Nanotheranostics and its role in diagnosis, treatment and prevention of COVID-19

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ABSTRACT: Microbe-related, especially viral-related pandemics have currently paralyzed the world and such pathogenesis is expected to rise in the upcoming years. Although tremendous efforts are being made to develop antiviral drugs, very limited progress has been made in this direction. The nanotheranostic approach can be a highly potential rescue to combat this pandemic. Nanoparticles (NPs) due to their high specificity and biofunctionalization ability could be utilized efficiently for prophylaxis, diagnosis and treatment against microbial infections. In this context, titanium oxide, silver, gold NPs, etc. have already been utilized against deadly viruses like influenza, Ebola, HIV, and HBV. The discovery of sophisticated nanovaccines is under investigation and of prime importance to induce reproducible and strong immune responses against difficult pathogens. This review focuses on highlighting the role of various nano-domain materials such as metallic NPs, magnetic NPs, and quantum dots in the biomedical applications to combat the deadly microbial infections. Further, it also discusses the nanovaccines those are already available for various microbial diseases or are in clinical trials. Finally, it gives a perspective on the various nanotechnologies presently employed for efficient diagnosis and therapy against disease causing microbial infections, and how advancement in this field can benefit the health sector remarkably.

KEYWORDS: nanotheranostics; nanovaccine; antimicrobial; antiviral; SARS-CoV-2

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1 Introduction

Nanotheranostics is an integrative approach and strategy employing various nanomaterials such as nanoparticles (NPs; 10–100 nm) and quantum dots (QDs; 1–10 nm) for diagnosis as well as treatment of different diseases that currently have a gloomy prognosis [1]. Nanotechnology has made rapid and consistent advancements in prime medical practices. The use of nanotheranostics gained attention in last decade as an emerging diagnostic tool, especially for cancer [2–3]. The main objective behind these new angles and an advanced class of nanomedicine approach was to improve all existing treatment modalities for fatal diseases. Treatment of fatal diseases such as cancer, neurodegenerative disorders, cardiovascular diseases as well as genetic disorders and hemoglobinopathies are limited to specific patients and are also selective of certain stages of disease development. Thus, nanotheranostics fosters a superior regime that can diagnose as well as treat disease at the cellular and molecular level without being subject-specific and are driven by the axioms of nanomaterials [1,4–5]. Nanomaterials used in this include a new generation of various types of nanocarriers such as polymer conjugates, metallic and nonmetallic NPs, inorganic NPs, dendrimers, micelles, and liposomes [2,6–11]. The nanotheranostic approach is superior because the therapeutic agents that are being delivered monitored and the therapy response is also concomitantly guided in real-time. This decreases the possibility of over and under dose. Multifunctional nanotheranostics comprises non-invasive imaging techniques for tumors and lesions mediated via radio labeling of nanomaterials such as gold, silver and silica-based NPs, carbon nanotubes (CNTs) with control for altering nanosize delivery, sustained release of drugs, transportation of drugs and also monitoring stimuli-responsive system [1–3,12]. Nanotheranostics media should allow the long-time circulation of nanomaterials in the blood, having efficient release behavior, specific tissue-targeting, penetration, good sensing ability, and efficient imaging with high target to background ratio as well as a low undesired side effect.

It was reported that nanosized particles easily navigate from the blood into tumor cells despite having poor lymphatic drainage compared to other functionalized macro-counterparts, which provoked the need for investigation in the development of novel strategies in nanoscale for improving imaging facility. Current research focus has been diverted from radiological imaging such as radiographs, ultrasound, computed tomography, and magnetic resonance imaging (MRI) to nuclear medicine imaging which is in vivo measurement of biological processes. Currently, nuclear medicine imaging is done using standard nanotechnology procedure and is reportedly helpful in early diagnosis, gathering of pathological information and is conveniently modified by linking, conjugation or coating with various ligands or motifs. An instance showed that traditional imaging detects cancer cells when it has attained a size of about 1 cm$^3$ containing around 1 billion cells. Early detection before the establishment of phenotypic chances is going to make a significant change in the effectiveness of therapies and treatments [12]. Optical, molecular, radiologic and nuclear medicine imaging methods are the various imaging modalities that have already featured four groups of NPs such as magnetic, fluorescent, radiolabelled and magnetofluorescent ones [13].

Magnetic NPs (MNPs) are synthesized either directly or via integration into a polymeric matrix and are said to have magnetic features, presently employed to locate cancer cell and neurological disorders. Because of their contrasting characteristics, they are a handful tool in diagnosing cancer, molecular imaging, hyper fusion region visualization, radiotherapy, and detecting apoptosis, angiogenesis, and gene expression. Similarly, fluorescent NPs have prime contributions in theranostics fields for their combination properties of magnetism as well as fluorescence. It has thus been crucial for various imaging techniques such as MRI and fluorescence microscopy. Thus, it can be aptly said that these MNPs have been revolutionizing fields of molecular biology through development of molecular sensors, innovative carrier agents, imaging techniques, therapeutic approach to gene therapy, biomarker identification, and targeting strategies [14].

2 Synthesis of nanomaterials

Various physical/chemical methods have already been optimized by different research groups for formulation of various NPs. Among them, mechanical milling, laser ablation, ultra-sonication, electron-beam evaporation, chemical vaporization, electrochemical methods, chemical reduction, electrochemistry, photochemical reduction, etc. are some physical/chemical methods for NPs formulations.
However, these conventional methods for NPs synthesis possess various limitations such as not simple or cost-effective. Additionally, it is also reported that these methods use various toxic chemicals during formulation of NPs and consume huge amount of energy, hence they are not eco-friendly [15]. To expand the application domain of nanotechnology in bio-medical science, development of eco-friendly, non-toxic and cost-effective approach for NPs formulation is essential. In this context, green synthesis approach which is based on synthesis of NPs using biological agents has drawn the attention of various research groups. Biological methods of NP synthesis employ various enzymes, bacteria, yeast, or other microorganisms, and plants as reducing agents and capping agents [15–17].

Additionally, green synthesis is a low-cost, environmentally friendly, and industrially scalable method for NPs formulation. Biologically synthesized NPs have been found to have improved stability and biocompatibility. Because particle shape and size play key roles in clinical applications, biosynthesis of NPs is a favorable choice owing to its greater control over particle size and morphology in comparison to chemical/physical methods for synthesis of NPs. Bioreduction or biosorption mechanisms are utilized for the green synthesis of NPs involving the reduction of metal ions by bacterial enzymes and the easy extraction of NPs from the reaction. These strategies allow synthesis of NPs by living organisms such as bacteria, plants, and fungi. The primary sources of precursors used for NPs synthesis also include biological extracts and enzymes. Substantial amounts of the reducing metabolites like flavonoids and phenolic acid are generated by plant extracts, and simultaneously also offer a high selectivity and efficient capping agents for NPs stabilization. The metal NPs produced with the help of bacteria offer rapid, easy and highly controlled synthesis owing to the high replication rate of bacteria and presence of specific pathways within them for metal metabolism. Like plants, the fungal enzymes too possess reducing ability and are utilized for metal NPs synthesis from metal salts. In biosorption, the metal ions and particles interact with cell membranes, so that NPs have to be further extracted. The physical parameters of NPs are adjusted to modify the size and shape of the particles. The few challenges associated with biogenic synthesis can be controlled by optimization of extract-metal salt solution concentrations; pH and temperature of reaction mixture.

The most frequently used NPs for therapeutics are metal NPs, lipid NPs, QDs, etc. [1–3,18–21] (see Fig. 1 [22]). The characteristic physico-chemical properties of NPs react with the infectious agents very effectively, thereby affecting the efficient diagnosis and cure. These interactions at the bio-nano interface are driven by colloidal forces and dictate their uptake, translocation, release, and effect as well as determine their fate. If the size of NPs is less than 20 nm, they get very well distributed within the body and also flushed out of our body quickly without getting accumulated. But if their sizes are more than 200 nm, then for their removal from the body macrophages are recruited [13,23–24].

### 2.1 Metallic NPs

Metallic NPs are most widely used in nanotheranostics,
just to name a few are zinc, silver, gold and titanium NPs [25‒26]. In infinitesimally small dimensions their uptake is highly ameliorated. Small size and high surface area induce more toxicity due to significant interaction with the surface of microorganisms and thus killing them. Also, some NPs agglomerate owing to their high intrinsic reactivity resulting in attenuated size-dependent activity when reacted with bacterial cells. Thus, surface fabrication of NPs with theranostics properties enhances their biocompatibility. Metallic NPs are already being employed in CT-scan and real-time visualized drug delivery. They can also be used in the case of photothermal and photodynamic therapy as well as in radiotherapy. Near-infrared (NIR) radiations are utilized by photothermal therapy to heat-kills the surrounding cells. This property has proven to be effective in treating benign as well as malignant cancerous cells. Nowadays, photothermal therapy is mostly preferred over photodynamic therapy owing to its oxygen-independent mechanism of action and deep penetrative power [9].

Silver NPs are amazing tools for the diagnosis process due to their pathogen-specific biochemical properties enhancing the diagnosis process, imaging, and drug delivery. Although AgNPs are very good source of nanotheranostics, their toxic effects at the cellular and genetic level pose the biggest hindrance in their usage. It has been reported that conjugating it with graphene QDs reduces their toxicity in the case of pancreatic tumor cells. The combinatorial effect of AgNP functionalized with 5-fluorouracil can initiate apoptotic pathways in the uracil phosphoribosyltransferase (UPRT) process which is utilized for gene therapy. AgNPs also display amazing optical properties for localizing the infection region. It is reported that, nanogel conjugated with silver NPs and pH-sensitive poly (N-isopropyl acrylamide-acrylic acid) gel act as a nanovehicle for dipyridamole drug (nonpolar). AgNPs are therefore being sought after as a highly potential candidate for nano-based treatment due to their varied advantages [1,11].

2.2 Magnetic NPs

These are frontline NPs for therapeutics and imaging purposes owing to their biocompatibility and low cost of designing. They are mostly used for attacking damaged genes and tissues, and biosensors in the medical research field [27]. Iron oxide, manganese, and nickel NPs are pioneers in these aspects. The combinatorial therapeutic approaches allow MNPs to be employed for diagnosis, gene delivery, phototherapy, bioimaging, and chemotherapy [28]. \( \text{Fe}_3\text{O}_4 \) (magnetite) and gadolinium (chelated organic gadolinium complexes) are mostly used as MNPs due to their capability to decompose into oxygen and iron in the body [28]. The iron oxide NPs (IONPs) have been shown to exhibit antibacterial effect against various bacterial species such as \textit{Bacillus subtilis}, \textit{Bacillus cereus}, \textit{Escherichia coli}, \textit{Aeromonas hydrophila}, and \textit{Staphylococcus aureus} [27,29].

2.3 Quantum dots

High photoluminescence and quantum yield and minimal photobleaching make QDs a very elegant candidate for nanotheranostics. The optical properties of these QDs vary with their varying size, which is not seen in their bulk counterpart. As particle size reduces, the QD absorption and emission shift to higher energy. The quantum confinement effect thus generated leads to enhanced band gap leading to improved optical properties for bioimaging purposes enhancing the detection of infections by multifold. Synergizing these NPs with repurposed drugs can be a potential way to inhibit bacterial efflux pumps and biofilms synthesis; impair their quorum sensing, and can combat multidrug-resistant development in bacteria [1,30‒31].

3 Potential nanomaterials for treatment of microbial diseases

NPs have antibacterial effects and exhibit significant antimicrobial activity against many infectious bacterial species like \textit{Enterococcus}, \textit{Klebsiella}, and \textit{Staphylococcus}. Different metal and metal oxide NPs such as silver, zinc oxide, and titanium oxide are extremely noxious to bacteria [27,32]. Silver NPs (AgNPs) having strong antimicrobial activity is an area of particular interest as they are being employed effectively exhibiting multiple pathways to exhibit antibacterial propensity. AgNPs have exhibited significant antimicrobial activity against both Gram-positive and Gram-negative bacteria and also are effective against various pathogenic bacteria such as \textit{Pseudomonas aeruginosa}, \textit{Escherichia coli}, and \textit{Streptococcus pyogenes} [33]. Additionally, they can be easily functionalized with biomolecules and antibiotics [17,34‒35]. Ag–Au nanoconjugates are highly efficient as
they combine the antimicrobial property of AgNPs and the solidness of AuNPs. Tellurium NPs are proven to be more efficient than AgNPs due to their high antibacterial activity and low toxicity in comparison to AgNPs. The reactive oxygen species generated due to interaction of metal oxide NPs with different biomolecules inside the biological milieu damage the cell segment, genetic component, crucial enzymes, and proteins of their target pathogen species [27,32]. There are number of mechanisms behind antimicrobial activity of metal-based NPs against different pathogens, hence are effective in neutralizing even the most highly mutant microbes, thereby preventing them from becoming multi-drug resistant. Oxidative by-products generated during fullerene preparation have very high antimicrobial activity against microbes. Also, the hydrophilic fullerene can be utilized for photodynamic treatment purposes because of their enhanced reactive oxygen species production. The drug rifampicin conjugated with hydrophobic modification of cleaved amplified polymorphic sequence (CAPS) has curative potential against all types of tuberculosis disease. These combinatorial methods of developing nanocarriers are very handy also for loading antibiotics and delivering at specific sites. Antimicrobial peptides (AMPs) also offer inhibition of proliferation of different antibiotic resistant pathogens [36–37]. The AMPs, playing a key role in the defense system of host cells, have some common features such as (i) typically have 12–100 amino acids (< 10 kDa), hence known as short peptide, (ii) cationic in nature, and (iii) have amphipathic stereogeometry [36]. In this context, Liu et al. have formulated a class of core–shell NPs which show strong antimicrobial activity against different bacteria, yeast, and fungi by self-assembling an amphiphilic peptide [37]. Additionally, Arakha et al. have reported the enhanced antimicrobial activity of AMPs like nisin upon conjugation with silver NPs [36].

The other properties that make NPs the most effective and stand-alone candidate against any pathogen infection are their sustained release, high cell-entry rate, and negligible efflux of toxic metal ions. Metallic NPs are highly effective against different viruses because metals inhibit a wide range of viruses. Also, the risk of multi-drug resistance is very low with metal NPs as compared to other antiviral drugs. AgNPs have both antibacterial and antiviral properties against HIV, herpes simplex virus, hepatitis B virus, H1N1, etc. Nanocolloid AgNPs also control viral proliferation in the respiratory tract and are administered through inhalation, thereby preventing the spread of the disease. Various reports have shown the antiviral activity of titanium dioxide (TiO2) NPs functionalized by embedding DNA in them against MDCK cell lines infected with influenza A subtypes. Graphene NPs have also been reported as a potential antimicrobial candidate [14].

4 Antimicrobial nanovaccine

Nanovaccines have been evoked as killing antibiotics and are useful in beating microbe enhancement, infection transformations and bio-manufacturing challenges. In this context, cationic liposomes have likewise been utilized as immunization adjuvants upon being conjugated with the plasmid DNA with additional advantage of being viable immunization adjuvants. For example, CAF01 is in the clinical trial phase, being proposed to improve insusceptible reactions of progression of various antibody applicants. In an examination for tuberculosis immunizations, CAF01 was conjugated with mycobacterial glycolipid. It cured the BALB/c mice to 100% after a deadly respiratory infection with B. pseudomallei [38]. Mice inoculated with nanovehicle-loaded drugs showed predominant protection against toxins and the survival rate was nearly 100%. Additionally, chitosan has already been employed against microorganisms like Chlamydia trachomatis and Streptococcus pneumoniae. Strangely, chitosan possessed intrinsic adjuvant properties due to release of cytokine. As far as antiviral therapies are concerned, nanotechnology should be considered as an important method, both for treatment and vaccine development, which will also help in winning the current battle against global pandemic-COVID-19, and also help in keeping ourselves prepared for the next pandemic which may come in future. For COVID-19 treatment we may employ virus-like NPs (VLNP) which are sphereshaped (20–200 nm) and with size in the range of SARS-CoV-2 (125 nm). These VLNPs include viral capsids proteins but do not contain any viral genetic elements. Attaching VLNPs with the appropriate antigens, they have the potential to trigger immune responses and also avoid any nuclear enzymatic degradation. Being small in size they can also penetrate and target cellular nuclei sites [14].

The most effective neutralizing antibody responses can also be escaped by HIV and influenza viruses. Therefore, scientists are trying to develop vaccines that could elicit
broadly neutralizing antibodies (bnAbs) for efficient recognition and neutralization of the majority of pathogens. In this context, a NP vaccine, eOD-GT8 60mer has been developed that elicits VRC01-class bnAbs, which deactivates 98% of HIV strains, and is presently in the first stage of the human clinical trial. However, tackling HIV is quite challenging owing to its glycosylation, antigenic vividness and immune evasion of its envelope, along with poor bnAbs generation. The problem is further aggravated as HIV envelope is constituted by ~50% glycans by mass rendering the binding with bnAb–glycan very weak. Thus, for effective viral neutralization nanovaccines must be designed that will allow strong binding of bnAbs to the glycans [39]. Due to the effective functionalization of NPs, they can be potentially very efficient in capturing the antigens, which cannot be achieved by standalone vaccines. This is evident in a study where the HA–ferritin nanovaccine exhibited 34 times more neutralization titres in immunized animals than that of flu vaccine available commercially, a trivalent inactivated influenza vaccine (TIV) [33].

5 Development of functionalized nanovaccines to tackle viral mutations and enhance immunogenicity

With traditional vaccine development, there is the potential risk of antibody-dependent enhancement (ADE) of the disease. SARS-CoV-2 vaccines are in clinical trials, but its ADE effect is yet not clear. NPs can help overcoming ADE in two ways, first by shielding the effect of ADE-promoting epitopes, and second, by enhancing safety through controlled and targeted delivery. NPs can also enhance the immunogenicity of the poorly immunogenic antigens by simultaneously packaging adjuvants in nanovaccines. Due to the highly mutant nature of the viruses, the vaccines that we develop are rendered unprotected within around 2 years. So, the need of the hour is to discover vaccines with a wide array of cross-protection against different viruses. The HA-SS NP vaccine has been proposed which is presently in phase I clinical trial which could theoretically protect against wide-ranging influenza subtypes.

A novel nanovaccine have been designed against influenza targeting two different conserved domains of the virus — the matrix protein 2 ectodomain (M2e) and the neuraminidase (NA) membrane glycoprotein possessing homo-tetramer polypeptides. Because of the minute size and low availability in virions in contrast to HA and NA, the M2e immunogen has poor immunogenicity. To enhance its immunogenicity, the nanovaccines are biofunctionalized with a layer of protein. High immunogenicity and immunity, strong cross-reactivity to a diverse set of influenza strain particularly against homosubtypic and heterosubtypic influenza A virus infection, and complete protection by nanovaccine-induced M2e antibodies were also reported after the biofunctionalization of vaccines. As stated above, these nanovaccines are exclusively antigens, and completely devoid of any vector components. They allow controlling the duration of antigen-release in physiological redox conditions by application of disulfide bond crosslinkers linking the primary amines in a protein, thus eliciting B-cell responses. When the soluble HA antigen binds to the desolvated double-layered NPs, it greatly reduces the risk of an unstable solution elicited by virus-like particles. It also offers the accurate immune reaction with the ability of their self-assembly. Also nonviral nanovaccines currently have overcome the two major challenges confronted by conventional vaccines, such as the poor immunogenicity and reversion risk associated with live/attenuated viral vectors. NPs can be functionalized to imitate the ability to transfer the genome of the viral vaccines possessing high pathogenicity and simultaneously transport molecular adjuvants. Many functionalized nanomaterials have an intrinsic adjuvant property that enhances the immune response in a host. This property is highly beneficial for vaccine development for immune-compromised patients [14].

The future of nanovaccines relies on the realm of reassessing the way we introduce the B-cell immunity which could ameliorate its T-cell counterpart. The approaches that we discussed for influenza could simultaneously be used against other pathogen diseases, such as malaria, Lyme disease, and possibly COVID-19. Many potential nanovaccines are already in pre-clinical trials. Particle vaccine, a proprietary virus-like, has been designed by a late-stage biotechnology company, Novavax, Inc., against MERS-CoV that included at least one trimer of S protein and their proprietary Matrix-M adjuvant. For a potential SARS-CoV-2 vaccine candidate, NVX-CoV2373, the similar technology is being employed by Novavax, Inc. as it used for MERS-CoV vaccine development. Messenger RNA-based nanovaccine platforms, such as a lipid NP encapsulated RNA vaccine,
are also encouraged for several microbial diseases. For example, the mRNA-1273 developed by Moderna, Inc. is in phase III trial for COVID-19 [31].

6 Diagnosis and therapeutics via NPs

The genetic element of the virus can be discarded, and the protein cage can be used to functionalize nanomaterials to be used for nanotheranostics. In the interior of the cage drug/therapeutic molecules could be added. The interface subunit can enclose imaging application compounds, and in the exterior layer RGD peptides can be added for enhancing cell attachment. So, VLNP can act as multifunctional theranostics NPs. Some important diagnosis and therapeutic strategies involving nanotechnology are discussed below:

6.1 DNA nanotechnology

DNA box with an oligonucleotide lock system have been reported for loading therapeutic drug, which can be released at specific sites. Efforts are being made to functionalize it in such a way that it can incorporate combinations of drugs, and also imaging agents. This approach has the potential to serve as a multiple targetting theranostic NP. Via their self-assembly process, X-shaped structures have been reported to be designed using four short oligonucleotides of DNA with specific properties at their edges for specific drugs, for example thrombin. For the drug delivery process at a specific location, cDNA specific for the thrombin binding site was used. cDNA forms complementary base pairing releasing the thrombin from that location. So, thrombin is released depending upon the concentration of cDNA applied. This is an amazing application of DNA nanotechnology for controlled drug delivery [40]. DNA origami nanopores which can be opened and closed by varying various parameters like temperature, light, pH, salt, and aptamers have been reported to be utilized as highly sensitive biosensors for various biological compounds like proteins, RNA, DNA, sugars, and drugs. When inserted in lipid bilayer, they act similar to potassium channels or sodium channels. This structural modification is being explored to be utilized for controlled drug delivery (Fig. 2(a)) [41].

6.2 Protein nanotechnology

Presently, nanofiber scaffolds are being utilized for three-dimensional (3D) cell culture. Protein-based nanotubes are also proposed to be used for drug delivery applications. Nanofiber scaffolds have stable beta-strands and beta-sheets with high water content in the matrix. The self-assembly property of peptide Lego is used to synthesize nanofiber scaffolds with ordered nanopores of 5–20 nm. It is quite beneficial for controlled differentiation of cells, regenerative medicines, and regulated drug release [42]. Various protein NPs that are in use for drug-delivery purposes are fibroins, albumin, gelatin, gliadine, legumin, 30Kc 19, lipoprotein, and ferritin proteins. These are prepared via emulsion, electrospray, and desolvation methods. These protein NPs are highly advantageous for drug delivery purposes due to their excellent biocompatibility and biodegradability properties. They also possess increased stability, and activity due to their ability to stay protected from enzymatic degradation, phagocytosis, immunogenicity, and renal clearance, thereby increasing the half-life of the drug [43]. Moreover, their encapsulation process does not require use of toxic chemicals or solvents, thereby nullifying the toxicity issues associated with protein NPs. The small size of proteins enables the protein NPs to be transmitted through the cells via endocytosis. The controlled and sustained release of protein NPs are enabled by encapsulating it into biodegradable polymers in microsphere structure [43]. Gliadin NPs have been reported to be employed for controlled-release system suitable for hydrophobic and amphiphilic drugs owing to their low solubility in aqueous solutions, excellent biocompatibility, biodegradability, non-toxicity, and stability [43].

6.3 Peptide- and carbohydrate-based sensors

Protein nanopores composed of α-hemolysin has 1 nm diameter pore through which ss-DNA can pass. The decay in current when ss-DNA passes is detected by the detector. This is being sought after for the DNA sequencing process [33]. GlycoNPs act as a very good biosensor. For example, lactose-gold NPs have the ability to check the concentration of pathogenic bacteria in the patient’s sample. In the presence of bacteria, these NPs agglomerate and give grey color. However, in absence of bacteria, they are free and discrete and hence give ruby-red color. For example, lactose-based glycoNPs are used as an anti-adhesive cancer therapy. Normally, the malignant tumor cells adhere to the endothelial cell and transmigrate through them causing abnormal growth at the
new location. The glycoNPs block the attachment of tumor cells and endothelial cells and prevent tumor formation. Similar mechanisms need to be explored for other pathogenesis of antiviral or antibacterial origin [33].

6.4 Carbon nanotubes and quantum dots

CNTs are used as a functional atomic force microscope tips by attaching certain biomolecules to its tip and measuring the force of interaction between the tip and sample. It is reported to be used for disease detection by attaching to probe DNA. When target DNA binds it, the electrical conductivity of CNT changes, which is measured by the detector. Hence it acts as a very good biosensor having properties such as high specificity, fast response, high sensitivity, and capture of a single molecule. It can also be used for targeted drug delivery. It is loaded with contrast agents for imaging, therapeutic molecules for treatment, antibodies for targeting CNT only to specific diseased cells and functional group for enhanced biocompatibility and circulation time for CNT. In this way it serves as a highly potent theranostics NPs (Fig. 2(b)) [44–45]. QDs are employed for disease detection due to their high fluorescent properties. Biomarkers attached to QDs specifically locate them to diseased sites which are visualized in the form of fluorescence by applying ultraviolet (UV)-light to the sample. In healthy cells no fluorescence is observed [44,46]. QDs are already in use for cancer diagnosis. But the problem with QDs is their toxic effects, which are well taken care of by replacing QDs with carbon dots. Carbon dots are discovered to have the same efficiency as that of QDs, and are also biocompatible and non-toxic to healthy cells [47].

7 NP-based therapeutics for COVID-19 and related future pandemics

The pathway of virus entry is initiated by the binding of the viral S protein into the ACE2 receptor. Following binding event the entry into the cell occurs via transmembrane serine protease 2 (TMPRSS2) through protease activity. Internalization is followed by the entry of virus into endosomes where the viral particles release their genetic material for protein synthesis resulting in synthesis of new infectious particles and host infection (Fig. 3) [48]. Nanotechnology offers a promising remedy for fighting the ongoing COVID-19 outbreak and also for the future pandemics. Both conventional and advanced biomimetic approaches including engineered biochemically functionalized NPs come under the realm of nanotechnology that could be employed against COVID-19. The nano-intervention is of the utmost requirement for advancing COVID-19 prophylaxis, diagnosis and treatment. Nanotechnology aims to develop safe, efficient, and targeted drug delivery and fabricating nanovaccines that are risk-free and invoke highly efficient immunization, thereby culminating the viral and host cell interaction and permanently destroying the viral particles.

7.1 Delivery of repurposed drugs via nanocarriers

For SARS-CoV-2, currently, the main focus is to repurpose
the existing molecules for developing specified/broad-spectrum antivirals [49]. For this purpose, a nanocarrier delivery system might be quite useful. The minimal aqueous solubility, degeneration, rapid-clearance and low bioavailability greatly hampers the delivery of drug cargoes containing peptide/protein, DNA/RNA, etc. to the target site. Varied properties of nanomaterials like large surface area-to-volume ratio, biofunctionalization, characteristic physicochemical properties, and multiple routes of administration will be extremely beneficial to tide over the challenges related to prosaic therapeutics. To effect efficient therapeutics with beneficial properties like control release, improved pharmacokinetics, and minimize drug resistance, biocompatible organic/inorganic NPs can prove to be a potentially promising candidate. Additionally, small in size and site-specific nanovehicles have the potential to cross the biological barriers thereby accessing the pathogen-infected protected sites of the body with higher specificity and simultaneously preventing the unwanted release of drugs at non-targeted regions, hence resulting in a reduction in the amount of dose needed and systemic toxicity. Nanotechnology further makes it possible to design personalized therapy [6].

Various research groups have shown the potential nano-based therapeutics, or modulation of immune systems against various viral infections like SARS-CoV-2, herpes simplex virus (HSV-1 and HSV-2) (treated by embedding acyclovir in chitosan NPs), Venezuelan equine encephalitis virus (VEEV) (treated by utilizing lipid-coated mesoporous silica nanocarrier to carry antiviral drug ML336), and bleomycin-induced pulmonary fibrosis (treated by introducing liposomes carrying cholesterol modified hydroxychloroquine). This successful bio-prevention of viruses achieved through nanoplatforms could guarantee promising nano-candidates to combat various viral infections including SARS-CoV-2. Nanomedicines have the potential to overcome antiviral drug site-specific delivery. In the case of COVID-19 disease, if scientists develop an effective drug against the SARS-CoV-2 virus, then optimized targeted drug delivery systems based on nanomedicines can help overcome the site-specific delivery challenge. Nanomedicines are also useful for the controlled release and maintenance of antiviral drugs in specific sites, which plays an important role in the treatment of viral infections, because a high dose of off-targeted antiviral drugs can cause severe side effects that can be as severe as a viral infection [50].

7.2 Combinatorial therapy: loading drugs-cocktail in a single nanosystem

Combinatorial therapy promotes crosstalk inhibition mechanisms producing synergistic effects which are currently being explored to be effectively utilized against SARS-CoV-2. Its advantages include minimum drug loading and insignificant side effects [51]. It also combats drug resistance to a very high degree. In this approach multiple drugs possessing different physicochemical properties are loaded within the same nanocarriers. Both hydrophobic and hydrophilic drugs can be carried within the same nanovehicle, and also ensure their sequential release. Scientists have recently designed combinatorial NPs enclosing endogenous lipid squalene, an adenosine-immunomodulator, and α-tocopherol for developing nanotherapy against acute viral inflammation [14]. Additionally, a lipid-based nanocarrier enclosing lopinavir, ritonavir, and tenofovir have been fabricated to treat lymphatic drug insufficiency [14]. This system was shown to contain 50-fold higher concentrations of the drugs in the lymph nodes in comparison to the contemporary oral therapy of free drugs. This system also has the potential to be employed against SARS-CoV-2. Frequent mutations in the SARS-CoV-2 genome continuously change the antigenic protein. A67V, H69del-V70del, T95I, G142D-V143del-Y144del-Y145del, N211del-L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F are the 32 mutation on the spike of Omicron. Furthermore, pseudo-typed viruses expressing S proteins from the other current variants of concern (VOCs; Alpha, Beta, Gamma, and Delta) and variants of interest (VOIs; lambda and mu) were tested and reported [52]. Hence, implementation of highly sensitive and specific diagnostic tools is an urgent demand to detect viral infections and to manage viral spreading [53], and the aim is to develop NPs functionalized with multiple antigenic moieties/proteins which will synergistically ameliorate the efficiency of vaccines in countering viral infections. These nano-based strategies will also expose antigenic proteins to antigen-presenting cells leading to the improved delivery and treatment [2,14,54].

7.3 Nanomaterials for diagnosis of viral infections

The magnetic, fluorescence and surface-enhanced Raman
scattering properties of metallic NPs aid in tracking the treatment response. Colorimetric assay administered by gold NPs is efficiently employed for timely, specific and visual diagnosis of positive COVID-19 patients in a very short time span. Capping the N protein of SARS-CoV-2 with AuNPs shows selective agglomeration of their antisense RNA strand and exhibits amended surface plasmon resonance (SPR). RNaseH application further cleaved the RNA, thereby causing precipitate formation. Antibodies-conjugated graphene sheets have the potential to detect rapidly the targeted viral proteins. They can also be employed for the development of COVID-19 biosensors. Theranostic NPs have also been proposed that could diagnose as well as neutralize the virus in a single go, inhibiting the virus survival and proliferation inside the host.

Potential nano-based therapy for COVID-19 outbreak includes fusogenic DNA vaccine which is based on proteolipid nanovehicle, mRNA vaccine (mRNA-1273) encapsulated in lipid NP, recombinant protein NP vaccine (NVX-CoV2373), etc. Researchers have also improvised the detection by developing a paper-based colorimetric RNA sensor. The sensor utilized a positively charged pyrrolidinyl peptide nucleic acid (acpcPNA) probe aggregating the negatively charged AgNPs. The acpcPNA probe hybridized with the viral RNA in the presence of MERS-CoV RNA, forming a negatively charged RNA-acpcPNA duplex. The duplex dispersed the AgNPs, resulting in a detectable color change because of electrostatic repulsion [55–56]. Researchers are considering a new mRNA vaccine that directly targets the Omicron receptor-binding domain (RBD). The failure of ARCoV vaccines to neutralize sera against Omicron variant highly emphasized the development of the mRNAs encoding the Omicron RBD and lipid NP formulation as a potent candidate. Out of the 18 proposed mRNA constructs with different untranslated regions (UTRs), two of them namely Omicron/1 and Omicron/2, were selected and found to be most apt upon intravenous injection. Both LNP-formulated mRNAs and ARCoV-Omicrons are potent in producing Omicron RBDs in mouse sera. The final clinical grade mRNA vaccine is currently being manufactured [57–59].

Employing the nanotherapeutics analogous to the way it is employed for cancer, COVID-19 and similar pandemics can also be countered successfully. 3D nanotechnology-based approaches have recorded a high potential for efficacy detection, prognosis, and conveyance. The tissue and cell targeting principle that we employ for cancer and neurodegenerative diseases via the administration of NPs can also be affected against antiviral infections to cure the infected patients. These theranostic NPs can also kill the virus simultaneously. NPs can be used for fabricating superfine filters for facial masks, personal protection equipment (PPE) and surface coatings. These nanotheranostic approaches will help to address COVID-19 and similar pandemics very promptly and effectively (Figs. 4 and 5) [14]. The list of the potential nanotherapeutic molecules under consideration against certain viral infection are summarized in Table 1 [3,30–31,60–70].

8 Conclusions

Nano-based therapy has a tremendous potential to diagnose, treat and also to prevent many deadly diseases like neurodegenerative diseases, cancer, and HIV-AIDS. Currently, the COVID-19 outbreak has left the world in chaos forcing everybody to stay confined to their own houses. These antiviral pandemic outbreaks can also be taken into radar by the holistic approach of nanotheranostics to cure the infection and also prevent such devastating outbreaks in the future. This review highlighted various metallic NPs, such as AuNPs and AgNPs, which have shown to induce antimicrobial activity owing to their characteristic optical and thermal properties. Additionally, the superparamagnetism and hyperthermia properties of MNPs makes them highly potential tool to treat the microbial infections. The nanovaccines have been discussed that has the ability to cure various microbial infections. Additionally, various nanotechnologies for drug loading, drug delivery, and biosensing are discussed in this review. For example, DNA box with an oligonucleotide lock system has been shown for loading and release of thrombin. Similarly, DNA origami and protein-based nanotubes are utilized for controlled drug delivery. For biosensing applications, the glycoNPs, and CNTs are proven to be highly efficient. This review also discussed briefly about the nano-based therapy for the ongoing battle against viral pandemic-COVID-19. For example, a lipid NP is designed which encapsulates mRNA vaccine (mRNA-1273), thereby serving as a potential DNA vaccine for COVID-19. The other mRNA constructs, such as Omicron/1 and Omicron/2 having potential to produce Omicron RBD in mouse sera, are in final stage of clinical trials. These advancements in the
Fig. 4 Nano-based technologies for COVID-19: role of nano-based technologies for pandemic diagnosis as well as prevention. NPs can be used as a synthetic platform for vaccines formulations and immunomodulation.

Fig. 5 Schematic diagram of the nanotheranostic approach to combat COVID-19. Reproduced with permission from Ref. [14].
Table 1  Nano-based therapy for some viral infections [3,30–31,60–70]

| NPs                        | Characteristics                                                                 | Theranostic uses                                                                 | Refs.                |
|----------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------|
| Magnetic NPs               | Biocompatibility; hyperthermia capability; high photothermal effect              | As a catalyst and biomarker; detection of location of cancer and neurological disorders; T-cell based radiotherapies; detection of angiogenesis | [3]                  |
| Metallic NPs such as zinc, gold, silver, and titanium | Small size, high surface area, unique optical properties, and functionalization abilities with PEG and folic acid | Antimicrobial and cytotoxicity propensity; cancer treatment; photothermal, photodynamic, radiotherapy; real-time imaging | [60]                 |
| Quantum dots (CdSe, ZnS)   | High photoluminescence and quantum yield, minimum photobleaching, enhanced and discrete band energy gap due to quantum confinement | Single molecule and single particle tracking in vivo; bioimaging | [30–31]              |
| Virus-like NPs             | Trigger immune response, avoid nuclear enzymatic degradation                     | Multifunctional theranostic NPs; drug loading; bioimaging                       | [61]                 |
| DNA origami nanopores      | Opened and closed by varying parameters like pH, temperature, salt, and light    | Controlled drug delivery                                                         | [62]                 |
| Nanofibre scaffold         | 3D cell culture, stable beta pleated sheet and strand, and self-assembly properties | Controlled drug delivery; regenerative medicine                                   | [63]                 |
| GlycoNPs                   | Multivalent interaction of sugar; size range of biomolecules; quantum size effect | Biosensors, anti-adhesive, cancer therapy, targeted drug delivery, efficient probe molecule | [64]                 |
| Carbon nanotubes (SWNT, MWNT) | Property of measuring change in electrical conductivity, high specificity, enhanced biocompatibility and circulation time | Disease detection by probe; targeted drug delivery | [65]                 |
| Amino acid-based nanobowl  | Property of self-assembly, high specific surface area; concave shape, high pore-volume, and low density | Stimulus-responsive carrier of anti-cancer drugs like Dox; pH-sensitive drug targeted drug delivery | [66]                 |
| Short di- or tri-peptides  | Property of self-assembly, redox-processes sensitive like NADP⁺/NADPH system, O₂/O₂⁻ system, GSH/GSSG system, etc. | Targeted drug delivery based on redox sensitivity | [67]                 |
| Liposomes                  | Property of fusing with cell membrane to release its content in cytoplasm; high circulation time, and targeted drug delivery upon functionalization with PEG | Cancer diagnosis and therapy; vaccine development; brain-targeted drug delivery; antimicrobial therapy | [60]                 |
| Dendrimers                 | Hyperbranched, compartmentalized structure; high monodispersity, very small size (1–15 nm) | Cavity ensures efficient drug carrying capacity, easy surface modification ensures targeted drug delivery like that of polyethylineimine, chitin, etc. | [60,68]              |
| Micelles                   | Sphere shaped shell made of hydrophilic component; core made of hydrophobic component | Deliver hydrophobic drugs; dynamic structure leads to versatile drug loading, conjugation, and low dissolution of drugs | [60]                 |
| Nanogels                   | Property of swelling, flexible size, high water content | Minimize drug leakage, same formulation carry various drug candidates like nucleic acid, cytokines, vaccines, and anti-tumor candidates | [60]                 |
| Nanodiamonds               | Contain sp² carbon on surface; contain chemically inert core | MRI; manufacture of contact lenses, drug delivery for tumors | [60]                 |
| Silica-based NPs           | Porosity, efficient functionalization property; large surface area for water adsorption, and stabilize therapeutic molecules | Constant drug delivery rate, stimuli responsive targeted drug delivery | [69]                 |
| Solid lipid NPs (SLNs)     | Aqueous colloidal dispersion                                                    | Encapsulate huge amount of lipophilic and hydrophilic drugs for cancers, pulmonary diseases, etc.; oral drug delivery purposes | [70]                 |

Field of nanotechnology have significant potentials to act as a cure as well as prevention against microbial outbreaks leading to epidemic or pandemic.

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