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State-of-art high-performance Nano-systems for mutated coronavirus infection management: From Lab to Clinic

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ABSTRACT

The emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants made emerging novel coronavirus diseases (COVID-19) pandemic/endemic/or both more severe and difficult to manage due to increased worry about the efficacy and efficiency of present preventative, therapeutic, and sensing measures. To deal with these unexpected circumstances, the development of novel nano-systems with tuneable optical, electrical, magnetic, and morphological properties can lead to novel research needed for (1) COVID-19 infection (anti-microbial systems against SARS-CoV-2), (2) early detection of mutated SARS-CoV-2, and (3) targeted delivery of therapeutics using nano-systems, i.e., nanomedicine. However, there is a knowledge gap in understanding all these nano-biotechnology potentials for managing mutated SARS-CoV-2 on a single platform. To bring up the aspects of nanotechnology to tackle SARS-CoV-2 variants related COVID-19 pandemic, this article emphasizes improvements in the high-performance of nano-systems to combat SARS-CoV-2 strains/variants with a goal of managing COVID-19 infection via trapping, eradication, detection/sensing, and treatment of virus. The potential of state-of-the-art nano-assisted approaches has been demonstrated as an efficient drug delivery systems, viral disinfectants, vaccine productive cargos, anti-viral activity, and biosensors suitable for point-of-care (POC) diagnostics. Furthermore, the process linked with the efficacy of nanosystems to neutralize and eliminate SARS-CoV-2 is extensively highligthed in this report. The challenges and

Abbreviation: COVID-19, Coronavirus Disease 19; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; +ssRNA, positive single-stranded ribonucleic acid; Acov, alpha coronavirus; Bcov, beta coronavirus; Γcov, gamma coronavirus; Δcov, delta coronavirus; MERS-CoV, middle east respiratory syndrome coronavirus; HCoV, human coronavirus; RT-PCR, reverse transcriptase polymerase chain reaction; Ct, computed tomography; Np, nanoparticle; Vlp, virus-like particles; MHC, major histocompatibility complex; HSV, herpes simplex virus; AuNps, gold nanoparticles; AgNps, silver nanoparticles; LNps, lipid or liposome-based nanoparticles; Dotma, 1,2-di-o-octadecyl-3-trimethylammonium-propane; DoOTAP, 1,2-dioleoyl-3-trimethylammonium-propane.

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opportunities associated with managing COVID-19 using nanotechnology as part of regulations are also well-covered. The outcomes of this review will help researchers to design, investigate, and develop an appropriate nano system to manage COVID-19 infection, with a focus on the detection and eradication of SARS-CoV-2 and its variants. This article is unique in that it discusses every aspect of high-performance nanotechnology for ideal COVID pandemic management.

1. Background: nano-biotechnology as emerging solution to tackle COVID-19 infection

The worldwide new coronavirus disease 2019 (COVID-19) epidemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is affecting individuals of all ages, children, and physically healthy people. The emergence of COVID-19, the third major epidemic of respiratory disorders in history has brought attention to the socioeconomic balance of the world. Millions of people's lives have been significantly impacted by the rising incidence of infectious illnesses. According to a cumulative collection of studies, SARS-CoV-2 infections are associated with greater cardiac involvement in both symptomatic and asymptomatic individuals. The epidemic has reached alarming proportions, paralyzing national healthcare systems and mandating global deployment. On the other hand, some randomized clinical studies targeted at therapy must give realistic advice on therapeutic interventions and pharmaceutical treatments.

The discovery of medications utilizing nanoparticles (NPs) is attracting a lot of interest nowadays, and it might result in the creation of novel, better pharmaceuticals (i.e., alternative antiviral and antimicrobial agents). The considerable desired physio-chemical properties of nano-systems include aggregation, agglomeration, crystallinity, chemical composition, shape, size, surface charge, and anti-microbial [for example silver (Ag), copper (Cu), zinc oxide (ZnO), graphene, MXenes, etc., NPs and polymeric nanostructures] properties [1]. Although there is enough literature on the symptomatology, epidemiological studies and spread, etiopathogenesis, diagnosis, and clinical manifestations of SARS-COV-2, as per our best knowledge, significant efforts are required to tune, promote, and execute state-of-the-art nanotechnology for developing point-of-care (POC) and personalized strategies for COVID-19 pandemic management efficiently. Researching bio-nanotechnology and nanomedicine, both of which are designed and developed for personalised health wellness, makes it possible to investigate very precise nanomedicine as a method of managing COVID-19 infection in a personalized approach. In order to lower the concentration of medicine required for biological processes due to extended and/or controlled administration, nanocarriers are researched to alter the pharmacokinetics features of the encapsulated nutraceutical

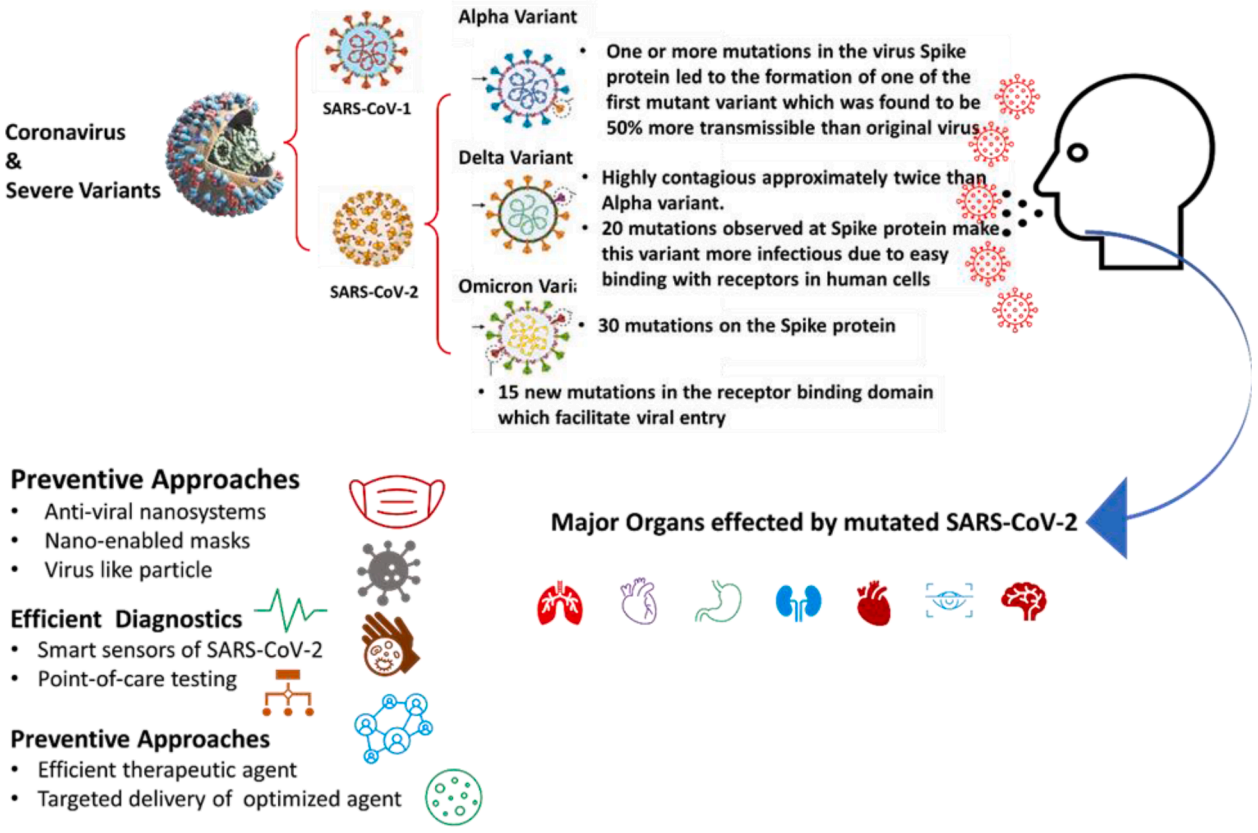

Fig. 1. Structural organization of the SARS-CoV02 variants and related COVID-19 infection.

treatment. Additionally, a particularly promising method for enhancing antibacterial characteristics is the application of specific ligands on the surface of nanocarriers to detect biological components of the targeted tissue.

2. Emergence of human coronavirus and associated pandemic

Even presently, the SARS-CoV-2 along with its variants is attempting to inflict chaos on people's health. This virus, which is mutating often, found to be highly contagious in humans and still spreading rapidly across the world affecting the global population and economy. Because of the rising number of illnesses, COVID-19 have been declared as a "pandemic" and there is ab active discussion to declare it as an endemic [2–4]. Coronaviruses (CoVs) represent one of the largest groups of viruses that belong to the order *Nidovirales*, family *Coronaviridae*, and further classified into four genera namely *Alphacoronavirus* (αCoV), *Betacoronavirus* (βCoV), *Gammacoronavirus* (γCoV) and *Deltacoronavirus* (δCoV) (Fig. 1) [5].

In humans and animals, however, alpha- and beta-coronaviruses have the potential of causing gastrointestinal and respiratory illnesses. The pandemic virus, meanwhile, is a member of the beta-coronavirus family, which also includes the human coronaviruses SARS-CoV and MERS-CoV. (HCoV). These beta-coronaviruses, including SARS-CoV (2002–03), MERS–CoV (2012–13), and SARS–CoV-2, are to blame for a number of the most devastating outbreaks and a pandemic (2019-Ongoing). The other four human coronaviruses (HCoV-NL63, OC43, 229E, and HKU1) have relatively mild effects on the respiratory tract but can be extremely dangerous to completely impervious hosts, such as elderly people and young children [6].

Due to its highly variable incubation period ranging from 3 to 9 days to 3 weeks, transmission efficiency, high mutability, and increasing frequency of asymptomatic infections, SARS-CoV-2 is difficult to detect (Fig. 2) [7,8]. Traditional methods of diagnosis such as RT-PCR and CT scan are widely used but the possibility of human error and risk of false negatives delay the medical intervention potentially leading to severe infection [9,10]. Thus, effective measure with an interdisciplinary approach is needed to combat this virus.

The SARS-CoV-2 is known to evolve regularly, and new variations like Alpha, Delta, and Omicron have emerged with greater

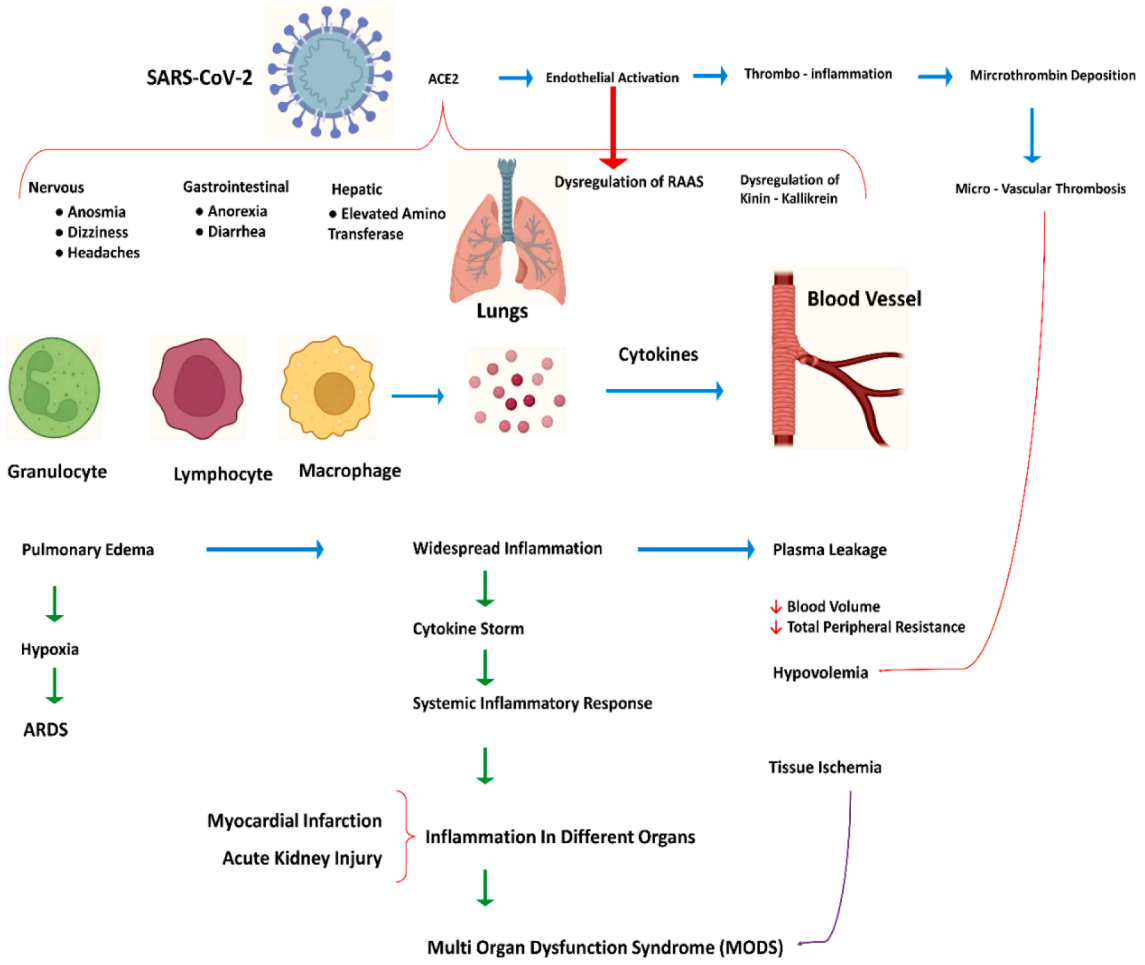

Fig. 2. Pathophysiology of SARS-CoV-2 associated viral infection.

virulence and transmissivity, with detrimental health effects (Table 1). The complexity of treating this unique COVID-19 infection strain has heightened the need for effective POC biosensors for SARS-CoV-2 detection, antiviral and antibacterial materials for SARS-CoV-2 eradication, and nano-theragnostic for capturing and eliminating mutants [11].

SARS-CoV-2 recently evolved into a new variety, Omicron (B.1.1.529), which is far more transmissible and infectious than the previously fatal Delta versions. This severity is linked to a higher number of mutations found in the receptor-binding region of the Omicron-SARS-CoV-2 spike protein [23]. Although there is no conceivable reason to explain the origin of Omicron variants, speculations like zoonotic mutation involving human-to-human transmission, random mutation among COVID-19 infections, and the association of SARS-CoV-2 with seasonal flu virus all contribute to the observed unexpected gap in genomic profiling between Delta and Omicron variants. Even if they are completely immunized, these Omicron mutations have major medical repercussions for people with compromised immune systems, such as those recuperating from COVID-19 [24].

Investigating very precise nanomedicine as a method of treating COVID-19 infection in a customized way may be done using bio-nanotechnology and nanomedicine, both of which are intended and developed for tailored health wellbeing [23]. The NPs have the potential to be used not just as immunogenic agents but also as targeted delivery systems for therapeutic drugs, even though vaccines are currently the most effective method of lowering the risks associated with severe SARS-CoV-2 infection [25]. Nanocarriers are being investigated for their potential to alter the pharmacokinetics of encapsulated nutraceutical medications and minimize the drug concentration required for biological processes due to extended and/or controlled delivery. Using targeted ligands on the surface of nanocarriers to detect biological molecules in the targeted tissue is also a viable technique for improving antibacterial capabilities [24, 26,27]. In the past decade, a newly emerged area of medicine called "theragnostic nanomaterials" has arisen to manage a targeted disease. It combines precise targeted therapy with diagnostic tools for the next-generation treatment of many different illnesses. Such nano systems are able to get past the many obstacles that stand in their way through different delivery routes thanks to their non-toxicity, structure, charges, and electrochemical conversion abilities [28]. The incorporation of nanotechnology, such as carbon-based NPs, can result in more accurate detection techniques for keeping track of a patient's long life. Customer firms should be streamlined from planning to flag identification while boosting local sensitivity and specialization. This is possible by merging all the features into a single device. The testing of COVID-19 in outlying places could benefit from the creation of a straightforward, adaptable, and wireless device [29,30]. Additionally, incorporating mobile apps developed using artificial intelligence (AI) and internet of medical things

Table 1
Time to time mutation on SARS-CoV-2 and related health consequences along with challenges.

Variant	Lineage	Origin	Year	Spike Mutations	Clinical Outcomes	Challenges	Ref.
Alpha (α)	B.1.1.7 and Q lineages	United Kingdom	Sep-20	Δ69–70 deletion, Δ144 deletion, E484K, S494P*, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N	50–100% higher transmissibility; 39–72% more lethal	There is no evidence that the variance impacts the illness's severity or the vaccine's efficacy.	[12] [13],
Beta (β)	B.1.351 and descendent lineages	South Africa	May-20	D80A, D215G, R246I, Δ241–243 deletion, K417N, E484K, N501Y, D614G, A701V	20–113% higher transmissibility	E484K, one of the spike protein mutations, may alter antibody neutralization by various polyclonal and monoclonal antibodies.	[14–16]
Gamma (γ)	P.1and descendent lineages	Brazil	Nov-20	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	70–140% higher transmissibility; evades immunity 21–46% more; 20–90% more lethal	The antigenic profile and transmissibility of the P.1 variety may be affected by mutations, which might impact how well the virus is recognized and neutralized by antibodies produced after a prior infection or during vaccination.	[17, 18]
Delta (δ)	B.1.617.2 and AY lineages	India	Oct-20	T19R, (G142D), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N	64% higher than B.1.1.7 (26–113% higher transmissibility	Target cells infected by the variant spike's pseudo virus more quickly and more severely because it unites with target cells with low levels of (hACE2) more efficiently.	[19]
Omicron (ο)	B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 lineages	South Africa	Nov-21	N211del/L212I, Y145del, Y144del, Y143del, G142D, T95I, V70del, H69del, A67V (N-terminal domain); Y505H, N501Y, Q498R, G496S, Q493R, E484A, T478K, S477N, G446S, N440K, K417N, S375F, S373P, S371L, G339D (Receptor Binding Domain); D796Y (Fusion peptide); L981F, N969K, Q954H (Heptad repeat)	70–100% higher transmissibility	Possibility of enhanced infectiousness; Possibility of decreased inactivation by various monoclonal antibody therapies against EUA; Possibility of post-vaccination sera decreasing neutralizing	[20–22]

(IoMT) will let you monitor a patient's health status when evaluating local health. Delivering antiviral NPs can be used in conventional therapy to start a secure defense against sickness [31]. Researchers believe that using nanotechnology to fight the COVID-19 outbreak and any potential epidemics is a good idea, but more study is required to give fresh, meaningful knowledge [32,33].

In the future, nanotechnology, specifically the development of functionalized nano-structures with tuneable high-performance, could be used to create viral disinfectants, preventive systems (filters and masks), drug delivery, and biosensors with the goal of quickly detecting and inactivating SARS-CoV-2 [13,14]. When opposed to alternative methods to medicine delivery strategies that circulate throughout the body, NPs are used particularly to target lymphatic tissue and interaction locations in order to trigger a long-lasting and robust immune response [15–17]. As a result of the demand for efficient, precise, and cost-effective theragnostic equipment, researchers have turned to nanotechnology [34]. Nanotechnology has been used to build vaccines based on NPs that can carry antigens and have the right size and surface area to act as effective vehicles for antigen transport and immune stimulation [35, 36]. The nano-vaccinations showed strong immune response activation, controlled drug pharmacokinetics, excellent cell and humoral response, and enhanced vaccination efficiency, making them ideal replacements for traditional vaccines [37].

3. Nano-conjugates developed for COVID-19 infection management

Despite substantial progress in developing effective quick sensing technologies and more effective nanotherapeutics, the current coronavirus disease i.e., COVID-19 pandemic remains uncontrollable so because severe acute respiratory syndrome virus i.e., SARS-CoV-2 (original and mutated) spreads rapidly from person to person and produces life-threatening respiratory ailments [22,38]. As a result, it's become critical to take safeguards and maintain the environment clean by utilizing high-performance anti-viral nano-materials to capture and eliminate SARS-CoV-2. Such an antiviral nano-system has successfully proved its usefulness in the control of COVID-19 pandemics and endemics [39].

The NPs-based vaccines can be regarded as appropriate substitutes for traditional vaccinations if they are induced in alternative pathways, their circulation is confined to regions, are thermo-stabilized, economically feasible, and can be synthesized in bulk and delivered broadly [40]. Such vaccines may not require a second, booster dose. Nano-biotechnology assisted platforms can provide a promising chance of increasing the intensity of humoral and cellular immune responses [41]. However, only vaccines are not enough for suppressing the upsurge of SARS-CoV-2 infections. It must be combined with efficient diagnostic, preventative, and clinical techniques [42]. In this review, the authors have described the applications of nano-conjugates discovered for therapeutics and the detection of COVID-19 infection. Furthermore, we have explored the clinical importance and drawbacks of several nano-systems that can be used as viral disinfectants, vaccines, medication delivery, biosensors, and antiviral agents as nano-strategies for the management of COVID-19 and its variations.

3.1. Virus-like particles

Virus-like particles (VLPs) are a class of protein-derived NPs that include envelope proteins without the viral genetic material and can generate an immune response without the risk of reproduction. VLPs acquire pathogenicity through mediating interactions amongst their distinctive envelope proteins (capsid proteins) and have effectively mimicked human infection by penetrating cells and expressing viral antigenic peptides via host cell replication processes [43]. They have a high immunogenic potential and may elicit long-lasting immune responses across a wide range of pathways, with the added benefit of not requiring the major histocompatibility complex, allowing them to be displayed on both MHC class I and II cells. When VLPs are combined with adjuvants (Pattern Recognition Receptors, Chitosan), immuno-regulators (cytokines such as interleukins), and preservatives, innate and adaptive immune responses are boosted [44]. They are stable and are used in viral diseases such as Hepatitis B, HSV, Malaria, and Norwalk Virus [45,46].

3.2. Inorganic nano-systems

Metal-derived compounds such as gold (Au), silver (Ag), copper (Cu), Mxene, and iron oxides $(FeO)_x$ NPs are being increasingly used for multifarious biomedical applications such as imaging, therapeutics, targeted drug delivery, and antiviral activity [47]. The AuNPs have proven to be resourceful for imaging owing to their light-scattering properties and can further be loaded with therapeutic molecules such as proteins, and RNA for in vivo or in vitro applications. Iron oxide NPs including Fe_3O_4, Fe_2O_3, etc. NPs are currently being used widely for non-invasive diagnostic bioimaging owing to their magnetic properties and for targeted drug delivery owing to their biodegradable properties [48].

3.3. Lipid-based nano-systems

Lipid or liposome-based nanoparticles (LNPs) are some of the most widely used NPs in recent times. They are widely used in therapeutics and drug delivery because conjugating mRNA with LNPs protects it from enzymatic degradation, increasing the levels of interferon interacting genes by 15–25 folds when compared to neutral or negatively charged NPs, mediating efficient drug uptake through a sophisticated permeation mechanism, and simultaneously ensuring targeted vaccine delivery [49]. As a result, the creation of a steady, powerful, and long-lasting immune response is aided, which might better protect the host from infection. The synthetic lipids have two unsaturated aliphatic hydrocarbon chains that are either bonded to a quaternary amine, unlike natural lipids [50].

The LNPs-based systems utilize two cationic liposomes namely, 1,2-di-O-octadecyl-3-trimethylammonium-propane (DOTMA) and 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) for nucleic acid delivery [51]. These liposomes serve as suitable drug and

nucleic acid delivery systems and are considered viable candidates not only for their utilization as nano-adjuvants in vaccines but are also currently being explored as potential candidates for drug carriers. Pfizer/BioNTech and Moderna Vaccine are two of the most widely used COVID-19 vaccines which are LNP-based mRNA vaccines used all over the world [52,53].

3.4. Polymer-based biocompatible nano-systems

For targeted medicine delivery with no side effects, electrospun nanomaterials are coupled with the target receptor on their surface. Because of their abrupt distribution in the treatment of viral infections, the tunability of nucleoside analogues with nucleoside analogues and nucleobases acting as antimetabolites is often associated with insufficient activation and instantaneous clearance, providing insights into the application of polymer NPs for anti-COVID activity [54]. The FDA has authorized many polymers for clinical use, including polyvinyl alcohol (PVA), polylactic acid (PLA), polyethylene glycol (PEG), and poly (lactic-co-glycolic acid) (PLGA), hyaluronate, alginic acid, and collagen. Their fundamental characteristics, including size, shape, and density, are quite variable and may be adjusted for better medication delivery. These can also be coupled with inorganic NPs to enhance their anti-viral effects and are employed in masks and personal protective equipment, in addition to medication delivery [55].

4. Nanotechnology-enabled preventative approaches

4.1. Vaccine production and nanotechnology

Vaccines have been seen as an important public health strategy for preventing virus outbreaks. The demand for vaccinations to protect against numerous illnesses by generating a powerful and long-lasting immune response has been steadily increasing in conjunction with the incidence of viral outbreaks [37]. The basic concept of a vaccine is that it uses an immune response that can be intentionally initiated by harmless inactivated or subunit viruses to stimulate the development of antibodies and memory cells that can prevent a severe infection from occurring in the future [37]. The use of pre-clinical and clinical studies to develop vaccines against COVID-19 variations has been explored, which will pave the road for their transfer from the laboratory to the market after FDA or WHO/EMP approval.

Vaccines that cause greater antibody titre counts (>13) are recommended; nevertheless, stronger antibody elicitation raises the potential of severe adverse effects [56]. Traditional inactivated or live attenuated vaccines are the most often approved vaccines against SARS-CoV-2; viral vector vaccines and subunit-based vaccines have been highly beneficial due to their potential to serve as adjuvants, infective agents, or stimulate innate immune responses in the human body. These vaccines are largely biocompatible to minimize viral mRNA degradation in the human body, which can reduce immune response induction and result in lower titre [57]. However, enhancing the potency, durability, and quality of vaccinations is a continuing problem. Vaccine delivery platforms like hydrogels, NPs, and micro-needles need to be customized to enhance immune system response by controlling vaccine release and targeting vaccine delivery to antigen presentation niches (lymph nodes and other secondary immune organs) [58]. For example, the spike protein (S) has notably become a prominent antigenic target for vaccine development. The discovery of mutations of SARS-CoV-2, on the other hand, has underlined the need for alternative structural (envelope protein) targets as prospective vaccine targets [59]. aluminum salts, graphene, silica NPs, carbon nanofibers, Au-NPs, liposomes, and polymerized NPs were employed as vaccine adjuvants by Sinopharm, a Chinese pharmaceutical drug development agency, in collaboration with the Wuhan Institute of Biological Products. It must be stored between 2 and 8 °Celsius to stay alive [7]. In addition, NPs have been effectively employed in the development of biosensors that have reliably identified the presence of SARS-CoV-2, which is much faster than previous approaches. These strategies were developed because of decades of study on how to effectively identify different viruses [60].

Plant-based recombinant virus-like particle vaccines for COVID-19 are being developed to generate economically viable, quickly growing, and large volumes of recombinant virus-like particles, which could assist in vaccine production at a large scale [2]. Medicago's vaccine candidate, a coronavirus-like particle (CoVLP), is a spontaneously self-assembling VLP with parts of SARS-recombinant CoV2′s spike protein incorporated in the lipid bilayer of the NPs. Transient infection of *Nicotiana benthamiana* is followed by conjugation with AS03 adjuvant (oil-in-water) before injection of the recombinant VLP. In Plants, a similar strategy was employed to make hemagglutinin-based VLPs [61]. These vaccinations are effective at temperatures ranging from 2 to 8 °C. and therefore do not require intense conditions, facilitating shipment into distant areas simpler. Phase 3 studies began in April 2021, following favourable interim Phase 2 findings, and are now being done with 30,000 participants from ten countries [62]. Placebo-controlled randomized studies with a defined pharmaceutical formulation of 3.75 g CoVLP conjugated with AS03 were conducted in people 18 years of age over 21 days to get more insight into the safety and immunogenicity by assessing neutralizing antibodies and the cell-mediated response. According to reports, CoVLP with AS03 caused a stronger humoral response in adults than older people and IFN-γ 30 response in both age cohorts, although the second dosage significantly boosted IFN-γ and IL-4 responses in both age cohorts [62] .

KBP-201, a plant-based VLP vaccine candidate that targets the S-protein, was produced in *N. bentha*miana, which produces both RBD and Tobacco Mosaic Virus at the same time. The difference between both CoVLP and KBP-201 is that both use an epitope and an independent virus to generate a Chimeric VLP or cVLP that can autonomously assemble. KBP-201 has access to a cutting-edge facility that can grow up to 3 million tobacco plants at a time, enabling fast vaccine manufacture [63]. Presently, 101 people participated in Phase 1 Clinical Trials, which were concentrating on an observer-blinded, randomized, placebo-controlled, parallel-group research to assess the safety and immunogenicity of the SARS-CoV-2 vaccination with CpG adjuvant in healthy adults of two age groups. The individuals were split into three groups: those who received a modest dosage with an adjuvant, those who received a high dose, and those who received a placebo. The trials are still underway, and the findings have yet to be released (NCT04473690).

To stabilize the antibody-inducing antigen as well as an enhanced immune response, nano-adjuvants such as virus-like particles, polymers, and inorganic adjuvants such as Au and Ag are being employed [64]. In mouse models to examine the efficacy of antibody formation when encapsulated and non-encapsulated HepBAg are delivered, chitosan NPs are utilized as an adjuvant and vaccine delivery method against Hepatitis-B surface antigen [65,66]. When compared to non-encapsulated Hepatitis-B antigen, Chitosan-NPs conjugated HepBAg produced many stable, long-lasting antibodies in a single, low dosage without serious adverse effects in mouse models. Comparable results can be predicted in COVID-19 due to similar properties, however, this must be confirmed using experimental data [65].

By introducing SARS-CoV-2 viral gene segments into a highly annotated *S. cerevisiae*-based D-Crypt™ platform, Mazumder and colleagues effectively created a triple antigen virus-like particle vaccination candidate, PRAK-03,202 [67]. The immunogenic potential of PRAK-03,202 was evaluated in conjunction with the adjuvant effect of aluminum hydrogel (AH), as well as against AH and placebo. To evaluate the effectiveness of this vaccine candidate, BALB/c mice were procured and vaccinated intramuscularly three times within a 14-day interval, further separating the animals into AH with PRAK-03,202, just AH, and placebo [67]. In animal models, PRAK-03, 202 proved successful in binding to ACE-2 receptors, preventing infection. Antibody titre counts in BALB/c mice were very similar to those in convalescent plasma, demonstrating the potential antigen neutralizing effects of PRAK-03,202, which elicited a significant immunological response to all three antigens and is thus considered a possible candidate for human trials [67].

In a recent investigation, Van Oosten et al. successful in synthesizing a baculovirus-derived SARS-CoV-2 vaccine based on the Spike Protein S1 component in a murine model using the AP205 VLP and tag/catcher system [68]. S1-VLP immunization produced efficient antibodies against SARS-CoV-2 in K18-hACE2 transgenic mice given adjuvant spike sub-unit vaccine and those given the same vaccine conjugated with the NPs-based AP205 VLP display system. As a result, further research is required before clinical trials may begin [68].

Inorganic NPs, like VLPs, are a hot topic of research because of their potential to be used as vaccine delivery vehicles. When utilized

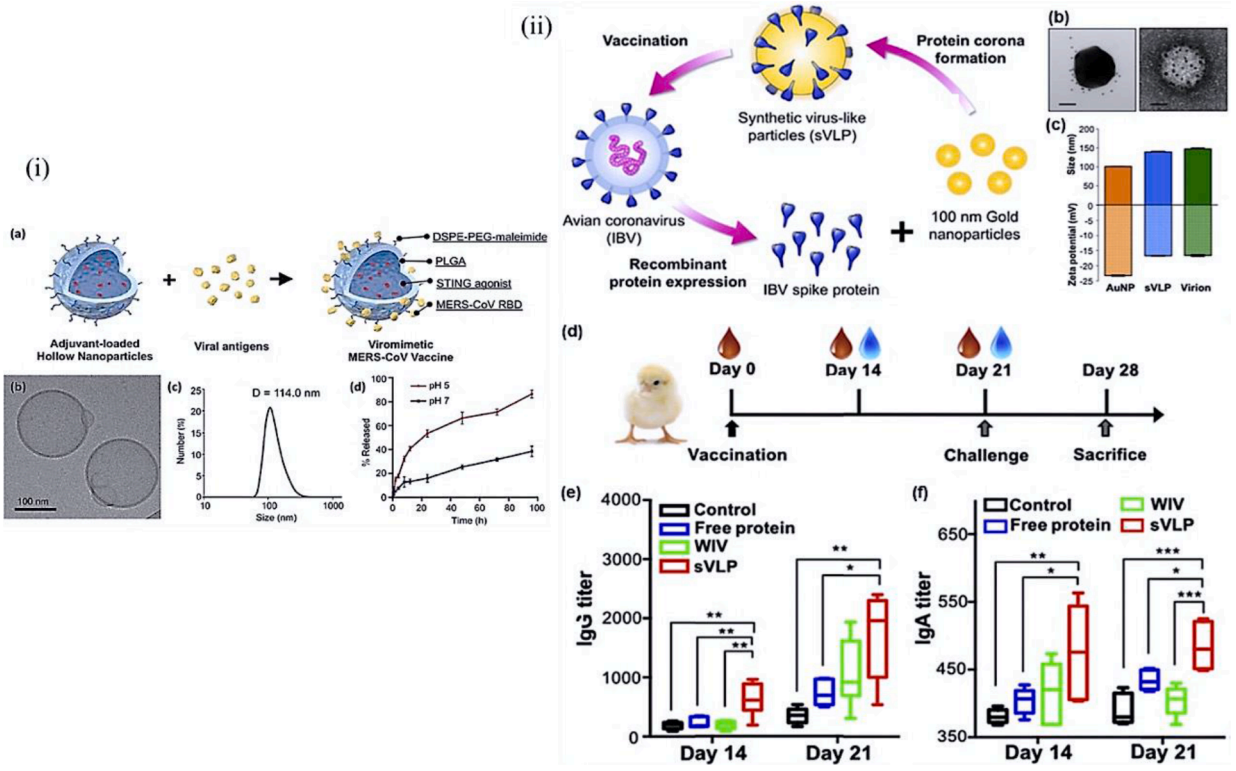

Fig. 3. **(i)** Viromimetic NPs with adjuvants. (a) Schematic of the viromimetic NPs vaccine formulation. Using a double-emulsion approach, hollow PLGA NPs containing encapsulated adjuvant and surface maleimide linkers were created. The surface of NPs was then coupled with recombinant viral antigens through a thiol maleimide linkage. (b) Cryo-electron microscopy of hollow cdGMP NPs. (c) Dynamic light scattering was used to determine the size distribution of NPs (DLS). (d) In vitro profiles of cdGMP release from PLGA hollow NPs at pH 5 and 7. Adapted from free acces permission from [80]. **(ii)** (a) The development of avian coronavirus sVLPs is explained in the section that follows. Through the mechanism of spontaneously peptide spike formation, virus particles and 100 nm gold NPsare combined in the best possible combinations to generate sVLPs. (b) Transmission electron imaging of IBV spike protein-immunogold-labelled sVLPs and wild IBV virions (right and left, respectively). (c) Zeta potential and size measurements made using NPs tracking analysis for native IBV virions, sVLPs, and AuNPs. (d) A schedule for tissue sample collection, immunization, and viral challenge in an avian model of coronavirus disease. (e) Animals administered with free proteins, a whole inactivated virus (WIV) vaccination, and sVLPs all resulted in serum IgG titers specific to the virus. (f) In animals given vaccines with medicinal quantities, serum IgA titers specific to viruses. Reproduced with permission from ref. [81]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for RNA transport, metals like Au produce steric hindrance, which protects the RNA from disintegration [69]. The FeO-based NPs, which are not only good carriers but also decompose and contribute to the human body's iron stores [70,71], are another inorganic NM for RNA delivery in vaccines. Animals were given Au-NPs that had been conjugated with the swine transmissible gastroenteritis virus (TGEV) in another investigation. When exposed to natural viruses, these conjugated antibodies induce a stronger immunological response (greater levels of IFN-γ). Immunization with an antigen-colloidal gold combination increased macrophage metabolic activity and the number of T cells in inoculated mice [72].

In another work, a recombinant adenovirus serotype 5 expressing the MERS-CoV spike protein gene (Ad5/MERS) and a ferritin-based NP complex controlled by RNA as a new molecular chaperone were produced as MERS-CoV vaccines. Although both types of vaccines were able to induce the production of specific IgG against MERS-CoV, only NP-based vaccines were able to induce neutralizing antibodies against MERS-CoV. As a result, both AuNPs and ferritin-based NP are considered viable pre-clinical NP candidates for improving the efficacy of SARS-CoV-2 vaccines [73]. Replicon RNAs containing sequences from the SARS-CoV-2 spike protein were produced by Erasmus and colleagues to test the capacity of repRNA-CoV2S to rapidly generate antibodies and immunological responses in an in-vivo model when coupled with a lipid inorganic nanoparticle (LION) emulsion. The electrostatic interaction of DOTAP with RNA shielded the RNA from degradative enzymes, resulting in a greater T cell response. It also promoted the formation of immune complexes of a size that could induce immunogenicity, and Phase 1/2 trials are currently being conducted in India (in collaboration with Gennova Biopharmaceuticals, Pune) [74,75].

Gu *et.al* has developed a protein-based NPs vaccine, REVC-128, against COVID-19 in which FeO-based NPs were conjugated with multiple trimeric spike proteins and administered in murine models via subcutaneous injection route with either NPs-conjugated spike protein or non-conjugated spike protein using the Sigma Adjuvant System. PBS was injected into the third set of mice as a negative control, and substantial levels of spike protein-specific IgG were observed in all vaccinated animals two weeks later. On days 14 and 28, the conjugated NP vaccination generated a 1.5-fold rise in IgG levels as compared to the non-conjugated NPs vaccine, with the titer count dropping on day 28. REVC-128 has the potential to be a vaccination candidate following clinical trials for individuals who have had an adverse reaction to mRNA vaccines, given that FeO-based NPs have already been approved for clinical usage [76].

The widely commercialized mRNA-based COVID-19 vaccines have proven dependency on NPs for their generation and efficacy in giving protection against developing strains of the viral pathogen, according to the above-mentioned pre-clinical investigations done *in-vivo* animals. By including DSPE-PEG-maleimide in the polymeric shell, the surface functionalization of the NPs was facilitated, allowing for additional antigen coupling for vaccine formulations. Characterizations by cryo-EM and the dynamic light scattering (DLS) study showed that the hollowed NPs had an average diameter of 114.0 nm, a shell thickness of 10 nm, and a unimodal particle distribution (Fig. 3). A sizable aqueous interior could be seen, and HPLC successfully confirmed that cdGMP had been successfully encapsulated. However, when hollow NPs were mixed directly with cdGMP, no peak of NPs-associated cdGMP was seen, showing that there was no contact between both the NPs and the adjuvant. By saturating 100 nm AuNPs in a mixture containing the spike S protein of the avian coronavirus infectious bronchitis virus (IBV), researchers created synthetic VLPs (sVLPs) using AuNPs. After unbound peptide were removed, antigen loaded AuNPs that matched viral proteins were found. The size of the NP was raised via protein corona creation to 139 nm, which remained constant over a period of seven days while retaining 200–250 spike proteins per particle (Fig. 3). These synthesized VLPs demonstrated improved lymphatic antigen transport (6-fold) compared to injection with free proteins, greater antibody titers, better T cell response, and decreased symptoms. Certain vaccinations are also authorized for commercial use and have the potential to be the most effective COVID-19 weapons [77–79]. Further testing is required as a surprisingly painstaking strategy to build an effective vaccine with fewer negative effects than standard vaccines.

4.2. Nanotechnology-based disinfectants to eradicate SARS-CoV-1/2 virus

Owing to the infectious nature of SARS-COV-2, disinfectants such as alcohol-based sanitizers and UV disinfection have become an essential part of our life [64]. Chemical disinfectants with a wide spectrum of antiviral activity, such as chlorines, peroxides, and alcohols, have been employed to disinfect and sterilize personal protective equipment and surfaces [82]. Disinfectants, on the other hand, have limitations such as the need for greater concentrations for 100% antiviral action, limited long-term efficacy, and negative environmental consequences [83]. In this study, researchers demonstrated the utilization of organic and inorganic NPs as viral disinfectants with antiviral activity.

Copper (Cu) alloy surfaces, an adequate cleaning regimen, and excellent clinical practice might all contribute to minimizing MERS and SARS transmission rates [84]. Other heavy metals, such as Au and Ag, also have strong antiviral effects. Because of their antiviral effects, Au, Cu, Ag, and other heavy metal NPs have been frequently employed in biomedical research [85]. The increased surface area accessible during NPs production, which increases the release rate of metal ions for dissolving the viral genome and inhibiting infection, might be a possible source of heavy metals' exceptional antiviral efficacy [86]. When sprayed on surfaces, such particles tend to stay active for a long period since they are relatively stable and unaffected by regular environmental changes. This eliminates the need to clean a contaminated region regularly, demonstrating that these NPs are not particular and have wide anti-viral efficacy [87].

The Cu was utilized as an anti-COVID agent in recent research, and the survival period for Human Coronavirus 229E (HCOV-229E) on Cu-containing surfaces was considerably shorter than on copper-free surfaces [77]. On surfaces that interact with polytetrafluoroethylene (Teflon; PTFE), polyvinyl chloride (PVC), ceramic tiles, glass, silicone rubber, and stainless steel, HCOV-229E can survive for at least 5 days [77]. On a variety of copper complexes (within a few minutes for simulated fingertip contamination) and Cu functionalized Zn brasses as an effective at a lower copper concentration, HCOV-229E was immediately inactivated owing to the destruction of the viral genome and permanent morphological alterations [77].

Neal et al. constructed two customized Ag-based preparations of redox-active nano-scale cerium oxide (AgCNP1 and AgCNP2),

with AgCNP1 inactivating Coronavirus OC43 (enveloped RNA virus) and AgCNP2 reactive to rhinovirus 14. (non-enveloped RNA virus). In situ results showed that AgCNP1 damaged the membrane's lipid bilayer whereas AgCNP2 disabled surface receptor proteins. This approach has the potential to be expanded to the inactivation of SARS-CoV-2, although more research is needed [88]. NMs coupled onto the surface of masks boosts their virucidal properties without impairing breathability, according to research by Chen et al. The superior capabilities of graphene oxide grafted with metal NPs may be employed to not only spread on the surface of a mask but also to prevent viral infection on personal protective equipment (PPE) [77]. Independent investigations have found that graphene-Ag nano-composite coatings and Ag nanoclusters in a silica composite coating have considerable virucidal characteristics and might become a commercially manufactured amenity in the future [89].

When it pertains to widespread materials, inorganic NPs are preferable since long-term exposure to free metal radicals has negative consequences that can't be investigated in a reasonable amount of time [90]. Electrospinning is one such dependable media, capable of creating nanofibers with a significant surface area, making them extremely specific apertures for inorganic nanoclusters. Because of their antibacterial capabilities, NPs may be filtered as well as organic pollutants can be absorbed and inactivated [91]. Multi-layered electro-spun membranes allow moisture to escape between layers, allowing the user to be comfortable for long periods. The curve of the mask might be customized via 3D printing to give the wearer with the most comfort [92].

The potential use of biodegradable cellulose acetate (CA)/cetyl pyridinium bromide (CPB) electro-spun nanofibers coupled with NaCl-NPs as a filter medium for surgical face masks were investigated, with samples of these nanofibers exhibiting anti-bacterial and anti-viral properties. With an air flow rate of 8 mL/min, the aerosol filtering performance of these samples was examined. Despite efficient filtering, the breathability parameters were not reached, postponing its application in mask manufacturing. Even though it must be improved in terms of design, it may be utilized as a filter in centralized air conditioning systems to avoid cross-contamination in hospitals, workplaces, malls, and public spaces [93].

By putting a few layers of graphene over low-melting-temperature non-woven masks, a self-cleaning reusable mask has recently been constructed. The mask's surface is very hydrophobic, preventing water droplets from adhering to it. The mask's surface temperature quickly increases to above 80 °C when exposed to sunshine, successfully sterilizing it using solar radiation. Despite the encouraging results, graphene's limited light absorption capacity prevented the mask from being heated sufficiently to accomplish 100% disinfection [94].

Li et al. used electrospinning polyvinyl alcohol (PVA), poly (ethylene oxide) (PEO), and cellulose nanofiber (CNF) to create an antibacterial and biodegradable mask, which was then esterified and a nitrogen-doped TiO_2 (N-TiO_2) and TiO_2 mixture was deposited. Because of its photocatalytic activity, the mask may be reused, filling in the gaps in the prior research. It has excellent breathability and might be utilized to meet the urgent demand for reusable, ecologically friendly, and effective personal protective equipment (mask) in the continuing COVID-19 epidemic [95]. Quantum dots, iron oxide, silicon oxide, polymeric and metallic NPs are attractive candidates, according to an ever-growing mountain of scientific literature, and should be used in the development of COVID-19 diagnostic instruments, vaccinations, disinfectants, and personal protective equipment (PPE) [96]. Higher metal NPs and organic NPs have a long history of antiviral action, paving the door for their future use in disease intervention.

Naked Ag-NPs have been proven in several trials to be effective in the control and prevention of several viral infections. The antiviral function of nano Ag, on the other hand, is yet unknown. The following pathways are linked to antiviral activity: Nano Ag can prohibit the virus from penetrating the molecular targets by preventing it from infiltrating the host cells and inhibiting it from connecting to the cell receptor (Fig. 4). The Ag-NPs could be able to attach to viral surface proteins and prevent the virus from interacting

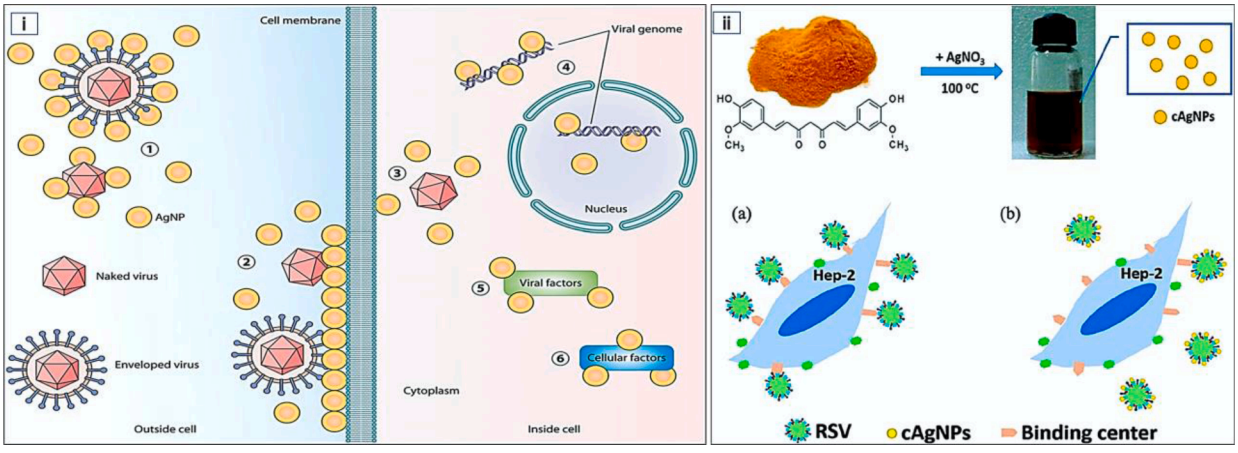

Fig. 4. Anti-COVID activity using Ag nanotechnology-mediated methods. **(i)** Ag-NPs have the potential to be antiviral. The Ag-NPs limit viral penetration, cellular routes of viral entry, viral genome, viral replication factors, and cellular components required for effective viral replication by interacting with viral envelope and/or surface proteins. Adapted with permisiion from ref. [98] **(ii)** A schematic illustration of the creation of cAg-NPs and their prevention of RSV infection by lowering the capacity of viruses to bind to the binding centres on the surface of cells when compared to those lacking cAg-NPs. Reproduced with permission from ref. [99]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with cellular membrane targets [97]. Curcumin has just been demonstrated to inhibit RSV proliferation and budding, however, its poor solubility and absorption hampered its therapeutic use. Curcumin was employed to create stable curcumin Ag-NPs (cAg-NPs) under physiological parameters by acting as a stabilizing agent. By directly inactivating the virus before entrance into the host cells, cAg-NPs were able to minimize the cytopathic effects generated by RSV and exhibited effective antiviral action against infection. It had a stronger antiviral impact than curcumin or unmodified Ag-NPs [97].

Another effective strategy is to lower the level of reactive oxygen species (ROS) in the host cells. The ROS scavenging can reduce infection toxicity by increasing cell survival, allowing the cell more time to activate its antiviral systems. As a result, this strategy may be able to prevent infection while also ensuring the survival of the host cell. Selenium NPs (Se-NPs) have been widely researched for

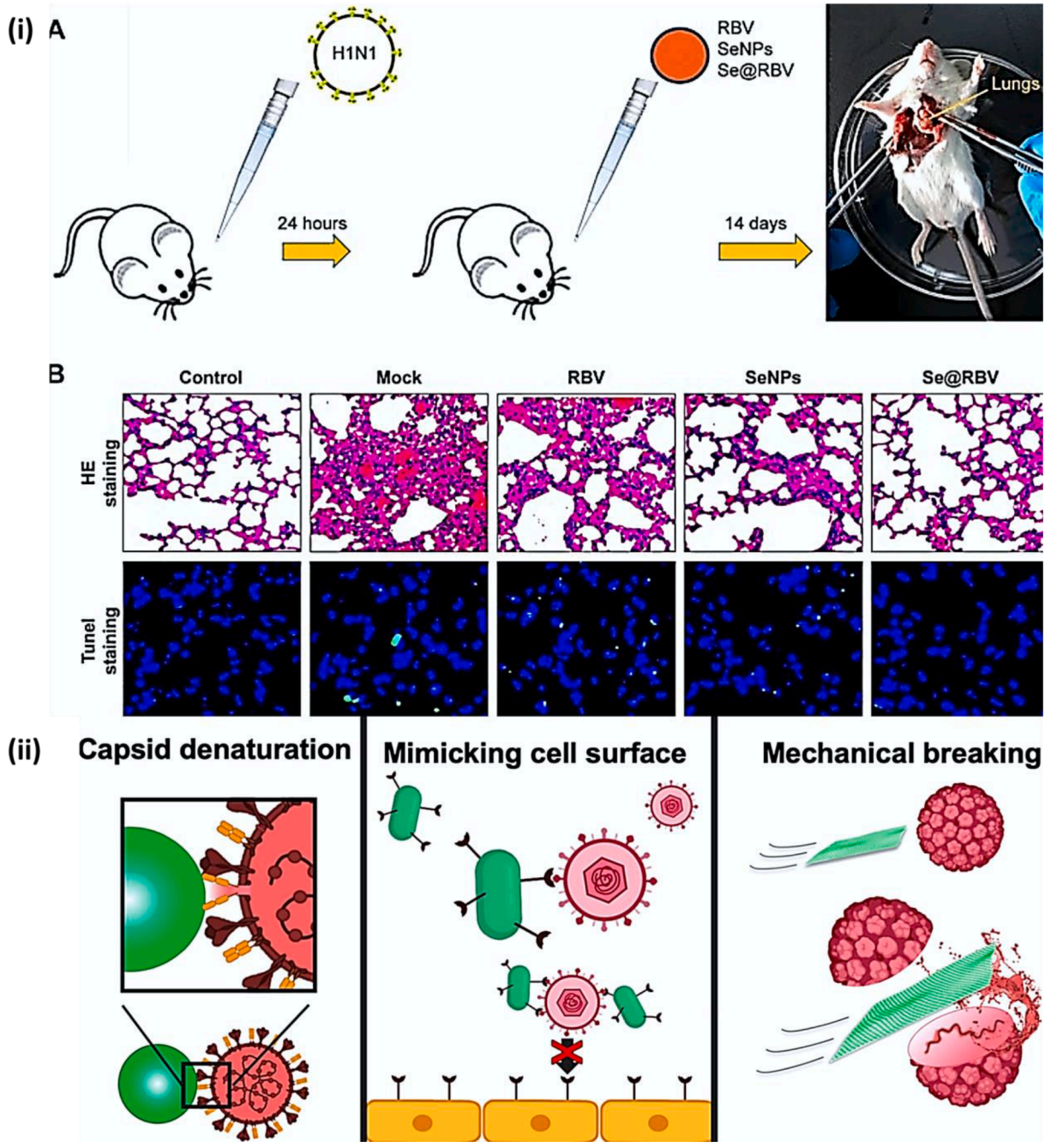

Fig. 5. Nanoparticles as a viral disinfectant. **(i)** In vivo antiviral efficiency of Se-NPs functionalized with ribavirin (Se@RBV).Adaptd with open access permission from ref. [100] **(ii)** Illustration of the main mechanisms of blocking virus entry into host cells: capsid denaturation, mimicking cell surface, and mechanical breaking of the virus. Reproduced with permission from ref. [97].

their antiviral action in this context (Fig. 5). The mechanism of action of these NPs is based on the infection-induced quenching of radicals in host cells, which prevents mitochondrial depolarization and the subsequent apoptotic cascade [97].

5. Nanotechnology-enabled diagnostic approaches to manage COVID-19 infection

The most often utilized commercialized approaches for the diagnosis of COVID-19 to accomplish quick detection for the existence of SARS-CoV-2 are reverse transcriptase-polymerase chain reaction (RT-PCR), and rapid antigen tests (RAT), and chest computed tomography (CT) [101]. However, rather than being employed alone, these tests are frequently used in conjunction to generate confirmed findings. A chest CT scan is commonly used to determine the severity of a lung infection. Recognizing the source of sequelae in individuals with a history of smoking or other forms of pre-existing respiratory infection, on the other hand, is difficult [102]. The most used diagnostic method, RT-PCR, has several drawbacks, including an increase in false negatives, which can lead to a significant underestimating of active cases, suggesting that a negative RT-PCR report does not rule out the potential of SARS-CoV-2 infection. The occurrence of false negatives has been attributed to inefficient testing, the lack of a defined standard, and testing at different points of the infection cycle [103].

The RATs are generally based on lateral flow immuno-chromatography or fluorescence immunoassays for the qualitative detection of SARS-CoV-2 and deliver a practically instantaneous response about the status of COVID-19 [104]. Despite differences between various brands of RATs, there is a risk of false positives, hence it is typically regarded as the least accurate method of testing, even though RATs must be confirmed by a related RT-PCR in most countries to be recognized as genuine [105]. Although there is no ideal way of diagnosing COVID-19, NPs have been employed in conjunction with not only RT-PCR methods but also enzyme-linked immunosorbent assay (ELISA) to improve viral detection effectiveness of diagnostic instruments [106].

Most metal NPs are made up of noble metals like Au, Ag, and Cu, which have a unique feature called localized surface plasmon resonance (LSPR), which has been exposed to additional research and modification approaches with varying degrees of nucleic acid detection sensitivity. Each approach is tailored to the type of virus to be detected, the lowest sensitivity concentration, and the test time, among other considerations [107]. As a result of this research, biosensors that precisely detect the presence of SARS-CoV-2 have been created. Biosensors have features that allow them to detect chemicals in liquids, solutions, and bodily fluids using biomarkers. When the material under investigation comes into touch with a biological element, a signal is formed, which is then translated into a measurable entry using a physical transducer. Physical transducers are primarily optical, electrochemical, and piezoelectric devices, whereas biological elements being studied include DNA, RNA, proteins such as enzymes or antibodies, organic and biological receptors, entire cells, and tissues [108]. Researchers have identified three types of biosensors that have demonstrated great clinical relevance in the laboratory and might be pushed to clinical trials once conjugated with NPs.

5.1. Nucleic acid-based coronavirus detection

Micro/nano technologies have aided the creation of very sensitive sensors, allowing them to be used as detection instruments for minor sequence alterations [31]. This complex detection approach has expanded its applicability beyond POC diagnostics to include reporting molecules, probes, electrode fabrication, electrode coatings, as well as NM conjugation [109–111].

A paper-based colorimetric technique for nucleic acid detection based on peptide nucleic acid-induced Au-NPs complex was utilized in another investigation to identify genetic material associated with the viral genomes of MERS-CoV, HPV, and MTB [112]. In response to these findings, scientists created a colorimetric test based on thiol-modified antisense nucleotides coated on Au-NPs, revolving around the fundamental mechanism in which oligonucleotides were specific for the SARS-CoV-2 N-gene (nucleocapsid phosphoprotein). The NPs coagulate in the presence of complementary RNA, and when RNase-H was added, the RNA-DNA hybrid decomposed, leading to the production of a visible precipitate (naked-eye test) that could be utilized to identify SARS-CoV-2 in isolated RNA samples within 10 min [113].

Kang and colleagues explored graphene field-effect transistor efficiency and created an ultrasensitive FET with a limit of detection (LoD) of 10–18 M (corresponding to 10–16 g mL-1) level. The FET was further modified by the inclusion of Spike S1 Protein, and the g-FET was able to detect the presence of SARS-CoV-2 in clinical blood samples in less than 2 min while demonstrating increased discriminating behavior. This biosensor showed great promise for commercial application and may be developed to detect different viruses [114].

SARS-CoV-2 RNA was isolated and amplified using nucleic acid sequence-based amplification (NASBA) and detected using specifically constructed to hold-based biosensors in a highly sensitive diagnostic test developed by Chakravarthy et al. employing tailored RNA biosensors. In an in vitro transcription-translation experiment, these sensors show remarkable complementarity toward target viral DNA while also accurately distinguishing between positive and negative human clinical samples [88]. In patient samples, the PHAsed NASBA-Translation Optical Method (PHANTOM) was able to detect many strains of SARS-CoV-2, including the highly infectious form. As a result, the designed RNA biosensor based on the PHANTOM platform provides a reliable approach for detecting SARS-CoV-2 and may be used commercially once manufacturing is up and running [88].

The detection of IgM antibodies against the SARS-CoV-2 virus is being evaluated as an alternate approach for COVID-19 diagnosis, as IgM is a key signal during the acute infection phase. Through the indirect immunochromatography (blotting) approach, a Lateral flow Assay coupled with Au-NPs was developed to achieve quick diagnosis and distant detection of the IgM antibody against the SARS-CoV-2 virus. The nitrocellulose Lateral flow strips have two barrier lines: the first is formed of the NP-conjugated antibody (detecting reporter), also known as the test line, and the second is designed to catch free antibodies by covering the membrane with SARS-CoV-2 nucleoprotein, known as control route. The AuNP-LF assay was tested on serum samples from infected and healthy people, with the

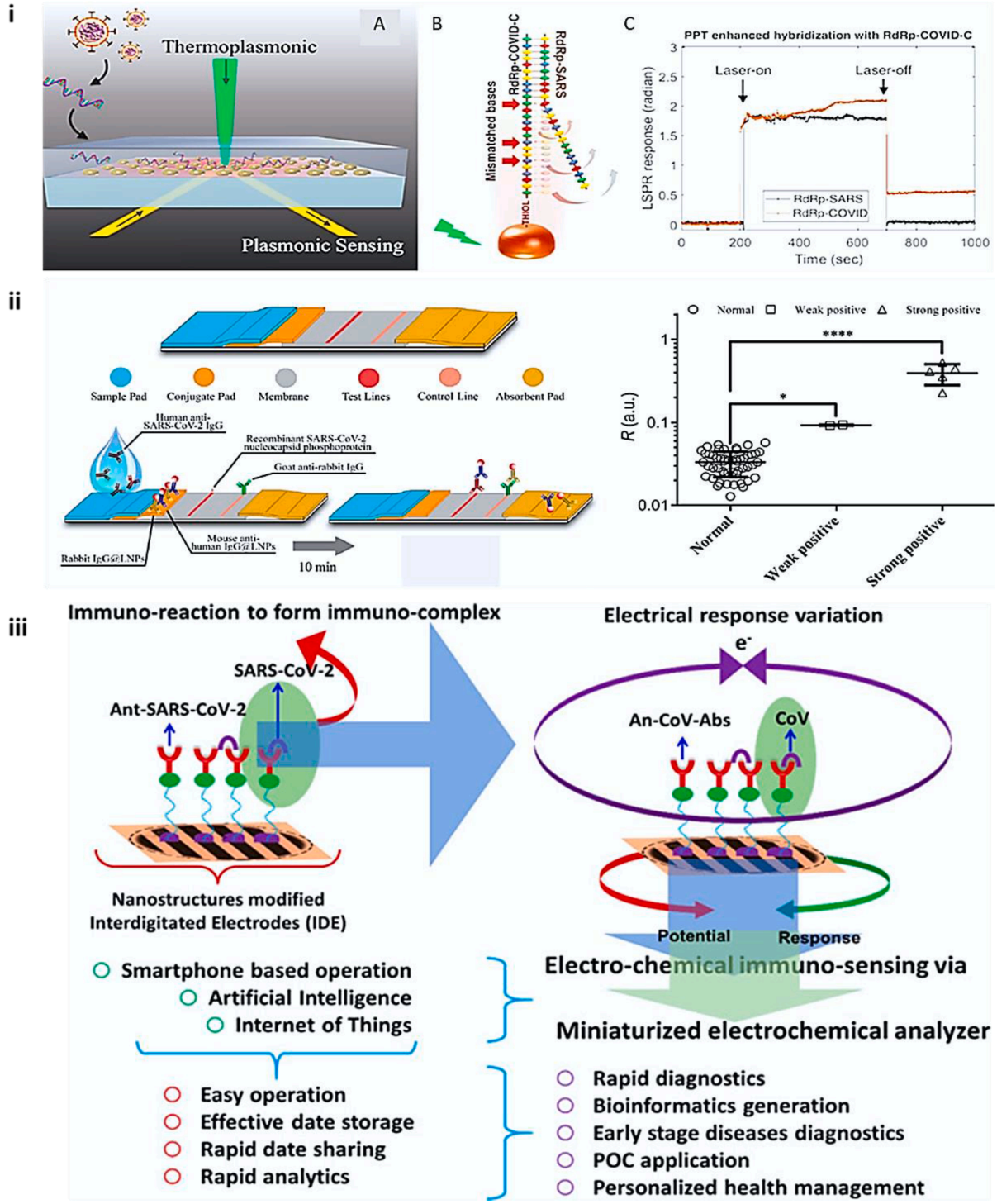

Fig. 6. Nucleic acid-based detection system **(i)** A) Plasmo-photothermal-based biosensor for selected viral sequences for SARS-CoV-2 detection. Adapted with open access permission from ref. [118] (B) 2D nano-island of Au serving as an immobilizing platform to formulate a thiol-cDNA ligand. Adapted with permisison from ref. [119] (C) Real-time monitoring of AuNI response and ability to demonstrate discrimination between two related and almost similar sequences. **(ii)** Schematic presentation of electrochemical SARS-CoV-2 immuno-sensing in the physiological range. **(iii)** Representations of LTR flow-based bioassay for selective detection of SARS-CoV-2 detection. Reproduced with open access permission from ref. [4].

findings compared to RT-PCR results. The Au-NPs-LF assay's sensitivity and specificity were calculated to be 100 and 93.3%, respectively. The AuNPs-LF test demonstrated excellent selectivity in the detection of IgM against the SARS-CoV-2, with minimal interference from other viruses. Within 15 min, this assay could reliably identify the presence of SARS-CoV-2, and each test only required a little amount of serum [115]. As a result, Au-NPs-LFA is a cost-effective, stable, and effective instrument for detecting and diagnosing SARS-CoV-2 in labs and hospitals, and its manufacturing might be significantly accelerated with additional financing. With the use of nanotechnology-based biosensors and bioassays, nucleic acid detection has gained major relevance in terms of diagnosing and monitoring pathogen infection. The basic and practical components of these approaches are combined with a proof-of-concept to give ultra-high sensitivity and specificity in DNA/RNA detection [116].

Chen et al. developed a lateral flow immunoassay (LFIA) based quick (10 min) and sensitive bioassay to detect anti-SARS-CoV-2 IgG for COVID-19 diagnoses in human serum utilizing a lanthanide-doped polystyrene nano-system (Fig. 6). IgG A was captured on a nitrocellulose membrane using SARS-recombinant CoV-2′s nucleocapsid phosphoprotein, and self-assembled nano-systems tagged with mouse antihuman IgG antibody served as a fluorescence readout. A total of 51 normal samples were used to assess the sensor's sensing capabilities. RT-PCR was used to confirm the device's testing performance, and the results of both procedures were quite

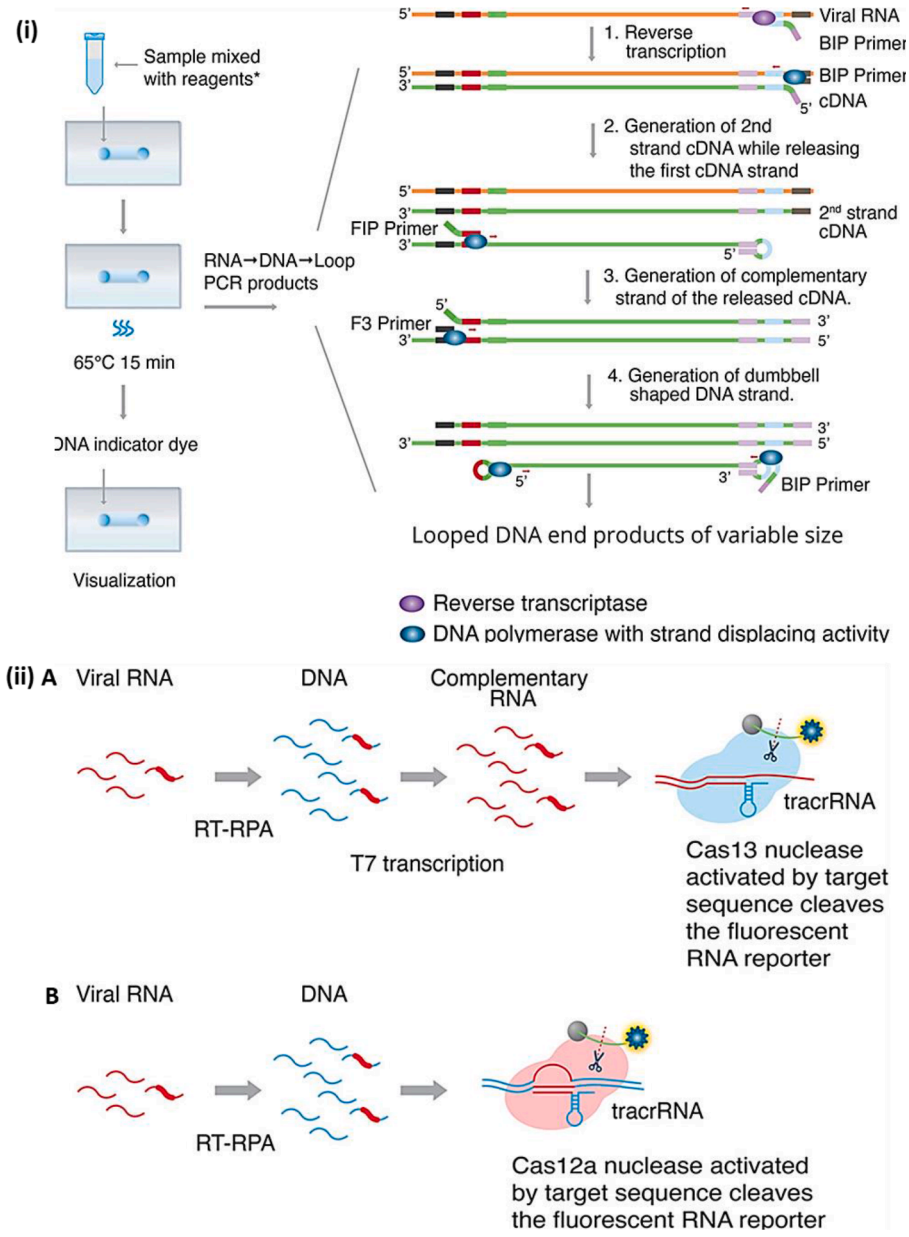

Fig. 7. Nucleic acid-based detection for anti-COVID-19 activity using **(i)** reverse transcription-polymerase chain reaction (RT-PCR). **(ii)** Reverse transcription loop-mediated isothermal amplification (RT-LAMP). Reproduced with Open access permission from ref. [117].

similar. Because of its selectivity, cost efficiency, and mobility, this COVID-19 diagnostic platform satisfies clinical difficulties and may be used to control COVID-2 infectious illness [4,117].

For SARS-CoV-2 testing, RT-LAMP was created as a quick and low-cost option. Fig. 7(i) depicts how RT-LAMP integrates LAMP with a reverse transcriptase process to identify RNA and needs a combination of multiple primers appropriate for the targeted gene/region to improve selectivity. Photometry may be used to identify the amplifying product by detecting the turbidity induced by amplification by product magnesium pyrophosphate precipitate in solution. The process could be monitored continuously by monitoring turbidity or by using intercalating dyes to fluoresce. The CRISPR-based approaches do not require complicated apparatus and may be read on paper strips to identify the presence of the SARS-CoV-2 virus without sacrificing sensitivity or specificity Fig. 7(ii) [120]. These tests are both inexpensive and may be completed in about an hour. These tests offer a lot of potential for diagnosis at the POC applications.

5.2. Nano-based system to detect coronavirus

Certain features of NPs, including their tiny size, surface charge, biodegradable nature, biocompatibility, bioavailability, and large surface to volume ratio, have made recognition and classification approaches fascinating applications within the biomedical arena with the advancement of technology. These methods have spawned a slew of applications that have proven useful in the creation of diagnostic kits to combat the SARS-CoV-2 virus [121].

Clinical experiments encouraging the use of nanomedicine are now underway, and they have presented options whose successful use is urgently needed [122]. Metal nano-islands (NIs), metal NPs, magnetic NPs (M-NPs), and quantum dots are the most promising options for medication administration among the several types of NPs explored for the diagnostics of respiratory viruses [79]. An assemblage of symmetrical zirconium quantum dots (Zr QDs) and Au-NPs was produced with the usage of L (+)-ascorbic acid as a substrate and chiral ligands employed as a chiral immune-sensor to identify the existence of respiratory syncytial viruses in chicken in recent research. The chiral Zr QDs' cytotoxicity was evaluated against rat brain glioma cells using a variety of analytical methods [123]. In an extended investigation, Zr QDs and magneto-plasmonic NPs (MPNPs) were coupled with coronavirus anti-infectious bronchitis virus (IBV) antibodies, and the virus content was quantified using the fluorescence emission intensity of the nano-hybrids, with a limit of detection of 79.15 EID/50 ml. The fluorescence of the SARS protein complex with Au-NPs was substantially greater than that of the protein complex containing no gold NPs [124].

Testing targeted antibodies in serum is an alternate technique to confirm SARS-CoV-2 infection, which has been resolved by the COVID-19 diagnostic and treatment guideline in China, in addition to detecting the virus that COVID-19 patients carried. Not just whether infected people develop clinical symptoms, but the level of IgM in their blood grows dramatically during the acute infection phase of infectious illnesses. A fast detection approach for the IgM antibody against the SARS-CoV-2 virus was conceived and developed, employing the SARS-CoV-2 NP produced by the research as the capturing antigen (Fig. 8). This Au NP-LF assay combines the benefits of the immunological lateral-flow technique with the unique features of Au-NPs in an enormous detection device that is simple to use and cost-effective [108].

When capped with appropriately designed thiol-modified antisense oligonucleotides (ASOs) specific for SARS-CoV-2 s N-gene (nucleocapsid phosphoprotein), AuNPs might be utilized to diagnose positive COVID-19 cases in minutes. The technology reported

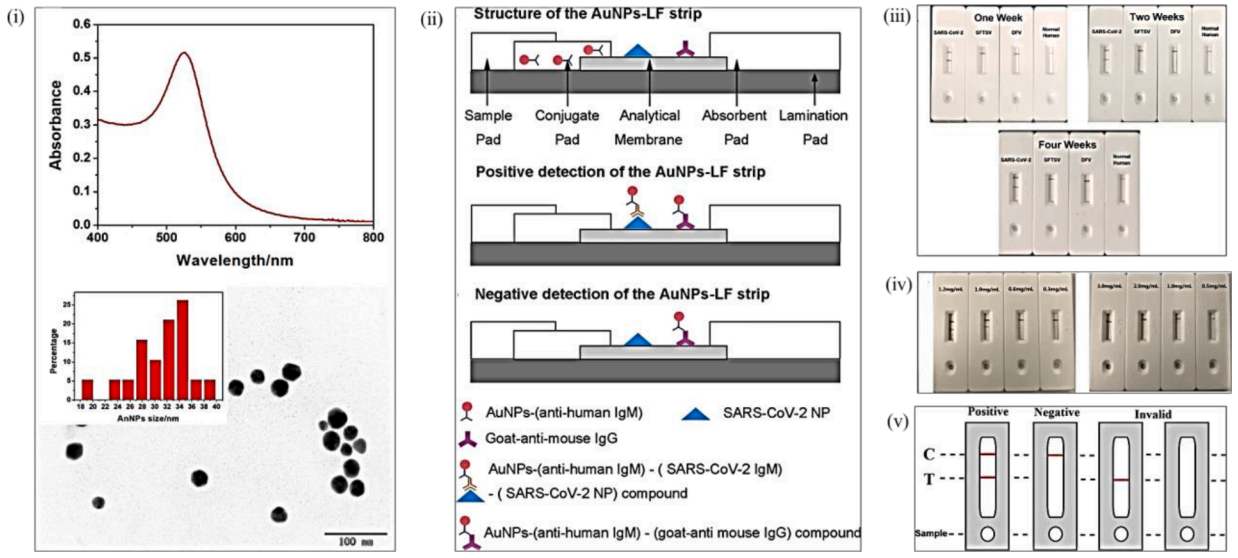

Fig. 8. NPse-based COVID-detection system. **(i)** (A) TEM image of Au-NPs. (B) UV–vis spectra of AuNPs. **(ii)** Description of operation principle of the Au-NPs-LF Strip. **(iii)** Stability of Au-NPs-LF strips. **(iv)** Performance of Au-NPs-LF based on different concentrations of (A) SARS-CoV-2 NPs and (B) goat–anti-mouse IgG. **(v)** Diagram of Au-NPs-LF strips' positive, negative, and invalid results. Reproduced with open access permission from ref. [108].

here employs an all-encompassing targeting strategy mediated by four ASO sequences that simultaneously cover two portions of the viral N-gene sequence [125]. These thiolated ASO-capped Au-NPs agglomerate exclusively in the presence of the SARS-CoV-2 target RNA sequence, resulting in a shift in surface plasmon resonance (SPR), which is increased further with the addition of RNaseH, resulting in the visually observable precipitation of gold NPs (Fig. 9). The diameter of the spike protein NPs was 35 nm, but when they formed with alum, it expanded to 80 nm. Th1/Th2 activation was balanced when utilized in combination with a recombinant adenovirus serotype 5 expressing the MERS-CoV spike gene (Ad5/MERS), resulting in a longer-lasting antibody response [126]. A ferritin template can help MERS-CoV protein NPs self-assemble and guarantee that target antigens are shown on the surface. The effectiveness of this VLP in MERS-infected mice is represented (Fig. 10).

5.3. Towards point-of-care (POC) COVID-19 diagnostics

The theory behind moving COVID-19 diagnostic procedures from laboratory conditions to the site of therapy is ground-breaking in terms of the speed and amount of testing that may be performed [130]. Testing for POC is defined as being done at home or in a setting where the patient is being treated with a kit or strip. The most crucial component of POC research is the biosensor, which is utilized to carry out a biochemical experiment to detect the pathogen [131]. The POC detection system meets the demand for illness diagnosis while also offering quick results, a simple handling mechanism, and a low cost of ownership and reliance on specialist equipment [132]. Many researchers working to combat COVID-19 have expressed interest in combining such diagnostic systems with NMs that can be used in biosensors, in-vitro diagnostics, and future generation devices that use carbon nanotubes (CNTs), Au NPs, magnetic NPs, and graphene, graphene oxides, for POC applications [133,134].

Ma et al. have developed a CRISPR-Cas12a photo-biosensor with smartphone readout for ultrasensitive and selective detection of

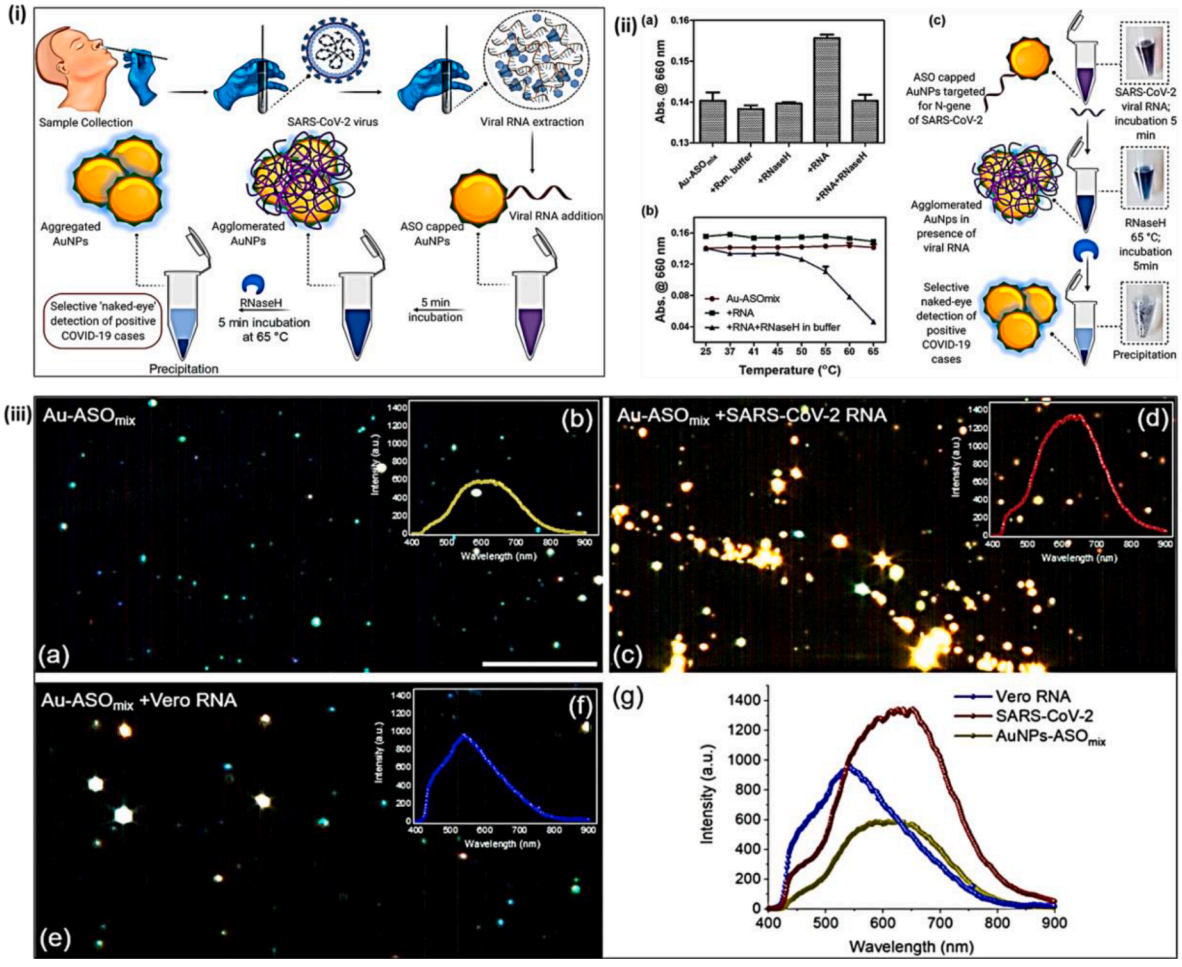

Fig. 9. **(i)** Schematic Representation for the selective naked-eye detection of SARS-CoV-2 RNA mediated by the suitably designed ASO-capped Au-NPs. **(ii)** The schematic representation for the visual naked-eye detection of SARS-CoV-2 with the treatment of RNaseH and comparison of the response of the Au-ASO mix NPs at 65 °C for 5 min. **(iii)** EDFM-HSI and hyperspectral data of the Au-ASO mix in the absence of RNA and the presence of RNA containing the viral SARS-CoV-2 gene is exhibited. Reproduced with open access permission from ref. [125].

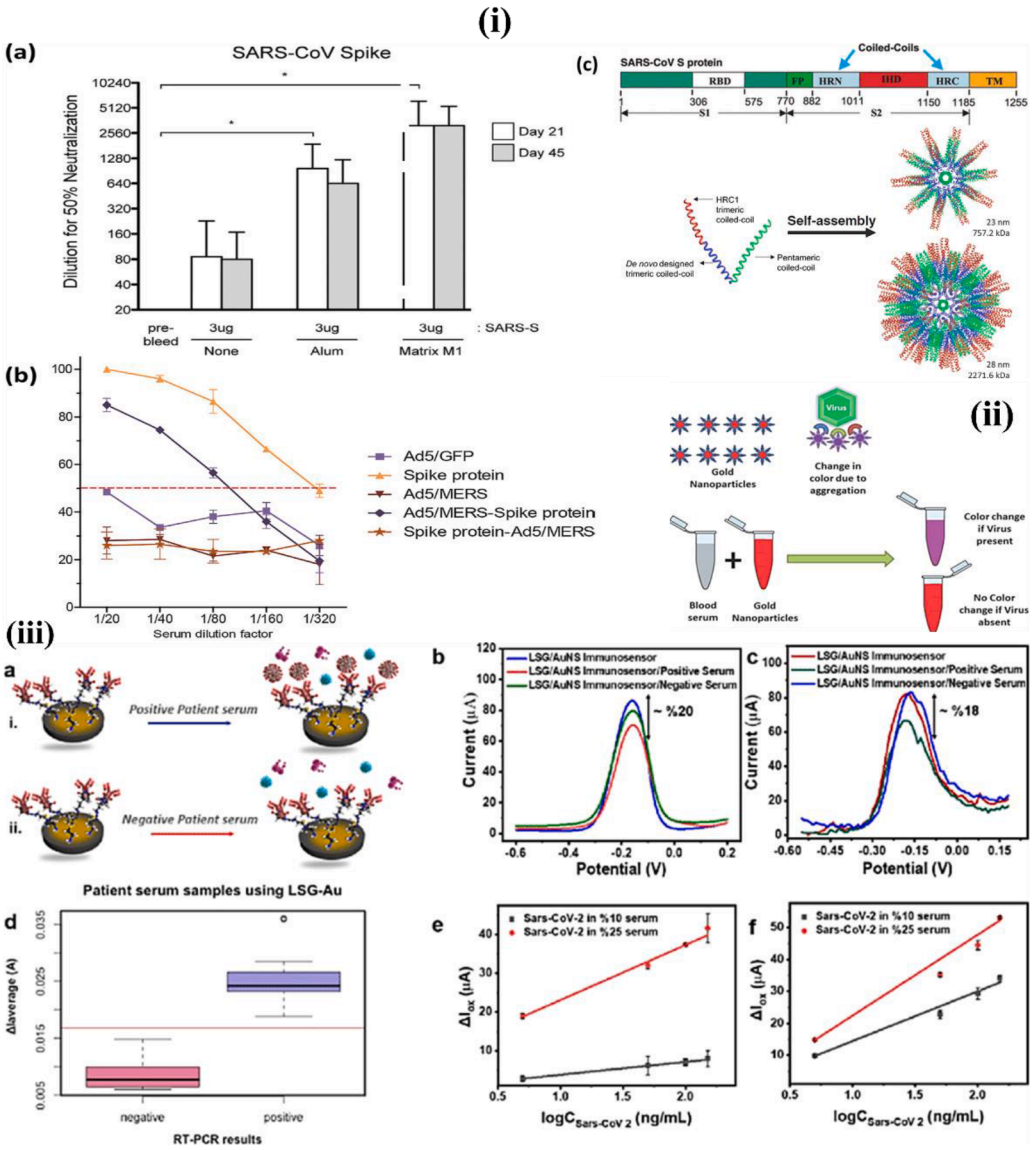

Fig. 10. NPs-based detection of SARS-CoV-2 efficiently. **(i)** Neutralization titres of coronavirus-spike-vaccinated mice. Adapted with free access permission from ref. [127] **(ii)** Schematic representation of detection system using NPs. Reproduced with permission from ref. [128]. **(iii)** Representation of SARS-CoV-2 detection in human blood serum. Reproduced with permission from ref. [129].

SARS-CoV-2 in clinical samples using CRISPR-Cas12a. Because of their complimentary base pairing, they constructed a linker ssDNA that functionalized with AuNPs-DNA pairs [132]. The linker ssDNA stays intact when the sample was deprived of the target dsDNA (SARS-CoV-2), but the AuNPs probes underwent DNA hybridization induced aggregation and were therefore precipitated. When the target dsDNA is present, Cas-12a's trans-cleaving activity is initiated, and the linker ssDNA is cut off, resulting in Au-NPs disaggregation and color changes (Fig. 11). This variation may be seen with the naked eye and measured using a 'colour picker' smartphone app. The suggested biosensor detected the SARS-CoV-2 gene in synthetic vectors, transcribed RNA, and SARS-CoV-2 pseudo-viruses with no cross-reactivity with other viruses [132]. When tested with 20 positive and 30 negative clinical swab samples, the developed biosensor provided 100% similarity (both positive and negative) with qPCR findings within a 90-minute time frame. As a result, more research is needed to see if this biosensor may be used instead of qRT-PCR [132].

Employing different strategies can sometimes provide positive outcomes. Ferreira et al. created a novel biosensor employing Au-NPs modified with human angiotensin-converting enzyme 2 (ACE 2). This biosensor was used to collect clinical samples and was coupled with a cotton swab. With a limit of detection of 0.154 pg mL-1 of SARS-CoV-2 spike protein, this COVID-19 low-cost Opto-diagnostic for Rapid testing (COLOR) could identify the presence of SARS-CoV-2 in the nasopharyngeal swab in 5 min. When examined by qRT-PCR, the color intensity of the swab correlated to the Ct value of the same sample. As a result, a COLOR biosensor is a low-cost and effective alternative testing tool that may be utilized for frequent testing, especially in underprivileged populations [135].

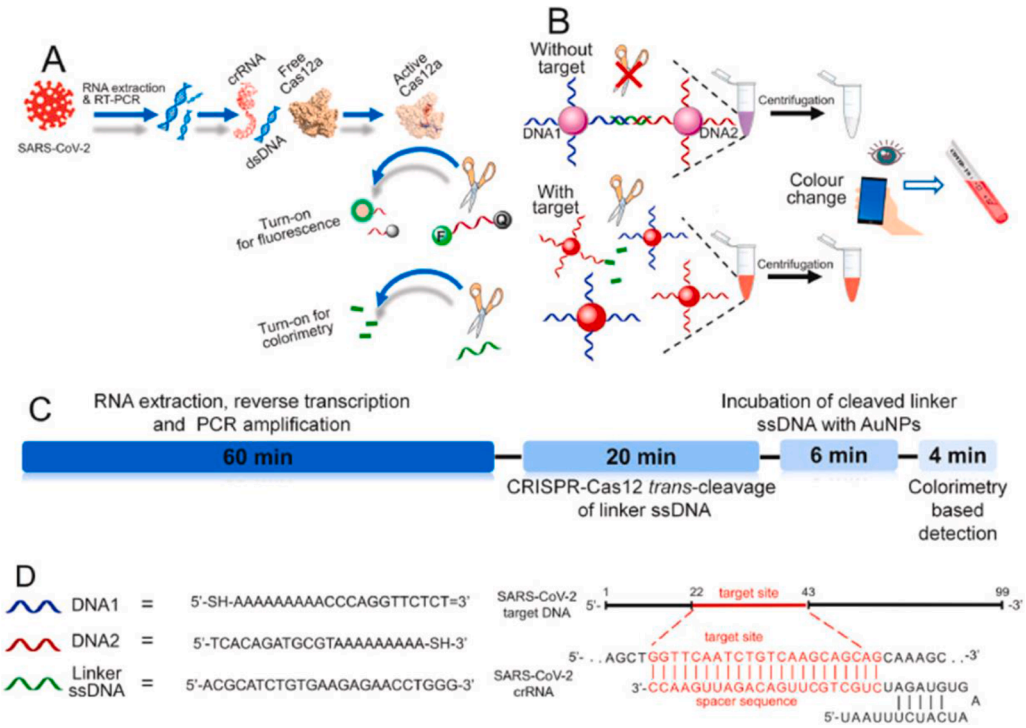

Fig. 11. The POC biosensor used for the management of COVID. (i)The trans-cleavage of CRISPR-Cas12a can be utilized to devise fluorescent and colorimetric biosensors for SARS-CoV-2 detection. Reproduced with permission from ref. [132].

Further, to detect SARS-CoV-2 spike protein in clinical samples, researchers developed a COVID-19 field-effect transistor (FET)-based bio-sensing device made from graphene sheets covered with a particular antibody against the virus [136]. The biosensor was tested against the grown virus, nasopharyngeal tissues, and antigen protein, and it was able to identify the virus in every case [125].

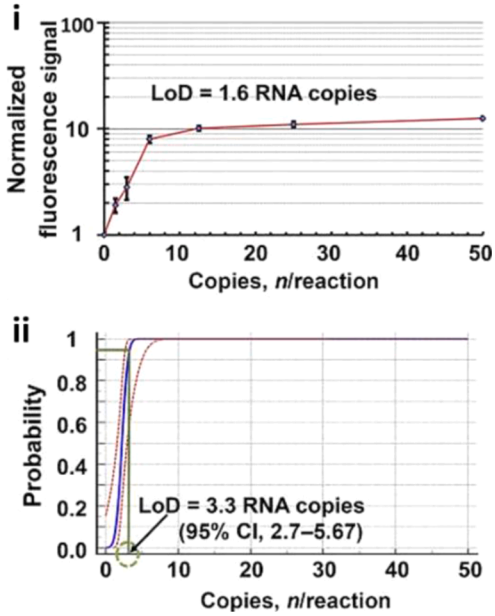

Fig. 12. (**i**): MMB fluorescence signals normalised in PCR-grade water from samples containing 0, 1.5, 3, 6, 12, 25, and 50 copies/reaction of in vitro transcribed E-gene targets. All samples passed via 40 rounds of amplification. The computed limit of detection (LoD) for each reaction is 1.6 copies. (**ii**) The dose-response experiment's probit regression analysis. Reproduced with permission from ref. [137].

The COVID-19 FET sensor could identify and differentiate between healthy and infected persons with a limit of 2.42 102 copies/mL, even though it had no cross-reactivity with MERS-CoV. This biosensor is thought to be a good technique to identify SARS-CoV-2 in samples without having to treat them first [125]. Cost-efficient, portable, user-friendly, and effective SARS-CoV-2 detection technologies are required. Clinical testing and increased manufacturing capability are also necessary for the commercial use of these biosensors.

Margulis *et.al* created a potential molecular test that uses ultrasensitive magnetic modulation biosensing (MMB) device, quick heat cycling, and a modified double-quenched hydrolysis probe to shorten the RT-PCR process. The limit of detection for the MMB-based E-gene molecular test paired with traditional RT-PCR methods was 1.6 copies/reaction. The MMB technique detected the presence of SARS-CoV-2 in clinical samples in as little as 30 min, which is one-third the time required by RT-PCR [137]. As a result, this molecular assay may be employed successfully in a clinical setting to facilitate high-throughput sample testing (Fig. 12).

SARS-CoV-2 spike (S1) proteins might be identified with higher selectivity and speed with the possible functionalization of a graphene oxide (GrO)-glazed double-interdigitated capacitive (DIDC) biosensing device. The DIDC bioactive surface developed utilizing the GrO/EDC—NHS/anti-SARS-CoV-2 antibodies (Abs) on a Pt/Ti integrating SiO2 substrate provided the engineered surface for Abs immobilization and amplified capacitance, resulting in a wide detection range (1.0 mg/mL to 1.0 fg/mL), low limit of detection (1 fg/mL) within 3 s of response time, good linearity (18.56 nF/g), and high sensitivity of 1.0 fg/mL [38].

Investigating plasmonic metasensor technologies for COVID-19 examinations, provides exquisite prospects in advanced healthcare programs and current clinical diagnostics, and can be one ideal alternative way to detect SARS-CoV-2 viral protein at low levels, i.e., femtomolar (fM). The capacity of plasmonic metasensors to compress electromagnetic fields concurrently in frequency, time, and space is one of its primary advantages. Furthermore, a common shortcoming of traditional metasensors is the detection of low-molecular-weight biomolecules at low densities, which has recently been solved utilizing toroidal meta surface technology [34].

5.4. Point-of-Care (POC) testing of SARS-CoV-2 for COVID-19 management

Since the development of biopharmaceuticals, efforts have been made to transform a tried-and-true sensing technology into an analytically diagnostic instrument for use in clinical contexts. Currently, electro-chemical, optoelectronic, thermal, and piezoelectric signal amplification technology-based sensing devices, whether wearable or non-wearable biosensors, have demonstrated promising record, particularly in the test results of glucose levels, lipids, triglyceride levels, prenatal care, contagious diseases, medicinal chemistry, blood assessment, and so on [138]. Using materials such as biopolymers, conducting polymers, metal oxides, Au, CNTs, graphene, QDs, composites, and hybrids, modern material science has made it easier to prepare and fabricate nano-enabled smart sensing substrates. Exploring innovative electro-active surface-functionalized nanostructures has become more necessary because of the necessity to accomplish high biomolecule loading to achieve wide detection range and signal amplification to enable sensing at a low level of biomarker. The efficient implementation of SARS-CoV-2 viral sensors with AI and IoMT allows for virus detection at the point-of-contact while also communicating information with the medical center for prompt treatment strategies. This method is also effective for task monitoring and controlling COVID-19 infection based on patient infections profile [139]. To prevent human-to-human SARS-CoV-2 viral transmissions, specialists recently created sensory perceptions nanotechnology enabled that can not only capture virus aerosol but also eliminate viruses when stimulated externally, such as nano enable photo-sensitive virus degradation [82]. By employing a particular anti-SARS-CoV-2 viral protein antibodies for effective analytical sensing within 30–40 min of operating interval, a miniature IDE-based SASR-CoV-2 biosensor may be developed. Perhaps a biosensor may be developed into POC advanced analytics to carry out SARS-CoV-2 at POC required to control COVID-19 in a thoughtful approach [140]. The need of creating effective nano-enabled sensing systems was outlined by Kaushik et al., employing the electrochemical monitoring of the SARS-CoV-2 as an instance. This system is capable of selectively detecting the COVID-19 virus at the pM level. Such low-level viral identification skills are necessary to comprehend the course of illnesses and to assess the effectiveness of recommended medication [111].

To achieve desired POCT, the microfluidic system integrates multicomponent assays (such as multiplication, preconcentration, and identification) together into single automated tiny device. For lab-on-a-chip technologies, a number of biosensing platforms, including as optical, electrochemical, piezoelectric, and surface-enhanced Raman spectroscopy, have been described [141]. In a previous work, square wave voltammetry (SWV) and electrochemical impedance spectroscopy (EIS) were implemented to determine dengue virus NS1 using gold electrodes that had been chemically functionalized with synthetic peptides. The created sensors displayed low LOD up to 1.49 g/mL in spiked fermentation broth and strong specificity against all four dengue serogroups. Additionally, POCT devices found that a sample included a number of pathogenic organisms [130]. The introduction of lanthanide-doped polystyrene nano-platform by Chen et al. increased the sensitivities of LFA and enabled SARS-CoV-2 detection within 10 min. This sensitive fluorescent IgG bioassay successfully detected SARS-CoV-2 recombinant nucleocapsid phosphoprotein on a self-assembled nano-systems. Tests on 12 individuals who had COVID-19 infections and comparisons with 51 uninfected samples were used to verify this nano-enabled LFA. The therapeutic use of this LFA diagnostic platform can be triggered by the required sensor performance and precision [119].

Biosensors based on MXenes have also been used to detect ions important in mammalian metabolism. An effective investigation of this kind was conducted by Hui et al. using a gold electrode that had been modified with layer-by-layer construction of $Ti_3C_2T_x$ and multi-walled CNTs nano-systems [142]. The limitless possibilities of these functionalities in revolutionary point-of-care bioanalytical devices are highlighted by several exciting publications regarding MXenes-based biosensors for genuine tracking of heartbeat and other physiological changes (respiration-humidity, sweat analysis, etc.) [143]. The integration of a 2D-borophene based miniaturized biosensing system with a shrunk transducer may be advantageous for the creation of an analytical diagnostics tool to manage recently emerging and re-emerging infectious diseases like COVID-19 [144].

It is interesting to note that A2Ms-based biosensors have become a strong contender for identifying viruses, particularly the coronavirus-2 that causes severe acute respiratory syndrome (SARS-CoV-2). MXene-graphene composites can be another promising candidate for biosensing applications [145]. A Ti_2C MXene-graphene-based field-effect transistor (FET) sensor, for instance, was described by Li et al. to monitor the SARS-CoV-2 and influenza viruses. The sensor showed a linear detection range of 125 copies ml-1 for H1N1 virus and 1FG ml-1 for recombinant 2019-nCoV spike protein within 50 ms. It also showed a linear detection range of 1–10 pg ml-1 for recombinant 2019-nCoV spike protein [146]. A DNA-functionalized $Ti_3C_2T_x$ MXene-based chemiresistive biosensor has also been reported to rapidly and accurately detect the SARS-CoV-2 nucleocapsid gene. With a substantial LOD of 105 copies ml-1 in saliva and good selective detection against SARS-CoV-1 and MERS, the manufactured sensor demonstrated its effectiveness [147]. Additionally, Mi et al. described the development of a tetrahedral DNA/aptamer cardiac troponin-I biosensor on an Au/Ti3C2-MXene analysis of the proposed upon something in situ hybrid chain reaction for the COVID-19 serious patients' assessment. With a LOD of 0.04 FM, the sensor showed a linear detection range of 0.1 fM, pM for cTnI. The manufactured sensor demonstrates a clever technique for screening COVID-19 patients in portable hospitals [148].

In a different investigation, Huang and colleagues employed the colloidal AuNPs-based lateral-flow (AuNP-LF) test to quickly diagnose and determine the level of IgM antibodies against the SARS-CoV-2 virus on-site. In attempt to develop AuNP-LF strips, the SARS-CoV-2 nucleoprotein (SARS-CoV-2 NP) was coated on a sample capture analytical membrane. Antihuman IgM was then coupled with AuNPs to create the detector reporter. Blood samples were taken from COVID-19 patients and healthy individuals were examined to assess the output of the AuNP-LF test. With just 10–20 L serum needed for each test, AuNP-LF's sensitivity and specificity were 100 and 93.3 percent, respectively, and results were available in only 15 min [108].

6. Nano-enabled drug delivery to recognize and eradicate SARS-CoV-2

Nano-carriers with a diameter of less than 100 nm shield the drug from direct interaction with the immune system except at the target location and promote in vivo circulation [149]. This contributes to the drug's life by ensuring that it is only released at the target spot when it is needed. The most common technique employs NPs that are enzymatically degradable and susceptible to changes in the environment such as pH and temperature, which help in the inactivation of the bond, permitting mutual dissociation of the drug as well as the carrier or destabilization of the carrier at the specified location [150]. Because of these major benefits, many various types of medications may be carried on nano-carriers to improve their efficiency. Remdesivir, one of the most used antiviral drugs against SARS-CoV-2, was conjugated with Cu nano-carriers. The Cu was chosen because it can destroy the virus's genome and envelope, inhibit RNA polymerase activity, and produce reactive oxygen species capable of killing the virus [151–154].

NPs, in addition to nanocarriers, can be employed to lower SARS-CoV-2 infection severity and incidence by reducing viral entry, replication, and cytokine storm. SARS-CoV-2 attaches to cells in the upper respiratory canal via binding to the Angiotensin-Converting Enzyme 2 Receptor, indicating that if the binding is blocked, viral entrance is also blocked. SARS-CoV-2 binding is inhibited by NPs when they attach to ACE-2 receptors [155]. In comparison to SARS-CoV, SARS-CoV-2 has a greater ability to fuse plasma membranes. S protein-mediated membrane fusion and, as a result, SARS-CoV-2 entrance was prevented by a nano-engineered lipopeptide (EK1C4) [156]. By attaching to the various receptors of the membrane proteins, either the antiviral NPs or the hybrid antiviral NPs have efficiently suppressed coronaviruses. Chitosan NPs targeting SARS-CoV nucleocapsid protein and spike protein have been shown to limit SARS-CoV entrance into cells in addition to acting as nano adjuvants [157,158].

In the instance of MERS-CoV, AuNPs have been observed for their capacity to prevent viral entrance. Multiple heptads repeat 1 (HR1) peptide antagonists were developed to prevent MERS-CoV and host cell transmembrane fusion by interfering with HR1/HR2 regulation of the process. Peptide pregnancy-induced hypertension (PIH) has a high inhibitory action with an IC50 of 1.171 M, and when conjugated with Au-NPs, the inhibitory effects increase 10-fold. This discovery might be used in the treatment of COVID-19 in a clinical setting [159]. As a result, it can be observed that NPs can not only operate as entrance inhibitors but also as medication delivery carriers. This provides an entirely new realm of possibilities for nanomedicine as a prophylactic measure. Materials that prevent or impede the reproduction of the virus are critical in the case of infectious disorders [160]. The capacity of transmissible gastroenteritis virus (TGEV) to proliferate in animals has been substantially hindered by the action of Ag NPs. In vitro, NMs such as NPs, nanowires, and colloidal mixes were used to find the most effective Ag NPs. By acting as a viral replication inhibitor, all Ag NMs were shown to be equally efficient in preventing TGEV infection [161].

In the last decades, theragnostic NPs have risen to prominence as a promising study area. Detection and in particular therapy of illness problems may be done simultaneously using these NPs. Nano-theranostics use NP-based targeted drug delivery to deliver medicines, vaccines, and other chemicals to their intended locations. Many researchers are attempting to use radio-labelled NPs, inorganic NPs such as IONPs and AuNPs, organic NPs such as polymers, carbon-based nanomaterials, lipid NPs, and vesicular nanostructures such as nanosomes to enhance drug delivery and bioimaging [162].

Because it is non-invasive, cost-effective, and simple to conduct, intranasal administration of conjugated NP serving as drug carriers is a viable alternative to established methods of drug delivery. Therapeutic medicines are delivered more effectively, siRNA is delivered more precisely, peptide inhibitors are delivered more efficiently, viral entrance into cells is prevented, and the host immune system is stimulated by theranostic NPs. Various prospective therapeutic drugs now under investigation against SARS-CoV-2, administered by biocompatible theragnostic NPs via the intranasal route, are likely to be significantly more effective than any other treatment for COVID-19 treatment [163]. In addition to lowering the severity of SARS-CoV-2 infection, NPs may be used to alleviate some of the virus's side effects, such as acute respiratory distress syndrome (ARDS). Inflammation-reducing IL-6 inhibitors can be used with NPs to enhance the patient's condition. To drive macrophage regeneration and minimize cellular inflammation, nano-diamonds are coupled with dexamethasone, an anti-fibrotic medication, and octadecyl amine [164].

The virus binds to the host via cell surface receptors in the initial phase of the viral infection cycle. In many viral infections, blocking virus entrance has been proven to be an effective anti-viral therapy (Fig. 13) [82]. Nanostructures are excellent for competitively binding and inhibiting viral entrance into cells due to their properties. Some nano-based approaches are designed to bind virus particles directly, preventing them from ever getting close to the host cell [165,166].

However over past decade, there has been improvement in the development of innovative NPs that have both medicinal and diagnostics components. For a variety of imaging techniques, including MRI, optical coherence tomography, computerized tomography (CT), ultrasonography, and nuclear imaging, including both positron - emission (PET) and single-photon emission computed tomography, theragnostic NPs have been developed (SPECT). Studies have extensively shown positive interest in nanoparticle-drug delivery systems (NDDS) and auditory stimulation demeanor [167,168]. Randomized trials for COVID-19 have evaluated antimicrobial drugs; among these, chloroquine, ritonavir, lopinavir, ribavirin, and remdesivir have demonstrated efficacy against the SARS-CoV-2 virus infection. For the administration of antiviral medications such acyclovir, zidovudine, dapivirine, and efavirenz, as well as to improve bioavailability of drugs, improve the effectiveness of drug administration, and targeted antimicrobial activities,

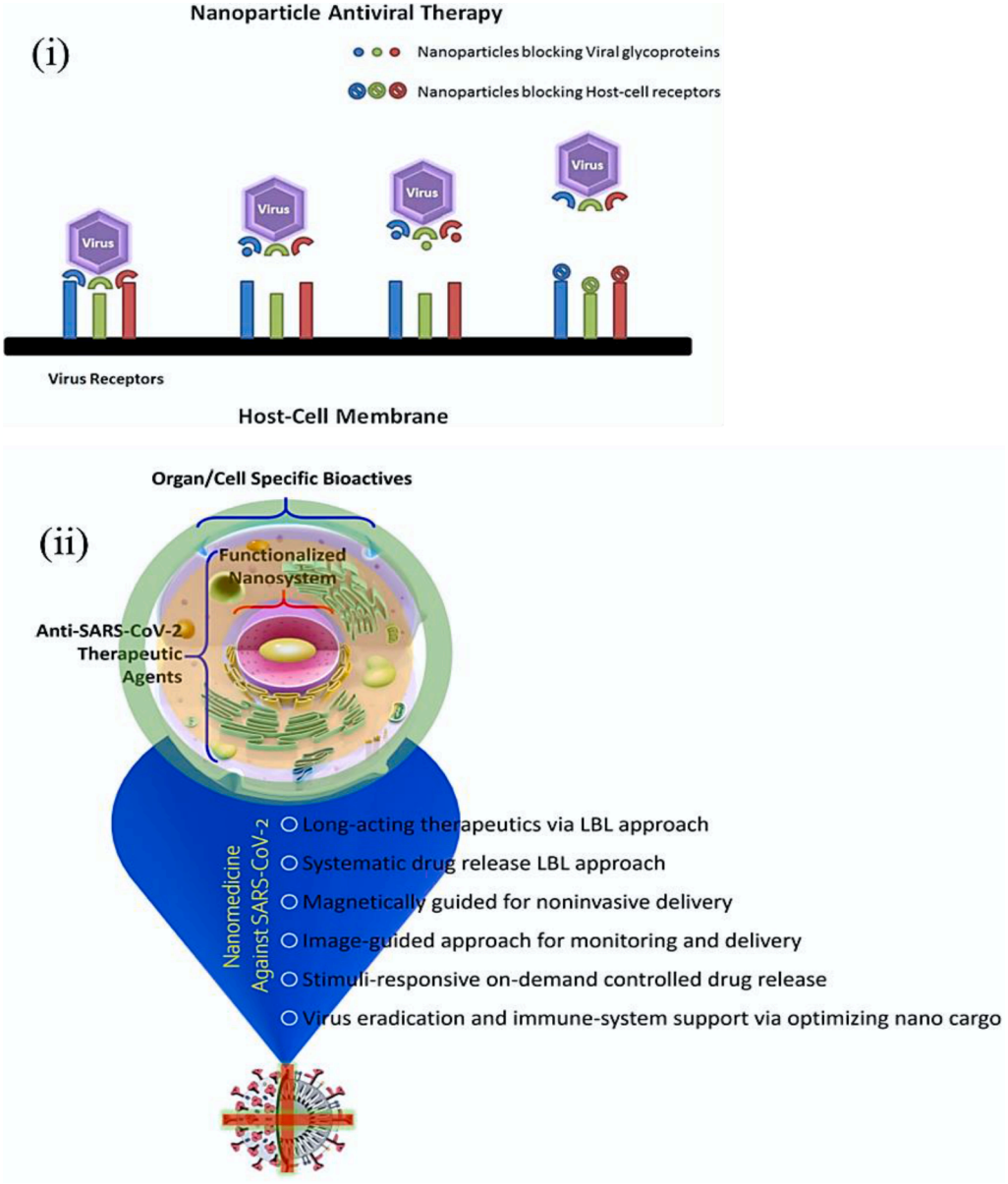

Fig. 13. NPs for delivering antiviral drugs for anti-COVID action. **(i)** High-performance nanomedicine using NSs for antiviral action. Reproduced with permission from ref for open access [128] **(ii)** Antiviral nano-therapy. The most prevalent location for viral infection inhibition is the virus's entrance into the host cell. NPs might disrupt the connection between the virus and the host receptor by attaching to either the virus or the host cell. Reproduced with permission from ref. [165].

organic NPs have been used [169]. The main weakness of antivirals is their lack of precise targeting, which results in cytotoxicity of the host cell and is remedied by organic NPs. The development of safer treatments for COVID-19 and other viral illnesses may be facilitated by the nanoencapsulation of antimicrobial medicines [170,171].

It is vital to clarify toxicological issues and their laws, even though nanotechnology has become extremely popular in the research sector owing to its superior efficacy when compared to the conventional alternatives. A major worry is the reactivity of the NPs after being exposed to the human body and their partial retention [172]. Additionally, it has been discovered that iron oxide particles have detrimental properties both in vitro and in vivo, mostly because of reactive oxygen species (ROS) production. Iron oxide NPs surface being coated with a polymer, significantly increases cell survival. Another strategy to lessen the negative effects of NPs is surface changes. For instance, gadolinium fullerene particles with hydroxyl groups reduces the production of ROS, which decreased their toxicity [173].

Enhancing the selective absorption of NPs-based therapies using peptides or receptors with high affinity for extracellular macrophage membrane components might reduce dysfunctional macrophage responses. Even though these synthetic NPs may perhaps be more likely than unmodified EVs and liposomes to trigger unfavorable immunological responses, clinical trials must extensively evaluate their biosafety. Although the effects of virus-like particles (VLPs) on immune responses mediated by macrophages are not fully understood, VLP treatment has been shown to have curative benefits in animal models of infection or chronic inflammation [36].

7. Emerging NPs as an anti-viral agent

When exposed to precise wavelengths of light, nanomedicine may also be employed in an in vivo setting through photosensitizing treatment, in which medications are supplied to specific cells and convert oxygen into ROS to destroy targeted cells [174]. Kipshidze et al. proposed employing micro-catheters to inject porphyrin-based photosensitizer medicines into the pulmonary artery to treat COVID-19 induced ARDS. The SARS-CoV-2 would initially connect to photosensitizer molecules rather than normal lung tissue, attacking healthy hemoglobin [175]. Using a fiber-optic catheter, the specified tissue is flashed at the photosensitizer's characteristic absorption wavelength (450–800 nm) to lower the viral load. This results in the generation of reactive oxygen species (ROS), which may peroxide and inactivate the SARS-CoV-2 virions bound to photosensitizer molecules. As a result, clinical performance is improved, and oxygenation is increased, increasing SpO2 [176]. The absence of important research in this sector is a severe problem that must be addressed as soon as possible by the scientific community. Techniques that have been utilized and tested against SARS and MERS-CoV can be adapted to be used against SARS-CoV-2 [176] .

The present necessity of the hour is for advancements in modern pandemic tactics to counteract developing SARS-CoV-2 strains. With recent advances in high-performance nano-systems, their diverse applications have a good chance of eliminating the virus by permitting sensitization and then using ultrasensitive tests with the focused identification of viral biomarkers [165]. Researchers have been focusing on point-of-care devices, bio-imaging appliances, antiviral therapeutics, photo-thermal techniques, and medication formulations because of the uncontrollable catastrophic health effects, making nanotechnology one of the strongest foundations of illness intervention [4,34]. Emerging medicative technologies have shown promise in targeted therapies delivery via virucidal NPs, photo/hyperthermia, lipid adjuvants, and nano-vesicles, as well as disinfection via antiviral coatings, nanotechnology-based PPE kits, antiviral photoactive compounds, and filter systems via various modes of transmission such as droplet, aerosol, virus particulate, and air-dispersed-aerosol. Thus, the strategy is clear in fulfilling their aim of tracking, predicting, regulating, and monitoring COVID-19 infection, resulting in accurate and successful illness treatment [165].

The regulated physical and chemical properties feature with inherent antiviral core have enhanced drug loading efficacy while also allowing for longer-term drug circulation regulation, directed distribution of hydrophobic medicines, and very sensitive diagnostic prospects [165]. Vaccines, medicines, and neutralizing antibodies are common antiviral techniques, such as dexamethasone, which is given intravenously to SARS-CoV-2 infected individuals to combat overactive immune cells. Nano-based antiviral vaccines, on the other hand, have the greatest impact in terms of efficacy and reliable administration, aiding virus entrapment and propagation suppression [177,178]. These tactics have also eliminated the constraint of detecting viral strains in and around the host, resulting in a lower detection limit and a faster reaction time, making them functionally adaptable to changing demands [140].

Using a graphene-based FET system with 2D-AuNPs coupled with complementary DNA receptors, a recent finding demonstrated the potential of plasmonic NPs with photo-thermal and LSPR capabilities for diagnosis and detection of SARS-CoV-2. These receptors were treated with nucleic acid hybridization to determine the infection [4]. The NSs' unique qualities, including tenability and charge distribution potential, set them apart from traditional techniques, allowing a medication with poor water miscibility to be delivered with little toxicity, higher bioavailability, and increased concentration [179–181]. Targeted identification by surface receptor binding NPs improves antiviral activities [182,183].

Light-triggered TiO_2-based photocatalytic coatings have been shown to have antiviral effects by causing damage to viral membranes, and therefore may be utilized to coat a wide range of equipment such as air conditioner vents, hospital mats, and metal surfaces [184]. Because aerosols are a particularly vulnerable route of viral transmission, hydrophobic NMs that are far more efficient than cotton masks can be used to prevent it. Similarly, nanostructured water in conjunction with a few functional agents has the power to disrupt the normal course of disinfectant action, whereas nanotechnology-based alternatives considerably lower the viral load of the H1N1 virus, which is associated with high cell viability [185].

The use of nanomedicine-based on high-performance nano-systems to protect antigens against degradation, deuteriation of stability, and interruption of sustained release have also been emphasized in vaccines. Moderna, the first mRNA vaccine, is referred to as a nano vaccine because it uses lipid NPs to encapsulate mRNA and create an immune response against MERS-CoV [186,187]. Other examples include the development of Epivax, which provides partial immunity against SARS-CoV-2, and the Matrix-M adjuvant, which

attracts and stimulates antigen-presenting cells at the site of infection, to establish passive immunity and mass immunization through the effective administration of neutralizing antibodies or convalescent plasma therapy [188,189].

As a result, we can reasonably conclude that the described techniques are not only practical, clever, and cost-effective, but they also have a good possibility of eliminating VOCs due to their innovative use in masks, sheets, and air conditioners, disinfectants, and hydrophobic coverings (Fig. 14). More research is needed, however, to get greater FDA clearances and constraints that will cover the high cost of essential biomarkers, storage conditions, and other resource arrangements [165].

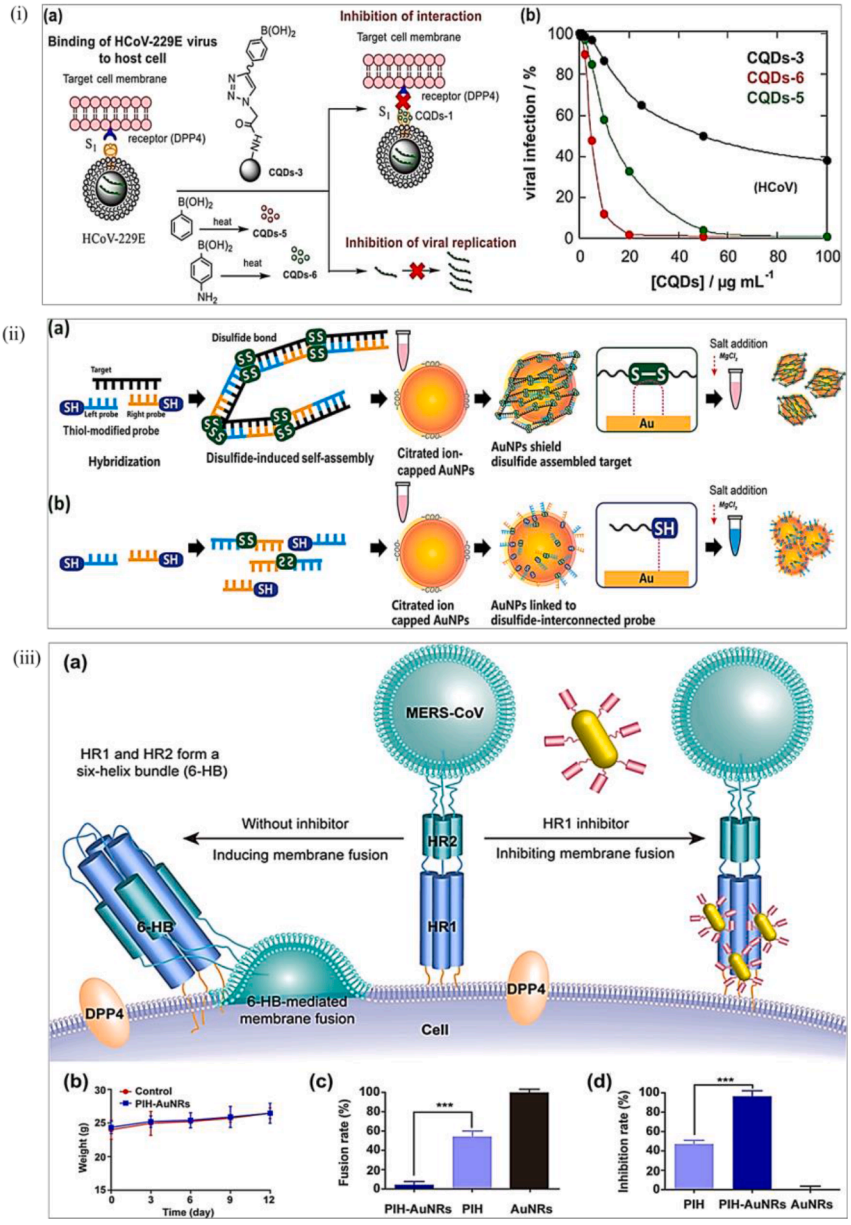

Fig. 14. Antiviral properties of functional NPs. (i) A disulfide-induced self-assembly technique is used to calorimetrically identify RNAs.Adapted with permission from ref. [190] (ii) Inhibition of S protein–receptor interaction (top) and viral RNA genome replication by CQD on HCoV (bottom). CQDs-3, CQDs-5, and CQDs-6 were used to suppress viral replication. Adapted with permission from ref. [191] (iii) Schematic representation of an HR1 inhibitor (left) inhibiting MERS-CoV S2-subunit-mediated membrane fusion; the HR1 inhibitor can inhibit the HR1/HR2 complex (6-HB) -mediated membrane fusion and infection with MERS-CoV (right). Reproduced with permission from [157] Copyright 2020 American Chemical Society.

Table 2
Application of nano-systems used for anti-COVID activity.

Nano-systems	Characteristics	Functionality	Ref.
Virus Like particles	Acquire the virulence by mediating interactions among their characteristic envelope capsid proteins. These systems have successfully imitated human infection through penetration into the cells while using host cell replication mechanisms for the expression of viral antigenic peptides. Such systems inherit immense immunogenic potential.	Vaccination	[51]
Au-NPs	Light scattering properties and can further be loaded with therapeutic molecules such as proteins, RNA for *in vivo* or *in vitro* applications	Anti-viral activity and bio-imaging	[56]
Iron oxide NPs	Magnetic and Biodegradable properties	Non-invasive diagnostic bio-imaging and targeted drug delivery	[55]
Lipid Based NPs (DOTAP & DOTMA)	Efficient uptake of drugs through a sophisticated permeation mechanism.	Nucleic acid and drug delivery.	[60]
Polymer-based NPs (PVA, PLA, PEG, PLGA)	Their basic properties such as size, shape, and density are highly variable and can be manipulated for optimized usage.	Besides, drug delivery they are also being conjugated with inorganic NPs to amplify their anti-viral properties. The usage of modified PBNMs in masks and personal protective equipment.	[62, 63]
Nano-enabled efficient detection system	Sensors demonstrated high sensitivity and specificity, with no cross-reactivity from non-SARS-CoV-2 templates.	The amplification reaction was visually assessed as a readout on a NPs -based biosensor platform.	[199]
Au-NPs along with thiol modified probes	The probes are conjugated to AuNPs via strong Au-S interactions. In the absence of a target, the AuNPs aggregate (in the presence of a positive electrolyte), leading to color change, which can either be visualized with the naked eye or detected by localized surface plasmon resonance (LSPR) shift.	Detection of lower amounts of the viral target. Such a colorimetric based assay allows low-cost and rapid diagnosis without sophisticated instruments	[124, 161]
Carbon electrodes coated with Au-NPs	Sensitivity of the sensor and signal response. The recombinant spike (S1) protein of MERS-CoV was immobilized to AuNPs.	The immobilized S1 protein competes with virus particles in the sample for binding to the antibody.	[200]
Peptide NPs	The small size of the immunogen and the repetitive presentation of the epitope, both of which were met underutilizing NPs lead to the potent immunogenic effect of the Np-based vaccine.	Repetitively displayed the B-cell epitope and elicited an adequate antibody response with the use of any adjuvants	[199, 201]
Nanowire based label-free electrochemical sensing of N-virus protein of SARS Virus N-Protein using an antibody mimic protein	The nanowire was utilized as an antibody immobilizing platform to design nano biosensors.	Selective detection of the virus protein.	[202]
2D nanostructure of Au	Combined features of plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) based transduction.	Utilized as a plasmonic platform, functionalized with complementary DNA to detect a specific sequence of SARS-CoV-2 based on the concept of gene hybridization.	[203]
Au-NPs, capped with efficiently designed thiol-modified DNA antisense oligonucleotides	The oligonucleotides are specific for N-gene (nucleocapsid phosphoprotein) of SARS-CoV-2.	The colorimetric assay was able to diagnose positive COVID-19 cases from the isolated RNA samples within 10 min.	[159]
VLPs with full-length glycoproteins adjuvanted with Matrix M1.	Stimulates Immunogenic Response	Longer-lasting antibody response was generated	[204]
RT-LAMP associated with NP based biosensor	Simplifies the viral extraction procedure for RT-PCR	The extracted viral RNA was efficiently absorbed onto magnetic NPs due to the strong interaction between the carboxyl groups.	[205]
N-protein of SARS Virus using an antibody mimic protein (AMP)	Antibody immobilizing platform	Selective detection of nucleocapsid	[202]
Au—NPs to modify carbon array electrodes	A virus is detected based on the measured change in current in competitive immunoassays.	Detection of MERS CoV and HCoV.	[206]
Ag-NPs have been used in paper-based analytical devices (PADs) for MERS-CoV detection	Aggregation of AgNPs to design a colorimetric assay	The cationic acpcPNA probes can bind to negative citrate ions on the surface of AgNPs, inducing NP aggregation together with a color change.	[207]
Magnetic NPs	Strong magnetic properties	Improve the selectivity of the target cDNA of SARS-CoV in the separation process.	[36]
Poly (amino ester) with carboxyl group (PC)-coated MNPs (pcMNPs)	Magnetic property	Used in RT-PCR process for viral RNA amplification without the use of an elution step.	[208]
Modified carbon QDs with functional groups, including NH_2, COO−, N_3, triazole, R-$B(OH)_2$, and PEG	Biocompatibility due to functionalized groups	Anti-COVID-19 activity	[209]

8. Challenges and alternative approaches

In comparison to other viruses, the properties of SARS-CoV-2 remain comparatively unexplored. As a result, scientists have relied on broad antivirals and studies on other coronaviruses to devise an effective treatment strategy. Hundreds of medications are being tried against SARS-CoV-2 every day in laboratories all around the world. Many of the antiviral medications that have been licensed are nucleic acid or protein-based therapies that are easily destroyed or produce inflammatory responses in humans [151]. The development of a treatment that checks all the boxes and successfully blocks SARS-CoV-2 entrance is a long way off, but pre-existing antiviral medicines employed against SARS-CoV-1/−2 and MERS-CoV can be utilized as references because they possess the same fundamental structure [192]. NPs that target virally infected cells' autophagy is being studied. Autophagy-targeting drugs promote autophagosome build-up, which leads to apoptotic cell death. These medications, on the other hand, have serious side effects such as neuropathy, myopathy, gastrointestinal problems, and osteoporosis [193]. It can be considered a beneficial vector that supports the mechanism of vaccine protection from premature degradation, resulting in an increased immune response, modulation of release dynamics, suppression of adverse anomalies, and target-specific antigen delivery, as well as an increase in intracellular absorption [194,195]. Polymers, graphene derivatives, inorganic/organic NPs, and CNTs, metals, metal oxides are among the potential nanostructures that have established key roles in the dramatic alteration of the existing method used to counter-balance biosafety-related difficulties [196]. As a result of the present method, it is feasible to bridge the gap between diagnostics and therapy. Nano-diagnostics, surveillance and monitoring, nano-vaccination, and nanotherapeutics are the face of innovative yet extremely dependable combatants, and they represent a turning point toward a next-generation strategy to outbreak control [197,198]. The potentials of NPs as anti-COVID-19 agent are summarized in Table 2.

The threat presented by the deadliest pandemic of the new century, which began with coronavirus, is still dynamically active, and with vaccines still in development, researchers can claim that there is no therapeutic cure in the works that really can immunize against the antigenic assaults of the viral protein. This circumstance necessitates the development of existing clinically marketed techniques by investigating the therapeutic potential of NPs with broad medical applications in biosensing, antibacterial therapy, and drug development [79]. The ongoing diagnostic methodologies, such as the use of antivirals, immunomodulators, protease inhibitors, nucleoside analogs, and plasma therapies, have not slowed the spread of the virus, and their administration is solely to alleviate clinical issues, resulting in a lack of effective and long-term clinical benefit [210]. Remdesivir (GS-5734), a virus-targeting antiviral (VTA) that inhibits viral replication while interacting with RNA-dependent RNA Polymerase, has been found to enhance the clinical condition of the US population (RdRp). The effectiveness factor related to the medicine was demonstrated in research including 53 SARS-CoV-2 infected individuals. Remdesivir has been linked to a lack of effectiveness and safety, as well as other side effects such as renal damage and an increase in liver enzyme levels [211–213].

Ribavirin, on the other hand, has been linked to high-risk anemia, and dose-dependent hematologic damage, and is a possible teratogen in pregnancy [214,215]. Apart from the VTA, host-targeted antivirals (HTA) such as convalescent plasma face obstacles such as high costs, little research, and short duration of elicited immunity against the SARS-CoV-2 virus [216–218]. To provide successful theragnostic therapy, these restrictions simultaneously demand the conjugation of NPs with existing techniques. The in vivo behavior of the viral pathogen, cytotoxicity generated by nanocarriers, and the bulk manufacture of the diagnostic on an industrial scale are the main hurdles in terms of nanomedicine's efficiency against the viral pathogen. Apart from these, several alarming factors must be addressed before the development of a novel technique, including a greater understanding of the multifaceted characteristics of disease pathophysiology, mechanisms at the nano-bio-interface, safety, regulatory kinetics, and biocompatibility [210].

According to reports, antibodies that attach to the S protein prevent viral entrance into the host cell. However, over time, mutations to this polypeptide may prevent antibodies from attaching, allowing the virus to slip past the immune response. However, mutations in the SARS-CoV-2 genome have resulted in several novel variants documented across Brazil, India, South Africa, and the United Kingdom. When comparing with the original strains, these new variants are deadlier and have a greater risk of transmission. Furthermore, these variations increase the likelihood of reinfection and reduce the efficiency of vaccine-induced immunity [219]. The complexity of the illness is increasing due to viral mutations, making it harder to treat with currently available medications. According to reports, antibodies that attach to the S protein prevent viral entrance into the host cell. However, over time, mutations to this polypeptide may prevent antibodies from attaching, allowing the virus to slip past the immune response. To understand how well nanomaterials work against COVID-19, it is important to thoroughly examine how they interact with various mutant viruses [220–222].

Since the virus cannot be eradicated with current medication molecules, genetic mutations of the virus pose the most difficult challenges to conventional therapy. Because the earlier reported drug molecules may be the prospective therapeutic molecules against SARS-CoV-2 with strong inhibitory effect, drug repurposing became an issue that urgently needs study. Regarding the fabrication of NPs for in vivo applications, toxicity of the nanomaterials is another criterion that needs to be given serious consideration. The assessment methods that should be used to each of the developing nanomaterials for antiviral applications should be biocompatibility and nanotoxicity features [221,223].

Due to the constraints associated with antibody detection such as identification, technical production, false-positive findings, and lack of appropriateness, NP-mediated sensing instruments are reported to have improved diagnostic performance when compared to time-consuming detection approaches such as Rt-PCR. As a result, the necessity for early detection, minimum contamination, and reduced chance of error persists, necessitating enhanced testing to ensure that the nanotechnology-driven detection approach is foolproof. Conventional vaccinations are inefficient against a wide range of pathogens, a high rate of viral mutation, and host-related complexity, all of which contribute to an incorrect immune response [224]. When compared to the biocompatible nano-based COVID-19 approaches, which facilitate non-invasive administration with reduced toxicity, treatment facilities provided by the

conventional approach lack stabilization in the systemic circulation, do not achieve sustained delivery, suffer from side effects due to high serum concentrations, have a lower surface area to mass ratio, and foster unstable chemical reactivity [225].

The worldwide debate over the risks connected with the control of NPs during nanostructure development necessitates the identification and legal application of marketed nanotechnology-driven goods. These items have the potential to inflict irreversible harm to persons and the environment [200]. A key issue that must be addressed is the indirect expenses associated with the use of nanomedicine, which disrupts the balance between health-care expenditures and quality, further complicating the use of NMs in the fight against worldwide Covid-19 transmission [199]. Industrially advantageous nanomedicine with higher safety, high sterilization capacitance, low dose pattern, repeatability, and eco-friendly alternatives is still a work in progress [201,226,227]. Complex stages in the creation of NP, the establishment of pure research designs with sensible sample sizes, and controlled methodologies are some of the other persistent obstacles [202,203].

Biomolecule disintegration, poor entrapment efficiency, unregulated release burst, accumulation in places other than the target site, and sterilization of parental formulations are all dangers that come with nano-formulations [204]. They're also concerned about scavenger cells' potential for undesired recognition [205]. Molecular damage, geno-immunotoxicity, fibrosis, inflammation, tiny granulomatous lesions, and oxidative stress resulting from NP build-up in the alveoli responsible for blood vessel penetration, alveolar cell injury, and proliferation to other organs are all safety concerns [206,207]. From a pharmaceutical standpoint, the favourable properties of developing nanotherapeutics necessitate the continuation of the search for antiviral therapeutic agents with minimal adverse side effects, dosage optimization, and delivery systems, resulting in biocompatible, immunomodulating, immune-supportive, multiple stimuli-responsive, and biofunctionalized products whose functionalization is bound to vary depending on the application [36].

The alpha and delta variants have been noted to be a growing source of worry due to their increased transmission capacity and decreased neutralization by antibodies, the negative consequences of which are visible post-vaccination. Recent research has found that immunizations are less effective against the delta version than against the other variations. The two vaccines typically used against the B.1.617.2 strain, BNT162b2 (a Pfizer-formulated mRNA vaccine) and ChAdOx1 nCoV-19 (an adenoviral vector-derived vaccine containing the spike protein), are known to have minimal effectiveness against the delta variation when provided with the first dose. Resistance to anti-NTD and anti-RBD antibodies was enhanced by the delta variant. When compared to the alpha form, the antibodies recovered from the convalescent patient's blood at 12 months post-infection showed a steady decrease in efficacy (by 4 times). However, when both doses of the aforementioned vaccines were administered against the delta form, they exhibited greater effectiveness (88 percent in the case of BNT162b2 and 67 percent in the case of ChAdOx1 nCoV-19) [208,209].

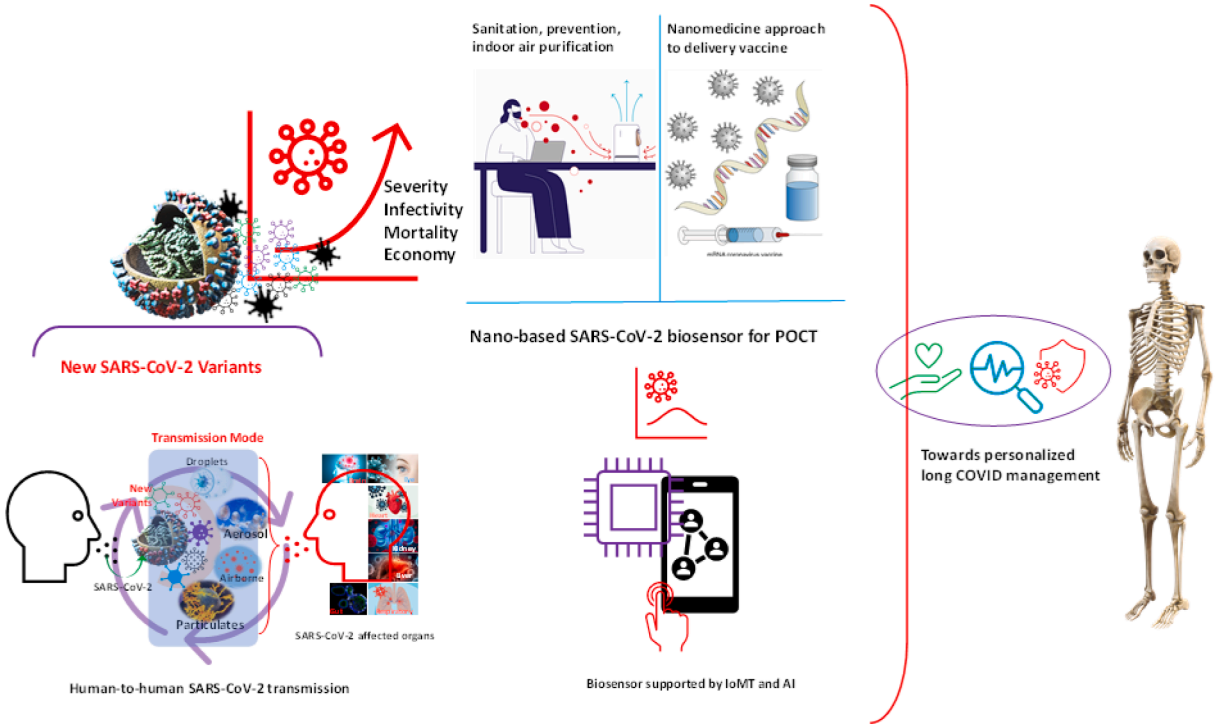

Fig. 15. Projection of mutated SARS-CoV-2 induced COVID-19 infection and its management using nanotechnology assisted prevention (disinfectants, anti-microbial agent, efficient mask, indoor air cleaning), diagnostics (biosensors to detect mutated SARS-CoV-2), and treatment (therapeutic agent of higher efficacy and targeted delivery using nano-systems) in the direction of personalized COVID-19 infection management.

9. Conclusion and viewpoint

The promise of several nanotechnology-based systems for enhancing coronavirus detection, disinfection, prevention, and multiplication inhibition is highlighted in this review paper with a focus of personalized COVID-19 infection management (Fig. 15). As adjuvants and delivery platforms, NMs have been effectively employed in vaccine conjugation. They have the potential to improve immune response by shielding antigens from early degradation, penetrating cell membranes, allowing for prolonged release, and increasing stability. Targeted immunogen delivery, vaccine release control, increased innate immune response, and vaccine delivery to immunological niches for antigen presentation are all aided by this characteristic of NPs (lymph nodes and other secondary immune organs).

Anti-viral characteristics of NPs allow them to coat surfaces and promote disinfection. The Au, Cu, Ag, and other heavy metal NPs are being researched and developed for use as surface disinfectants and on masks. These NPs hasten the destruction of the viral DNA outside of the host body, preventing the virus from spreading. To identify and diagnose SARS-CoV-2, traditional instruments, and techniques such as RT-PCR and Chest CT are employed. These methods, however, are unreliable. Metal NPs are employed in POC devices to improve the accuracy of results due to their inherent qualities such as chemical stability and high electrical conductivity. They showed LSPR, which improves detection systems' sensitivity and specificity. Magnetic NPs and quantum dots have also been used in nanomedicine as detecting and medication delivery agents.

Antimicrobial NPs aim physiochemical features shared by many different types of viruses, in contrast to standard therapies, which typically target a single viral species and may lose their effectiveness as the virus acquires mutations. The use of DNA-based nanostructures to capture viruses or the use of modified polymers as cell membrane spoofs are two contemporary examples of antiviral methods. Other antiviral tactics involve rupturing viral membranes to avoid infection. Because they may be created fast and have action against a variety of virus families, several of these nanomaterials may be advantageous in the context of pandemic countermeasures.

To identify nucleic acids with the naked eye, many colorimetric techniques have been devised. Biomimetic NPs, in addition to serving as nano-carriers, lessen the severity of SARS-CoV-2 infection by decreasing viral entrance, replication, and lifespan, as well as lowering the cytokine storm syndrome. As a result, NPs can play a crucial role in COVID-19 infection at several phases, initially by limiting viral entrance and infected cell protein fusion during early attachment and membrane fusion, and secondly by functioning as drug delivery vehicles. It may also be employed as a vaccine delivery platform and for the development of self-disinfecting surfaces for clinical and commercial usage, making it a prophylactic tool.

In-depth research is needed to comprehend the disease's transmission, host interactions, and mutations to create a viable vaccine. As a result, current advancements in the field of nanotechnology may be able to improve the diagnosis, prevention, and detection of COVID-19 and its variations, while also offering insight to the reader and scholar into SARS-CoV-2 variants induced COVID-19 infection treatment. Clinically effective translation has, however, been stymied by the fact that, upon dispersion, such medications lose their effectiveness when the virus-compound combination dissociates, allowing viruses to resume their reproduction cycle. Nevertheless, it has been demonstrated that this restriction may be removed by creating NPs that upon binding are capable of inhibiting viral pathogenic potential irreversibly by permanently harming the viral genome, reigniting hope for a real, wide antiviral medication. The SARS-CoV-2 epidemic presents an advantage to consider the possibilities of nanotechnology for vaccine adjuvant development, despite the fact that it uncertain that innovative additives will be deployed in the circumstances of the present epidemic. To choose potential candidate materials that may be investigated for use in clinical trials as vaccine adjuvants, it is crucial to establish cohesive networks encompassing in vitro and in vivo research in this approach. Clinical trials on NPs-based treatments and diagnostics for future variations and the present pandemic are expected based on the findings of the investigations. Molecular docking, molecular dynamics, and computational chemistry are examples of in silico methods that are now employed for medication repurposing and are useful tools to support preclinical and clinical research of nanomaterials intended for disease therapy. In silico evaluations may be especially helpful in directing the logical design of novel NPs-based formulations needed to combat SARS-CoV-2, given the urgent need for nanomedicine against the present pandemic. In this review, the importance of NPs in the development of effective vaccines has been explored, as well as various preclinical research that has been shown and discussed. It's worth noting that NPs have had a lot of success in improving the efficacy of mRNA, protein, and subunit vaccines by preventing enzymatic degradation, making nanotechnology a powerful ally in the fight against COVID-19 by bringing new potentials in terms of disease diagnosis, treatment, and prevention.

Author Contributions

The manuscript was conceptualized by RB and AKD. AG and BB accumulated the data from different sources, analysed and modified the manuscripts. RB and AKD worked on the illustrations and finally the manuscript was proof-read and cured by AKD and AK. YM, EM, AK supervised and mentored the entire project.

Consent for publication

All authors have consented to the manuscript for publication.

Conflict of interest

The authors declare no conflict of interest.

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