	Title	Strategy for the use of AgNPs in mouthwashes	Outcome
Lu et al., 2018 [52]	Redox/pH dual-controlled release of chlorhexidine and silver ions from biodegradable mesoporous silica nanoparticles against oral biofilms.	They manufactured biodegradable disulfide bridge (MSNs) mesoporous silica nanoparticles to co-deliver AgNPs and CHX (chlorhexidine) for biofilm inhibition, (Ag-MSNs @ CHX).	Ag-MSNs @ CHX exhibited dose-dependent antibacterial activity against planktonic formation and *Streptococcus mutans* clones, and had an increased, long-term ability to restrict the growth of S. mutans biofilms compared to free CHX, and was less toxic to oral cells, even *in vivo*
Ahrari et al., 2015 [53]	The antimicrobial sensitivity of *Streptococcus mutans* and *Streptococcus sanguis* to colloidal solutions of different nanoparticles applied as mouthwashes.	Was evaluated the antibacterial effects of colloidal solutions containing zinc oxide, copper oxide, titanium dioxide and silver nanoparticles in *Streptococcus mutans* and *Streptococcus sanguis* and compared the results with those of chlorhexidine and sodium fluoride mouthwashes.	The antibacterial effect of silver nanoparticles was not desirable against *Streptococcus mutans*.
Besinis et al., 2014 [54]	The antibacterial effects of silver, titanium dioxide and silica dioxide nanoparticles compared to the dental disinfectant chlorhexidine on *Streptococcus mutans* using a suite of bioassays.	This study investigated the toxicity of silver (Ag), titanium dioxide and silica nanoparticles (NPs) against the oral pathogenic species of *Streptococcus mutans*, compared to the routine disinfectant, chlorhexidine	AgNPs were the best disinfectants and performed better than chlorhexidine

agents (Table II), 08 articles bring the use of mouthwashes against SARS-CoV- 2 (Table III) and finally, 03 articles expose AgNPs in mouthwashes (Table IV). These were articles in the English language, published between 2014 and 2021, covering experimental studies “*in vitro*” and “*in vivo*”.

DISCUSSION

The SARS-CoV-2 has already caused millions of deaths worldwide and due to its rapid spread it is difficult to contain the transmission [9]. Person-to-person contact through respiratory droplets generated by sneezing and coughing in infected individuals has been shown to be the main route of transmission of SARS-CoV-2 [10,43,44,46]. In addition to the efficient use of personal protective equipment, such as masks, and maintaining social distance, it is necessary to implement more active prevention strategies.

One of the main approaches to minimize the risk [37] of transmission of SARS-CoV-2 would be to reduce the viral load of SARS-CoV-2 in the saliva of infected patients [37], which is particularly important in high-risk procedures, such as dental treatment [37,47]. When a symptomatic or asymptomatic patient goes to the dental office, he can transmit the SARS-CoV-2 through contact with other people, direct transmission to the dentist or indirect transmission through contamination of surfaces, even more so today with the flexibility in use of masks [55].

The use of antiseptic mouthwash has been suggested as a pre-procedural infection control measure by health authorities since the early stage of the COVID-19 pandemic [37], when they recommended the use of mouthwashes with povidone-iodine (PVP-I) [47,48,49], hydrogen peroxide [49,50] or cetylpyridinium chloride (CPC) [43,46] as a pre-procedure preventive measure. However, it is important to emphasize that these recommendations were not based in robust scientific evidence. The first case report on the effectiveness of mouthwashes in reducing the viral load of SARS-CoV-2 in saliva was reported in Korea [13,37,56]. Other studies suggested that mouthwash with PVP-I could reduce the SARS-CoV-2 salivary viral load [47,48,49], and the efficacy of virucidal mouthwash activity against SARS-CoV-2 [46,51].

Silver nanoparticles are antiviral agents against several types of viruses [44,48,49,52,57,58,59,60,61,62,63], in addition to the antimicrobial activity against Grampositive and Gram-negative bacteria [53,54]. A possible antimicrobial mechanism of AgNPs is attributable to suppression of respiratory enzymes and interference in DNA functions by released Ag^{+} ions [44,52].

Elechiguerra et al. (2005) [57] in their study showed that silver nanoparticles undergo size-dependent interaction with HIV-1 and that they inhibit virus infectivity in vitro. El-Mohamady et al. (2018) [60] studied the inhibitory effect of silver nanoparticles on bovine herpesvirus-1 and showed that in non-toxic concentrations, AgNPs were able to inhibit BoHV-1 when administered before viral infection. Several other studies in the literature report the effectiveness of AgNPs as a potent antiviral against in humans and animals diseases, such as HIV [57,58,59], influenza [27,44], herpes type 1 and type 2 [60], respiratory syncytial virus, norovirus and hepatitis B [27,28].

Since the effectiveness of silver nanoparticles is known to be a potent antiviral agent, it is suggested that AgNPs may be effective in combating the transmission of SARS-CoV-2. In this sense, several studies are being developed and aim to test whether the AgNPs are also effective against SARS-CoV-2. In that way, AgNPs would have an antiviral effect on SARS-CoV-2 by disrupting disulfide bonds in spike protein and ACE2 receptors [28], inactivating the virus and preventing its replication or decreasing viral load in situ (Figure 2).

In their study, Jeremiah et al. (2020) [28] assessed numerous silver nanoparticles with varying sizes and concentrations. They found that silver nanoparticles with a diameter of approximately 10 nm were successful in inhibiting the extracellular growth of SARS-CoV-2 at concentrations ranging from 1 to 10 ppm, while concentrations of 20 ppm and above showed cytotoxic effects. Furthermore, the luciferase-based pseudo virus entry assay indicated that AgNPs effectively impeded the viral entry process by disrupting the virus's integrity.

The shortage of personal protective equipment and crucial medical supplies, such as surgical masks, is a major worry amid the COVID-19 outbreak [45]. The researchers aimed to create a cost-effective and straightforward study to enhance the antimicrobial capabilities of surgical

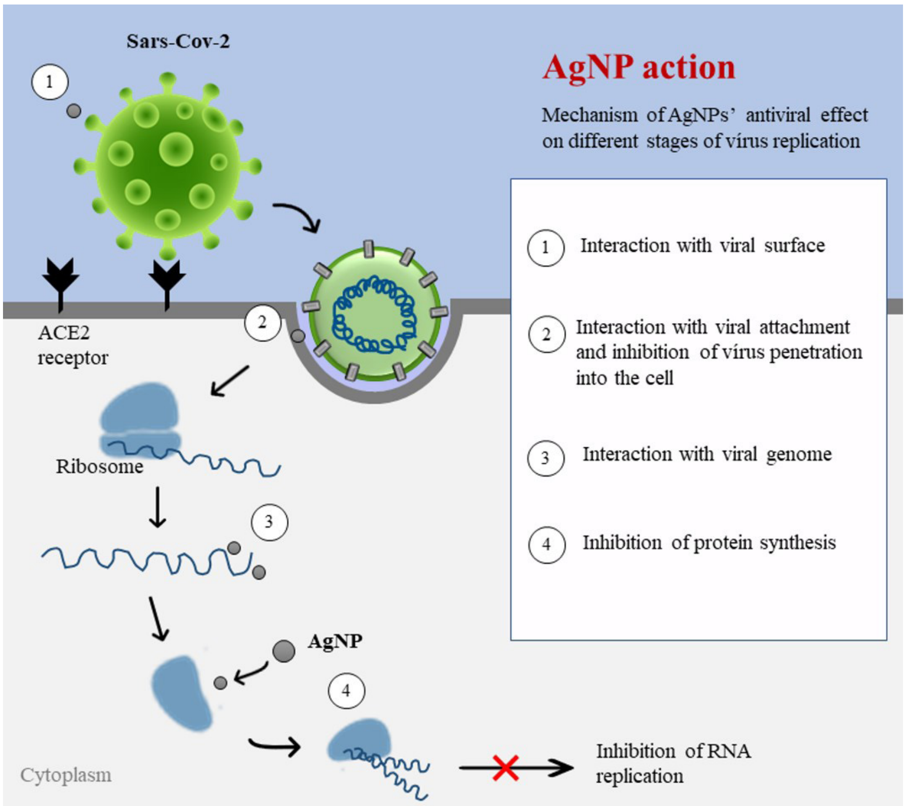

Figure 2 - Representation of the SARS-CoV-2 viral replication pathway. AgNP in mouthwashes would act on SARS-CoV-2 spike protein receptors and ACE2 receptors breaking their disulfide bridgs and preventing their viral replication.

masks by incorporating AgNPs. Their findings showed a microbial reduction rate exceeding 99.999% against various microorganisms, and the method of reusing surgical masks did not affect the filtration effectiveness, indicating no harmful alterations. This nano-disinfectant method offers a beneficial approach for efficient decontamination, reuse, and promotion of antimicrobial properties of surgical masks, particularly for frontline clinical staff [45]. Chang et al. (2021) [44] conducted a study where they combined AgNPs with other metallic nanoparticles in a compound called TPNT1. They used an in vitro cell assay to demonstrate that the compound was effective in inhibiting six significant subtypes of SARS-CoV-2 at concentrations suitable for use as food additives. TPNT1 was observed to block viral entry by preventing the binding of SARS-CoV-2 spike proteins to ACE2 and disrupting syncytium formation. Thus, this study suggests that this composite of metallic nanoparticles could serve as a prophylactic for preventing SARS-CoV-2 infections. To decrease the risk of transmission in patients with COVID-19, the viral load in the oral cavity must be decreased. Several studies have concluded that mouthwashes containing cetylpyridinium chloride (CPC) or povidone-iodine (PVP-I) can decrease the severity of COVID-19, reducing the oral viral load of SARS-CoV-2 and can decrease the risk of transmission by reducing the load viral in droplets generated in normal life or in aerosols produced during dental procedures [64]. In addition, if we look at mouthwashes that are marketed as containing antiviral molecules, other compounds may be of interest in the fight against SARS-CoV-2, such as hydrogen peroxide, chlorhexidine, cyclodextrin, Citrox, essential oils, among others [10,65]. The effectiveness of mouthwashes against SARS-CoV-2 may support their use as additional hygiene measures in patients with COVID-19 [47], thereby reducing the viral load in ambulatory and clinical environments [47], and their use may be adjunctive to personal protective equipment for dentists and healthcare professionals during COVID-19 outbreaks [48,49,66]. A randomized trial conducted by Santos et al. (2021) [67] showed promising results where the use of a mouthwash with an antiviral derivative of phthalocyanine reduced symptoms, spread of infection, and hospital stay period in patients with COVID-19. This reinforces the importance of conducting further studies in this area.

Our work aimed to map the current evidence on the use of AgNPs in mouthwashes for patients with COVID-19, the limitation of this study was that we were unable to include in the review any study where an AgNPs mouthwash was used for SARS-CoV-2. But this hypothesis is supported by the fact that the nanoparticle has antiviral properties well described in the literature and allows for a call for controlled clinical studies on the topic of considerable importance. Given this information and considering the various studies on AgNPs and its antiviral potential, it is suggested, with this scoping review, new studies that associate AgNP with mouthwashes and in this way it is possible to use this nanotechnology appropriately as a way to help combat SARS-CoV-2.

In conclusion, this study mapped the evidence around the use of AgNPs as an antiviral agent and the use of mouthwashes with potential against SARS-CoV-2. With the findings presented in this study, we can suggest that mouthwashes with AgNPs have the potential to act against SARS-CoV-2, as a way of reducing viral load, preventing viral multiplication, but studies need to be done to prove the hypothesis.

Author's Contributions

KFM: Conceptualization. MFNF: Methodology. MFNF: Formal Analysis. KFM, CROGM: Investigation. KFM, CROGM, CAFO: Data Curation. KFM, CROGM, CAFO: Writing – Original Draft Preparation. AMQ: Writing – Review & Editing. KFM: Project Administration. KFM: Funding Acquisition.

Conflict of Interest

No conflicts of interest declared concerning the publication of this article.

Funding

The authors declare that no financial support was received.

Regulatory Statement

A regulatory statement is not applicable as this is a scoping review article.

REFERENCES

1. Mohamadian M, Chiti H, Shoghli A, Biglari S, Parsamanesh N, Esmaeilzadeh A. COVID-19: virology, biology and novel laboratory diagnosis. J Gene Med. 2021;23(2):e3303. http://dx.doi.org/10.1002/jgm.3303. PMid:33305456.

2. Pike J, Kompaniyets L, Lindley MC, Saydah S, Miller G. Direct medical costs associated with post–COVID-19 conditions among privately insured children and adults. Prev Chronic Dis. 2023;20:220292. http://dx.doi.org/10.5888/pcd20.220292. PMid:36757854.

3. Mürbe D, Kriegel M, Lange J, Schumann L, Hartmann A, Fleischer M. Aerosol emission of adolescents voices during speaking, singing and shouting. PLoS One. 2021;16(2):e0246819. http://dx.doi.org/10.1371/journal.pone.0246819. PMid:33566852.

4. Tang S, Mao Y, Jones RM, Tan Q, Ji JS, Li N, et al. Aerosol transmission of SARS-CoV-2? Evidence, prevention and control. Environ Int. 2020;144:106039. http://dx.doi.org/10.1016/j.envint.2020.106039. PMid:32822927.

5. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564-7. http://dx.doi.org/10.1056/NEJMc2004973. PMid:32182409.

6. Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: the status and perspectives in delivery points of view. Adv Drug Deliv Rev. 2021;170:1-25. http://dx.doi.org/10.1016/j.addr.2020.12.011. PMid:33359141.

7. Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med. 2004;350(17):1731-9. http://dx.doi.org/10.1056/NEJMoa032867. PMid:15102999.

8. Kang M, Wei J, Yuan J, Guo J, Zhang Y, Hang J, et al. Probable evidence of fecal aerosol transmission of SARS-CoV-2 in a high-rise building. Ann Intern Med. 2020;173(12):974-80. http://dx.doi.org/10.7326/M20-0928. PMid:32870707.

9. Ambrose JM, Kullappan M, Patil S, Alzahrani KJ, Banjer HJ, Qashqari FSI, et al. Plant-derived antiviral compounds as potential entry inhibitors against spike protein of SARS-CoV-2 wild-type and delta variant: an integrative in silicoapproach. Molecules. 2022;27(6):1773. http://dx.doi.org/10.3390/molecules27061773. PMid:35335139.

10. Carrouel F, Gonçalves LS, Conte MP, Campus G, Fisher J, Fraticelli L, et al. Antiviral activity of reagents in mouth rinses against SARS-CoV-2. J Dent Res. 2021;100(2):124-32. http://dx.doi.org/10.1177/0022034520967933. PMid:33089717.

11. Fazio S, Affuso F, Bellavite P. A review of the potential roles of antioxidant and anti-inflammatory pharmacological approaches for the management of mild-to-moderate symptomatic COVID-19. Med Sci Monit. 2022;28:e936292. http://dx.doi.org/10.12659/MSM.936292. PMid:35256581.

12. Negrini TC, Carlos IZ, Duque C, Caiaffa KS, Arthur RA. Interplay among the oral microbiome, oral cavity conditions, the host immune response, diabetes mellitus, and its associated-risk factors-an overview. Front Oral Health. 2021;2:697428. http://dx.doi.org/10.3389/froh.2021.697428. PMid:35048037.

13. Yoon JG, Yoon J, Song JY, Yoon SY, Lim CS, Seong H, et al. Clinical significance of a high SARS-CoV-2 viral load in the saliva. J Korean Med Sci. 2020;35(20):e195. http://dx.doi.org/10.3346/jkms.2020.35.e195. PMid:32449329.

14. To KK, Tsang OT, Yip CC, Chan KH, Wu TC, Chan JM, et al. Consistent detection of 2019 novel Coronavirus in saliva. Clin Infect Dis. 2020;71(15):841-3. http://dx.doi.org/10.1093/cid/ciaa149. PMid:32047895.

15. Fini MB. Oral saliva and COVID-19. Oral Oncol. 2020;108:104821. http://dx.doi.org/10.1016/j.oraloncology.2020.104821. PMid:32474389.

16. Almanza-Reyes H, Moreno S, Plascencia-López I, Alvarado-Vera M, Patrón-Romero L, Borrego B, et al. Evaluation of silver nanoparticles for the prevention of SARS-CoV-2 infection in health workers: in vitro and in vivo. PLoS One. 2021;16(8):e0256401. http://dx.doi.org/10.1371/journal.pone.0256401. PMid:34411199.

17. O'Donnell VB, Thomas D, Stanton R, Maillard JY, Murphy RC, Jones SA, et al. Potential role of oral rinses targeting the viral lipid envelope in SARS-CoV-2 infection. Function. 2020;1(1):zqaa002. http://dx.doi.org/10.1093/function/zqaa002. PMid:33215159.

18. Wall G, Lopez-Ribot JL. Current antimycotics, new prospects, and future approaches to antifungal therapy. Antibiotics. 2020;9(8):445. http://dx.doi.org/10.3390/antibiotics9080445. PMid:32722455.

19. Vazquez-Munoz R, Lopez-Ribot JL. Nanotechnology as an alternative to reduce the spread of COVID-19. Challenges. 2020;11(2):15. http://dx.doi.org/10.3390/challe11020015.

20. Brydson R, Hammond M. Generic methodologies for nanotechnology: classification and fabrication. In: Kelsall RW, Hamley IW, Geoghegan M, editors. Nanoscale science and technology. Chichester: John Wiley & Sons Ltd; 2005. p. 1-55. http://dx.doi.org/10.1002/0470020873.ch1.

21. Sim W, Barnard RT, Blaskovich MAT, Ziora ZM. Antimicrobial silver in medicinal and consumer applications: a patent review of the past decade (2007–2017). Antibiotics. 2018;7(4):93. http://dx.doi.org/10.3390/antibiotics7040093. PMid:30373130.

22. Dilnawaz F, Acharya S, Sahoo SK. Recent trends of nanomedicinal approaches in clinics. Int J Pharm. 2018;538(1-2):263-78. http://dx.doi.org/10.1016/j.ijpharm.2018.01.016. PMid:29339248.

23. Pelaz B, Alexiou C, Alvarez-Puebla RA, Alves F, Andrews AM, Ashraf S, et al. Diverse applications of nanomedicine. ACS Nano. 2017;11(3):2313-81. http://dx.doi.org/10.1021/acsnano.6b06040. PMid:28290206.

24. Huh AJ, Kwon YJ. "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J Control Release. 2011;156(2):128-45. http://dx.doi.org/10.1016/j.jconrel.2011.07.002. PMid:21763369.

25. Teixeira MC, Carbone C, Sousa MC, Espina M, Garcia ML, Sanchez-Lopez E, et al. Nanomedicines for the delivery of Antimicrobial Peptides (AMPs). Nanomaterials. 2020;10(3):560. http://dx.doi.org/10.3390/nano10030560. PMid:32244858.

26. Ghedini E, Pizzolato M, Longo L, Menegazzo F, Zanardo D, Signoretto M. Which are the main surface disinfection approaches at the time of SARS-CoV-2? Front Chem Eng. 2021;2:589202. http://dx.doi.org/10.3389/fceng.2020.589202.

27. Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. Molecules. 2011;16(10):8894-918. http://dx.doi.org/10.3390/molecules16108894. PMid:22024958.

28. Jeremiah SS, Miyakawa K, Morita T, Yamaoka Y, Ryo A. Potent antiviral effect of silver nanoparticles on SARS-CoV-2. Biochem Biophys Res Commun. 2020;533(1):195-200. http://dx.doi.org/10.1016/j.bbrc.2020.09.018. PMid:32958250.

29. Niska K, Knap N, Kędzia A, Jaskiewicz M, Kamysz W, Inkielewicz-Stepniak I. Capping agent-dependent toxicity and antimicrobial activity of silver nanoparticles: an *in vitro* study. Concerns about potential application in dental practice. Int J Med Sci. 2016;13(10):772-82. http://dx.doi.org/10.7150/ijms.16011. PMid:27766027.

30. Yin IX, Zhao IS, Mei ML, Lo ECM, Tang J, Li Q, et al. Synthesis and characterization of fluoridated silver nanoparticles and their potential as a non-staining anti-caries agent. Int J Nanomedicine.

2020;15:3207-15. http://dx.doi.org/10.2147/IJN.S243202. PMid:32440119.

31. Molina GF, Cabalén MB, Aranguren JP, Palma SD, Pino GA, Burrow MF. Color changes and shear bond strength to simulated caries lesions treated with a novel solution of 20% silver nanoclusters in polymethacrylic acid. Sci Rep. 2022;12(1):15418. http://dx.doi.org/10.1038/s41598-022-19757-6. PMid:36104473.

32. Yin IX, Yu OY, Zhao IS, Mei ML, Li QL, Tang J, et al. Developing biocompatible silver nanoparticles using epigallocatechin gallate for dental use. Arch Oral Biol. 2019;102:106-12. http://dx.doi.org/10.1016/j.archoralbio.2019.03.022. PMid:30999064.

33. Dias HB, Bernardi MIB, Marangoni VS, Bernardi ACA, Rastelli ANS, Hernandes AC. Synthesis, characterization and application of Ag doped ZnO nanoparticles in a composite resin. Mater Sci Eng C Mater Biol Appl. 2019;96:391-401. http://dx.doi.org/10.1016/j.msec.2018.10.063. PMid:30606547.

34. Teixeira JA, Costa e Silva AV, Santos VE Jr, Melo PC Jr, Arnaud M, Lima MG, et al. Effects of a new nano-silver fluoride-containing dentifrice on demineralization of enamel and *Streptococcus mutans* adhesion and acidogenicity. Int J Dent. 2018;2018:1351925. http://dx.doi.org/10.1155/2018/1351925. PMid:29853891.

35. Han J, Chen L, Duan SM, Yang QX, Yang M, Gao C, et al. Efficient and quick inactivation of SARS coronavirus and other microbes exposed to the surfaces of some metal catalysts. Biomed Environ Sci. 2005;18(3):176-80. PMid:16131020.

36. Talebian S, Wallace GG, Schroeder A, Stellacci F, Conde J. Nanotechnology-based disinfectants and sensors for SARS-CoV-2. Nat Nanotechnol. 2020;15(8):618-21. http://dx.doi.org/10.1038/s41565-020-0751-0. PMid:32728083.

37. Seneviratne CJ, Balan P, Ko KKK, Udawatte NS, Lai D, Ng DHL, et al. Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: randomized control trial in Singapore. Infection. 2021;49(2):305-11. http://dx.doi.org/10.1007/s15010-020-01563-9. PMid:33315181.

38. Khan FR, Kazmi SMR, Iqbal NT, Iqbal J, Ali ST, Abbas SA. A quadruple blind, randomised controlled trial of gargling agents in reducing intraoral viral load among hospitalised COVID-19 patients: a structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21(1):785. http://dx.doi.org/10.1186/s13063-020-04634-2. PMid:32928313.

39. Ziaeefar P, Bostanghadiri N, Yousefzadeh P, Gabbay J, Bonjar AHS, Ahsaie MG, et al. The efficacy of mouthwashes in reducing SARS-CoV-2 viral loads in human saliva: a systematic review. New Microbes New Infect. 2022;49-50:101064. http://dx.doi.org/10.1016/j.nmni.2022.101064. PMid:36530834.

40. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015 Sep;13(3):141-6. doi: 10.1097/XEB.0000000000000050. PMID: 26134548.

41. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. http://dx.doi.org/10.1186/2046-4053-4-1. PMid:25554246.

42. Molena KF, Pinto LC, Dalben GS. The use of hyaluronic acid in individuals with cleft lip and palate: literature review. J Cleft Lip Palate Craniofacial Anomalies. 2021;8(2):143-8. http://dx.doi.org/10.4103/jclpca.jclpca_2_21.

43. Steinhauer K, Meister TL, Todt D, Krawczyk A, Paßvogel L, Becker B, et al. Comparison of the in-vitro efficacy of different mouthwash solutions targeting SARS-CoV-2 based on the European Standard EN 14476. J Hosp Infect. 2021;111:180-3. http://dx.doi.org/10.1016/j.jhin.2021.01.031. PMid:33582201.

44. Chang SY, Huang KY, Chao TL, Kao HC, Pang YH, Lu L, et al. Nanoparticle composite TPNT1 is effective against SARS-CoV-2 and influenza viruses. Sci Rep. 2021;11(1):8692. http://dx.doi.org/10.1038/s41598-021-87254-3. PMid:33888738.

45. Valdez-Salas B, Beltran-Partida E, Cheng N, Salvador-Carlos J, Valdez-Salas EA, Curiel-Alvarez M, et al. Promotion of surgical masks antimicrobial activity by disinfection and impregnation with disinfectant silver nanoparticles. Int J Nanomedicine. 2021;16:2689-702. http://dx.doi.org/10.2147/IJN.S301212. PMid:33854315.

46. Xu C, Wang A, Hoskin ER, Cugini C, Markowitz K, Chang TL, et al. Differential effects of antiseptic mouth rinses on SARS-CoV-2 infectivity in vitro. bioRxiv. 2020. https://doi.org/10.1101/2020.12.01.405662. In press.

47. Pelletier JS, Tessema B, Frank S, Westover JB, Brown SM, Capriotti JA. Efficacy of povidone-iodine nasal and oral antiseptic preparations against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2). Ear Nose Throat J. 2021;100(2S):192S-6S. http://dx.doi.org/10.1177/0145561320957237. PMid:32951446.

48. Bidra AS, Pelletier JS, Westover JB, Frank S, Brown SM, Tessema B. Rapid in-vitro inactivation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) using povidone-iodine oral antiseptic rinse. J Prosthodont. 2020;29(6):529-33. http://dx.doi.org/10.1111/jopr.13209. PMid:32511851.

49. Bidra AS, Pelletier JS, Westover JB, Frank S, Brown SM, Tessema B. Comparison of in vitro inactivation of SARS CoV-2 with hydrogen peroxide and povidone-iodine oral antiseptic rinses. J Prosthodont. 2020;29(7):599-603. http://dx.doi.org/10.1111/jopr.13220. PMid:32608097.

50. Gottsauner MJ, Michaelides I, Schmidt B, Scholz KJ, Buchalla W, Widbiller M, et al. A prospective clinical pilot study on the effects of a hydrogen peroxide mouthrinse on the intraoral viral load of SARS-CoV-2. Clin Oral Investig. 2020;24(10):3707-13. http://dx.doi.org/10.1007/s00784-020-03549-1. PMid:32876748.

51. Koch-Heier J, Hoffmann H, Schindler M, Lussi A, Planz O. Inactivation of SARS-CoV-2 through treatment with the mouth rinsing solutions ViruProX® and BacterX® Pro. Microorganisms. 2021;9(3):521. http://dx.doi.org/10.3390/microorganisms9030521. PMid:33802603.

52. Lu MM, Ge Y, Qiu J, Shao D, Zhang Y, Bai J, et al. Redox/pH dual-controlled release of chlorhexidine and silver ions from biodegradable mesoporous silica nanoparticles against oral biofilms. Int J Nanomedicine. 2018;13:7697-709. http://dx.doi.org/10.2147/IJN.S181168. PMid:30538453.

53. Ahrari F, Eslami N, Rajabi O, Ghazvini K, Barati S. The antimicrobial sensitivity of Streptococcus mutans and Streptococcus sangius to colloidal solutions of different nanoparticles applied as mouthwashes. Dent Res J. 2015;12(1):44-9. http://dx.doi.org/10.4103/1735-3327.150330. PMid:25709674.

54. Besinis A, Peralta T, Handy RD. The antibacterial effects of silver, titanium dioxide and silica dioxide nanoparticles compared to the dental disinfectant chlorhexidine on Streptococcus mutans using a suite of bioassays. Nanotoxicology. 2014;8(1):1-16. http://dx.doi.org/10.3109/17435390.2012.742935. PMid:23092443.

55. Du T, Lu J, Liu L, Dong N, Fang L, Xiao S, et al. Antiviral activity of graphene oxide-silver nanocomposites by preventing viral entry and activation of the antiviral innate immune response. ACS Appl Bio Mater. 2018;1(5):1286-93. http://dx.doi.org/10.1021/acsabm.8b00154. PMid:34996232.

56. Guimarães TC, Marques BBF, Castro MV, Secco DA, Porto LCMS, Tinoco JMM, et al. Reducing the viral load of SARS-CoV-2 in the saliva of patients with COVID-19. Oral Dis. 2022;28(Suppl 2):2474-80. http://dx.doi.org/10.1111/odi.14118. PMid:34963033.

57. Elechiguerra JL, Burt JL, Morones JR, Camacho-Bragado A, Gao X, Lara HH, et al. Interaction of silver nanoparticles with HIV-1. J Nanobiotechnology. 2005;3(1):6. http://dx.doi.org/10.1186/1477-3155-3-6. PMid:15987516.

58. Lara HH, Ixtepan-Turrent L, Treviño ENG, Singh DK. Use of silver nanoparticles increased inhibition of cell-associated HIV-1 infection by neutralizing antibodies developed against HIV-1 envelope proteins. J Nanobiotechnology. 2011;9(1):38. http://dx.doi.org/10.1186/1477-3155-9-38. PMid:21923937.

59. Fayaz AM, Ao Z, Girilal M, Chen L, Xiao X, Kalaichelvan P, et al. Inactivation of microbial infectiousness by silver nanoparticles-coated condom: a new approach to inhibit HIV- and HSV-transmitted infection. Int J Nanomedicine. 2012;7:5007-18. PMid:23049252.

60. El-Mohamady RS, Ghattas TA, Zawrah MF, El-Hafeiz YGMA. Inhibitory effect of silver nanoparticles on bovine herpesvirus-1. Int J Vet Sci Med. 2018;6(2):296-300. http://dx.doi.org/10.1016/j.ijvsm.2018.09.002. PMid:30564612.

61. Lv X, Wang P, Bai R, Cong Y, Suo S, Ren X, et al. Inhibitory effect of silver nanomaterials on transmissible virus-induced host cell infections. Biomaterials. 2014;35(13):4195-203. http://dx.doi.org/10.1016/j.biomaterials.2014.01.054. PMid:24524838.

62. Mori Y, Ono T, Miyahira Y, Nguyen VQ, Matsui T, Ishihara M. Antiviral activity of silver nanoparticle/chitosan composites against H1N1 influenza A virus. Nanoscale Res Lett. 2013;8(1):93. http://dx.doi.org/10.1186/1556-276X-8-93. PMid:23421446.

63. Morris D, Ansar M, Speshock J, Ivanciuc T, Qu Y, Casola A, et al. Antiviral and immunomodulatory activity of silver nanoparticles in experimental RSV infection. Viruses. 2019;11(8):732. http://dx.doi.org/10.3390/v11080732. PMid:31398832.

64. Herrera D, Serrano J, Roldán S, Sanz M. Is the oral cavity relevant in SARS-CoV-2 pandemic? Clin Oral Investig. 2020;24(8):2925-30. http://dx.doi.org/10.1007/s00784-020-03413-2. PMid:32577830.

65. Carrouel F, Viennot S, Ottolenghi L, Gaillard C, Bourgeois D. Nanoparticles as anti-microbial, anti-inflammatory, and remineralizing agents in oral care cosmetics: a review of the current situation. Nanomaterials. 2020;10(1):140. http://dx.doi.org/10.3390/nano10010140. PMid:31941021.

66. Pilaquinga F, Morey J, Torres M, Seqqat R, Piña MLN. Silver nanoparticles as a potential treatment against SARS-CoV-2: a review. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2021;13(5):e1707. http://dx.doi.org/10.1002/wnan.1707. PMid:33638618.

67. Santos PSS, Orcina BF, Machado RRG, Vilhena FV, Alves LMC, Zangrando MSR, et al. Beneficial effects of a mouthwash containing an antiviral phthalocyanine derivative on the length of hospital stay for COVID-19: randomised trial. Sci Rep. 2021;11(1):19937. http://dx.doi.org/10.1038/s41598-021-99013-5. PMid:34620904.

Kelly Fernanda Molena
(Corresponding address)
Pós Graduanda do Programa de Odontopediatria, Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil
Email: kelly.molena@usp.br

Date submitted: 2022 Dec 02
Accept submission: 2023 Apr 17