

Therapeutic and Diagnostic Approaches by using Nanotechnology in SARS-CoV-2 Infections

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Abstract

Severe Acute Respiratory Syndrome Corona Virus-2 infection is a universal threat in recent days, hence early diagnosis and treatment play a pivotal role in controlling the spread thereby preventing them to become endemic. A newer promising approach by Nanotechnology plays an essential role in targeting the specific pathogens for therapeutic and diagnosis of Viral infection. Certain Nano platforms like Microneedle array delivered Virus S1 subunit vaccines, spike protein nanoparticles, Lumazine synthase Nanoparticles, Silver Nanoparticles, Self-Assembling Protein Nanoparticles against Viral therapy are the upcoming applications as a therapeutic approach. Nucleic acid amplification techniques and Surface-enhanced Raman Spectroscopy shows a high specificity with the immunoassay strategy. In recent days, Colloidal Gold - Nanoparticles and silicon nanoparticles have been widely used as a point of care for quick detection of IgG and IgM antibodies obtained from the virus as a diagnostic approach. Additionally, the Nanoparticles serve as a significant improvement in Personal Protective Equipment and protect against exposure to the virus. As a result of repurposing as well as for the development of the drug, apparently, Nanoparticles themselves and their concomitant therapy or their carriers will be advantageous in making a therapeutic and diagnostic approach against Severe Acute Respiratory Syndrome Corona Virus-2 infections.

Keywords: Severe Acute Respiratory Syndrome Corona Virus-2, Nanotechnology, Nano-particles, Therapeutic and Diagnostic Approaches, Immunoassay Strategies

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Abbreviation: SARS-CoV-2 - Severe Acute Respiratory Syndrome Corona Virus-2, WHO – World Health Organization, MNA – Micro Needle Array, NPs – Nano Particles, SAP NPs – Self Assembling Protein NPs, M NPs – Metallic NPs, Au NPs - Gold NPs, AgNPs - Silver NPs, SiO₂NPs - Silica NPs, ZnO NPs - Zinc Oxide NPs, CuO NPs - Cuprous Oxide NPs, CuI NPs - Copper (I) Iodide NPs, MBTs - Molecular Based Techniques, ICT - Immunochromatography technique, SERS - Surface-enhanced Raman Spectroscopy, POC - Point of Care, C NPs - Carbon particles, INF – Interferons, ISG - Interferon stimulating genes, IFNAR - Interferon α/β Receptor (IFNAR), QDs - Quantum Dots, PPEs - Personal Protective Equipment's, NBS - NP-based biosensors.

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INTRODUCTION

Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) infection is a global threat in recent days as it has affected more than 506 million population including 6.2 million deceased all over the globe according to the World Health Organization (WHO) till 17th April 2022. Hence early diagnosis and treatment be a matter of great importance in controlling the spread thereby preventing them to become endemic.^{1,2}

Certain Nano platforms Microneedle array (MNA) that released SARS-CoV-2 S1 subunit vaccines, spike protein nanoparticles, Lumazine synthase Nanoparticles (NPs), Self-Assembling Protein NPs (SAP NPs) against SARS-CoV-2 treatment are the upcoming applications.^{3,4} Metallic NPs (MNPs) such as Gold NPs (Au NPs), silver NPs (AgNPs), Silica NPs (SiO₂NPs), etc, are upcoming novel repurposing therapy to inactivate SARS-CoV-2 infection.^{5,6} (Figure 1). Thus, NPs

as antiviral drug carriers are more promising in improving their drug activity and bioavailability which in turn has manifested in delivering drugs at the targeted spot with fewer consequences.⁷⁻¹⁰

Molecular Based Techniques (MBTs) like Nucleic acid amplification techniques, Immunochromatography technique (ICT), and Surface-enhanced Raman Spectroscopy (SERS) are emerging in order to help in the timely detection of the infection.^{11,12} Globally, RT-PCR helps in the determination of RNA in SARS-CoV-2.¹³ Followed by RT-PCR, SERS was invented which was reliably used as Point of Care (POC) Testing for Coronavirus and it ensures the presumptive identification of analytes at an ultra-low concentration without processing the samples (Table).¹⁴⁻¹⁹

Moreover, the novel therapeutic agents against SARS-CoV-2 will be developed as a result of the regulation of viral gene expression by, microRNA and shRNA.^{20,21} Hence, the main purpose of this review is to discuss the forthcoming newer

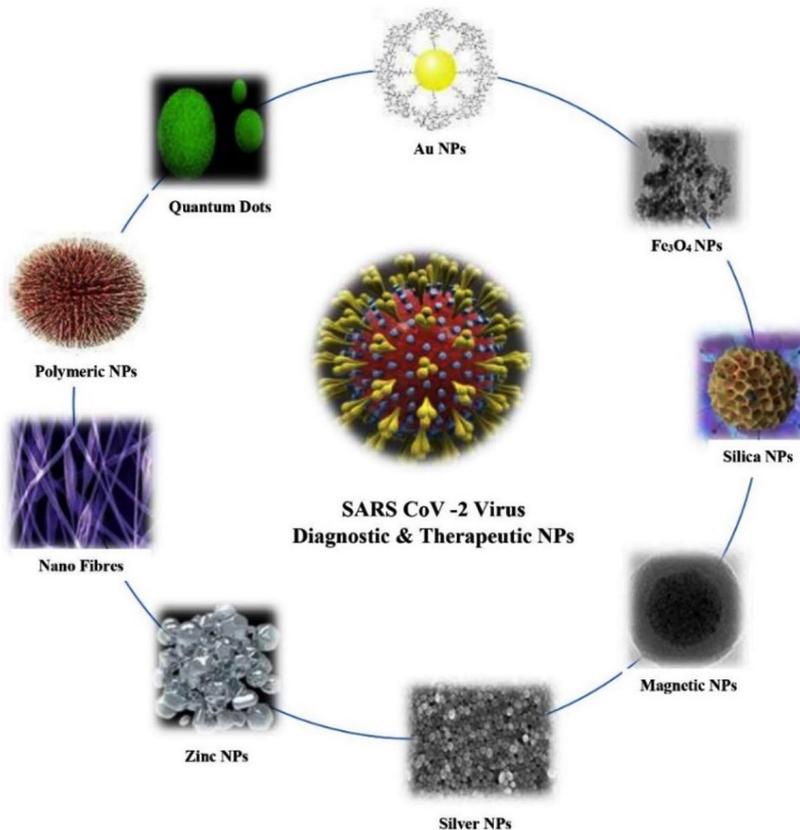


Figure 1. Diagnostic and Therapeutic NPs for SARS-CoV-2 Virus

advances in NT among diagnostic and therapeutic approaches in SARS-CoV-2 infections.

Preclinical Evaluation of Nanoparticles in SARS-CoV-2 Therapy

For treating SARS-CoV-2 infection, various forms of carbon dots (Carbon particles – CNPs) have been researched and procured from modified boronic acid ligands and citric acid/ethylene diamine.²² This helps in inactivating and inhibiting the SARS-CoV-2 entry in a concentration-dependent manner by repurposing the antimicrobial agents like Ribavirin, Lopinavir/Ritonavir, Chloroquine and

IFN- α . Thus, drug repurposing involve preclinical testing, safety assessment, and thus reducing the time required for the drug development.²³

Chloroquine: Chloroquine, inhibits viral entry into the host cell, reduction of viral load and endosomal pH enhancement by endosome–lysosome fusion.²⁴ Since chloroquine has been used for over 70 years and is both affordable and efficient, it has the potential to be therapeutically helpful for SARS-CoV-2.²³

Hydroxychloroquine: Hydroxychloroquine is coated with the nano-carriers alike albumin NPs, liposomes and micelles which helps in the supply

Table. Nanoparticle used for prevention and detection of SARS-CoV-2 infection

Name of product (company)	Type of nanoparticles	Function
Detection and Diagnosis		
COVID-19 Rapid POC CE-IVD Test (NanoComposix)	Gold nanoparticles	Has sensitivity and reliability of visual detection so used in point-of-care tests (detection kit)
COVID-19 Rapid Test Cassette (SureScreen Diagnostics Ltd)	Gold nanoparticles	Detection kit
COVID-19 point-of-need diagnostic test (Mologic Ltd)	Gold nanoparticles	Detection kit
Lateral flow (Sona Nanotech, Inc.)	Gold nano-rod	Detection kit
PPE		
Graphene mask (Flextrapower, Inc.)	Graphene nanomaterial	Virus protective respiratory mask
Guardian G-Volt (LIGC Applications Ltd)	Graphene nanomaterial	Virus protective respiratory mask
G + Fabrics (Directa Plus PLC)	Graphene nanomaterial	Antiviral fabric is used in the production of medical devices such as masks, gloves and gowns to ensure better prevention against the spread of virus
Antiviral fabrics (Promethean Particles Ltd)	Copper nanoparticle (with Promethean particles)	PPE
Nanofiber mask (YAMASHIN-FILTER CORP.)	Nanofibers made from synthetic polymers	Respiratory protective mask
NANO HACK (Copper 3D Antibacterial Innovations)	Copper oxide nanoparticles	Protective respiratory mask
Disinfectants and Sanitizers		
Nano Silver sanitizer (SHEPROS)	Silver nanoparticle (suspension)	Hand sanitizer (kills 99% of germs and bacteria)
Silvo Clean Spray (Weinnovate Biosolutions)	Silver nanoparticle (colloidal solution)	Sanitizer and disinfectant
NanoSeptic (NanoTouch Materials, LLC)	Mineral nanocrystal (creates an oxidation reaction, continuously oxidizing organic contaminants)	Surface disinfectant

POC: Point of care; PPE: Personal protective equipment. All the data mentioned in this table were obtained from the Nanotechnology Product Database <https://statnano.com/>

of cargo to the respiratory system and thereby declines the consequences in the systemic clinical manifestations like cardiac disease, myopathy and retinopathy.²⁵

Lopinavir/Ritonavir

Mpro, a vital enzyme for coronavirus replication, may bind to lopinavir and ritonavir. This prevents activity of SARS-CoV-2.²³

Interferons

Interferons (INF) are a cluster of cytokines that are secreted by dendritic, plasmacytoid and other types of cells. The interferon stimulating genes (ISG) are principally concerned about signaling, inflammation and immunomodulation which are activated on Interferon α/β Receptor (IFNAR) receptors by the INF fixation present on the plasma membrane of most of the cells. The ISGs are also involved in the activation of the adaptive immunity through decreasing the metabolism or the secretion of cytokines by means of interfering with viral replication. Further, they prevent membrane fusion by reducing the membrane fluidity and sensitize the cells to pathogens thereby inhibiting the virus-cell cycle steps. As of now, there is no established regimen for INF in treating SARS-CoV-2 and several clinical

trials with INF alone and in combination with other drugs have been initiated. (Figure 2).²³

However, NT takes a leading role in the SARS-CoV-2 vaccine development also. Novavax notified that the development of Matrix-MTM ADJUVANT (rn 1235341-17-9) Vaccine by formulation of virus-like particles (VLP; recombinant NPs) resulted in targeting one trimer of an S protein.²⁶ A novel development of vaccine described an antigen presentation platform as human SARS-CoV-2 involving peptide NPs which are self-assembling with deposition of viral transcription factor as N- and C-termini and containing non-structural protein.²⁷

Therapeutic Nano Particles in SARS-CoV-2 Treatment

Metallic Nanoparticles

Metallic NPs (MNPs) such as Gold NPs (Au NPs), silver NPs (AgNPs), Silica NPs (Au-SiO₂NPs), Zinc Oxide NPs (ZnONPs), magnetic NPs, Cuprous Oxide NPs (CuONPs) and Copper (I) Iodide NPs (CuINPs) are nanocarriers that show a newer approach to inactivate SARS-CoV-2 infection. The broad-spectrum antimicrobial activity was discovered in AgNPs and it enhances the sulfasalazine drug by silver ion from silver-sulfasalazine pharmaceutical product.²⁸ Ag ion

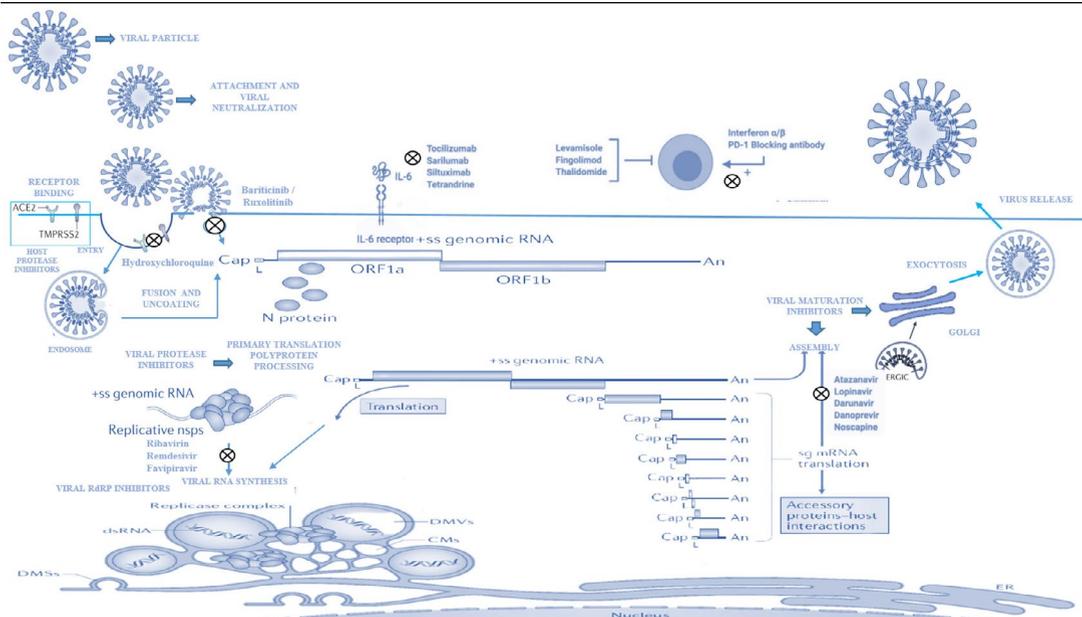


Figure 2. Mechanism action of Antiviral Drugs towards SARS-CoV-2 Infection

have noted anti-inflammatory, anti-cancer, antibacterial, antiplatelet, anti-angiogenesis and antifungal activities and also AgNPs are undergoing research for viricidal effects.²⁹

Polymeric Particles

These nanocarriers are being fabricated with liposomes, cyclodextrin complexes, polymeric nanoparticles, which are carried out through natural, synthetic, and semi-synthetic materials.³⁰

Liposomal Targeted Delivery

It is otherwise called lipid bilayer vesicles, widely meant for hydrophobic-hydrophilic drugs delivery.³¹ As a result of their biodegradable and biocompatible nature, they are mostly selected as a carrier for the drug formulation. It can also be utilized as a prospective stage for the development of novel drug formulations in treating SARS-CoV-2 infection. In 2009, Ohno et al conducted a study and reported that SARS-CoV infections are treated with synthetic peptides-based liposomes.³² Cytotoxic T lymphocytes are effectively induced with the chemically conjugated peptide-liposomes that can be likely treated for clearing the viral load against SARS-CoV-2.³³ Hence, liposomes act as a supporting system that has distinctive value for delivering the antiviral drug for the purpose of management in SARS-CoV-2 infection.³⁰

Cyclodextrin Complexes

It is a naturally occurring cyclic polysaccharide. They are composed of primary units such as α , β , and γ . cyclodextrin nanoparticles bear cyclodextrin in numerous units so that it could dissolve a drug in large quantity when compared to native cyclodextrin because of which they have greater importance.³⁴ In recent times, the cyclodextrin-based Remdesivir formulation is used for SARS-CoV-2 treatment which are authorised by FDA.³⁵ In the clinical scenario, it showed a promising effect against many other viruses such as the MERS-CoV and Nipah virus infection.³⁶ Hence, they are believed to be an efficient delivery vehicle for confined drug delivery to the lungs. Formulation of Cyclodextrin-based Remdesivir is used for the management of SARS-CoV-2 infection in which it showed great success.³⁷⁻³⁹

Polymeric Solid Colloidal Nanoparticles

The design of nanoparticle (NP) like size, shape and surface chemistry has a significant impact on their performance and they can be engineered into different sizes, shapes and surface chemistries to meet these requirements. Most NPs have a spherical shape. With advanced nanofabrication techniques, different shapes and forms of NPs have emerged in recent years with unique geometrical, physical and chemical properties which aids in drug binding.⁴⁰ Polymeric NPs have demonstrated significant capacity for binding and targeted drug delivery for the treatment of SARS-CoV-2.⁴¹ It has special feature in safe drug administration in vivo by targeted drug delivery, controlled drug release and improved efficacy. Due to its nano-size property, it helps to reduce the side effects because of high dose administration and permeability across the cell membrane.³⁹ Various approaches can be applied for the production of particles as they depend on the drug type to be loaded in the polymeric NPs as well as their requirements in appropriate route of administration.⁴¹ By fabricating human macrophages membrane-coated nano sponge with PLGA and human lung epithelial type II cells makes it essential for the SARS-CoV-2 entry into host cells. Therefore, during the course of viral incubation, artificial cellular nano sponge serves as a receiving target where it turns to be neutralized and incapable of infecting the host cells. Accordingly, the polymeric nanoparticle also acts as an efficient nanocarrier system in order to deliver antiviral drugs for SARS-CoV-2 treatment.⁴²

Nanotech as a Promising Approach for SARS-CoV-2 Diagnostics

In the course of universal catastrophe, there exist an emergency to formulate a diagnostic kit for the timely interventions of SARS-CoV-2 infection to hold down its spread. The standard test was RT-PCR, Chest Computed Topography, point of care against SARS-CoV-2.⁴¹ MNPs were used for SERS- based detection and it has a key role to refine the signal of analytes and their identification by electrical, immune fluorescent, and optical methods.⁴² Immunochromatography methods (lateral flow assay) colloidal gold NPs (CG NPs) were used for antigen detection. In recent

days, CG-NPs has been used as a POC for the prompt identification of IgG and IgM antibodies obtained from the virus.⁴³

Real-time Reverse Transcriptase-polymerase Chain Reaction using Nanoparticles

RT-PCR is a standard technique used for identification of SARS-CoV-2 virus from nasopharyngeal and oropharyngeal swab, tracheal aspirates or bronchial alveolar lavage (BAL).⁴⁴ Certain genes such as E protein (envelope protein), NP (nucleoprotein), and RdRp enzyme (RNA Dependent RNA Polymerase) are amplified.^{45,46} Though, these assays have certain limitation that they need high viral RNA with high viral load.⁴⁷ So, more interest was intrigued in the preparation of samples with the application of magnetic NPs.⁴⁸ While sample preparation, they can be effortlessly isolated with the help of an external magnetic field from the media.⁴⁹ Over the past few years, a promising consideration was gained as solid-phase adsorbents of various biomacromolecules by magnetic NPs. They are superior to other conventional methods as a result of reduced consumption of chemicals, the easier process by means of automation and lesser time for processing.⁵⁰ In this connection, Zhao et al made magnetic NPs coated by carboxyl group-(PC) with poly (amino ester) (pcMNPs) especially during the extraction of RNA.⁵¹ Ultimately this led to the sensitive identification of SARS-CoV-2 in RT-

PCR.⁵² On analogues to column-based nucleic acid extraction methods, a simple and quick extraction was shown by pcMNPs with high productivity and purity of an external magnet. Unfortunately, this method results as time-consuming in the prognosis of SARS-CoV-2 by RNA extraction.⁵³ In sum, NPs for extraction and detection of infections might be a reassuring matter. Additional experimentations are quite essential to appraise their potency and protection.

Surface-enhanced Raman spectroscopy – Aan Upcoming Advancement

SERS is a newer novel emerging diagnostic strategy for the quantification of SARS-CoV-2 performed in the real samples on its biological nature, including virus detection.⁵⁴ In 2021, Zhang et al resulted that detection of SARS-CoV-2 using SERS and they are correlated with their statistical analysis.⁵⁵ In their analytical system, ACE-2@SN-SERS substrate (Silver nanorod SERS arrays were physisorbed in human cellular receptor ACE-2 deposited on silicon wafers) and the recognition of functional receptors of spike glycoprotein of SARS-CoV-2 by ACE-2 enzyme particularly in its S1 subunit region.^{55,56} Therefore, ACE-2 worked as a reporter molecule as well as the molecular recognition element in which Raman signal occurred using an excitation wavelength of 780nm, when the Spike protein involves in binding and recognition of the Receptor Binding Domain.⁵⁷ In

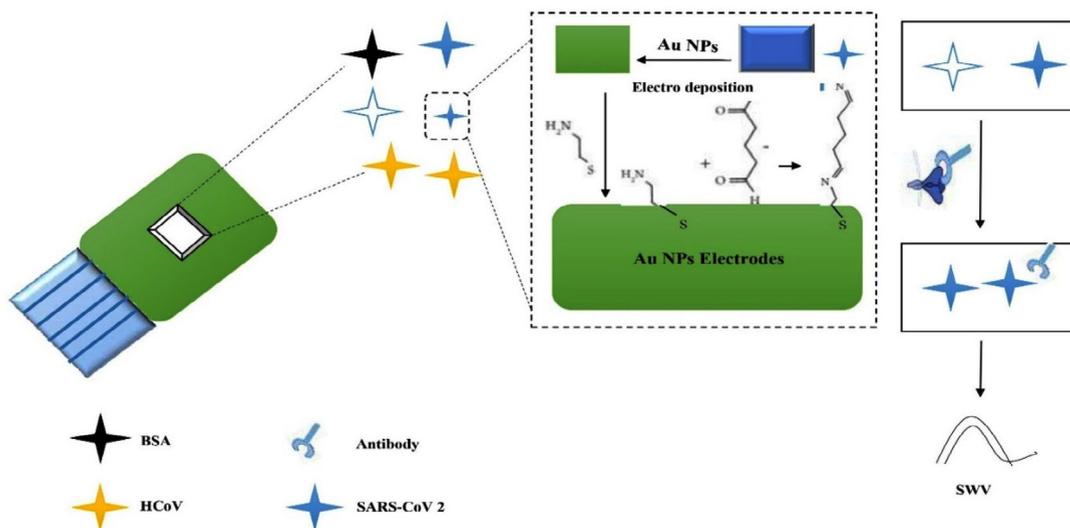


Figure 3. Nanotechnology in Electrochemical Sensing of SARS-CoV-2 Infections

addition to SERS immunoassays, various analytes can be tested, which absolutely exhibits a high versatility of the SERS technique, in contrast to PCR which works by testing samples with nucleic materials.

Electrochemical Sensing

It has been evolved as a novel diagnostic methodology for the identification of SARS-CoV-2 infection.^{58,59} The standard electrochemical sensors comprise a diffusion barrier, an electrode, a counter-reference electrode and a sensing electrode (as transduction element) carrying out an electrical signal by interacting with the target analyte and resulting in recognising the sensing electrode layer.⁶⁰ Some of the exquisite properties of semiconductor and metallic NPs containing high catalytic properties, surface area and conductivity have resulted to use in (i) effective catalysis, (ii) labelling biomolecules, (iii) biomolecules immobilization and (iv) enrichment of electron transfer.⁶¹ The electrochemical immunosensors are incorporated with a recognition compound of an electrode surface immobilisation (i.e., antigen

or antibody) and has obtained promising focus being efficiently and reliably detecting SARS-CoV-2 infections.⁶² These sensors are sensitive, user-friendly and cost-effective and provide an alternative approach for the detection of various infections. All the sensors are developed on the basis of N and S proteins and they are used for the detection of individual targets involving viral nucleic acids, nucleocapsid, spike antigen and immunoglobulin. Moreover, biosensors are capable of simultaneously recognizing nucleic acid as well as N or S proteins in order to detect SARS-CoV-2.⁶³ Possibly, they also have the ability to sense N or S proteins, nucleic acid, and IgG and IgM antibodies, although antibodies take a long period of time to establish once the infection has occurred. Thus, electrochemical sensors can be very selective and sensitive for the detection of infection⁶⁴ (Figure 3).

Quantum Dots

Evolution of Bio-Sensors (BS) was employed by Quantum Dots (QDs).⁶⁴ Newly, Roh developed a BS by modifying QD-Conjugated

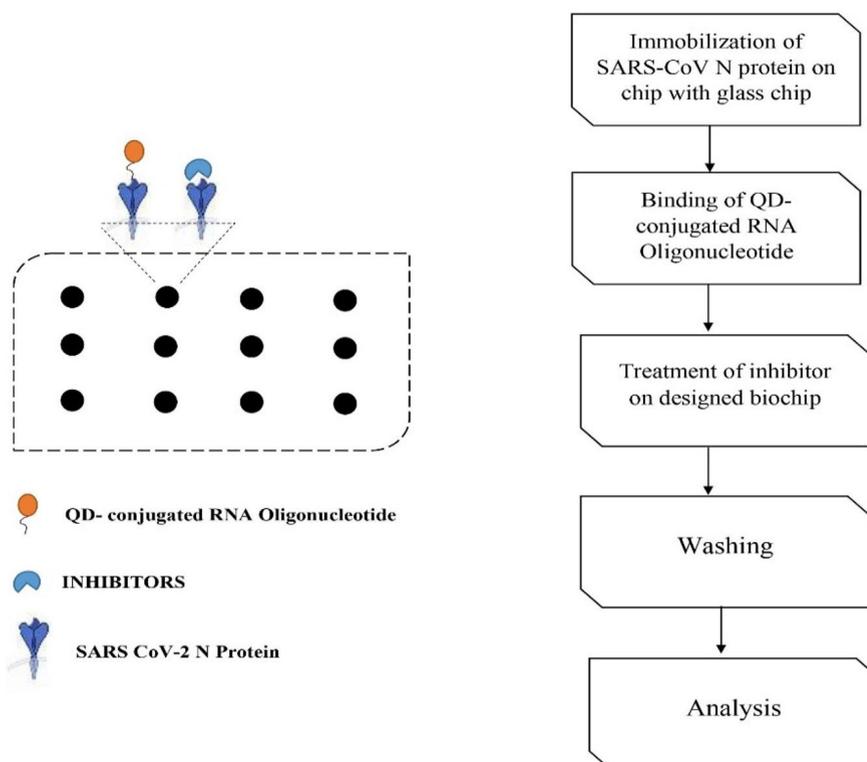


Figure 4. Quantum dots (QDs) Sensing of SARS-CoV-2 Infections

RNA oligonucleotide and SARS-CoV-2 N protein and tested the inhibitor screening by several polyphenolic compounds as-fabricated biochips.^{65,66} QDs are a newer Nano approach due to their distinctive features like electric and optic properties used as a therapeutic and diagnostic agent.^{67,68} Anti-HIV properties of gallate and (-) - galocatechin gallate on a QDs-RNA oligonucleotide biochip demonstrated high and maximum inhibitory concentration (IC50) rates while comparing with different polyphenolic compounds.^{69,70} The introduction of biochips not just directed the particular determination of the viral N protein plus it also showed their possibility for using as an inhibitor.⁷¹ Also, Zhu and work colleagues on using reverse transcription loop-mediated isothermal amplification (RT-LAMP) coupled NP-based biosensors (NBS), especially for SARS-CoV-2 diagnosis which leads to the identification of SARS-CoV-2 in a sensitive and selective manner. Thus, it is a propitious approach applied to sense SARS-CoV-2 infection (Figure 4).^{72,73}

Nanoparticles for Improvement of Personal Protection Equipment

Personal Protective Equipment's (PPEs) are essential for HCWs. Effectiveness of PPEs were improved by NPs-based solution with antiviral property and exhibit potent.⁷⁴ In a study carried out by Bhattacharjee et al., presented that metal grafted graphene oxide (GO) has an antimicrobial property used for utilization of PPEs.⁷⁵ GO is hydrophilic in nature and they allow interfacial bonding with various polymers and fibers. GO is further modified into rGO by removing majority of oxygenated functionalities through thermal, microwave and chemical treatment.⁷⁶ GO loaded with Cu or Ag NPs produces the effective antiviral properties upon enveloped and non-enveloped viruses. It is also reported to present antiviral activity over SARS-CoV-2 virus.⁷⁵⁻⁷⁶ When the 'virus-nanoparticle' complex come in close proximity, the active centres on the viral capsid are suppressed by local field enhancement which in turn disable the chemical bonds within the capsid. Modification of these receptors present on the viral capsid will

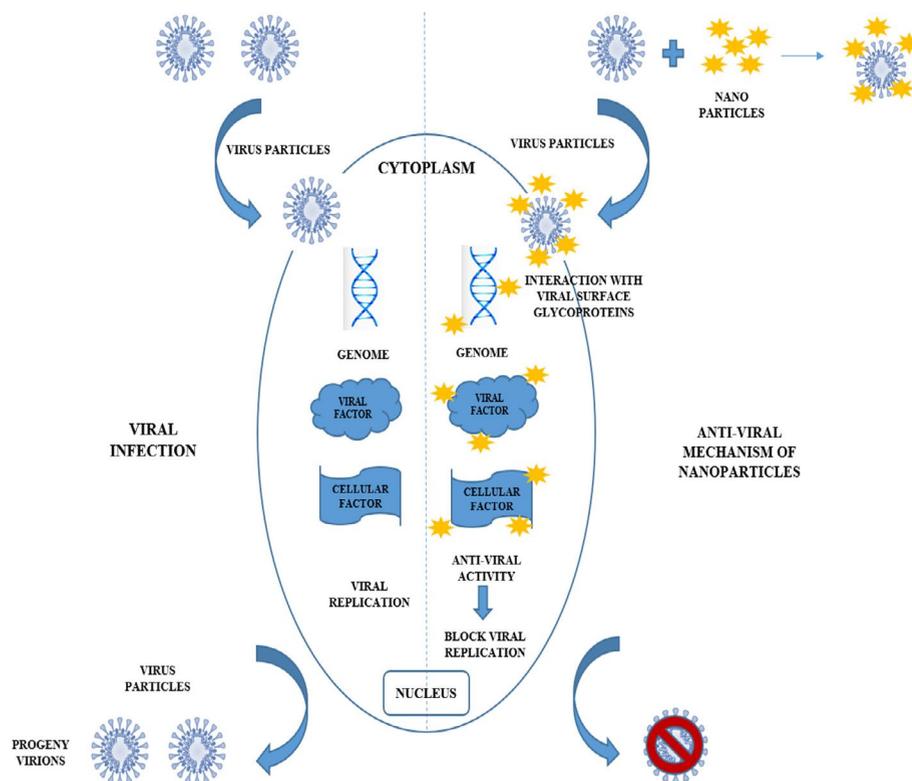


Figure 5. Anti-Viral Mechanism of Nanoparticle effect on SARS-CoV-2 virus

render the virus harmless while it would have lost its ability to infect nor the host cells penetration. These mechanisms on local field interactions and binding energies have presented several nanomaterials by generating a progressive novel area of research in nanoscience.^{77,78} The newer approach against SARS-CoV-2 by developing silver nano-cluster silica composite facial mask by studying anti-infective property of Ag and can also use in glass, ceramic and metallic surfaces and application against populated areas like schools, supermarkets, and hospitals for controlling the increase in SARS-CoV-2 infection. It was exhibited that filling of polypropylene masks by CuO are protected against the influenza virus.⁷⁹ Likewise, in 2020 Ahmed et al incorporated into face masks to inactivate the Viral particles with GO and CuO NPs into electrospun nanofibers. There is a possibility for sterilizing face masks for re-use by Graphene NPs.⁷⁸ The Graphene has vital properties of electric and thermal to enable the sterilization of the fabric respirators, facemasks, and filters. Hence, the NPs serve as a significant improvement in PPEs with the purpose of protecting and preventing from SARS-CoV-2 virus⁸⁰ (Figure 5).

Barriers to Overcome

With the global raising of SARS-CoV-2 pandemic, the strength of the newer drugs is always very essential to understand as they are supposed to be reviewed better. Concurrently, nano drugs serve like double-edged sword. Besides certain exceptions regarding the toxic natures, they never fail to boost the drug potency or act for inhibiting the virus attachment by nano-drug, its pathogenicity or by subsequently controlling the damaging and inflammatory cascade of viral infection in patients.⁸¹ There are numerous reports that are linked with tumorigenicity, penetration into the brain, mutagenicity, producing free radicals of metallic NPs. Therefore, penetration into the brain, toxicity, biodistribution, biodegradability of NPs and size dose-dependency should be cautiously maintained.⁸² NPs prove cell death mechanisms and drugs showing cross-reaction against a virus such as ferroptosis, autophagy are alternative crucial points that are related to them. Thus, the clinical investigations involving translation of *in vivo* studies showed irreversible damages by NPs'

biocompatibility without involving any conclusive studies.⁸³

CONCLUSION AND FUTURE PERSPECTIVE

Nanomedicine has set up a novel and powerful period through the interpretation as well as treatment of SARS-CoV-2 infections. At the same time, there was concern about translation of clinical applications involves size-efficacy, safety of nanoparticles and dose-response. Sketching of the nano platform is very much necessary in determination and management of SARS-CoV-2 infections limits the human cell tissue damage cascade activation. In pursuit of this objective, manipulation of viral structures and the enzymatic structures by nanoparticles are more pivotal for precise understanding of cell death mechanisms and by engaging human cells with virus receptor binding using NP. Designing of nanoparticles meanwhile, concerns the increase in circulation time, limitation of drug metabolization by its biodistribution, efficacy of drug entrapment and delivery in unwanted tissues and organs. The significant feature of the designed NPs amplifies the ability of delivering the antiviral drug as it may be functionalized for the active targeting of certain antibodies and ligands. As a result of repurposing as well as for the development of the drug, apparently NPs itself and its concomitant therapy or their carriers will be advantageous in making a therapeutic and diagnostic effect against SARS-CoV-2 infections.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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