Applications of nanomaterials in COVID-19 pandemic

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Abstract The novel coronavirus 2019 (COVID-19) pandemic represents one of the biggest global health threats in the last two decades, so researchers around the world are searching for solutions and treatments for COVID-19. At the time of writing, there are no specific drugs that have demonstrated suitable effectiveness in treating COVID-19. The current challenge involves designing tools for the prevention, rapid and accurate diagnosis, drug delivery, and effective treatment of this novel coronavirus. In this short review, we discuss how nanotechnology offers new ways to combat COVID-19, and how nanomaterials can be applied to control the COVID-19 outbreak. We also summarize relevant studies regarding the use of nanomaterials for preventing viral spread, preparing vaccines, and diagnosing coronavirus, as well as studies that show how nanoparticles can be used as drug delivery systems for the treatment of viral infections. Research on nanotechnology-based diagnosis, drug delivery, and antiviral therapy is currently in the early stages. However, the unique chemical properties of some nanomaterials highlight the broad prospect of nanomaterials in the future, and we propose that they will play an important role in the fight against COVID-19.

Keywords Coronaviruses; COVID-19; Nanomaterials; Viral control

1 Introduction

Severe acute respiratory syndrome coronavirus 2 (known as SARS-CoV-2 for short) was identified and named by the World Health Organization (WHO) as a novel coronavirus disease in 2019 (abbreviated as COVID-19) [1], referring particularly to the pneumonia caused by a novel COVID-19 infection. By around December 2019, several cases of pneumonia with unknown causes yet a common exposure to a seafood market in South China had been identified in a hospital in Wuhan, Hubei Province and were later confirmed to have resulted from acute respiratory infectious disease caused by the novel COVID-19 infection; since that time, such viral infections have spread globally [2]. Compared with the relatively recent severe acute respiratory syndrome (SARS) pandemic, COVID-19 has induced higher levels of transmission risk (reaching pandemic status), because the effective reproductive number of COVID-19 (2.9) was greater than that reported for SARS (1.77) during the initial stage [3].

Because the reported cases exhibit symptoms ranging from mild to severe infection and even death, the complete set of data covering the clinical expression of COVID-19 has not yet been clarified. The majority of COVID-19 patients present symptoms that mainly include headache, runny nose, fever, and a phlegm-producing cough, among others [4]. Patients with mild infections showed improved health within a week, while those with severe infections developed severe respiratory problems, which resulted from alveolar damage and often ultimately led to death [5].

COVID-19 transmission is most likely to occur via spreading from person to person in the form of droplets that are produced during sneezing, coughing, and talking [6]. However, it can also spread when a healthy person is in close contact with an infected person or their goods. The

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duration of symptoms and infections can range from 2 to 14 days [1]. To date, there are no reliable drugs or effective vaccines for COVID-19 [7].

It is believed that nanoscience and technology can play a significant role in the effective control of COVID-19 [8]. Nanoscience and technology usually involve the design and development of materials with particle sizes ranging from one nanometer to hundreds of nanometers, which makes it possible to manufacture materials with defined structures and molecular architectures. As a result of their nanoscale structure, such nanomaterials display unique and excellent optical, electrical, and biological performances [9, 10]. Nanotechnology, and nanomaterials in particular, can offer new applications in biomedicine, such as intelligent and controlled drug delivery, or diagnosis and treatment of various diseases, including viral infections [11]. Currently, thousands of laboratories around the world are involved in working to develop preventative measures and treatments for COVID-19. The results of these research efforts have revealed various biomedical applications of nanomaterials; for example, filters with nanometer coatings, vaccines with nanometer adjuvants, drug delivery systems prepared with nanometer carries, and medical apparatus and instruments, among others. Prior to the fight against COVID-19, many researchers had established that nanomaterials could be used to fight various viruses, particularly coronaviruses. Recently, Alphandery [8] reported that nanomaterials could offer some effective methods to fight the spread of COVID-19 by (i) developing an affordable and rapid test that could be used to diagnose COVID-19 in all global populations, (ii) preventing viral replication and RNA composition by using nanomaterials that inhibit interactions between COVID-19 and the cellular receptor, ACE-2, and (iii) developing a novel nanoparticle vaccine to restore innate immunity in infected patients [1]. In this short review, we consider these facts and focus on how nanomaterials can be implemented as promising tools for preventative, diagnostic, drug delivery, and treatment aspects related to COVID-19, thereby providing a reference for the prevention and treatment of future viral pandemics.

2 Critical nanomaterial properties for fighting COVID-19

2.1 Nanomaterials and virus prevention

It is well known that most cases of COVID-19 infections occur when people inhale droplets of the virus. These droplets are produced when COVID-19-infected patients cough or sneeze, and then the droplets can float or stick to

surrounding surfaces, such as doorknobs, desktops, and even protective equipment for health care workers. The guidelines for COVID-19 treatment issued by the National Institutes of Health (NIH) state that healthy people can also become infected with COVID-19 by touching surfaces contaminated by the virus. In a study regarding the survival time for COVID-19, researchers detected a live virus on the surface of surgical masks seven days after exposure to the virus [12]. Therefore, it is crucial to investigate potential face masks based on nanomaterials with excellent self-disinfection properties to enhance the efficiency of masks for blocking COVID-19.

In terms of disinfecting surface pollutants, many hospitals and medical institutions use traditional disinfection methods, such as ultraviolet disinfection or spaying hydrogen peroxide. However, these types of disinfection methods are often one-off. As soon as the ultraviolet lamp is switched off or the hydrogen peroxide decomposes, the virus can brazenly adsorb onto the surface of the disinfected materials, just as it had before the disinfection. With the development of nanoscience and technology, self-disinfection of nanomaterial surfaces can provide a possible solution to solve this problem.

Copper, silver, and other heavy metal ions have been widely used in the medical field due to their antiviral properties, which may result from the fact that heavy metal coatings can slowly release heavy metal ions after contact with the bacterial virus. When combined with the protein shell of the bacterial fungus, these ions deactivate the proteins, thereby achieving self-disinfection of the pollutants. In a coronavirus study, the survival time for coronavirus 229E (HUCOV-229E) on copper-containing surfaces was significantly reduced compared with that on non-copper-containing materials [13]. The use of copper alloys for doorknobs and bed bars in medical facilities is also based on this principle. In a study involving the effects of silver, researchers found that silver ions demonstrated high affinity for sulfur, so silver has been added to some antiviral drugs to block viral DNA replication [14]. In addition to silver and copper, other heavy metals have also exhibited excellent antiviral properties [15]. If such metallic materials are prepared as nanoparticles (NPs), these materials present even better biological properties. For example, metal nanoparticles can increase the contact area between materials and viruses and accelerate the release rate of metal ions. Additionally, nanoscale materials possess some unique properties. For instance, under light irradiation with a specific wavelength, gold nanoparticles can catalyze reactions to generate reactive oxygen species (ROS), which deactivate viruses and bacteria [16]. After treatment, the nanomaterials are relatively stable, indicating that they can maintain chemical activity

for long periods. Spraying such nanomaterials on a contaminated surface not only disinfects the surface but also protects it from the virus for an extended period.

In a study of non-metallic nanomaterials, a team of researchers synthesized a super-hydrophobic nanoscale graphene material, which was applied to the surface of medical masks. The emergence and application of these nanometer-scale self-disinfection methods have reduced the burden of disinfection for medical personnel to some extent.

In addition to the disinfection of contaminated surfaces, the barriers provided by masks to protect against viruses represent another important research direction for the prevention and treatment of COVID-19. Since COVID-19 virus particles are on the nanoscale (~ 100 nm), it is reasonable to envision applying nanomaterials to achieve virus blocking [17]. Recent reports indicated that masks treated with nanomaterials possess better virus-blocking effects than ordinary masks. For example, the filtration efficiency of an ordinary mask was significantly enhanced after incorporating electrospun yarn (~ 100 nm in diameter), which caused different fabrics to rub against each other, thus giving the barrier an electrostatic charge that made the mask better at absorbing viruses [18]. Nanofiber air filters developed based on this principle can filter more than 94% of viruses at low pressure (~ 30 Pa). If a nanoscale TiO_2 fiber coating is applied on the surface of the filter, the filtration efficiency can be improved even further, even to the point that it can capture sub-micron-sized droplets. Such nanoscale TiO_2 fiber coatings can also possess properties related to photodynamic therapy. Specifically, the coating can transform O_2 into ROS under natural ultraviolet light irradiation, thus deactivating the virus adsorbed on the coating surface [19].

In another study, it was determined that composite nanomaterials can also be integrated onto the surface of masks to improve their virus-blocking effects. A research group from India found that graphene oxide grafted with metal nanoparticles and spread on the surface of a mask can prevent the mask from becoming contaminated with viruses [20]. Balagna et al. [21] demonstrated that the filtering facepiece-3 mask, which contained silver nanoclusters in a silica composite coating, was effective to against COVID-19. This study showed that the silver nanocluster/silica composite coating deposited on the mask had efficient antiviral activity. Additionally, Chen [22] reported that masks with graphene-silver nanocomposite coatings also exhibited antiviral properties.

Although various heavy metal ions have demonstrated certain degrees of antiviral properties, it cannot be ignored that when they are applied to masks, these ions come into close with the skin and can cause discomfort. If a face mask is used frequently over a long period of time, facial

skin lesions, irritant dermatitis, or worsening acne may occur. Therefore, it is critical to develop a new type of personalized, non-disposable, and high-quality medical-grade mask based on functional fiber antibacterial materials. Achieving this goal would make it possible to provide environmentally friendly, non-disposable, reusable masks and is expected to enhance the protection of medical workers and increase sales of high-quality masks. Already, nanofibers produced via electrospinning and three dimensional (3D)-printed to a personalized face shape guarantee superior comfort and high filtration (99% efficiency) [23]. Using 3D printing to obtain a personalized design required consulting a 3D head library compiled by scanning the head and neck of representative medical workers [24]. The nanofibers have a large surface area to volume ratio, so they possess an extraordinary ability to filter nanoparticles and absorb biological and chemical contaminants, while also demonstrating excellent thermal radiation cooling properties [25]. Therefore, face masks based on double-layer electrospun membranes embody moisture pump technology and exhibit high levels of filtration.

Inorganic nanoclusters (NCs) with custom characteristics that modify the surface of the fibrous material can take advantage of their chemically driven intrinsic bactericidal and antiviral activity, thus enabling an aggressive approach to minimize the accumulation of harmful pathogens in the nanofiber pores [26]. To fully disinfect pathogens that may remain, the nanofibers should be modified with nanoparticles exhibiting high photo-thermal efficiency over a broad absorption spectrum to trigger light-assisted photo-thermal disinfection [27]. In fact, the ability of plasma nanoparticles to convert monochromatic light into heat (photo-thermal effects) reveals their potential for application in the treatment of cancer and other diseases via photo-thermal therapy (PTT) [28].

This concept has created a visionary branch in the field of PTT-based applications due to the possibility of exploiting the extraordinary photo-thermal sensitivity of custom plasma nanoparticles to develop light-assisted photo-thermal disinfection techniques [29]. Meanwhile, the combination of the nanostructured electrostatic spinning desiccant layer with the photo-thermal-responsive nanofiber membrane enables the multifunctional mask to act as a hygroscopic pump, which can help dissipate the humidity normally generated in the mask, thereby greatly improving the mask user's comfort [30]. Additionally, this breakthrough technology allows the production of new masks and personalized personal protective equipment (PPE) with outstanding comfort, high filtration functionality, low humidity levels, chemically assisted internal sterilization, and antiviral activity. Gold nanoparticles in particular are effective for converting monochromatic light into heat energy, thus solidifying their potential for use in the

treatment of cancer and other diseases through photo-thermal therapy [31]. Similarly, the thermal properties of nanoparticles can be designed to locate and improve their thermal production and penetration capabilities, thus creating a new path for realizing synergistically combined photo-thermal treatments of bacteria and viruses [3]. Recently, Zhong et al. [32] utilized a graphene layer with photo-thermal properties to develop a new generation of reusable and self-cleaning photo-thermal auxiliary face masks. Although the results were promising, one of the limitations was that graphene has low light absorption, which reduces the material's photo-thermal conversion performance. Therefore, it is possible to develop an efficient photo-thermal disinfection process using custom nanoparticles with extraordinary photo-thermal properties, which opens a breakthrough path in the field of PTT disinfection masks.

Gold nanoparticles (Fig. 1a, left) absorb light under suitable light illumination, and the absorbed energy induces an electronic transition in the Au nanoparticles (Fig. 1a, middle), which generates heat that can be dissipated into the ambient medium (Fig. 1a, right). A water dispersion of Au nanoparticles (Fig. 1b) was dropped onto a respirator and dried for ~ 20 min before the analytical test was

performed. Thermographic analysis (Fig. 1c) before the laser irradiation ($t = 0$) shows a uniform temperature distribution of about 20°C , which is in contrast to the near-infrared (NIR) exposure, where the light absorption by Au nanoparticles is effectively converted into heat through the plasma photo-thermal effect, ultimately reaching 75°C (Fig. 2d). A circular region highlighting the illuminated area in the time-temperature profile (Fig. 1e, red curve) indirectly verified the aforementioned results. This experiment employed the original areas of N95 masks (Fig. 1b, outside the black circle). The results showed that the temperature did not increase significantly (Fig. 1e, blue curve), which again confirmed the excellent performance of Au nanoparticles for converting resonant light into heat [33]. This study indicated that there is a need for a new generation of face masks with excellent properties in terms of high filtration capacity, high comfort level, and self-disinfection.

2.2 Nanomaterials and diagnosis of COVID-19

To obtain rapid diagnostics, early disease detection, and identification of pandemic-causing infectious pathogens, nanotechnology can be used as a tool in medical and environmental applications, particularly in the form of

Fig. 1 **a** Schematic illustration of photo-thermal conversion process of Au NRs upon light irradiation; **b** photo-thermal responsive FFP2 (N95) respirator containing a drop-casted Au NRs dispersion (black circle) along with a thermographic view of the same region exposed to NIR laser ($\lambda = 810$ nm; $I = 200$ mW·cm $^{-2}$) acquired at **c** $t = 0$ s, and **d** $t = 22$ s; **e** temperature profiles of pristine (blue curve) and Au NRs treated respirator by turning On and Off NIR laser beam (water dispersed Au NRs ($C = 3.2 \times 10^{-9}$ mol·L $^{-1}$) have longitudinal and transversal LSPR bands centered at 775 and 524 nm, respectively; dynamic IR thermographic analysis was carried out using a FLIR (A655sc) thermal-camera that produces thermal images of 640×480 pixels with an accuracy of $\pm 2^\circ\text{C}$; thermal-camera was suitably equipped with a close-up IR lens characterized by a magnifying factor of 2.9x, a spatial resolution (IFOV) of $50\ \mu\text{m}$, and a reduced working distance). Reproduced with permission from Ref. [33]. Copyright 2020, Wiley

Fig. 2 Field-effect transistor (FET) sensor and its related operational process for diagnosis of COVID-19. Reproduced (adapted) with permission from Ref. [51]. Copyright 2020, American Chemical Society

nanobiosensors that improve the efficiency and quality of the detection process [34, 35]. In addition, nanotechnology inspired by virology has led to the development of new delivery tools to eradicate the viruses that cause epidemics, by enabling the development of devices on a scale ranging from one nanometer to several hundred nanometers [36, 37]. At the nanoscale, novel nanostructures and nanosensors exhibit properties not observed at the macro-level, especially in terms of nanoscale detection [38, 39]. Traditional testing methods depend on nucleic acid testing and have various disadvantages, including (i) low sensitivity and painstaking experimental procedures, (ii) low detection accuracy, (iii) long duration from sample collection to results interpretation, and (iv) lack of specificity, which may lead to the misdiagnosis of other infections in patients. Therefore, some researchers found that nanomaterial-based biosensors are one of the most important tools to help identify individuals affected by pathogens. In a recent report, sensory systems based on nanomaterials have been successfully applied to other microorganisms [40].

The development of new nanomaterials and nano-fabrication technologies has prompted researchers studying biosensors to search for ways to increase the surface area of biosensor structures to achieve higher sensitivity and shorter detection time relative to traditional methods [41]. These sensors can effectively recognize antibodies and antigens of the virus, as well as other biological components on the surface of the signal sensor [42, 43]. Therefore, the construction of the biosensor interface is of great significance in terms of verifying the efficiency and performance of nanobiosensors [44].

Many researchers have enhanced the specificity and sensitivity of sensors by utilizing nanocomposites, including nanoparticles, nanowires, nanorods, or carbon nanostructures and exploring their surface chemistry [45, 46]. Meanwhile, the preparation of 3D microstructures, nanostructures, and columns can have a significant impact on controlling the detection mechanisms [47]. The detection properties of nanobiosensors can be improved through incorporating various nanostructures. In particular, the rapid detection and immediate response characteristics make these sensors suitable for medical and environmental applications. Because of the urgency of the situation, the detection of COVID-19 is critical for major preventative applications in the medical field. Another important advantage associated with nanobiosensors is their ability to detect bacteria and viruses at very low concentrations [48]. The early and rapid detection of COVID-19 can help alert doctors before symptoms appear, which can ultimately reduce the impact of the virus.

To date, unique technologies have been developed for nanosensor chips based on silicon on insulator (SOI) structures. Compared with single-grown cylindrical nanowires and other nanomaterials, the principal advantage of SOI-based nanomaterials is that the synthetic method is compatible with complementary metal-oxide-semiconductor technology. Ivanov et al. [49] found that SOI-based nanomaterials can be mass-produced as portable high-sensitivity diagnostic systems. When detecting COVID-19 antibodies with Immunoglobulin M (IgM) or Immunoglobulin G (IgG) used as the antigens, antigen-antibody complexes could be conducive to the formation of

the detecting element. In this case, the detection time is very short and the detection accuracy is very high.

Zhao et al. [50] also developed a COVID-19 biosensor system based on nanomaterials. This biosensor was based on nanomaterials combined with one-step reverse transcription loop-mediated isothermal amplification, and the developed COVID-19 biosensor was successfully used to diagnose COVID-19 patients. In addition, the required time from sample collection to testing result was only about 1 h, which was higher than the traditional testing time.

One biosensor device that was developed based on a field-effect transistor (FET) can efficiently detect the COVID-19 virus in medical samples, and its performance and effectiveness were evaluated and confirmed using cultured viruses, antigenic proteins, and nasopharyngeal swab samples from COVID-19 patients. The biosensors were synthesized from graphene nanosheets modified with the COVID-19 spike antibody using N-hydroxysuccinimide 1-butyrate, and they could efficiently identify the COVID-19 spike protein at concentrations of $100 \text{ fg}\cdot\text{ml}^{-1}$ medical transfer vehicle and $1 \text{ fg}\cdot\text{ml}^{-1}$ in buffered saline. The biosensor prepared using this method exhibited excellent sensitivity for the diagnosis of COVID-19 without labeling or other sample pretreatments, and it also demonstrated an improved signal-to-noise ratio (Fig. 2) [51].

Recently, Seo et al. [51] presented a novel biosensor that was fabricated by coating the graphene sheets of a field-effect transistor with an antibody to the COVID-19 spike protein. The COVID-19 antibody was fixed to the synthetic device using a highly effective interfacial coupling agent (i.e., succinimide-1 butyrate). The limit of detection for this biosensor for the COVID-19 target antigenic protein was $1 \text{ fg}\cdot\text{ml}^{-1}$, which was significantly lower than traditional detection concentrations, and reduced the difficulty of sampling.

A color bioassay based on gold nanoparticles coated with thiol-modified antisense oligonucleotides and targeting the COVID-19 N-gene was prepared by Moitra et al. [52] and could accurately diagnosis COVID-19 in a few minutes. Meanwhile, gold nanoparticles coated with thiol-modified antisense oligonucleotide were also applied in a naked-eye test for COVID-19 that was effective in less than 10 min (Fig. 3).

Traditional testing strategies, including polymerase chain reaction (PCR) methods, can sometime provide false positive results, causing delayed treatment in patients and infections in more healthy people. Some researchers found that using nanoparticles can improve the ability, efficiency, and accuracy of PCR to detect the COVID-19 virus. This can be achieved by coupling fluorescent nanoparticles to specific probes for viral RNA and then performing fluorescence detection on the coupled nanoparticles, which can

be detected a low concentration ($1 \text{ fg}\cdot\text{ml}^{-1}$) [8]. The magnetic nanoparticles and zirconium quantum dots were combined with coronavirus antibodies and then bound to the coronavirus, which could then be detected at 412 nm by fluorescence spectroscopy [53]. Compared with the fluorescence of the protein complex without gold nanoparticles, the fluorescence of the complex with gold nanoparticles bound to the SARS protein showed a significant change. Based on the reports discussed in this section, detection methods based on nanomaterials have many advantages compared with traditional detection methods, especially in terms of their low detection concentration, high accuracy, and speed for the detection of COVID-19.

2.3 Nano-adjuvant in COVID-19 vaccines

In general, infectious disease outbreaks have highlighted the need to develop effective vaccines. Immunization is a process through which an antigen is introduced, and the immune system of an individual is triggered to form adaptive immunity to the corresponding pathogen [54]. However, traditional vaccines possess many limitations in terms of effectively inducing an immune response, low blood flow stability, and inability to elicit a sustained and adequate immune response [55, 56]. In general, the higher the vaccine titers are, the better their therapeutic effects are; however, vaccines with higher titers often generate greater side effects [57]. Recently, researchers found that novel vaccines based on nanoparticles demonstrated strong immune-stimulating effects and were expected to be an effective substitute for traditional vaccines [58]. It was also determined that the novel vaccines had numerous other benefits, including adjustable sizes, high payloads, controllable drug kinetics, and enhanced stability [59]. Meanwhile, some researchers have determined that DNA- and RNA-based vaccines required a second enhancement with DNA and a recombinant protein from another vector. Vaccine adjuvants derived from nanoparticles are expected to have various advantages, such as slow release, improved vaccine efficacy, and strong induction of humoral and cellular responses, allowing them to serve as substitutes for vaccine-targeted immune cell delivery [60].

There is an urgent need to develop new vaccines to promote a cellular immune response because COVID-19 is an extremely severe global pandemic. The antigens of most current COVID-19 vaccines are attenuated or inactivated pathogens, or deactivated or chemically modified toxins (i.e., toxoids). These antigens have their own limitations for various reasons. For example, to prevent harm to inoculated people, the attenuated pathogen will pass through several differential passages in human cells, which requires the attenuated virus to possess certain biological

Fig. 3 Selective naked-eye detection of COVID-19 RNA mediated by specially designed ASO-capped Au nanoparticles. Reproduced (adapted) with permission from Ref. [52]. Copyright 2020, American Chemical Society

compatibility, which hinders the immune system from producing a strong immune response. Inactivated and toxoid vaccines contain materials derived from pathogens and inherent microbial components that may increase the risk of adverse side effects (e.g., excessive inflammation) in the body, so the dosages should not be too high in the vaccine; however, insufficient dosage will not generate an adequate immune response.

For this reason, researchers in immunology often add nanomaterials, known as nano-adjuvants, to vaccines. Nanoparticles applied as vaccine adjuvants are typically classified as inorganic (e.g., silver, gold, iron oxide nanoparticles, etc.) or organic (e.g., polymeric, virus-like particles, etc.). The use of such nanoparticles as adjuvants and potential delivery carriers of vaccine antigens has attracted the attention of researchers because the nanoparticles can both stabilize vaccine antigens and act as adjuvants [61]. The application and subsequent evaluation of vaccine adjuvants are critical during vaccination. Therefore, because of their immunogenicity, various types of nanoparticles (e.g., gold nanoparticles, spike protein nanoparticles, and hollow polymer nanoparticles) have significant potential for inducing anti-coronavirus immune responses in animal models and in vitro [62]. For example, silver nanoparticles can be used as a mucosal vaccine adjuvant for deactivated influenza viruses to stimulate significant antigen-specific immunoglobulin A formation with low toxicity by stimulating the regeneration of bronchial-associated lymphoid tissue [63]. Additionally, Sekimukai et al. [64] investigated gold nanoparticles and Toll-

like receptor agonists (surgical adjuvants for UV-inactivated SARS coronavirus vaccines) for the application of recombinant S proteins as vaccine adjuvants. Figure 4 illustrates the possible mechanism associated with this nano-vaccine.

In such nano-vaccine adjuvants, liposomes can encapsulate antigens to help deliver them to specific targeted cells; on the other hand, aluminum salts can stimulate the production of NLRP3 inflammasome and IL-13 in immune cells, thus prompting a stronger immune response. Currently, a deactivated vaccine developed by China Pharmaceutical Group Sinopharm in collaboration with the Wuhan Institute of Biological Products uses aluminum salts as adjuvants [65]. In addition to aluminum salts, some reports have used graphene, silica nanoparticles, gold nanoparticles, liposomes, and polymerized nanoparticles as vaccine adjuvants [3]. For example, the excellent behavior of the lipid vector has led to its application in the transport of COVID-19 vaccines. On May 16th, 2020, the first batch of COVID-19 patient volunteers was injected with the mRNA vaccine (mRNA-1273) developed by Moderna; this vaccine technology employed lipid encapsulation, and the project has now entered the emergency use in several countries [66]. Meanwhile, researchers found that polymeric nano-adjuvants were effective for preparing hepatitis B and Newcastle disease vaccines because of their slow antigen release and high biocompatibility. Additionally, they determined that carbon nanoparticles demonstrated facile encapsulation of proteins and high chemical stability and had used such materials in oral vaccine adjuvants [3].

Fig. 4 Nanoparticles (NPs) as antigen delivery system and immune response. Reproduced (adapted) with permission from Ref. [64]. Copyright 2020, Wiley

Based on the immunogenicity exhibited by these nanoparticles, many studies have reported that various types of nanoparticles, including gold nanoparticles, hollow polymeric nanoparticles, and spike protein nanoparticles, have the potential to induce a human immune response against coronaviruses [62].

When modified appropriately, nano-adjuvants can be tuned to perform specific functions. For example, gold nanoparticles modified with cetyltrimethylammonium bromide, polydiallyl dimethyl ammonium chloride, and polyethylene imide can promote DNA uptake by specific cells, which is an important step in the preparation of DNA-based vaccines [67]. Additionally, amino-modified graphene has negligible toxicity and can activate STAT1/IRF1 interferon signals in monocytes and T cells, leading to a polarized immune response from macrophage 1(M1)/T helper 1(Th1) [68]. In a recent study regarding COVID-19, Th1 polarization was strongly associated with infection control by the immune system [69].

Following these results, it was proposed that vaccines based on nanoparticles should be more safe, effective, economical, and convenient than traditional vaccines. Vaccines based on nanoparticles can provide a promising future if the following goals are achieved: (i) exploring novel vaccines via alternative administrative paths; (ii) inducing vaccine release at specified locations; and (iii) making nanoparticle-based vaccines that are stable at ambient temperature. Such vaccines may require only one

dosage, unlike traditional vaccines, which often need to be enhanced several times. Nanoscience and technology platforms can provide a promising opportunity to enhance humoral or cellular immune responses.

2.4 Nanomaterials and antiviral drugs

Hundreds of drugs against COVID-19 are currently being studied in laboratories across the world. Although COVID-19 shares similarities with other viruses and our understanding of its antiviral mechanisms continue to grow, the efficacy and side effects of drugs currently used to treat COVID-19 are not sufficient. Nanomaterials, such as liposomes and PLGA nanoparticles, can be used to encapsulate antiviral drugs; realize long-term circulation, sustained release, and co-administration of multiple drugs; and improve the overall therapeutic effect. Therefore, by modifying antibodies targeting the COVID-19 protein, nanomaterials can improve drug availability while reducing side effects, thereby ensuring better therapeutic outcomes. Nanomaterials may soon be used to deliver angiogenic factors in combination with antiviral drugs, resulting in enhanced treatment of COVID-19.

Most antiviral drugs are protein, DNA, or RNA drugs, which hinders the application of these drugs because of the physical and chemical properties of the human body to some extent. For example, these drugs can degrade during transport, and they are easily flagged by immune cells as

foreign and cleared by macrophages. In previous reports, researchers have found that nanocarriers can provide an effective solution to this problem. The introduction of nanocarriers significantly improves the efficiency of drug transport compared with traditional methods, such as the free diffusion of drugs in the body. A drug encapsulated in a carrier material can effectively evade immune surveillance by using a specific nano-fabrication technique, which has attracted significant attention due to its high encapsulation rate and high drug load. Many researchers also reported that some issues, such as low drug efficiency and inferior water-solubility, could be addressed through the delivery rate of nanocarrier antiviral drugs. Active targeting nanocarriers reach therapeutic concentrations in hidden virus reservoirs, which can provide the opportunity to cross biological barriers [70]. Many clinical trials have indicated that nanocarriers with controlled drug release properties are the best choice to alleviate the risks of poor compliance and viral rebound during viral infection treatment in patients. Therefore, the nanocarriers approach to antiviral therapy is an effective tool for adapting the use of antiviral drugs, which can significantly improve the management of COVID-19 treatments [71].

To date, nanocarrier technology has played a key role in the development of RNA interference (RNAi), proteins, peptides, and other biological agents [72]. Biologic prodrugs based on nanocarriers can prevent untimely release and degradation of drugs to ensure longer half-lives of the biological materials [73]. Additionally, targeted nanoparticles can provide an enhanced endocytosis rate to ensure therapeutic nanoparticle delivery to the target cells. Finally, nanocarriers with a higher drug load require fewer nanoparticles to provide controlled drug release inside the target cells, which ensures fewer side effects [74–76].

Based on the aforementioned reasons, many active substances, including antiviral drugs, nucleic acids, and biological agents can be loaded and transported by nanocarriers. Linking therapeutic candidates to disease-specific nanocarriers could be key in the fight against COVID-19. Such nanomedicine requires the reformulation of approved drug candidates and those currently being tested in order to enhance the therapeutic index, which mainly involves moderating the toxicity or side effects. Developing a treatment method for COVID-19 is fundamentally similar to many cancer studies; therefore, to promote the development of a treatment method, suitable nanomedicine must be considered [77, 78]. In fact, the high-profile Remdesivir EIDD-2801 and many other drugs have adopted nanocarrier-assisted drug transportation, thus verifying the advantages of antiviral drugs based on nanocarriers [79].

In addition to encapsulating drugs and aiding in drug transport, nanomaterials are expected to mitigate the

overreaction responses in the human immune system. Severe COVID-19 patients often have difficulty breathing, which is associated with excessive inflammation and necrosis of CD169⁺ macrophages; stimulated macrophages tend to excessively secrete IL-6. Prior to the COVID-19 health crisis, many researchers had developed IL-6 inhibitors, including the curcumin nanoparticles, Actemra, and Kevzara. The excellent properties of the latter two inhibitors have also led scientists to add them to the list of drugs being tested as IL-6 inhibitors for COVID-19 patients. Currently, both inhibitors are undergoing clinical trials [80]. Some reports indicate that nanomaterials can be used to treat and improve various symptoms. For example, nanodiamonds modified with octadecylamine and dexamethasone can reduce inflammation and improve the regeneration of macrophages in vitro [81]. In addition, adjusting the pore size of graphene can effectively remove pro-inflammatory cytokines from the blood in the body [82].

Nanomaterials have the potential to be used to deliver anti-inflammatory drugs, introduce antioxidant nanomaterials, or provide inhalation methods for platelet-derived nanomaterials, which can actively target inflammatory sites. These strategies provide timely solutions, while also inspiring future exploration. For example, nanomaterials originating from platelets can be coated with thiophen-3-carboxylamide to target pneumonia sites to quell cytokine storms [83]. Additionally, antioxidant nanomaterials, such as cerium dioxide nanoparticles, can be used to effectively eliminate ROS at inflammation sites [84].

In addition to applications involving nanoparticle carriers and immune system inhibitors, the emergence of photodynamic therapy (PDT) has made it possible for nanomedicines to be employed in vivo against COVID-19. Photodynamic drugs (i.e., photosensitizers) are delivered to specific cells and convert oxygen into ROS to attack and deactivate target cells when exposed to specific wavelengths of light. Because of their low toxicity and high selectivity, such photodynamic drugs have been widely used for treating tumors [85]. As early as 1970, researchers began to study the role of PDT in antiviral activity. Nanomaterials such as fullerene and graphene have been shown to successfully destroy the Semliki Forest virus and the Vesicular Stomatitis virus [86]. The excellent properties of photodynamic nanomaterials in anti-tumor and antiviral therapies led photodynamic drugs to provide great confidence in terms of current prospects against COVID-19. In October 2020, Kipshidze et al. [87] used a photosensitizer molecule that was not activated by light as a bait and reported that the COVID-19 virus was preferentially attached to the photosensitizer molecule, rather than attaching to healthy lung tissue or attacking healthy hemoglobin. Then, the target lung tissue and illuminated fiber optic tubes revealed the low-power photosensitizer

characteristic absorption wavelength range (typically 450–800 nm) that caused photosensitization, meaning that such illumination would generate highly reactive oxygen that could destroy the bound COVID-19 viruses via the peroxide photosensitizer molecule. The affinity between COVID-19 viruses and the photosensitizer's heme structure predicted high virus destruction titers confined to the photoactivation zone [87]. Based on this concept, it was proposed that PDT combined with an existing therapy would comprise the most effective COVID-19 treatment method [88]. For example, Schikora et al. [89] successfully used photodynamic treatments for COVID-19 infections. They also found that the treatment exhibited profound clinical efficacy in all age groups of patients affected by COVID-19, and there were no suspected or apparent treatment-related adverse events. Such photodynamic treatments are particularly relevant for patients with severe disease complications (e.g., advanced age), as well as potential asymptomatic carriers who may continue to unwittingly become participants in the COVID-19 pandemic.

3 Unsolved problems and perspectives

Respiratory infections, particularly coronaviruses, are one of the most common causes of death worldwide, and viral respiratory infections (especially the COVID-19 pandemic) continue to spread around the world. As of February 22nd, 2021, COVID-19 has infected more than 100 million people in 215 countries, resulting in nearly 2.5 million deaths, and has also triggered an exceptional economic crisis. Although there are several drugs or vaccines available to treat or prevent COVID-19, most of the existing antiviral drugs are re-used drugs that are effective against a limited number of human pathogens. Therefore, in addition to conventional approaches, more and more researchers are urgently trying to identify and develop suitable nanomedicines. It is clear from the reports discussed herein that nanomaterials play an important role in the prevention, diagnosis, vaccine production, and treatment of viral diseases, and nanoparticles additionally have great potential in the field of biomedicine, especially for patients who relapse after completing a conventional antiviral therapy. Nanoparticle-based technologies may provide solutions to the problems faced by conventional treatments, due to their large surface to volume ratio, surface charge, size, shape, antiviral resistance, and optical, electronic, biological, and functional properties [90]. In addition, treatment approaches based on nanomaterials exhibiting feasible, cost-effective, non-toxic, and biocompatible properties represent a convenient strategy for dealing with various types of viral infections, especially COVID-19.

Despite the vast efforts of researchers around the world to understand the causes and treatments of COVID-19, there are still many challenges surrounding this virus. First, many East Asian countries have imposed travel restrictions, which seem to be very effective so far [5]. Considering China as an example, travel restriction measures have effectively controlled the spread of COVID-19 in the short term. Second, the accurate and rapid detection of COVID-19 enables health care workers to identify the source of infection and reduce the transmission of the virus within the population to a certain extent, thus effectively reducing the number of infected people. Therefore, the application of nanotechnology for the rapid detection of COVID-19 is an important direction in the next stage of research. Third, the search for a reliable, safe, and effective COVID-19 vaccine is ongoing. Since the emergence of this, several candidates have been developed, but at the time of writing this review, there is still no licensed vaccine against it. Based on data obtained for other types of coronaviruses, nano-vaccines have been shown to elicit a stronger immune response. Thus, future investigations regarding the application of nanomaterials in COVID-19 vaccines are recommended in order to create effective, safe, and highly biocompatible nano-vaccines that could potentially provide long-term widespread immunity. Finally, although numerous studies have investigated the clinical symptoms of COVID-19 in patients, there is currently no specific and effective treatment. To date, some cases wherein Remdesivir was used for in vitro studies or to treat COVID-19 patients in the USA have shown promising results [91]. Another study found that Remdesivir combined with chloroquine was an effective combination therapy for COVID-19 [92]. However, the mechanism describing the efficacy of Remdesivir and chloroquine for treating COVID-19 is unclear. Therefore, it is crucial to explore a safe and effective treatment method for COVID-19 based on nanotechnology in future research efforts.

It is well known that the COVID-19 pandemic is not the first and will not be the last of its kind. Therefore, researchers studying nanomaterials for medicinal sciences must ensure that any developed nanomaterials can deal with COVID-19 and future pandemics. The nanomaterials community should thus be encouraged to actively leverage its impressive nanotechnology background to face the global health emergency.

4 Summary

Global health is facing an extremely dangerous problem with COVID-19. In this short review, we discussed the latest strategies involving nanomaterials for the prevention, rapid and accurate diagnosis, drug delivery, and effective

treatments related to COVID-19. The prevention and rapid diagnosis of COVID-19 represent vital control measures, because rapid detection in infected patients can limit the spread of the virus. Nanotechnology may be the best way to control COVID-19 in the absence of vaccines or other effective treatments. We also propose that COVID-19 vaccines based on nanomaterials may be the most effective way to protect the uninfected population and ultimately reduce the number of infected people. In addition, we discussed a variety of nanomaterials that can be used to fight this disease, classified as nano-vaccines and nano-drugs according to their mode of action and revealed the ways in which they are active against COVID-19. Based on the literature review presented herein, we believe that with rapid developments in materials chemistry, biology, and technology, it will be possible to control the emergence of new viral infections and to manage infectious diseases more effectively and comprehensively.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interests.

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