Review Article

Possible Insights into the Use of Silver Nanoparticles in Targeting SARS-CoV-2 (COVID-19)

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ABSTRACT

Aim: The aims of this review are to assess the anti-viral and targeting strategies using nano materials and the possibility of using Silver nanoparticles for combating the SARS-CoV-2. **Background:** The novel Coronavirus (SARS-CoV-2) has become a global pandemic and has spread rapidly worldwide. Researchers have successfully identified the molecular structure of the novel coronavirus however significant success has not yet been observed with the therapies currently in clinical trials and exhaustive studies are yet to be carried out in the long road to discovery of a vaccine or a possible cure. Another hurdle associated with the discovery of a cure is the mutation of this virus which may occur at any point in time. **Hypothesis:** Previous studies have identified a wide number of strains of Coronaviruses with differences in virulent properties. Silver nanoparticles have been used extensively in anti-viral research with promising results *in-vitro*. However, it has not yet been tested for the same in clinical subjects. It has also been tested on two variants of coronavirus *in-vitro* with significant data to understand the pathogenesis and which may be implemented in further research possibly in other variants of coronavirus. Another interesting targeting approach would be to test the effect of Silver Nanoparticles on TNF-α as well as Interleukins in SARS-CoV-2 patients. **Conclusion:** Sufficient evidence is required for its therapeutic potential and it still has to go a long way in SARS-CoV-2 research.

Key words: SARS-CoV-2, Pandemic, Immunomodulation, Silver nanoparticles, *In-vitro*.

INTRODUCTION

Persistent viral diseases that cause severe illnesses are primarily due to an impaired immune system activity. To understand recurrent infection, it is important to consider the very complex structure and role of the innate and adaptive divisions of the immune system. Prevention with the use of prophylactic vaccination is the only solution to the issue of chronic infection.[1] Viruses may be defined as parasites with an obligate nature and possess either an RNA or DNA genomes and protected with a virus coded protein coat. These are mobile genetic elements of cellular origin and proliferation is dependent on the specialized host cells with the complex machinery as in eukaryotes or prokaryotes. The entire structure can be referred to as virion and its prime function is to transport the DNA or RNA into the host followed by its transcription and translation process.[2] Viruses can be placed in one of the seven following groups:[2]

- I: dsDNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses)
- II: ssDNA viruses (+ strand or «sense») DNA (e.g. Parvoviruses)
- III: dsRNA viruses (e.g. Reoviruses)
- IV: (+) ssRNA viruses (+ strand or sense) RNA (e.g. Coronaviruses, Picornaviruses, Togaviruses)
- V: (−) ssRNA viruses (− strand or antisense) RNA (e.g. Orthomyxoviruses, Rhabdoviruses)
- VI: ssRNA-RT viruses (+ strand or sense) RNA with DNA intermediate in life-cycle (e.g. Retroviruses)

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- VII: dsDNA-RT viruses DNA with RNA intermediate in life-cycle (e.g. Hepadnaviruses)

When compared with one another, RNA viruses have shown to be more problematic, since there have been observed correlations between the mutations and its subsequent virulence. Many researchers suggest that the increased mutations enhance adaptability and the pathogenesis depends on the rare or de novo mutations.[3] Coronaviruses belong to the ssRNA with the (+) strand. Coronaviruses (CoVs) are one of the largest groups of viruses of the *Nidovirales* order including the families of *Coronaviridae*, *Arteriviridae*, *Mesoniviridae* and *Roniviridae*.

The family of *Coronaviridae* is subclassified into two sub families namely *Coronavirinae* (alpha, beta, gamma and delta coronaviruses) and *Torovirinae*

Studies carried out by cryo-electron tomography and cryo-electron microscopy identified its structure and the size was around 125nm.[4,5] Coronavirus is an RNA virus with a size of 25 to 31.4 kb and a distinguishing feature identified among coronaviruses was the appearance of spike projections which is club-shaped and the nucleocapsid (helically symmetrical) was found to be located within the virion. This peculiar nucleocapsid structure was found to be more common in negative-sense RNA viruses. The structure of coronavirus may be categorized into four main proteins encoded with 3' end viral genome, (Figure 1)

- The Spike(S)
- Membrane(M)
- Envelope (E)
- Nucleocapsid (N)

The S protein (~150 kDa) is extensively N- linked glycosylated and enters the Endoplasmic reticulum using the N- terminal signal sequence. The surface spike is made up of homotrimers encoded with S protein.[6,7]

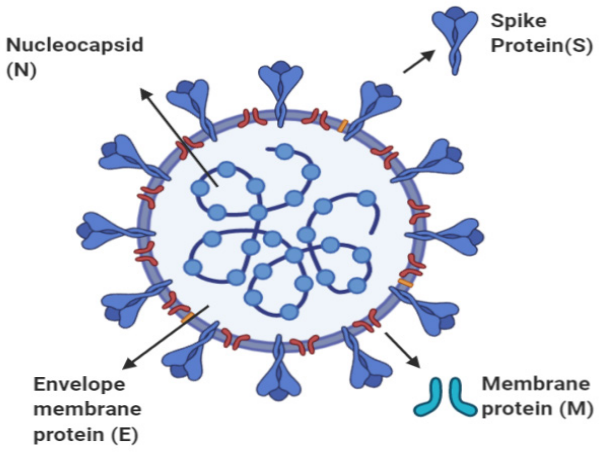

Figure 1: Structure of SARS-CoV-2-.

It belongs to the Fusion protein of class I[8] and enables binding to the host receptor.[9] The transmembrane spike glycoprotein is made up of two functional subunits S1 and S2 and both ensure the entry of the coronavirus by forming homotrimers from the surface of the virion and binding with the host cells receptors and membranes respectively. Hence it is utilized as one of the main sites for neutralizing antibodies (Abs) on the infection.[10]

There have also been significant scientific findings which point out that both the spike proteins of SARS and SARS-CoV-2 have an interaction with the angiotensin-converting enzyme 2 (ACE2) which is considered as the key receptor for both these variants.[11]

The M Protein is highly seen in the virion and is small (~25–30 kDa) possessing three transmembrane domains and believed to provide shape to the virion.[12]

The E protein (~8–12 kDa) is present in minor quantity inside the virion, is highly divergent and possesses a similar structure. It contains N- and C- terminal ectodomains along with ion channel activity.[13]

The last protein which is N Protein is present only within the nucleocapsid and consists of two distinct domains namely N- and C- terminal domains both of which attach to RNA *in-vitro* but using different mechanisms.[14,15]

The Figure depicts the structure of the novel coronavirus containing the spike glycoprotein, membrane protein, envelope small membrane protein as well as the nucleocapsid.

MUTATIONS AND CORONAVIRUS

The mutational capabilities differ between viruses and studies have shown that RNA viruses multiply more rapidly than DNA viruses and the mutations are at much higher rates in single-stranded viruses and negatively correlated with the genomic size. The mutational rates can be altered by polymerase fidelity, sequence context, template secondary structure, cellular microenvironment, replication mechanisms, proofreading and access to post-replicative repair.[16] Mutations are essential to be understood to obtain transparency on the evolution and possible vaccination strategies. From the perspective of epidemiological and evolutionary levels, it is one of the factors which ascertain the risk level of the infection in terms of the crossing of pathogens among species.[17]

The novel coronavirus appears to have innate proofreading machinery where it decreases the error rates and decelerates the mutation speed. The mutations occur abruptly. In some cases, the mutation aids in replication and transmission among humans whereas

sometimes its inability to infect may result in death of the virus- this was stated by Shweta Chelluboina clinical virologist at the Interactive Research School for Health Affairs in Pune.

She has further stated that the coronavirus was successful in moving into humans from animals with no containment as of now.[18]

Several reports have suggested that the novel coronavirus has undergone two possible mutations, the primary strain which is the S-type had its origin in Wuhan whereas the second strain, the L-type which was evolved from the S-type was found to be prevalent in countries like the U.S. which was initially discovered by scientists in Peking University's School of Life Sciences and the Institute Pasteur of Shanghai.[18]

Though both these mutations are not significantly different, the L-type was explained as more aggressive whereas there was no difference in virulence. The S-type had initially developed when the virus entered humans and on further transmission into other humans resulted in the L-type was hypothesized. Researcher's further caution against precautionary measures to be taken as further mutations can take place. However, due to limited population samples, the preliminary studies determined the possible mutations in the preliminary studies.[18]

Some studies have shown the possibility that both the Spike moieties S1 and S2 had a certain level of interchange ability which could affect the host. The reverse genetics system had identified introduced mutations in the genome regions of CoV at 3' of ORF1 which was based on the interchange ability of the tropism altering property in Spike ectodomain as well as the coronavirus targeted recombination in the intrinsic facility.[19] The modification of the functional regions of S1 and S2 may play a possible role in the mediation of CoV increase, however further studies are essential to elucidate the mechanisms related to the S2-modulated expansion *in- vitro* as well as *in vivo* along with the interchangeability between the S domain. Hence it will provide a better understanding of the emergence of novel strains and development of cross strain therapeutic products.[20]

VARIANTS OF CORONAVIRUSES

The various coronaviruses discovered up to date from the date of discovery of the first coronavirus which was at the 1960s.[21]

- 229E (alpha coronavirus)
- NL63 (alpha coronavirus)
- OC43 (beta coronavirus)
- HKU1 (beta coronavirus)
- MERS-CoV (beta coronavirus)
- SARS-CoV (beta coronavirus)
- SARS-CoV2
- Transmissible Gastroenteritis Virus (TGEV)
- Porcine Respiratory Coronavirus (PRCV CoV) Bovine CoV (BCoV)
- Feline CoV (FCoV)
- Infectious Bronchitis Virus (IBV)[22]

MERS CoV- had resulted in over 36% fatality with around 50-89% requiring mechanical ventilation.[23]

SARS CoV resulted in 10% mortality with 20-30% requiring mechanical ventilation.[23]

The first four types of HCoVs resulted in 10-30% of upper respiratory tract infections.[23]

NANO BIOMATERIALS IN DRUG DELIVERY

Targeting Systems for Antiviral Agents

Various targeting approaches have been adopted in the treatment of viral infections. A handful of them have been mentioned below.

a) Engineered antiviral T cell immunity through stem cells and chimeric antigen receptors

In a particular study, hematopoietic stem cells were changed genetically so they proliferate into Cytotoxic T Lymphocytes- matured which possess the ability to target and attack HIV infection. The stem cells recognize HIV virus or infected region since they are transduced with non-HLA restricted chimeric antigen receptors.[24]

b) Gum based hydrogels

Malik *et al*. identified the possible use of four different polymers namely monomer 2-acrylamido-2-methylpropane sulfonic acid (AMPS), chitosan (CS), xanthan gum (XG) and initiator potassium persulfate with cross linking by N' N'-methylene bis-acrylamide (MBA) for delivering Acyclovir, an effective treatment against HSV infections.[25]

c) Nanogels

Macchione *et al*. worked on preparation of poly(N-vinylcaprolactam) nanogels with differing concentrations of monomers and crosslinking agent. It was the first time the inhibitory potential of this nanogel was exposed against HIV infection. The initial concentration of this nanogel with 80mg of vinylcaprolactam along with 4% cross linking agent showed potential anti-viral activity.[26]

d) siRNAs targeting through cell-degradable multilayered polyelectrolyte films

Dimitrova *et al*. discovered novel approach to treat viral infections using gene silencing using RNA interference (RNAi). The multi-layered polyelectrolyte films showed

an enhancement inefficiency and was a relatively simple approach for targeting using siRNA for viral infections.[27]

e) miRNA inhibition

miRNA is complicated to target and requires advanced delivery. Antisense oligonucleotide delivery may be enhanced by conjugation with cell peptides in certain miRNAs. Another particular type of viral-based delivery is the use of inhibitors utilizing miRNA sponges which contain multiple miRNA targets competing with endogenous target. RNAi techniques may be used to cause overexpression of miRNA.[28]

f) DNA Aptamers

Yadavalli *et al.* demonstrated that topical applications of small DNA aptamers can be used to target HSV-1 envelope glycoprotein gD, which is essential for viral entry and spread resulting in ocular infection. Their studies revealed strong potential in inhibiting viral entry as well as replication in both *in vitro* and *ex vivo* studies.[29]

Nanomaterial's as Antiviral Agents or Carriers

Nanotechnology is an innovative field and is a result of physical and chemical changes enabling the formation of nano-sized materials. They have a broad range of applications in pharmaceutical sciences and are composed of micron-sized material (<1μm) for monitoring and diagnostic studies. Nanomedicines have also been used in targeting several antiviral drugs for viral infections (Table 1).

Organic Nanomaterials

Organic nanoparticles are the most extensively researched type of nanoparticle for drug delivery and the most widely approved system for therapeutic use in humans.[37]

Polymeric nanoparticles

They range at the size of 10 to 1000 nm and are a group of colloidal solids. Due to the minor size, the movement into cells is enhanced at targets.[38]

However, modifications are essential with hydrophilic polymers to decrease other possible non-specific interactions as well as vulnerability to opsonization and other techniques to prolong half-life and distribution.[39]

A study done by Abo-zeid *et al.* analysed the activity of fluorescently labelled polymeric nanoparticle to study the uptake in human hepatoma cells containing Hepatitis C viral genomes and compared with non-infected ones.[40]

Nanocapsules

They range at 50 to 300 nm possess low density and increased loading capacity.[38]

Studies carried out with HIV protease inhibitors loaded with Solutol® HS15 nanocapsules showed better uptake into the brain as well as testes in mice models in comparison with the control group with only indinavir administration.[41]

Nanospheres

Matrix systems with uniform distribution of the drug and ranging from 100 to 200 nm.[42] Nanospheres have been used in Hepatitis B treatment as well as Herpes simplex virus and influenza.[43]

Liposomes

Spherical shaped carriers of the size range 20 to 30 nm in size with the ability to directly fuse with the microbial membrane due to the mimicking property of phospholipid bilayer. Both types of drugs such as hydrophilic and lipophilic types can be incorporated

Table 1: Antiviral drugs in nano preparations.

Antiviral drugs	Targeted virus	Nano preparation	References
RALTEGRAVIR	HIV	Gold nanoparticles conjugated with Raltegravir	30
ZIDOVUDINE		PF-68 coated alginate conjugate nanoparticles	31
GLYCODENDRIPROTEIN	EBOLA	Biomimetic Glycodendriprotein Nanoparticles	32
ACYCLOVIR	Herpes Simplex Virus	Solid lipid nanoparticle	33
LAMIVUDINE	Hepatitis B Virus	Stearic acid-graft-chitosan oligosaccharide micelles loaded with Lamivudine stearate	34
IVERMECTIN	Zika Virus	Synthetic nanoparticles	35
GANCICLOVIR	Cytomegalovirus	Solid lipid nanoparticles	36

due to its versatile nature and aqueous core. These formulations have been studied in vaccines due to their property to behave as immunological adjuvant and additionally, they are also non-toxic and easily biodegradable.[43] Studies carried out by Pollock *et al.* showed the antiviral potential of Polyunsaturated ER liposomes (PERLs) which on treatment with HCV, HBV and HIV infections showed a decrease in viral infectivity and secretion.[44]

Micelles

These substances range from about 10-100nm, where inner core is lipophilic and outer layer is made up of hydrophilic polymer such as Polyethylene glycol. These have grown in importance as therapeutic agents and the encapsulation of drugs into polymeric micelles have also shown to enhance solubility in water. It has also shown better dissociation and enhanced retention time.[45] The micelle of hexadecyloxypropyl-cidofovir was found to be relatively safe on rabbits and guinea pigs and efficacy was estimated on HSV-1 model.[46]

Dendrimers

These are globular in shape and contain three main parts central core, branches and terminal functional groups.[47] They possess increased utility since they can encapsulate several chemical moieties and possess multisurface properties.[48]

Crespo *et al.* formulated carbosilane dendrimers which were conjugated along with Tenofovir and Maraviroc against HIV-1 infection. This combination was assessed for the anti-HIV activity and exhibited a higher action when compared to given alone.[49]

Solid lipid nanoparticles

This group is an alternative drug delivery system and makes use of the benefits of nanocarriers without the potential drawbacks. The production of polymeric nanoparticles on a large scale is a major difficulty whereas these SLNs can be prepared much easier.[50]

Stability, safety and low toxicity are also some of the advantages associated with them.

A study carried out by Kondel *et al.* compared the efficacy of Acyclovir solid lipid nanoparticles along with individual administration of the same with positive results.[33]

Inorganic Nanoparticles

Metallic nanoparticles can be smaller than organic nanoparticles, ranging between 1 nm and 100 nm in size, while their loading efficacy is much higher.

Gold nanoparticles

They possess immense conductivity, biocompatibility as well as flexibility. The inner gold core is inert as well as non-toxic and these NPs also possess photophysical properties and functionalization due to thiol linkages.[51]

The gold nanoparticles of Allium sativum were found to be efficient in blocking the viral particles by strong virucidal activity and the results suggest that it may be useful in treating measles virus and other such enveloped viruses.[52]

Silver nanoparticles

One of the most effective NPs against bacteria, virus and other such organisms mainly due to the inhibitory action of silver. The mechanism by which they act is by silver ion release and disruption of DNA and cell membrane.[53] Numerous research work has been published on the virucidal activity of AgNPs.[54]

Other metallic nanoparticles

Several other metallic NPs have also demonstrated anti-viral potential including Zinc,[55] Copper,[56] Titanium.[57] Whereas some are yet to be evaluated.

SILVER NANOPARTICLES

Silver nanoparticles (AgNPs) are widely used among nanomaterials for their various biomedical applications. They play imminent roles in nanoscience, nanotechnology as well as in nanomedicine. They have found to be useful in numerous applications such as anti-bacterial agents, household, health care, coating of medical devices, pharmaceutical industry, drug delivery, oncology research, food industry.

Synthesis of Silver Nanoparticles

The synthesis of such nanoparticles involves three methodologies:[58]

- Physical Method
- Chemical Method
- Biological method

Physical Method

The principle behind the physical method involves evaporation followed by condensation in atmospheric pressure and carried out in a tube furnace. Other conventional techniques involve spark discharge and pyrolysis process.[58]

The advantages of this method are the rapidity, use of radiation as reducing agents and the absence of perilous chemicals. However, the possible drawbacks associated

with them include the immense consumption of energy, possibility of contamination of solvent and improper distribution.[58]

Chemical Method

One of the differences between physical and chemical methods is the use of organic solvents or water in the preparation of AgNPs which utilizes three components namely- metal precursors, reducing agents, as well as stabilizing agents. The two steps in the process of reduction of silver salts are nucleation and subsequent growth. "Top down" and "Bottom up" are the two distinct methods to synthesize AgNPs. The former makes use of colloidal protecting agents to stabilize the grinding of metals in bulk mechanically. The latter process is done by chemical reduction, electrochemical technique as well as sono-decomposition.[58]

The benefits of this process of preparation of AgNPs is the economic benefit, production and yield but the main downside is the use of chemical agents which may be detrimental to humans.[58]

Biological method

This method has emerged as an alternative to the chemical technique and has also proven to be economical, reliable and environmentally friendly. This method has been focussed on of late to produce an increased yield of AgNPs employing biological components including fungi, bacteria, herbal extracts and biomolecules (Vitamins and amino acids).[58]

Application of Silver Nanoparticles as Anti-Viral Agents

Retroviridae

The first study on metal nanoparticles as anti-viral agents was performed by Elechigure *et al.* where they studied the possible interactions between AgNPs and Human Immunodeficiency Virus-1 (HIV-1). They studied the ability of these AgNPs using *in-vitro* assays to inhibit the infection of laboratory-adapted HIV-1 strain as well as the interactions between the nanoparticles and capping agent molecule due to physicochemical characteristics.

They reported a dose-dependent inhibition on viral infectivity.[59]

Among the nanoparticles used, those coated with Bovine Serum Albumin (BSA) and Polyvinylpyrrolidone (PVP) exhibited decreased inhibitory potential which was expected to be due to the direct binding of nanoparticle and encapsulation with capping agent.

However, in particular, the AgNPs which were released from carbon matrix showed an enhanced inhibitory activity due to the presence of a wider free surface area which indicates possible evidence for a possible interaction with gp120 and hence other assays were used to understand the possible mechanism against HIV-1.[60]

The infectivity was hindered to 50% with a concentration of 0.44 to 0.91 mg/mL. As determined by several viral infectivity assays, AgNPs proved virucidal and eradicated the infectivity within a short duration of exposure.[60]

Herpesviridae

This family is composed of an excess of 100-double stranded DNA viruses that can be segregated into α, β and γ subgroups, yet only 8 of these are known to infect humans whereas the rest affect animals. After the primary transmission, it remains dormant in neurons which is one of the key properties of α-herpesviruses.[61]

Mercaptoethane sulfonate-based (MES) gold and AgNPs were synthesized and analysed for anti-viral potential using several anti-viral assays on wild-type HSV-1 McIntyre strain. Vero cells along with virus solutions were given Ag-MES and Au-MES at altered time points to determine at which stage the infection could be hindered. The study concluded with the understanding that those sulfonate-capped silver and gold nanoparticles blocked the HSV-1 infection by interfering with the attachment and entry of the virus into the cell and avoiding cell-cell spread.[61]

Paramyxoviridae

The notable virus of this family is the Respiratory Syncytial Virus (RSV) which targets lung epithelia leading to a serious respiratory disease in people of a higher age group as well as lower. To date, there hasn't been any treatment of vaccine available which brings into consideration a need to develop novel RSV treatments.

The use of AgNPs have been exploited in the study to inhibit the RSV infection in Hep-2 cell culture by Sun *et al.*[62] Three different types of capping agents were used in the preparation of nanoparticles namely PVP, BSA and recombinant F protein from RSV (RF 412).

The initial studies were performed by Transmission Electron Microscopy (TEM) where the results indicated that BSA-conjugated with the nanoparticle showed possible interactions with RSV without any specified association which was in contrast with the RF 412-conjugated nanoparticles which did not exhibit any proof of attachment but floated freely. The PVP-coated AgNPs had shown potential in binding to the surface of viruses with regular spatial arrangement, hence signifying the possibility of G protein interaction on the envelope of RSV. The hypothesis that mentioned the PVP nanoparticle and its interaction with the G-protein

was due to the minor size and uniformity (4–8 nm) in comparison with the other two coating agents which was (3-38nm) suggesting the superior binding efficiency.[62]

Hepadnaviridae

A partially double-stranded DNA virus with an envelope coat composed of lipids is the Hepatitis B virus (HBV). It has a strong affinity for hepatocytes and it moves towards the nucleus on entering into the cell where the genome forms a covalently closed circular DNA (cccDNA) serving as template in other phases of transcription in viral mRNA resulting in pre-genomic RNA (pgRNA) formation. This, in turn, produces new viral genomes by acting as a template in reverse transcription process from the viral-encoded reverse-transcriptase.[63]

A study carried out by Lu *et al.*[64] studied the monodispersing of AgNPs and the capacity to block HBV multiplication. The AgNPs were prepared from $AgNO_3$ in (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) HEPES and were of the sizes ~10 nm (Ag10Ns), ~50 nm (Ag50Ns) and ~800 nm (Ag800Ns). In comparing each of the dimensions, the AgNPs were highly lethal at 800nm as antiviral agents whereas the former two showed less toxicity. Both these sizes of nanoparticles showed immense anti-HBV activity where Ag10Ns achieved at 5 and 50μM concentration, an inhibition of 38% and 80%, whereas the Ag50Ns showed improved efficacy with inhibitions at the same concentrations to be 53% and 92%. This study showed the possible inhibitory effect of AgNPs in decreasing the production of HBV RNA as well as the extracellular virions through interactions between the NPs and double-stranded DNA of HBV or a direct binding mechanism.[64]

Poxviridae

An example of this family of viruses is the Monkeypox virus (MPV) which is similar to the variola virus that affects several species of non-human primates but also affects humans with the clinical manifestations resembling smallpox. Still, therapies are being devised to target this virus as it remains a major threat to humans.[65]

Rojers *et al.* worked with a variety of different NPs with distinct sizes which were synthesized by the plasma gas method analysed by plaque reduction assay.[66]

Two types of coated -10 (Ag-PS-10), 25 (Ag-PS-25) and 80 (Ag-PS-80) nm and uncoated 25 (Ag-NP-25), 55 (Ag-NP-55) and 80 (Ag-NP-80) nm NPs were used, the coating material was polysaccharide.[66]

The concentrations used for the study were from 12.5 to 100 μg/mL and studied for inhibitory activity against plaque reduction assay and among the NPs used, Ag-PS-25 (polysaccharide-coated, 25 nm) and Ag-NP-55 (non-coated, 55 nm) exhibited maximum plaque formation inhibition of MPV however the mechanism through which it took place was not elucidated.[66]

Advantages of silver nanoparticles in anti-viral therapy over other agents

Several advantages of AgNPs as drug carriers over conventional therapies include an increased stability of the nucleic acids bound to the surface, adjustable size and shape, absence of any harsh transfection agents in transmembrane delivery, protection from degradation from attached therapies, enhanced controlled intracellular delivery.[67]

POTENTIAL OF SILVER NANOPARTICLES ON CORONAVIRUSES

Coronaviruses (CoVs) of late have been very common throughout the world and among the different types of CoVs, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) andthe Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have been found to be most deadly of them all. A particular form of porcine coronavirus known as Transmissible gastroenteritis virus (TGEV)[68,69] had caused increased mortality in pigs and the vaccination to piglets provided protection to suckling piglets, however, on a larger scale, it did not promote enhancement of immunity and did not control the spread of the infection.[70,71]

Hence the development of an alternative therapeutic strategy is imminent in the control of such an infection. AgNPs have already shown significance in antiviral research however their potential is to be understood in TGEV infection.

Although Silver Nanomaterials (AgNMs) have displayed an appealing effect on antiviral research,[72] their potential inhibitory effect on TGEV infection has not been studied and reported until now.

A recent study carried out by Lv X, *et al.* determined the potential of these AgNPs on TGEV strain PUR46-MAD propagated in Swine Testicle Cells (ST).[72]

AgNMs were synthesized and characterized by TEM and the nanowires were found to be 60- 400nm. On an average, the size of silver colloids was found to be 10nm. The characterization was done by nanoparticle tracking analysis (NTA) which makes use of dynamic light scattering.[73] MTT assay was used to determine the potential cytotoxic activity and ST cell viability with concentrations of 3.125 to 50mg/mL for 48 h. most cells were not affected until 12.5 mg/mL by at

a concentration above 50mg/mL AgNPs exhibited toxicity.[72]

In elucidating the activity of AgNMs, the ST cells were merged with TGEV with concentrations of 3.125-12.5mg/mL. The genes which were meant to be targeted were S-X gene and 3CLpro gene sequences estimated by the qRT-PCR. Both gene expressions were decreased in a dose-dependent manner with AgNPs, AgNW60 and AgNW400. There was no statistical variation observed in the amplification of the two genes by the silver colloids. The data obtained signified that AgNPs as well as Ag Nano wires showed potential in inhibiting TGEV activity whereas silver colloids were found to be relatively inert to it. Among the nanomaterials used, AgNMs, AgNPs and two types of silver nanowires showed substantial inhibition on TGEV which induced host cell infection and multiplication.[72]

Chen *et al.* carried out research using graphene oxide (GO) sheets individually and with a combination with AgNPs (GO-AgNPs) with targets on enveloped and non-enveloped viruse's especially feline coronaviruses (FCoV).[74]

The preparation of nanoparticles was done by dispersion of GO in silver solution followed by pulse microwave-assisted (MA) synthesis for growth of silver seeds. The product was then vacuum dried overnight. The study showed a possible concentration-dependent activity with GO and GO-Ag in inhibition of infection of Fcwf-4 cells. When a low concentration of FCoVs was exposed to higher concentrations of GO and GO-Ag with enhanced activity being observed with the GO-Ag. A concentration of 0.1mg/mL exhibited 24.8% inhibition of infection.

The possible anti-viral mechanisms were explained as blockage of viral entry as well as hindrance with viral membrane fusion.[75,76] The proposed mechanism was found to be possible due to the presence of Ag on GO sheets and the size range was GO sheets were 5 to 25 nm, with 50% Ag particles spread at 10 nm or fewer than 10 nm. However, the inhibition was comparatively lower with coronaviruses in comparison with the influenza virus where it showed 97% inhibition in the latter.[75,76]

Immunomodulatory Properties of AgNPs

TNF-α may possess several essential therapeutic implications when it comes to SARS with the increased availability of inhibitors of TNF-α are available for human use. Since the initial lung injury begins with TNF-α, inhibiting this could lead to decreased lung damage. Hence, according to Tobinik, using anti-TNF therapy to reduce SARS coronavirus therapy may disrupt this cascade and could provide a more specific and effective method.[77]

Among the top host targets predicted for SARS Tumour Necrosis Factor (TNF-α) and Interleukins (IL) are some. The Immunomodulatory properties of AgNPs were studied for its potential in anticancer research for murine fibrosarcoma. During the end of the study, the important serum levels of TNF-α and IL-6, were analysed for its role in cancer and tumour progression. The levels were found to be positively correlated with the progression of tumour with the control group.

The AgNP-treated group showed cytokine levels consistent with the physiological parameters.

The tumour microenvironment has distinctive proteins or cellular environments and the NPs which were exposed to various *in-vivo* systems, resulted in the formation of bio/nanocomplexes hence down regulating the activity of proinflammatory cytokine levels.AgNPs have shown significant potential in decreasing the cytokine levels in tumour environment and needs to be further exploited in anti-viral research since interleukins and TNF-α are few of the main targets of SARS-CoV-2.[78]

CONCLUSION

Coronaviruses possess unique mutational mechanisms and pathways of transcription and recombination. The observations regarding spike protein which is involved in the pathogenesis in the host have contributed to further studies in SARS CoV. An observation involving the spike protein of SARS-CoV and its accessory proteins as well as its association with the pathogenesis is undergoing further investigations. Among the insights available from research data, it is highly evident that these coronaviruses will continue to transmit between species and cause a new emerging disease which is in the case of the current SARS-CoV-2. The knowledge gathered from animal coronaviruses will help us in identifying the pathophysiology and create new forms of therapies. The use of AgNPs has been observed in several forms of viral infections and is effective in *in-vitro* studies. Targeting therapies on TNF-α and ILs may also be exploited in the therapy of SARS- CoV-2. These results open new windows to another alternative approach but further studies are required to test its efficacy in clinical subjects and determine its anti-viral potential.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

Abs: Antibodies; **ACE2:** Angiotensin-converting enzyme 2; **Ag-MES:** Silver Mercaptoethane sulfonate; **AgNMs:** Silver Nanomaterials; **AgNPs:** Silver nanoparticles; **AgNW:** Silver Nanowires; **Ag-PS:** Silver Nanoparticle Polysaccharide coated; **AMPS:** 2-acrylamido-2-methylpropane sulfonic acid; **Au-MES:** Gold Mercaptoethane sulfonate; **BCoV:** Bovine Corona Virus; **BSA:** Bovine Serum Albumin; **cccDNA:** Covalently closed circular DNA; **CoVs:** Coronaviruses; **CS:** Chitosan; **DNA:** Deoxyribonucleic acid; **dsDNA:** Double stranded DNA; **FCoV:** Feline Coronaviruses; **Fcwf-4:** Felis catus whole fetus cell line; **GO:** Graphene oxide; **GO-AgNPs:** Graphene oxide Silver Nanoparticles; **HBV:** Hepatitis B Virus; **HCoVs:** Human Coronaviruses; **HIV:** Human Immuno deficiency Virus; **HLA:** Human Leukocyte antigen; **HSV:** Herpes Simplex Virus; **HEPES:** 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; **HCV:** Hepatitis C Virus; **IBV:** Infectious Bronchitis Virus; **IL:** Interleukins; **kDa:** Kilodaltons; **MA:** Microwave-assisted; **MBA:** N' N'-methylene bis-acrylamide; **MERS-CoV:** Middle Eastern Respiratory syndrome- Coronavirus; **MES:** Mercaptoethane sulfonate; **miRNAs:** Micro RNAs; **MTT**:3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **NPs:** Nanoparticles; **NTA:** Nanoparticle tracking analysis; **PERLs:** Polyunsaturated ER liposomes; **pgRNA:** pre-genomic RNA; **PRCV CoV:** Porcine Respiratory Coronavirus; **PVP:** Polyvinylpyrrolidone; **RNA:** Ribonucleic Acid; **RNAi:** RNA interference; **RSV:** Respiratory Syncytial Virus; **SARS-CoV-2:** Severe Acute Respiratory Syndrome- Coronavirus-2; **siRNA:** Small interfering RNA; **SLN:** Solid lipid Nanoparticles; **ssDNA:** Single stranded DNA; **ssRNA:** single stranded RNA; **ssRNA-RT:** Single stranded RNA- Reverse transcriptase; **ST:** Swine Testicle Cells; **TEM:** Transmission Electron Microscopy; **TGEV:** Transmissible Gastroenteritis Virus; **TNF:** Tumour Necrosis Factor; **XG:** Xanthan gum.

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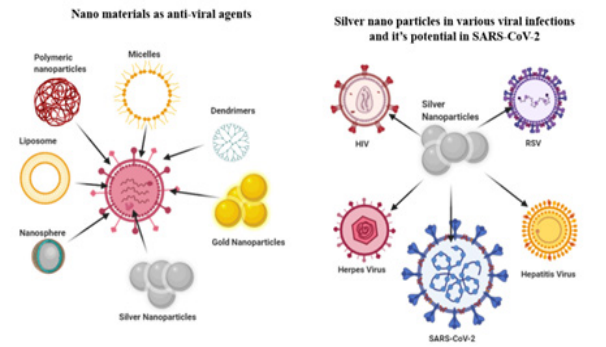
PICTORIAL ABSTRACT



SUMMARY

This review focuses on the SARS-CoV-2 coronavirus which belongs to the ssRNA and also one of the largest groups of viruses of the *Nidovirales* order. The basic structural characteristics of SARS-CoV-2 were elucidated along with some mutational aspects. This is then followed by the introduction to nano-biomaterials and its possible use in viral infections. Several applications of silver particles have been mentioned in other viral infections in along with *in-vitro* data. The application of silver nanoparticles was then explored in coronavirus species in *in-vitro* as well as animal models. The possible role of TNF-α and IL is then assessed in targeting SRAS-CoV-2 infection.

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