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ADVANCED REVIEW

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Silver nanoparticles as a potential treatment against SARS-CoV-2: A review

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Abstract

Several human coronaviruses (HCoVs) are distinguished by the ability to generate epidemics or pandemics, with their corresponding diseases characterized by severe respiratory illness, such as that which occurs in severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and, today, in SARS-CoV-2, an outbreak that has struck explosively and uncontrollably beginning in December 2019 and has claimed the lives of more than 1.9 M people worldwide as of January 2021. The development of vaccines has taken one year, which is why it is necessary to investigate whether some already-existing alternatives that have been successfully developed in recent years can mitigate the pandemic's advance. Silver nanoparticles (AgNPs) have proved effective in antiviral action. Thus, in this review, several *in vitro* and *in vivo* studies of the effect of AgNPs on viruses that cause respiratory diseases are analyzed *and discussed* to promote an understanding of the possible interaction of AgNPs with SARS-CoV-2. The study focuses on several *in vivo* toxicological studies of AgNPs and a dose extrapolation to humans to determine the chief avenue of exposure. It can be concluded that the use of AgNPs as a possible treatment for SARS-CoV-2 could be viable, based on comparing the virus' behavior to that of similar viruses in *in vivo* studies, and that the suggested route of administration in terms of least degree of adverse effects is inhalation.

This article is categorized under:

Nanotechnology Approaches to Biology > Nanoscale Systems in Biology

Therapeutic Approaches and Drug Discovery > Nanomedicine for Respiratory Disease

Toxicology and Regulatory Issues in Nanomedicine > Toxicology of Nanomaterials

KEYWORDS

COVID-19, *in vitro* studies, *in vivo* studies, SARS-CoV-2, Silver Nanoparticles

1 | INTRODUCTION

Viruses are pathogens that cause significant increasing morbidity and mortality around the world. For instance, viruses have been reported to cause 2 M human deaths annually worldwide (Colpitts, Verrier, & Baumert, 2015). Their

potential negative health impacts stem from their highly contagious nature and a lack of effective control systems (Morens, Folkers, & Fauci, 2004). The limitation of current detection systems potentially increases the incidence and outbreak of viral infections (Gushulak & MacPherson, 2004).

In nature, viruses exist in different morphologies, ranging from 20 to 900 nm (Passi, Sharma, Dutta, Dudeja, & Sherma, 2015). Their infectious material usually comprises defined units of proteins and nucleic acids that assemble to form nanoparticle (NP) structures called virions. The difficulties involved in establishing a virus detection system stem from their nano size and simple structure compared to other specimens.

In recent years, a specific virus type has caught the attention of the scientific community. Human coronaviruses (HCoVs) have caused severe respiratory diseases, such as those caused by severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and, currently, SARS-CoV-2. *The search for a drug against this last virus has become a race against time*. At the end of January 2021, 92 M people had been reported as infected, and 1.9 M people have died (WHO, 2021).

Nanotechnology has shown promise in fighting viruses. Nanotechnology in biomedicine involves the development of individual components with nanoscale features (10^{-9} m) that allow for the creation of revolutionary biomolecular machines that can recognize certain types of cells, viruses, bacteria, and fungi. These systems are capable of transferring information from the nano level to the macromolecular level (Al-Nemrawi, AbuAlSamen, & Alzoubi, 2020). NPs are often studied because of their unique properties, such as small size, improved solubility, surface adaptability, and multifunctionality, which can lead to the development of better and safer drugs, tissue-targeted treatments, personalized nanomedicines, and early diagnosis and prevention of diseases (Soares, Sousa, Pais, & Vitorino, 2018). Many nano-based formulations have been found to improve the target delivery and therapeutic efficacy of antiviral drugs (Lembo, Donalisio, Civra, Argenziano, & Cavalli, 2018). Thus, interest in nanotechnology has grown greatly since the beginning of the COVID-19 pandemic, and various studies related to its potential contribution in different areas have been published (Abdul, Muhammad, Atta Ullah, Asmat, & Abdul, 2020; Aranda et al., 2020; Cardoso et al., 2020; Jindal & Gopinath, 2020; Jones et al., 2020; Talebian, Wallace, Schroeder, Stellacci, & Conde, 2020).

Countless NPs, and the different ways of using them, have been studied in recent years regarding their effectiveness against certain viruses that cause major respiratory diseases (Zhang, Salieb-Beugelaar, Nigo, Weidmann, & Hunziker, 2015). NPs can be used as part of a vaccine or can deliver drugs to a specific organ or tissue (Karthik Pandiyan & Prabaharan, 2020). Some NPs have been used in vaccines for certain types of respiratory diseases caused by H1N1 influenza (g-PGAa, chitosan, ferritin, Au), human parainfluenza virus type 3 (HPIV3) (PLGA), and respiratory syncytial virus (RSV) (polyanhydrides). NPs allow for the stabilizing and release of the active components of vaccines in the body; they can also act as transport vehicles (Lee & Wang, 2006). For the transport of vaccines through mucosa, NP size is important; it is very difficult for NPs with a diameter of over 100 nm to penetrate the mucosal barrier, unlike those of fewer than 50 nm.

A wide range of nanomaterials are used for virus detection, such as metal NPs (Cho & Glenn, 2020; Dougan, Karlsson, Smith, & Graham, 2007; Shan et al., 2020), polymeric NPs (Zhang et al., 2020), dendrimers (Kandeel, Al-Taher, Park, Kwon, & Al-Nazawi, 2020; Paull, Castellarnau, Luscombe, Fairley, & Heery, 2020), carbon nanotubes (Aasi, Aghaei, Moore, & Panchapakesan, 2020; Pinals et al., 2020; Sengupta & Hussain, 2021; Yang, 2020), graphene (Kumar Raghav & Mohanty, 2020; Srivastava et al., 2020), and virus-like NPs (VLN) (Medhi, Srinoi, Ngo, Tran, & Lee, 2020), among others. These NPs are widely described as being suitable for numerous biosensing functions and applications that interact specifically with various biomolecules, like antibodies, DNA, and RNA, and represent the principal strategy of a large number of virus detection systems (Liao, Nehl, & Hafner, 2006).

Metallic NPs have been used in a myriad of ways. Some types of metallic NPs, like silver (Galdiero et al., 2011; Ghiuță & Cristea, 2020), copper (Jagaran & Singh, 2020), titanium (Khaiboullina, Uppal, Dhabarde, Subramanian, & Verma, 2020), zinc oxide, and iron oxide (Sarkar & Das Mukhopadhyay, 2021), have been incorporated into consumer products, including personal protective equipment (PPE) (masks and biosecurity suits) (Campos et al., 2020; Palmieri, De Maio, De Spirito, & Papi, 2021), disinfectants (Talebian et al., 2020), and cosmetics (Raj, Sumod, Jose, & Sabitha, 2012), among others (FDA, 2020). However, Talebian et al. (2020) proposed an alternative use of silver, copper, and titanium dioxide metallic NPs because of their broad-spectrum antiviral activity, persistence, and ability to be effective in much lower doses. Regarding detecting SARS-CoV-2, the principal technique is the real-time RT-PCR (reverse transcription polymerase chain reaction) test, which consists of correctly and effectively extracting viral RNA; to expedite this process and analyze a larger number of samples, magnetic NPs have been used (Zhao et al., 2020).

In recent months, biosensors utilizing metallic NPs have been developed that are sensitive to detecting the sequence of the SARS-CoV-2 N gene, such as in the naked-eye virus screening approach using gold NPs (AuNPs) capped by properly designed antisense oligonucleotides (Moitra, Alafeef, Dighe, Frieman, & Pan, 2020). In another example of NPs as

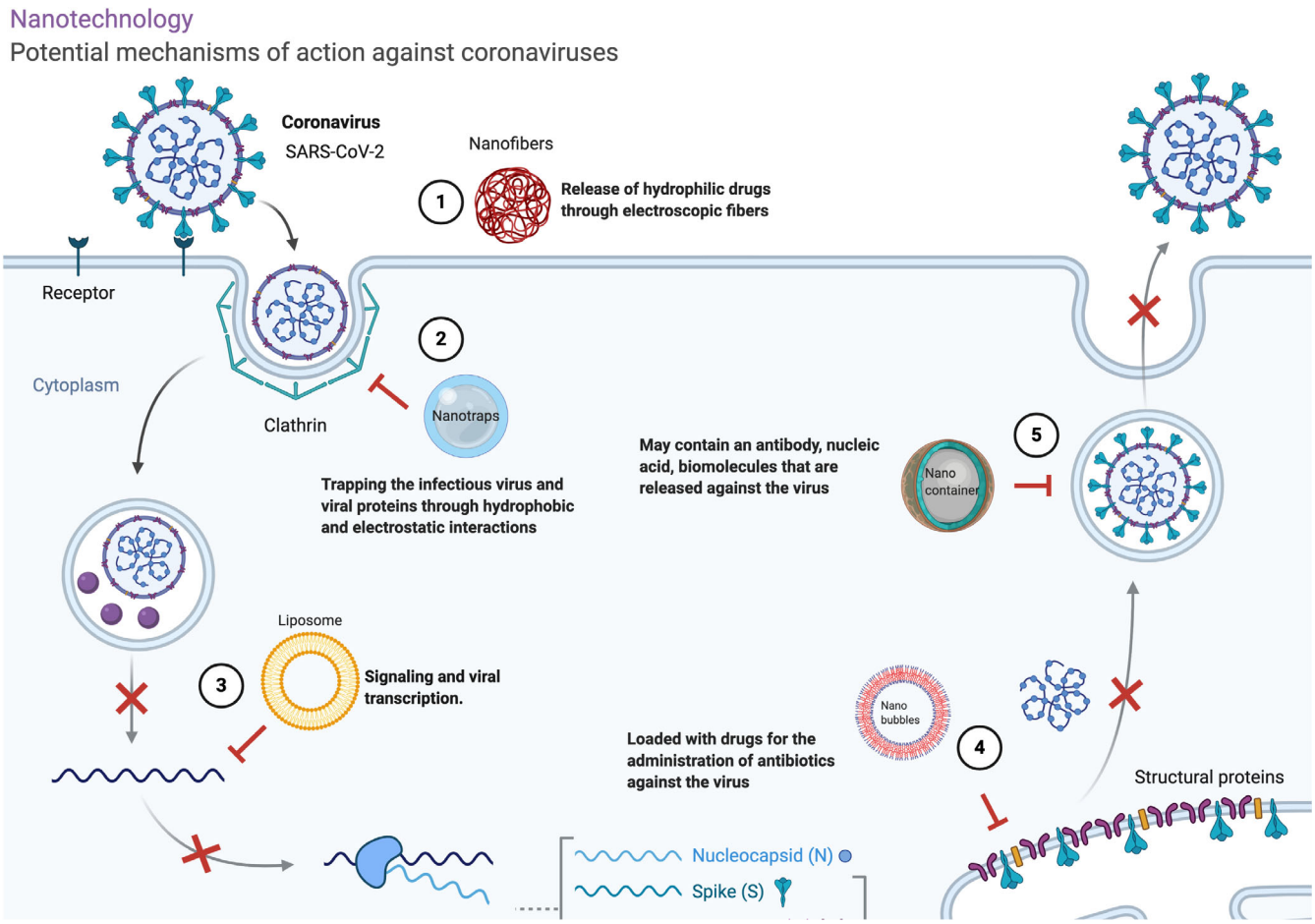

FIGURE 1 Possible mechanisms of the use of nanotechnology through nanobubbles, nanofibers, nanotraps, nanorobots, nanopolymers, nanodiamonds, and nanotransporters of biomolecules and drugs with antiviral action

electrochemical biosensors, ssDNA-capped AuNPs were placed on graphene-coated filter paper (Alafeef, Dighe, Moitra, & Pan, 2020). Further, used with porous nanomaterials, such as metal-organic frameworks (MOF), which is a class of porous polymers consisting of clusters and metal ions coordinated with polytopic organic linkers, NPs can detect different viruses, including SARS-CoV-2 (Rabiee et al., 2020; Seo et al., 2020). Another biosensor using cobalt-doped titanium dioxide nanotubes showed excellent results in detecting SARS-CoV-2 virus within 30 s in a wide range of concentrations (Vadlamani, Uppal, Verma, & Misra, 2020).

Although NPs' antiviral properties have been determined, the reaction of the human body and, therefore, the efficacy of NPs as drugs depends on the distribution of plasma proteins on their surface. NPs are designed to direct their action toward binding and penetration and in that way block the replication of viruses. They use mechanisms that either directly or indirectly inactivate the virus, which prevents the virus from binding to the host cells and blocks viral replication, as seen in Figure 1. Other mechanisms of action of NPs are related to their local action against receptors on the surface of the virus, where they alter the membrane potential and block virus penetration to a great extent (Abdul et al., 2020; Gurunathan et al., 2020).

Among the different types of metallic NPs, the antiviral activity of silver NPs (AgNPs) on SARS-CoV-2 is of particular interest (Argentiere, Cella, Cesaria, Milani, & Lenardi, 2016; Das et al., 2020; Durán, Silveira, Durán, & Martinez, 2015; Hossain, 2020; Teirumnieks, Balchev, Ghalot, & Lazov, 2021). AgNPs are known for their high antimicrobial activity, biocompatibility, and low toxicity in eukaryotic cells. There are few *in vitro* studies regarding the use of AgNPs against SARS-CoV-2 (Jeremiah, Miyakawa, Morita, Yamaoka, & Ryo, 2020), as *in vivo* studies are a more urgent need.

This study presents a review of the use of AgNPs against SARS-CoV-2. The properties of AgNPs and their possible interaction, *in vitro* and *in vivo* studies on viruses causing respiratory diseases, the toxicity of AgNPs induced by inhalation, dermal, and oral routes for AgNPs, and the dose extrapolation to humans, as a possible treatment for this virus.

2 | CORONAVIRUS SARS-CoV-2

The Coronaviridae family of viruses has affected mankind since the beginning of the twentieth century, and these virus' sudden mutations in short periods have complicated the development of a specific treatment to limit their spread and lethality (Bonilla-Aldana et al., 2020; de Wit, van Doremalen, Falzarano, & Munster, 2016; Lin, Hsu, & Lin, 2014). For example, SARS-CoV crossed the species barrier in late 2002: the bat that carries the virus transferred it to an intermediate species, which then transferred it to humans, and its transmission was nosocomial and presented a lethality of 30% (Aguanno et al., 2018; Lin et al., 2018). Another HCoV disease, MERS-CoV, was reported in the 1980s in camels; however, it did not begin to spread in humans until 2012, with a mortality of 36% (Chan et al., 2013). Two other HCoVs, HCoV-NL63 and HCoV-HKU1, appeared in 2004 and 2005, respectively; only minimal control efforts were needed, so their lethality is not fully known (Kasmi, Khataby, Souiri, & Ennaji, 2020).

SARS-CoV-2 was first detected in December 2019 in Wuhan City, Hubei Province (China); it has a percentage of lethality of 2% to 3% but is extremely contagious (Scavone et al., 2020; Weiss & Navas-Martin, 2005). The virus produces symptoms similar to those of a common cold and more serious diseases such as severe pneumonia and respiratory failure. It particularly affects elderly people with preexisting conditions (Chen et al., 2020). The main route of infection is through the respiratory tract, although various sources of infection, such as tears and feces, have been reported (Li et al., 2020). The virus can survive as a particle suspended in the air for 3 h, and its incubation period is from 2 to 14 days (Dong, Du, & Gardner, 2020).

SARS-CoV-2 is the seventh type of coronavirus isolated in humans; it belongs to the genus β CoV, is round in shape with a crown appearance, and measures 60 to 140 nm in diameter under an electron microscope (Lu et al., 2020). It has a positive-sense, single-stranded genome made of RNA (+ssRNA), contains 29,891 nucleotides encoding 9880 amino acids (−29.8 kbp), and has a 5′ cap structure and 3′ poly-A tail. The genomic RNA between ORF1a and ORF1b (open reading frames) is used for the direct production of two polypeptides: polyprotein 1a/1ab (pp1a/pp1ab), which encodes nonstructural proteins (nsps) (Guo et al., 2020).

The physiological binding of SARS-CoV-2 in the body is via epithelial cells containing surface sialic acids that bind with galactose α-2,6. Sialic acid is an abundant molecule in all cells and defines the particular tropism of respiratory viruses, the epithelial cells that line the human trachea contain mainly carbohydrates and have an α-2,6 bond (Allen, Tennant, & Franklin, 2019; Diefenbach, Gnafakis, & Shomrat, 2020; Kumazaki, Shimomura, Kiyono, Ochiya, & Yamamoto, 2020), which is why SARS-CoV-2 generally first enters the body here.

SARS-CoV-2 binds to its receptor in the host cell through the transmembrane spike protein (S), which forms homodimers that leave the viral surface. It is composed of two units, S1 and S2, which are responsible for binding with the host cell receptor and viral membrane fusion. The virus has been shown to bind to the angiotensin-converting enzyme 2 (ACE2) receptor and is a significant determinant for the pathogenesis of CD209L infection (a C-type lectin, also called L-SIGN, and dipeptidyl peptidase 4 [DPP4], also known as CD26), which promotes transmission to humans and other species and their cellular infection (Li, Geng, Peng, Meng, & Lu, 2020). The envelope protein (E) is located in an intracellular traffic site, such as the Golgi complex, where it participates in its self-assembly and is considered very important in the production and maturation of the viral particle (Schoeman & Fielding, 2019). The nucleocapsid protein (N) directs the genome to replicate, transcribe, and package. Additionally, the membrane protein (M) collaborates in the fixation of the nucleocapsid to the membrane of internal structures such as the Golgi complex and is responsible for the transmembrane transport of nutrients, the release of the virion, and the formation of the envelope (Cui, Li, & Shi, 2019). Once the viral genome is inside the cytoplasm and translates into two polyproteins and structural proteins, it begins to replicate (Huang et al., 2020). The envelope (E) glycoproteins are inserted into the Golgi endoplasmic reticulum membrane, and the nucleocapsid is formed by the combination of genomic RNA and the N protein. In these vesicles containing the virus particles, viral replication and transcription occur (Kasmi et al., 2020).

3 | AgNPS: *IN VITRO* AND *IN VIVO* STUDIES

One of the most commonly used inorganic materials for fighting bacterial and viral diseases is silver (Sondi & Salopek-Sondi, 2004). Silver is a noble metal that has been used since antiquity. In ionic form, it is used in concentrations higher than 40% to treat skin diseases such as warts and granulomas. As 1% silver sulfadiazine, it is used for burns and skin ulcers (Murthy, 2007; Ramírez, 2013). Currently, the use of ionic colloidal silver as an alternative treatment for

SARS-CoV-2 has gained popularity through the Internet. However, the Food and Drug Administration (FDA) does not recognize it as a safe and effective agent (Morrill et al., 2013).

Like NPs, AgNPs have a wide range of biomedical applications (Prabhu & Poulose, 2012) because of their antibacterial capacity and selective toxicity against microorganisms (Wong & Liu, 2010). Various studies have indicated that AgNPs can adhere to the cellular membrane, altering cellular permeability, and the cell's respiratory functions. It is possible they not only interact with the membrane surface but also penetrate the bacteria. Further, silver ions can link with thiol groups of biomolecules and with phosphorus sulfide compounds, such as when DNA inactivates bacteria. Many studies concerning AgNPs' antimicrobial activity have been published (Alafeef, Moitra, & Pan, 2020; Devanesan, Ponmurugan, AlSalhi, & Al-Dhabi, 2020; Elmehbad & Mohamed, 2020; Garibo et al., 2020; Rao, Saptami, Venkatesan, & Rekha, 2020; Sharma et al., 2020; Taghavizadeh Yazdi et al., 2020).

AgNPs have a highly reactive surface area in addition to unique optical and catalytic properties, unlike ionic colloidal silver (Marimuthu et al., 2020). Their surface chemistry controls AgNPs' properties and functionality. Various studies have demonstrated that silver nanoconjugates can easily enter living cells (Abdellah, Sliem, Bakr, & Amin, 2018). The use of organic compounds to stabilize AgNPs, whose function is to coat the surface and avoid coalescence phenomena that induce aggregation and, consequently, loss of characteristic properties. Stabilizing agents can be simple molecules or polymers, with or without surfactant characteristics, that interact with the surface of the AgNPs through their hydrophobic segments (Du et al., 2018; Randazzo, Fabra, Falcó, López-Rubio, & Sánchez, 2018).

The size and shape of AgNPs play a very important role in antiviral activity. Several studies have shown that dimensions smaller than 10 nm produce much more reactive surfaces (Marimuthu et al., 2020). The shape can also vary—for example, triangular, bar, or spiral—which drastically affects the mechanism of viral action; those of the spherical and cylindrical type are more phagocytosed (Soiza, Donaldson, & Myint, 2018).

Many studies have pointed out the antiviral activity that AgNPs exert on different virus types that cause respiratory illness, such as influenza (Mehrbod et al., 2009), HPIV3 (Galdiero et al., 2013), human adenovirus serotype 3 (Ad3) (Nana Chen, Zheng, Yin, Li, & Zheng, 2013), *respiratory syncytial virus* (RSV) (Yang, Li, & Huang, 2016), and Rift Valley fever (RFV) (Borrego et al., 2016). In a recent *in vitro* study using polyvinylpyrrolidone-coated AgNPs in Vero cells infected with SARS-CoV-2, the almost complete inhibition of the virus' replication was confirmed using NPs with diameters of 10 nm, as well as lower toxicity compared to NPs of smaller and larger sizes (Jeremiah et al., 2020). Other viruses for which AgNPs have been assayed, include the human immunodeficiency virus (HIV) (Elechiguerra et al., 2005; Lara, Ayala-Nuñez, Ixtepan-Turrent, & Rodriguez-Padilla, 2010), herpes (HV) (Baram-Pinto, Shukla, Perkas, Gedanken, & Sarid, 2009; Hu et al., 2014; Orlowski et al., 2014), hepatitis (HBV) (Lu et al., 2008), Ebola virus (Yen et al., 2015), Tacaribe virus (Speshock, Murdock, Braydich-Stolle, Schrand, & Hussain, 2010), monkeypox virus (Rogers, Parkinson, Choi, Speshock, & Hussain, 2008), African swine fever virus (Thi Ngoc Dung et al., 2020), porcine epidemic diarrhea virus (PEDV) (Du et al., 2018), polio virus (Huy et al., 2017), and dengue virus (Suresh et al., 2015), among others.

Both *in vitro* and *in vivo* studies have been conducted with AgNPs and various viruses. When comparing studies on AgNPs' antiviral activity with that of other metallic NPs (e.g., iron oxides NPs, ZnONPs, AuNPs, TiO_2NPs, CaONPs, and ZrONPs) for a specific virus like influenza A, we find a higher number of both *in vitro* and *in vivo* studies (Wieczorek, Szutkowska, & Kierzek, 2020). The first study related to the antiviral properties of AgNPs was conducted by Mehrbod et al. (2009), which demonstrated the 78% reduction of viral load after exposing the influenza virus to the treatment.

Finally, AgNPs have been tested in an influenza vaccine as an adjuvant to improve the immune response by increasing the production of immunoglobulin IgA, a predominant antibody in seromucosal secretions and an important defense against viral infections (Sanchez-Guzman et al., 2019).

Table 1 summarizes the most important information of *in vitro* and *in vivo* studies of AgNPs antiviral activity on different viruses that cause respiratory diseases, such as SARS-CoV-2, influenza, HPIV3, Ad3, *RSV*, *and* RFV.

According to the studies carried out, AgNPs act directly with the viral genome through the proteins found on its surface (Mehrbod et al., 2009; Xiang et al., 2011). Infection with influenza viruses H1N1 and H7N3, HPIV3, Ad3, RSV, RVF, and SARS-CoV-2 starts by binding protein S to the specific host receptor (Borrego et al., 2016; Chen et al., 2013; Fatima et al., 2016; Galdiero et al., 2013; Huang et al., 2020; Park et al., 2018; Yang et al., 2016). This protein allows the virus to bind with the ACE2 receptor conversion enzyme (Jiang & He, 2012). According to its crystal structure, SARS-CoV-2 contains disulfide bonds Cys336-Cys361, Cys379-Cys432, and Cys391-Cys525. Cys480-Cys488 is key in the junction between the virus crest and the N-terminal helix of ACE2 (Kang et al., 2020; Walls et al., 2020).

TABLE 1 *In vitro* and *in vivo* studies of silver nanoparticles' (AgNPs) effects on viruses that cause respiratory diseases

Virus	Antiviral NPs	Size (nm)	Concentration, (Time), Route of Administration	Type of Cells/ Model	Brief Results	References
SARS-CoV-2	AgNPs-polyvinylpyrrolidone (PVP)	2–100	0.1 to 10 ppm	Vero	Different sizes of AgNPs-PVP were analyzed. At 10 nm, a larger percentage of viral replication inhibition was shown	Jeremiah et al. (2020)
Influenza H1N1	AgNPs	10	6.25, 12.5, 25, 50, 100, 200 μg/ml (24 and 48 h)	Madin-Darby Canine Kidney (MDCK)	Binding of AgNPs with glycoproteins of the viral envelope, inhibiting viral entry into the host cell	Xiang, Chen, Pang, and Zheng (2011)
Influenza H1N1	AgNPs	5–20	4, 2, 1, 0.25, 0.125, 0.06, and 0.03 μg/ml (48 h)	MDCK	AgNPs form a disulfide bond that blocks virus binding receptors, increasing antiviral activity	Mehrbod et al. (2009)
Influenza H1N1	AgNPs-chitosan	3–12	Viral suspension in Phosphate-buffered saline PBS (250 μl, titer ca. 1,000 $TCID_{50}$)	MDCK	Increased antiviral activity by chitosan and inhibition of virus reproducibility	Mori et al. (2013)
Influenza H1N1	AgNPs-oseltamivir (OTV)	2–3	0.3125, 0.625, 1.25, and 2.5 μg/ml (24 h)	MDCK	OTV reduces the toxicity of AgNPs and also inhibits neuraminidase and hemagglutinin, preventing binding with the virus	Li et al. (2016)
Influenza H1N1	AgNPs-peptides (FlulPed)	10	0.008 to 0.2 nmol L^{-1}	MDCK	The peptide disables the formation of a viral surface in healthy cells, enhanced by the antiviral properties of AgNPs	Alghrair, Fernig, and Ebrahimi (2019)
Influenza H1N1	AgNPs-zanamivir	2–3	1.25, 2.5, 5, and 10 μg/ml (2 h)	MDCK	Functionalized AgNPs inhibited neuraminidase activity; in addition, the cytopathic effect demonstrated that the nanomaterial withstands the attack of the virus and prevents the death of healthy cells	Lin et al. (2017)
Influenza H1N1	AgNPs-amantadine	2–3	20 μl solution well MTT (5 h)	MDCK	The presence of functionalized AgNPs increased cell viability by 90% and inhibited virus proliferation by deactivating hemagglutinin and neuraminidase	Li et al. (2016)
Influenza H1N1	AgNPs–SiO_2	400	10×10^{10} particles/ml (1, 6, 12, and 24 h)	MDFK	AgNPs reduce virus infection due to their interaction with the viral components of the membrane	Park et al. (2018)

TABLE 1 (Continued)

Virus	Antiviral NPs	Size (nm)	Concentration, (Time), Route of Administration	Type of Cells/ Model	Brief Results	References
Influenza H7N3	AgNPs–*Cinnamomum cassia* (cinnamon)	42	15.6, 31.25, 62.5, 125, 250, and 500 μg/ml (24 h)	Vero	Cinnamon-reduced AgNPs exhibited improved viricidal activity against the virus; the concentration used was nontoxic to cells	Fatima, Zaidi, Amraiz, and Afzal (2016))
Influenza A subtype (H3N2)	AgNPs	9.5 ± 0.8	6.25, 12.5, 25, and 50 μg/ml (48 h) 5 and 20 mg/kg (14 days), inhalation	MDCK Mice BALB/c	*In vitro*, at lower concentrations than 12.5 μg/ml, virus replication decreased due to the decrease in hemagglutinin levels Infected mice without inhalation of AgNPs died on day 7, while those exposed to the nanomaterial had a survival rate of 75% to 88%. However, they showed weight loss. Pulmonary analysis indicated that the virus spread was less with the use of AgNPs	Xiang et al. (2013)
HPIV3	AgNPs-Alternaria AgNPs-Phoma *AgNPs-F. oxysporum *AgNPs-Curvularia	46 40 20 30	1, 5, 10, 50, and 100 μg/ml (1, 3, 10, 24, and 36 h)	Vero	Phenolic compounds extracted from rosemary *Rosmarinus officinalis L* prevented entry and inhibited viral DNA replication	Galdiero et al. (2013)
Ad3	AgNPs	11.4 ± 6.2	3.125, 6.25, 12.5, 25, 50, 100, 200, and 400 μg/ml (48 and 96 h)	Hela	The presence of AgNPs increased the viability of the cells and decreased the fluorescence intensity of the virus; this was potentially caused by the destruction of the viral structure	Chen et al. (2013))
RSV	AgNPs-Curcuma longa (ginger)	11.95 ± 0.23	0.008, 0.015, 0.03, 0.06, 0.12, and 0.24 nmol/L (24 and 72 h)	CCK-8	*Curcuma longa* better stabilizes AgNPs, increasing antiviral properties that inhibit virus entry and replication	Yang et al. (2016)
RSV	AgNPS-PVP	10	10, 25, and 50 g/ml (24 and 48 h) 2 and 4 mg/kg, (16 days), inhalation	A549 (type II) and HEp-2 Mice BALB/c	*In vitro*, the concentrations used did not generate cytotoxic effects after 24 h, but concentrations less than or equal to 10 g/ml increased virus replication *In vivo*, the concentrations used inhibited the replication of the virus between 45% and 55%; the mice did not lose weight or show adverse effects due to AgNPs	Morris et al. (2019)

(Continues)

TABLE 1 (Continued)

Virus	Antiviral NPs	Size (nm)	Concentration, (Time), Route of Administration	Type of Cells/ Model	Brief Results	References
RVF	AgNPs-PVP. Argovit	35 ± 15	1/5000, 1/10,000 (24, 48, and 72 h) 1/1000, 1/100, 1/10 (10 to 15 days), Parenteral	Vero Transgenic Mice 129Sv/Ev IFNAR −/−	*In vitro*, the Argovit did not abolish viral production in its entirety; the reduction in virus production was 50% compared to the use of uncoated AgNPs. With 12 μg/ml of metallic silver, a reduction in infectivity of 98% could be achieved *In vivo*, mice with a lethal dose of the virus (1.2 mg/ml silver) showed disease and late clinical mortality; their survival was 60%	Borrego et al. (2016)

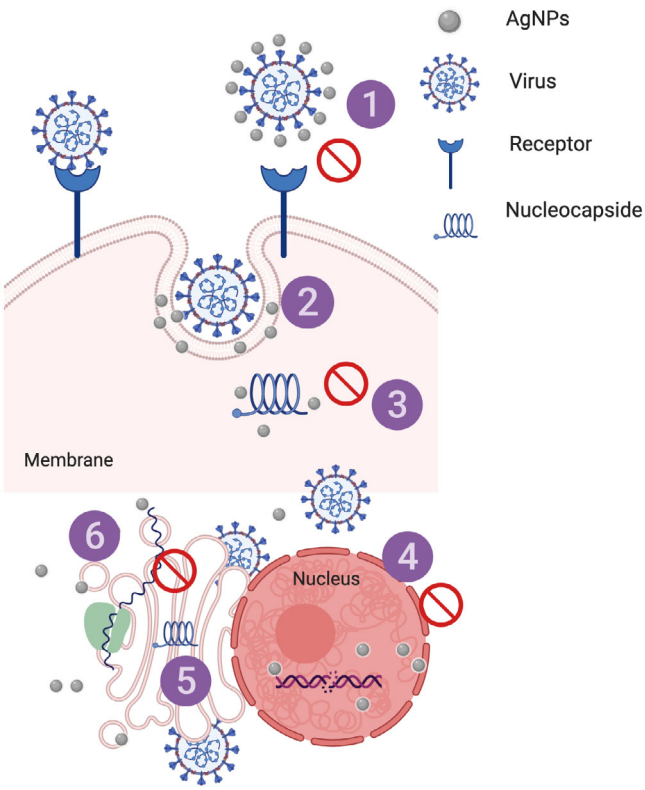

FIGURE 2 Mechanism of AgNPs' antiviral effect on different stages of virus replication: (1) interaction with viral surface, (2) interference with viral attachment, (3) inhibition of virus penetration into the cell, (4) interaction with viral genome, (5) inhibition of genome replication, (6) inhibition of protein synthesis

As Figure 2 shows, AgNPs bind to membrane of spike (S) glycoprotein through disulfide bonds, due to their chemical affinity for sulfur (Chung, Chen, & Chen, 2008; Yuan, He, Huang, & Su, 2019). This interaction hinders the internalization of the virus in the cells by inhibiting the interaction between the glycoprotein and its specific receptor. Cellular absorption of AgNPs occurs through the processes of endocytosis and macropinocytosis. Once inside the cell, the AgNPs inhibit the virus's replication capacity (Galdiero et al., 2011).

AgNPs also appear to exert an effect on H (hemagglutinin) and N (neuraminidase) proteins, which are the main determinants of pathogenicity. If AgNPs are also combined with oseltamivir (OTV), FlulPed, zanamivir, and amantadine (Alghrair et al., 2019; Li, Lin, Zhao, Guo, et al., 2016; Li, Lin, Zhao, Xu, et al., 2016) drugs, which possess antiviral properties and are currently used against SARS-CoV-2, reactive oxygen species (ROS) are produced, which minimize the destruction of MDFK cells and inhibit the neuraminidase and hemagglutinin activity of viruses with healthy cells (Li, Lin, Zhao, Xu, et al., 2016). Coatings also modify AgNPs' effects; for example, chitosan stabilizes AgNPs and allows them to increase their virucidal capacity, though their size modifies the mechanism of action (Mori et al., 2013). The use of other types of coatings, such as chitosan (Mori et al., 2013), SiO_2 (Park et al., 2018), *Cinnamomun cassia* (Fatima et al., 2016), *Curcuma longa* (Yang et al., 2016), and polyvinylpyrrolidone (Borrego et al., 2016; Morris et al., 2019), markedly reduce cellular cytotoxicity compared to uncoated AgNPs. The antioxidant, anti-inflammatory, and antibacterial properties from the plant from which the coating is derived.

4 | TOXICITY OF AgNPs: *IN VIVO* STUDIES

Despite the marked antiviral effect of AgNPs, currently in Europe, there is no specific legislation for NPs, although they are classified as a "substance" in the European Regulation of Chemical Substances (REACH) (Regulation No. 1907/2006 of the Parliament, December 18, 2006). In the United States, the regulation of AgNPs by the FDA is limited by the impact that silver, as an element, can have on the environment (Sood & Chopra, 2018)

The use of AgNPs is in the preclinical phase, and a general assessment of public health risk is not yet possible, although several products are on the market. Due to their applications, especially in relation to pandemic control, we must assume that human exposure to AgNPs will increase substantially in the immediate future. The main factors that determine the toxic effects of AgNPs in organisms are classified according to the route of exposure (entry,

concentration, and duration), factors that depend on the exposed organism, and those related to AgNPs' intrinsic toxicity (del Rocío Coutiño, Ávila, & Helguera, 2017), bioavailability, and accumulation in the body.

There are three main routes of exposure to AgNPs: inhalation, dermal/parenteral, and oral. Table 2 shows various published *in vivo* studies on toxicity that have used AgNPs. According to these studies, AgNPs' cytotoxic effect depends on their size, tissue distribution, penetration capacity, and cellular absorption (Khandelwal et al., 2014).

After entering the body, the largest AgNPs can be exhaled, while the smallest AgNPs can be deposited in the lungs and can reach other organs through the bloodstream. With average sizes of 15 to 30 nm and in concentrations of 0.5 to 381 μg/m^3, according to histopathological analysis, no significant changes regarding AgNPs presence after exposure were found in the nasal cavities (Hyun et al., 2008), lungs (Song et al., 2013), or liver (Kim et al., 2011), among other organs (Ji et al., 2007). However, at high concentrations above 2.9 mg/m^3, AgNPs can produce brain injuries after being inhaled (Kwon et al., 2012). Further, the existence of an electric charge on NPs' surface can affect their adhesiveness in biological tissues (Sharma, Mukkur, Benson, & Chen, 2009). Negatively charged NPs allow for efficient DNA encapsulation, although their stability is very low. In contrast, positively charged NPs form complexes with DNA plasmids through electrostatic interactions, promoting their encapsulation and increasing their stability. Furthermore, it has been shown that AgNPs improve immunogenicity when they are administered through the mucosa. However, they also have the ability to form electrostatic interactions with blood proteins, ions, and others (Kumar et al., 2002).

In parenteral injections, AgNPs cytotoxicity increases with a size of 20 to 100 nm and concentrations of 0.1 to 1000 mg/kg, causing lung (Wang et al., 2014), liver (Tiwari, Jin, & Behari, 2011), renal (Tang et al., 2009), and cerebral lesions (Rahman et al., 2009).

The level of toxicity from oral ingestion is intermediate. AgNPs ranging from 3 to 60 nm were used (Gaillet & Rouanet, 2015), but NPs size were not as decisive as dose for oral toxicity. The dosage range was from 0.5 μg to 500 mg/L. Doses of 10 mg/kg caused weight loss (Shahare & Yashpal, 2013), doses higher than 300 mg/kg led to liver disorders (Kim et al., 2008), and doses higher than 1000 mg/kg generated oxidative stress (Adeyemi & Faniyan, 2014). In terms of the spread of ionic colloidal silver and AgNPs, less distribution was observed with AgNPs in organs such as the liver, spleen, and kidneys, among others (Loeschner et al., 2011; Park, 2013). However, accumulation is minimal compared to the subcutaneous or parenteral injection route; this is because many of the applied doses are largely expelled in feces (Gaillet & Rouanet, 2015).

Regarding dosage of AgNPs, few studies have involved human participants, so extrapolation of *in vivo* toxicological information from rats to humans is of great importance. Certain dosimetric concepts can be considered, adapted to the parameters for each species because of their organic structural differences (Kim et al., 2011). Extrapolation to estimate human exposure through AgNPs inhalation has already been performed (Oller & Oberdörster, 2010). Specifically, rats have an alveolar surface area of 0.409 m^2, while that of humans is 62.7 m^2. Correlation is done through multipath particle dosimetry modeling, using exposure concentration in relation to the deposited mass per alveolar surface area. Using this model, through aerosol tests and measuring the elimination of AgNPs 90 days after exposure, it was determined that rats exposed to 100 μg/m^3 is equivalent to 19 μg/m^3 in humans (Ji & Yu, 2012).

Nevertheless, it is difficult to determine AgNPs toxicity for humans because studies on exposure in humans are still scarce (del Rocío Coutiño et al., 2017). A study carried out on workers exposed to AgNPs showed that exposure time is not the most important factor for the generation of toxicity; in certain cases, the exposure exceeded five years with concentrations of 0.35 and 1.35 mg/m^3, and in none of these cases were there hematological or blood changes (Lee, Mun, Park, & Yu, 2012). Further, exposure levels depend on the activity. A person who recovers silver in close proximity to soluble compounds has concentrations of 1.3 to 20 mg/L, while jewelry manufacturers present concentrations of 0.2 to 2.8 mg/L, showing that concentrations for the manufacturers of AgNPs are much lower than the limit. Therefore, long exposure time does not affect workers' health (Armitage, White, & Wilson, 1996). With medium-level exposure, blood levels of AgNPs should range between 0.1 and 23 mg/L, while for sporadic exposure, levels should be around ≤0.1 mg/L (Armitage et al., 1996; Lee et al., 2012). However, studies of NPs conditions should be expanded, especially those focusing on levels in the lungs, as highest exposure is by inhalation.

5 | CONCLUSION

AgNPs' inhibitory effects on SARS-CoV-2 may be a new clinical strategy for the prevention of infection during its early dissemination stage. This review analyzed the *in vitro* and *in vivo* effects of AgNPs on some viruses that produce respiratory diseases. To initiate animal studies, according to the *in vivo* toxicological analysis, the routes of exposure to AgNPs

TABLE 2 *In vivo* studies on toxicity of silver nanoparticles (AgNPs)

NPs	Size (nm)	Dose, (Time), Route of Exposure	Model	Tissue Accumulation	Brief Results	References
AgNPs	13–15	0.5, 3.5, 61 μg/m^3 (28 days), inhalation	Rats Sprague Dawley	Nasal cavity and lungs	Exposure to AgNPs increased the neutral mucins of the animals, while the nasal cavity and lungs were not altered	Hyun et al. (2008)
	15	49, 117, 381 μg/m^3, (90 days), inhalation	Rats Sprague Dawley	Lungs	Animals did not show a decrease in lung function during or after the exposure period	Song et al. (2013)
	18	0.8 μg/ml (90 days), inhalation	Rats Sprague Dawley	Lungs and liver	Exposure to AgNPs of the indicated concentration did not induce genetic toxicity in animals during exposure period	Kim et al. (2011)
Ultrafine elemental silver particles	15	133 μg/m ^{3} (6 h), inhalation	Rats Fischer 344	Liver, kidney, spleen, brain, heart, and lungs	The nasal cavities and lymph nodes related to the lungs showed silver accumulation. In the case of the brain and heart, accumulation was almost zero	Takenaka et al. (2001)
Nonagglomerated/ aggregated AgNPs	15	0.5, 3.5, 61.4 μg/m^3 (28 days), inhalation	Rats Sprague Dawley	Bladder, testicles, ovaries, uterus, heart, esophagus, tongue, prostate, lungs, kidneys, liver, pancreas, and brain	Animals did not show significant changes in their body weight nor hematological changes; the concentrations used did not show any effects	Ji, Jung, Kim, et al. (2007))
Inhalation of metallic AgNPs	20–30	2.9 mg/m^3 (6 h), inhalation	Mice C57BL /6	Lungs, heart, spleen, and testicles	Inhalation of AgNPs caused pulmonary toxicity with spread to various organs. After 24 h exposure, toxicity decreased	Kwon et al. (2012)
Polyvinylpyrrolidone-(PVP) and citrate-stabilized AgNPs	20 110	0.1, 0.5, 1.0 mg/kg (24 h), parenteral	Mice C57BL/6	Nasal cavity and lungs	Size and coating affect cell toxicity and enhance lung lesions	Wang et al. (2014))
AgNPs-ethylene glycol	15–40	4, 10, 20, 40 mg/kg (32 days), parenteral	Rats Wistar	Liver	Animals showed hepatological changes with doses of 20 and 40 mg/kg, an increase in ROS in the blood was also reported	Tiwari et al. (2011)
AgNPs-DMEM	50–100	62.8 mg/kg (24 h), parenteral	Rats Wistar	Kidney, liver, spleen, brain, and lungs	AgNPs induced destruction of blood vessels and inflammation of astrocytes, causing long-term neuronal degeneration	Tang et al. (2009)
AgNPs-deionized water	25	100, 500, 1000 mg/kg (24 h), parenteral	Mice C57BL/6N	Brain (caudate nucleus, frontal cortex, and hippocampus)	AgNPs can cause neurotoxicity due to the generation of oxidative stress that kills brain cells	Rahman et al. (2009)

(Continues)

TABLE 2 (Continued)

NPs	Size (nm)	Dose, (Time), Route of Exposure	Model	Tissue Accumulation	Brief Results	References
Citrate-capped AgNPs-deionized water	7.9 ± 0.95	1.58 ± 0.25 μg/ml (24 h), oral	Rats Sprague Dawley	Liver, kidneys, and lungs	Silver distribution occurred to a greater extent with colloidal silver than with AgNPs; there were no weight changes; an increase in the platelet count occurred with AgNPs. Treatment with AgNPs (2 or 20 mg/kg) also raised AST	Park (2013)
AgNPs	60	30, 300, 1000 mg/kg (28 days), oral	Rats Sprague Dawley	Bladder, testicles, ovaries, uterus, tongue, lungs, and kidneys	Both female and male rats showed no changes in body weight. However, the values of alkaline phosphatase and cholesterol were altered. Exposures greater than 300 mg/kg can cause liver problems	Kim et al. (2008)
AgNPs-hydrazine-PVP	14 ± 4	9 mg/kg (28 days), oral	Rats Wistar	Liver, kidneys, lungs, and brain	The highest concentration of AgNPs was found in the liver and kidneys. PVP used as core-shell does not intervene in any of the conditions, since it was only used as a vehicle and stabilizer	Loeschner et al. (2011)
AgNPs-distilled water	10–20	0.25, 2.5, 25 mg/L (28 days), oral	Mice NMRI	Spleen	All analyzed doses had a significant, albeit different, effect on splenocyte activity. With the lowest dose, a decrease in T cells was observed; the intermediate dose stimulated the proliferation of B cells, and the highest dose generated adverse effects	Małaczewska (2014)
AgNPs-tannic acid-PVP	8–20	100, 1000, 5000 mg/kg (7,14, and 21 days), oral	Mice Wistar	Kidney, liver, testicles, and brain	AgNPs increased the concentration of malondialdehyde and superoxide dismutase, although they also decreased glutathione, S-transferase, and catalase levels; this indicates that AgNPs may be agents of oxidative stress	Adeyemi and Faniyan (2014)
AgNPs-sodium hydroxide-hydrazine	3–20	5, 10, 15, 20 mg/kg (21 days), oral	Mice Swiss-albino	Kidney, liver, spleen, brain, and lung	The animals presented a significant reduction in their weight; maximum weight losses were observed at doses higher than 10 mg/kg	Shahare and Yashpal (2013)

by inhalation present fewer adverse effects, unlike oral and parenteral administration. With an average AgNPs size of 10 nm and in concentrations of 0.5 to 381 μg/m^3, there were no significant changes in the nasal cavities when AgNPs were inhaled. If extrapolated from rats to humans, 100 μg/m^3 of AgNPs is equivalent to 19 μg/m^3, respectively. Available studies on the toxicity of AgNPs are scarce and sometimes contradictory. Further, evidence for coating AgNPs to reduce their toxicity and enhance their specificity is still emerging. Therefore, it is necessary to carry out a greater number of studies on the effective dose and possible toxic effects of the use of AgNPs to establish safe conditions for humans against highly virulent viruses such as SARS-CoV-2.

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Fernanda Pilaquinga: Writing-original draft. **Jeroni Morey:** Writing-review and editing. **Marbel Torres:** Writing-original draft. **Rachid Seqqat:** Writing-original draft. **María de las Nieves Piña:** Writing-review and editing.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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