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# Antibacterial and antiviral high-performance nanosystems to mitigate new SARS-CoV-2 variants of concern

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## Abstract

The increased severity of the COVID-19 infection due to new SARS-CoV-2 variants has resonated pandemic impact which made health experts to re-evaluate the effectiveness of pandemic management strategies. This becomes critical owing to the infection in large population and shortcomings in the existing global healthcare system worldwide. The designing of high-performance nanosystems (NS) with tunable performances seems to be the most efficient method to tackle infectious SARS-CoV-2 variants including recently emerged omicron mutation. In this direction, experts projects the versatile functionalized NS and their capabilities to mitigate SARS-CoV-2 propagation pathways by sensitization, anti-pathogenicity, photocatalysis, photothermal effects, immune response, developing efficient diagnostics assays or associated, selective biomarkers detection, and targeted drug delivery systems. To achieve these tasks, this opinion article project the importance of the fabrication of nano-enabled protective gear, masks, gloves, sheets, filtration units, nano-emulsified disinfectants, antiviral/bacterial paints, and theranostics to facilitate quarantine strategies via protection, detection, and treatment needed to manage COVID-19 pandemic in personalized manners. These functional protective high-performance antibacterial and antiviral NS can efficiently tackle the SARS-CoV-2 variants transmission through respiratory fluids and pollutants within water droplets, aerosols, air, and particulates along with their severe infection via neutralizing or eradicating the virus.

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## Abbreviations

NS, Nanosystem; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus diseases 2019; FDA, Food and Drug Administration; FET, Field-effect-transistor; LBL, Layer-by-Layer.

## Keywords

Multifunctional nanosystem, Trapping and mitigation of COVID-19, Intelligent nano-healthcare, Effective management of virus.

## Introduction: emergence to manage COVID-19 pandemic

The recent viral infection outbreak namely coronavirus diseases 2019 (COVID-19 pandemic/endemic or both) is not still in control because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mutating continuously to produce more infectious variants [1–4]. The technological advances, active scientific collaborations, and immediate responses by developed counties and pharmaceutical industries were rewarded by the discovery of vaccines of higher efficacy to combat COVID-19 infection. Vaccines developed by Pfizer, Moderna, CoVaxin, Johnson & Johnson, and others were deemed to be very effective against the first stage of COVID-19 infection. However, mutations, varied human physiology, and regional changes make it difficult to manage the multiform virus. As of today, thousands of deaths are ascribed to the SARS-CoV-2 infection, and

the number of affected people is still growing even after the vaccination [5]. All the infectious SARS-CoV-2 variants are now characterized as variants of high concern (VOCs): Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529), whereas few others are under variants of interest (VOIs): Lambda: C.37, Mu: B.1.621, Epsilon: B.1.427/B.1.429, Zeta: P.2, Eta: B.1.525, Theta: P.3, Iota: B.1.526, and Kappa: B.1.617.1; and variants under monitoring (VUMs) [5]. Moreover, highly infectious and easily transmissible new SARS-CoV-2 variants, such as delta and omicron (B.1.1.529) variant, have a wider reach and probably can further mutate to affect the global younger population. Although the pandemic situation in many countries such as China, USA, Canada, UK, New Zealand, and others were relatively better owing to proper vaccination drives and public health orders. It is observed that a small underestimation of the COVID-19 pandemic situation may lead to catastrophe, as observed by a sudden rise in the number of cases all over India during the second and third wave, which was similar to the rapid spread at the first stage in Italy, Brazil, China, and the USA [6–8]. Presently, a highly infectious and transmissible omicron variant is spreading globally (more than 80 countries by Dec. 18, 2021). Therefore effective treatment (vaccines and boosters) and precautions are required to avoid the next wave of COVID-19 infections.

A viral outbreak is not new to human existence, but what makes SARS-CoV-2 a significant threat is its 40-fold higher transmission efficiency than SARS-CoV-1 and a 3.3% higher fatality rate. All statistics highlight the mutation or evolution of infectious diseases over earlier infections, such as the 1967 or 1918 Influenza (0.6% or 2%, respectively) pandemics. Moreover, the consistent genetic mutations in the viral genome make it difficult to subdue its effect. The coronavirus SARS-CoV-2 infection is not limited to the lungs infection, but also causes biological complications, syncytia, and an unpredictable increase in blood clotting chemicals. Different drug formulations are under trial, while some have already been approved by the Food and Drug Administration (FDA) for vaccination (Emergency Use Authorization, EUA) against the catastrophic effects of COVID-19 infection. However, limited efficacy, safety, and adverse immune responses have restricted the generalized application of few of these vaccines. The strategy to revive the essential facilities during/after pandemic situations involves the innovation in healthcare industry imbibing the very essence of nanotechnology. The imbalance in population and the rate of vaccine production, vaccine stocks, and other medical facilities, especially in developing or economically challenged countries, has also suggested the requirement of alternate ways to utilize small quantity of functional material for a larger population without

compromising the efficacy [9–12]. Nanotechnology supported strategies such as nanostructured high-performance materials, development of ultrasensitive diagnostic platforms, improved bioimaging modalities, advanced point-of-care devices, antiviral therapies, and drug formulations in response to manage emerging viral diseases are abundant in the scientific literature [3,13]. We hypothesize that the consequences and impact of new SARS-CoV-2 variants could be managed more efficiently using advanced nano-assisted approaches, as illustrated in Figure 1a. Although prevalent for a few decades, nanotechnology has found new relevance in health care due to the present scenario when controlling SARS-CoV-2 and managing preinfection/postinfection consequences are the main priority of health agencies and experts, as illustrated in Figure 1b. [14–16].

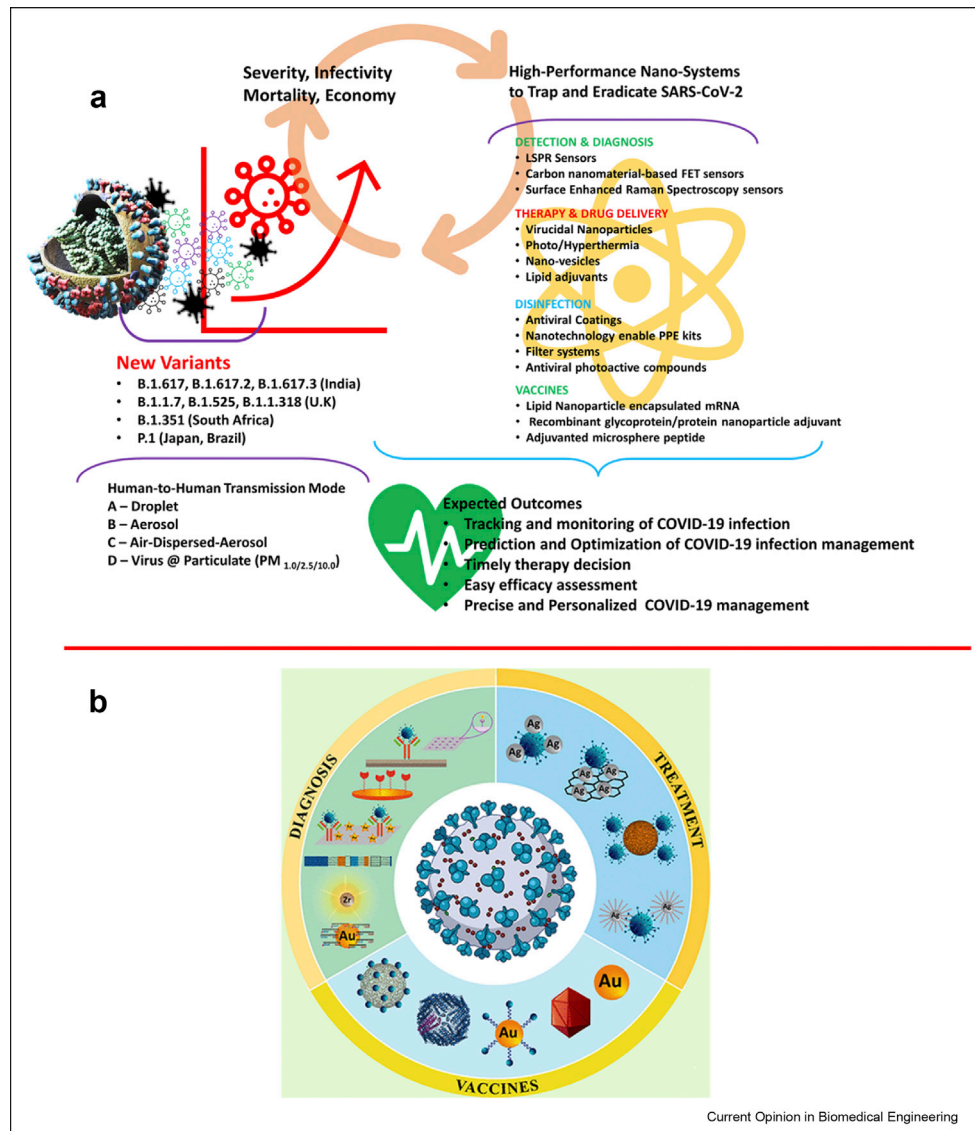
In this report, our focus is on exploring the potential routes of NS-assisted strategies such as antibacterial/viral coating and membranes, lipid-encapsulated drug formulations of improved efficacy, and immune capture assisted sensors to combat COVID-19 infection and a way forward to assess the limitations of nanotechnology [17–19].

### NS-supported COVID-19 pandemic/endemic mitigation

The potential of high-performance NS with desired functional properties in biomedicine is well documented. However, their clinical application is still under consideration, but their prospects are immense, specifically in antiviral research [20]. Some common advantages of nanomaterials against viral diseases include, **i)** tunable physicochemical properties with inherent antiviral/antimicrobial abilities, **ii)** improved drug loading efficacy owing to high specific surface areas, **iii)** increased circulation time in the body, modulating drug circulation time *in-vivo*, **iv)** assistance in delivery of water-insoluble drugs, and **v)** ultrasensitive detection capabilities based on superior optical/electronic behavior such as localized surface plasmon resonance (LSPR).

The current antiviral strategies, include neutralizing antibodies, vaccines, and encapsulated drug based nanoformulations, are driven using the NS-supported approaches (Figure 2a) which can be scaled up according to global demand. For example, the limited efficacy of dexamethasone to treat hyperactive immune cells is subjugated by intravenous delivery of nanoformulations in patients with SARS-CoV-2. Similarly, the neutralizing antibodies (LY3819252\REGN10933\REGN10987) and fragments (INOSARS) have been developed for fighting SARS-CoV-2 consisting of nanoscaled Ab fragments, known as nanobodies. Nano-enabled antiviral vaccines have the most sought out, strongest, and efficient response to the viral outbreak. The efficacy

Figure 1



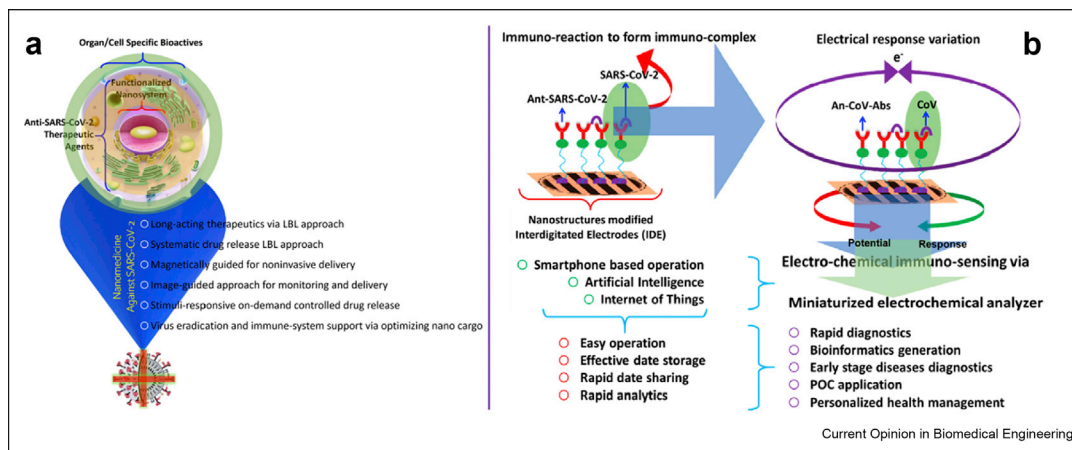
Spreading of the COVID-19 pandemic and possible nanotechnology-based intervention. **(a)** Prospective of NS-supported approaches and strategies to mitigate COVID-19 viral infections caused by new SARS-CoV-2 variants of concerns. **(b)** Illustration of state-of-the-art nanosystems investigated for diagnosis, treatment, and vaccine delivery to manage COVID-19 efficiency (Copyright ACS 2021). NS: nanosystem.

predominately depends on the stability of its delivery vehicle, which are in the nano regime [21,22]. For example, the lipid molecules in the mRNA-1273 from Moderna Inc. or the ChAdOx1 nCoV-19 from Oxford University require a nonreplicating adenovirus vector, all of these can be considered as NS. The objective is mostly the implementation of a nano-enabled medical platform to trap the virus, enhance detection capability, and improve the protection efficiency, thereby restricting the viral propagation.

Before vaccination, rapid detection of the viral strain within or outside the body has been a challenge. NS-based methodologies have been reported which can

overcome this limitation in the detection of viral load concentration. These NS become highly suitable for quick response strategies at airports, hospitals, and quarantine centers owing to shorter response time, lower detection limit, biofunctionality, tunability, and other enhanced surface phenomena [23]. One such example includes the development of a testing kit by eidgenössische polytechnische schule (ETH) Zurich in Switzerland, thereby tapping the multiplexing effect of the nanomaterials [24]. A combination of photothermal and LSPR characteristics of the plasmonic nanoparticles allowed true SARS-SARS-CoV-2 detection with promising potential for sensitive clinical diagnosis. The graphene-based field effect transistor (FET) system

Figure 2



The NS-assisted high-performance nanomedicine (a, Copyright Dovepress 2020) and biosensing approach, (LBL: Layer-by-layer) (b, Copyright ACS 2020) to combat COVID-19 infection intelligently in a personalized manner. NS, nanosystem; LBL, layer-by-layer.

could detect SARS-CoV-2 spike in proteins at a concentration as low as femtomolar (fM) levels in a clinical transport medium. Furthermore, the two-dimensional gold (Au) nano-islands, functionalized with complementary DNA receptors selective for SARS-CoV-2, allowed detection through nucleic acid hybridization, which was affirmed using thermoplasmonic heat mapping in the picomolar (pM) range [3]. The aspects of the nano-enabled biosensor to manage COVID-19 infection intelligently and in a personalized manner are illustrated in Figure 2b. These technologies should be further optimized for a broader future application where the detection of virus at point-of-care (POC) applications is crucial.

### NS-infused surface coatings, protective sieves, and disinfectants

The NS with highly sensitive multifunctional properties can check the pathogens' genesis, replication, and genetic makeup. Thus, they can be highly effective in containment protocols, drug formulation, rapid testing kits, and mitigation strategies. Nanotechnology addresses most of the present concerns for viral infections. It has also proven to be a successful alternative against existent viral pathogens such as human immunodeficiency virus (HIV), herpes, and other respiratory viruses [25–27]. The NS are distinguished by their high specific surface area, functional values, optical and electrical tunability, efficient charge transfer abilities, and inherent photocatalytic and antiviral/microbial properties. They have rightfully drawn researchers' interest around the world to tackle adversities.

NS-supported approaches such as nanosensors, nano-assisted assays, delivery agents, and antiviral agents/sterilizers are addressing various challenged associated with viral infection [4,13,23,28,29]. Drugs with poor aqueous

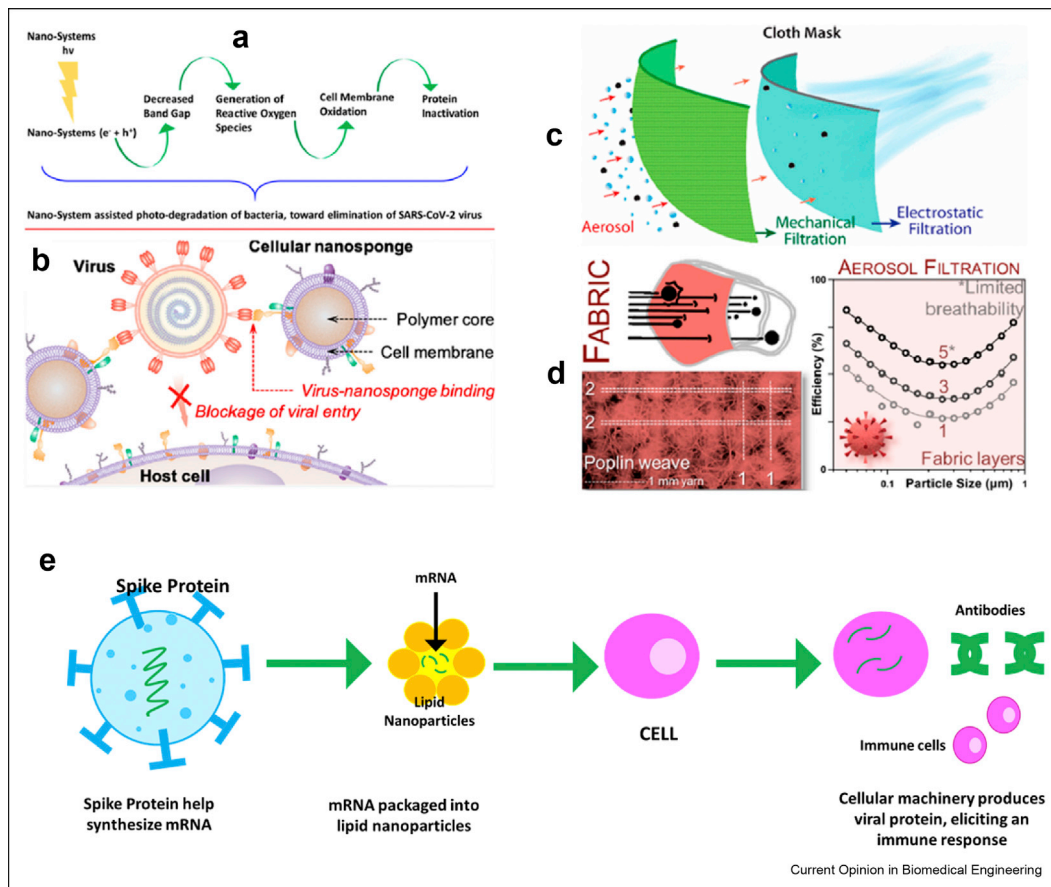
solubility but high inhibition abilities can be easily delivered intravenously with controlled concentration and lowered toxicity. Drug nanocarriers such as nano-emulsions, polymersomes, nanosomes, lipid-protein based vehicles, etc., have been established for high drug encapsulations, ability to influence the drug pharmacokinetics, and sustained drug release. Moreover, improved surface binding ability of nanoparticles nanoparticles with specific recognizing molecules bring specificity and are known to boost antiviral properties [18,30]. The encapsulation of drugs within the nanocarriers improved their shelf lives and therapeutic effect during *in-vivo* applications. These strategies would certainly work well with COVID-19 and cytokine storm or excessive proinflammatory cytokines [31,32]. Composite materials such as boric-acid-carbon quantum dot composite can target HCoV-229 E human coronavirus by readily interacting with the viral receptors and the viral S protein interference with cellular binding restricts replication [33]. Modified Au-NS, mimicking heparan sulfate proteoglycan (HSPGs), have inhibited viral attachment, entry, and spread [34]. The siRNA-assisted approach or nanoencapsulation-cum-delivery can contain SARS-CoV-2 spread by targeting pathogenicity caused by S protein and 3'UTR of the virus [30,35]. CRISPR-based systems have also been highlighted as an alternative for SARS-CoV-2 inhibition. Viral degradation and inhibition were brought about with Cas13d RNA endonucleases and targeted RNA synthesis using guide RNA [36]. The siRNA and CRISPR might not directly involve nanoparticles for viral restriction, but they have been identified as nanomachinery working toward antivirulence. Other than blocking the viral entry and replication, nanoparticles can also assist in improving the drug efficacy by improving bioavailability.

Viral infection in the atmosphere may affect others and can be responsible for the rapid spread of the disease.

Kampf [37] and van Doremalen [38] have reported the persistence of SARS-CoV-2 in the air and on various surfaces for days at temperatures above 30 °C [37,38]. Strong disinfectants or chemicals can kill the pathogens, but its over use can also make them resistant or cause mutations. At the same time, nanomaterials with high specific surface areas, localized drug release, slow disinfectant release profiles, stimuli responsiveness, and indigenous antimicrobial or self-cleaning properties could be one of the effective alternatives. They could address major concerns such as deparaffination, volatilization, and degradation associated with the conventional alcohol-based disinfectants [39,40]. The NS composed of ZnO, Mn, Fe, CuO, CeO<sub>2</sub>, graphene oxide, Ti, Ni, Ag, Au, etc., can be spray coated on cloth or maybe infused within the fiber to develop the anticontaminated platforms. These NS promote oxidation reactions on their surfaces with the help of the trapped oxygen moieties, are stimuli (light/electrochemical) responsive, and can undergo several charge–

discharge cycles. Functionalized nanostructures can trap the virus or other germ particles and disinfect the same by inherent variation in the magnetic field (hyperthermia), electric, or optical fields. Nano-enabled surface coatings based on titanium dioxides, silica composites, nanocellulose fibers, graphene, and metal ions with inherent antiviral abilities could be very effective even at low concentration. Such as silver nanoparticle/ nano-cluster based disinfectants, have been recently used to clean the buildings in Milan (NanoTech Surface, product.statnano.com) and was reported to be an effective self-sterilizing formulation limiting microbial buildup [2,41]. The TiO<sub>2</sub>-based photocatalytic coatings developed by FN Nano Inc., also have been tested to be an effective antiviral agent owing to the ability to damage viral membranes upon light activation (Figure 3a) [42]. The coating of such viable functional materials over metal surfaces, air conditioner vents, hospital floor mats, and equipment can enhance the protection mechanism.

Figure 3



Few mechanisms (external stimulation, restricted transmission, filtration, and delivery) involved in the eradication of SARS-CoV-2. (a) Nano (TiO<sub>2</sub>)-assisted approaches to eradicate micro-organisms on light stimulation [52]. (b) Antiviral biopolymer-coated surface to eradicate virus (Copyright ACS 2020) [45]. (c) Cloth-based mask (three-layered, a combination of cotton silk, chiffon, and flannel fabric) to trap SARS-CoV-2 containing aerosol (<300 nm and efficiency of 85%) for avoiding transmission (Copyright ACS 2020) [47]. (d) Fabric (synthetic/cotton blend, wool, cotton, synthetic, and synthetic blend)-dependent performance of a mask to trap aerosol virus useful to avoid infection transmission (Copyright ACS 2020) [46]. (e) NSs-assisted approach to deliver vaccine inside the viral infected cell.

Alternatively, fabricating nano-scaled three-dimensional (3D) structures with hydrophobic nanomaterials has also been known to prevent droplet accumulation through indulging a self-cleaning abilities. Nanomaterials can be used to develop antimicrobial textiles for use in personal protective equipment (PPE), masks, and sheets. Nano-engineered polymers, quaternary ammonium salts, peptides, and metal oxides restrict microbial growth by facilitating microbial membrane dissociation through oxidation. The high surface area of NS enables them to be easily functionalized with other nanomaterials to restrict viral replication on the surface. The ability to generate reactive oxygen species through photothermal and photocatalytic properties present them as a potential disinfectant with high viability [29]. Similarly, LIGC Applications Ltd. developed reusable masks made out of graphene foam (Guardian G-Volt), which can protect and be sterilized against SARS-CoV-2 [43,44]. Even biopolymers in nano-assemblies have been reported to generate potential antiviral properties, such as nanocellular sponges fabricated from human epithelial cells (Type-II) functionalized with inherent protein receptors can neutralize the SARS-CoV-2 (Figure 3b) [45]. The films or surface coating over the PPE kit can produce optimum inhibition sites against viruses and other inflammatory diseases.

Even nanomaterial-infused face masks, lab coats, gloves, and instrument surfaces are engineered to include new features such as antimicrobial, hydrophobic, self-cleaning, and healing properties (Figure 3c and d) [46–49]. Toxicity is a big concern since the development of these functional materials; however, the adhered nano-entities on the surface of such material would only enhance the beneficial aspects over others. It increases the reusability, improves the active surface regeneration via stimuli-responsive mechanisms, and even reduces the cost of the material in the long run. Tuned nanomaterials with high hydrophobic characteristics can act as an effective barrier against aerosol-mediated viral transfer, which happens to be the most probable infection route at the present moment. Compared with regular cotton/three-layered cloth face masks, combining a billion smaller fragments builds up significant surface tension allowing prevention of droplet absorption simultaneously with antiviral/bacterial response to the environment. Engineered nano-disinfectants based on nanostructured water with active agents can significantly reduce viral reduction, including influenza H1N1. The high surface areas allowed a significant reduction in dosage to nanograms indicating high viability [50]. NanoSeptic formulated self-cleaning, crystal nanoparticles have also presented environmentally sustainable alternatives with no residual discharge [51]. However, consequential effects on prolonged use, wear-off properties during washing, possible skin irritations, and allergies require testing for

nanotechnology-enabled materials for broader applications.

### Antiviral nanovaccines and delivery vehicles

High-performance NS contribute to vaccines by acting as adjuvants or carriers as well as effective barriers. NS-supported vaccines (i.e., nanomedicine) protect antigens against premature degradation, can cross cell membranes, allow sustained release, enhance stability, and encourage targeted immunogen delivery [41]. The BNT162b, one of the effective COVID-19 vaccines, BioNTech and Pfizer, contains lipid-based nano-formulation. As a result, the prefusion conformation of S protein and the receptor-binding domain are maintained, allowing the effective neutralization of immune cells (Figure 3e) [29]. Imperial College, London, and Acuitas Therapeutics, Canada, also jointly developed a self-amplifying RNA–lipid nanoparticle encapsulated with prefusion SARS-CoV-2 protein to produce a second-generation vaccine variant [30]. Encapsulation of genetic matter in lipid nanoparticles allows protection from enzymatic degradation while increasing cellular uptake. Moderna (Patent WO2017070626 and WO2018115527), the very first mRNA-based nanovaccine, encapsulates an mRNA mix into lipid nanoparticles, such that it could encode MERS-CoV S protein in mice to elicit an immune response. Novavax Inc. developed a recombinant SARS-CoV-2 vaccine with mutations at different sites in S protein to protect it from cleavage and to maintain the previrulence stage configuration. The NVX-CoV2373 is presently in Phase III of clinical trials. In addition to the commonly targeted S protein, a mix of proteins, such as nucleoproteins and nonstructural antigens, also make good candidates for vaccine production [41,53]. The EpiVax works on this concept of a ‘cocktail’ vaccine that aims to provide partial protection against the SARS-CoV-2, whereas the specific vaccines are underway. In another such effort, Matrix-M adjuvant improves immunological response by stimulating the antigen-presenting cells at the injection site. Different immunomodulatory therapies are prevalent to induce passive immunity, neutralizing antibodies, or convalescent plasma to mankind to achieve mass immunization against the SARS-CoV-2 [29,30,41]. However, the critical needs of more effective vaccine against all COVID-19 variants, understating immune parameters governing the host and precluding any adverse reactions, is still required. Careful observation and more clinical studies are needed to develop widely acceptable antiviral nanovaccine.

### Challenges, viewpoint, and future aspects

We anticipate more approvals by FDA to antiviral/bacterial NS for managing COVID-19 or other infections via trapping and neutralizing, thus effectively eradicating existing VOCs. The existing NS are smart,

Table 1

## Few of the many NSs with multifunctional abilities.

S.No.	Platform	Inhibition activity/functionality	Ref.
1.	Plasmonic gold nanoparticles	Naked-Eye Detection of SARS-CoV-2 Limit of detection as 0.18 ng/ $\mu$ L	[28]
2.	Functionalized gold nanoparticles	Femto molar detection with ultranarrow line shapes in the terahertz (THz) frequencies	[13]
3.	Silver nanocluster/silica composite coatings	Virucidal effect on SARS-CoV-2, flexible ceramic with practical applications	[16]
4.	Lipid nanoparticles	Immunization response against pseudotyped and wild-type SARS-CoV-2 virus	[30]
5.	Carbon quantum dots	Inactivation of CoV strain through inhibition of protein S–receptor interaction	[33]
6.	Electrospun nanofibers, ZnO Nanorods and Ag Nanoparticles	Antibacterial, antiviral, self-cleaning, and sensing mats for clothing applications	[39]
7.	Nanostructure substrate (cellular nanosponges)	Trapping and neutralization of SARS-CoV-2	[45]

affordable, acceptable, and have shown the potential (i) as a protective agent in forms of surface coverings, membranes, masks, and gloves, (ii) for enhancing drug efficacy by increasing the retention, bio-circulation, and bio-availability of drug, targeted delivery (i.e., nanomedicine toward personalized treatment), and (iii) as an efficient biosensor for early-stage diagnostics suitable for POC application. Overall, these approaches could be considered as an intelligent COVID-19 management in a personalized manner. However, such NS are limited, and scaling up must be a future direction owing to the significance of demonstrated applications. Advanced techniques including microfluidics, cold plasma, and supercritical formulation methodologies could also be explored for the rapid fabrication of such nanoformulations. Furthermore, engineered lipid-based nanoformulation would be largely exploited in the recent future in biomedicines, antiviral/antibacterial, and coating technologies with possible biomodifications using proteins or other biodegradable plant-based macromolecules.

In this unprecedented scenario of the COVID-19 pandemic, avoiding SARS-CoV-2 transmission is a top priority, as new VOCs and VOIs have emerged with rapid transmission and severity. Additionally, the airborne and particulate-assisted transmission of SARS-CoV-2 is detrimental. This raised concerns and projected the need of developing new approaches such as NS-assisted antiviral/antibacterial devices for protection against infection. We believe that using these NS in filter technology, air conditioners, exhaust, masks, hydrophobic coverings, sheets, clothes, and in other forms of disinfectant would be revolutionary. This approach may not seem fully functional owing to limited resources and lack of execution, but the potential of NS in improving these strategies cannot be ruled out. Table 1 highlights few of the many NS which have been proved to be

highly efficient against pandemic situations. However, there are several challenges to overcome which include the high cost of specific biomarkers, storage infrastructures, and skilled personals to improve nanomedicines implication at various stages for example from laboratory to home.

The spread of nanobiotechnology tools and techniques improving our lives is undoubtedly fascinating. However, efficient drug packaging in nanovesicles/nanopores or simply on their surfaces and prolonged retention in the tissues are still to be perfected for large-scale production/population. In this regard, protein-based nanoemulsions which can simultaneously neutralize SARS-CoV-2 and deliver essential drug molecules could be one of the alternatives. Due to similarity with cancer, viral infection showing severe heterogeneity due to a certain degree of mutation over alternating physiological parameters thereby emphasizing the need for personalized nanomedicine. The possibilities of sensing platform failure due to fundamental alteration on recognition sites of SARS-CoV-2 structure is an additional roadblock. To overcome selective sensing related concerns, developing alternative approaches such as smart artificial intelligence (AI) driven nanosensors would be suitable for early-stage selective diagnostic of infection associated with new SARS-CoV-2 variants. Besides, re-evaluating the state-of-art, treatments, and neutralizing capabilities is required to overcome the severity of SARS-CoV-2 VOCs to combat COVID-19 infections globally.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.



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- \* of special interest
- \*\* of outstanding interest

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