Nanotechnology-based promising strategies for the management of COVID-19: current development and constraints

Mahendra Rai, Shital Bonde, Alka Yadav, Yulia Plekhanova, Anatoly Reshetilov, Indarchand Gupta, Patrycja Golińska, Raksha Pandit, and Avinash P. Ingle

ABSTRACT
Introduction: COVID-19 pandemic has been declared as a global emergency by the World Health Organization which has mounted global pressure on the healthcare system. The design and development of rapid tests for the precise and early detection of infection are urgently needed to detect the disease and also for bulk screening of infected persons. The traditional drugs moderately control the symptoms, but so far, no specific drug has been discovered. The prime concern is to devise novel tools for rapid and precise diagnosis, drug delivery, and effective therapies for coronavirus. In this context, nanotechnology offers novel ways to fight against COVID-19.

Area covered: This review includes the use of nanomaterials for the control of COVID-19. The tools for diagnosis of coronavirus, nano-based vaccines, and nanoparticles as a drug delivery system for the treatment of virus infection have been discussed. The toxicity issues related to nanoparticles have also been addressed.

Expert opinion: The research on nanotechnology-based diagnosis, drug delivery, and antiviral therapies is at a preliminary stage. The antiviral nanomedicine therapies are cost-effective and with high quality. Nanoparticles are a promising tool for prevention, diagnosis, antiviral drug delivery, and therapeutics, which may open up new avenues in the treatment of COVID-19.

1. Introduction
The first known case of severe illness in humans due to coronavirus was reported in 2003 in China which resulted in the outbreak of Severe Acute Respiratory Syndrome (SARS) pandemic [1,2]. In 2012, the second outbreak of coronavirus occurred in Saudi Arabia leading to the Middle East Respiratory Syndrome (MERS) epidemic [23]. Recently, the third outbreak of this disease was reported in Wuhan, China, in December 2019 and named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Based on the confirmed cases of coronavirus, on 11 February 2020 the official name ‘COVID 19’ was announced for the novel CoV variety that infected and destroyed the lower respiratory tracts of a person suffering from Coronavirus in Wuhan, China [1].

Coronaviruses are a wide group of viruses belonging to the Coronaviridae family [1]. They are reported to cause infection in humans and a few animals. These viruses can be identified by the presence of crown-like spikes on their surface [4]. The causative agent of COVID-19 i.e. SARS-CoV-2 consists of four different proteins and more than 30,000 nucleotides in its RNA genome. The studies on the surface morphology of the proteins revealed that there are three structural proteins on the surface which include small envelope protein (E), spike surface glycoprotein (S) and matrix protein (M). Among these, S protein is responsible for more than 80% of the interactions with the cellular membrane [5]. Figure 1 represents the structure of SARS-CoV-2. To date, four sub-groups of the coronavirus have been identified which are named as alpha, beta, gamma, and delta [1]. They are one of the largest known spherical RNA viruses enveloped by a positive-sense single-stranded RNA genome [6]. Their stability is low, but the potential for mutation is quite high [4]. This virus has been considered as a smart virus because it shows different reactions and symptoms in living organisms and also has the ability to optimize these reactions and symptoms by increasing the proliferation of its genetic material for survival [7].

In comparison to SARS-CoV, SARS-CoV-2 has shown an enhanced level of pandemic and transmission risk. The data generated from the research studies have revealed that COVID-19 exhibited similar behavior and pathogenesis as that of beta-CoV identified in bats [4]. However, complete and clear data on the clinical expression of COVID-19 patients is not yet elucidated as the reported cases show symptoms from mild to severe infection and even result in the death of patients. The possible symptoms of COVID-19 mainly include headache, diarrhea, runny nose, fever, hemoptysis, and phlegm producing cough, etc [4]; however, there are many reports available about asymptomatic positive cases across the world. The patients mildly
affected show improved health conditions within a week while those severely infected experience severe problems in the respiratory tract due to alveolar injury that finally leads to death [2].

The person to person transmission of the disease is more likely to occur through respiratory droplets produced during coughing, sneezing, and talking [8]. Transmission can also occur when a healthy person comes in close contact with infected persons or their belongings. The period of infection and appearance of symptoms ranges from 2 to 14 days [1]. Although it is not yet fully studied, the health and economic losses caused to date are very high and these will rise dramatically in the future also till the discovery of the most effective and reliable solution such as vaccine [9]. However, there are some reports presenting that antiviral drugs such as remdesivir (GS-5734), a 1’-cyano-substituted adenosine nucleotide, etc. can be effective in the management of RNA viruses. Further, the reports suggested that chloroquine (CQ) can also inhibit coronavirus [4]. Unfortunately, as of now, there are no efficient treatment strategies available that can be used against SARS-CoV-2 infection [10].

In this context, it is believed that nanotechnology can play a pivotal role in the effective management of COVID-19 [11]. Nanotechnology usually deals with the designing and development of materials having dimensions in the range of 1 nanometer (nm) to hundreds of nanometers, which enables the design and fabrication of materials with a defined structure and molecular architecture. These materials exhibit unique and promising optical, electrical, chemical, physical, and biological properties. Nanotechnology in general and nanomaterials, in particular, has provided a novel platform for various applications in biomedical fields such as smart, specific and controlled drug delivery, diagnosis and treatment of many diseases including viral infections. [12,13]. Alphandéry [11] reported that nanotechnology can provide effective solutions for the management of COVID-19 through (i) the development of an affordable and rapid test for the diagnosis of COVID-19 which can be used globally for the entire population, (ii) the prevention of viral replication and RNA synthesis is possible by using nanomaterials that possess the ability to inhibit the interaction between SARS-CoV-2 and the cellular receptor ACE-2, (iii) the development of a new nanoparticles-based vaccine, and (iv) the restoration of innate immunity among infected patients. Considering these facts, in the present review, we have mainly focused on the COVID-19 pandemic and nanotechnology as a promising tool for the diagnosis, drug delivery, and treatment of COVID-19.

2. Diagnosis of COVID-19

Presently, the laboratory diagnostics of the viral infection is based on the following techniques:

2.1. Polymerase chain reaction (PCR) and sequencing

It is the predominant method to determine all kinds of coronaviruses [14]; however, RT-PCR has been found to be the most effective tool for the detection of SARS-CoV-2 [15]. After the genetic code of 2019-nCoV was published in China in early January, PCR-based tests are considered as a gold standard throughout the world for the detection of COVID-19 [16]. The identity of the viral RNA by the PCR technique (smears from the oral cavity and throat are taken) is determined. In addition, next-generation sequencing can also be useful for the rapid detection of SARS-CoV-2 [17].

2.2. Computer tomography

This method reveals ground-glass opacity in the lungs, which is a sign of viral pneumonia [18,19].

2.3. Plain chest radiography

It investigates inflammatory foci caused by the virus, fibrosis, and connective tissue occlusions in the lungs that may develop after the disease. In this connection, there are several studies available for the detection of COVID-19 using chest X-ray radiography. In addition, the current research makes use of artificial intelligence [20,21].

2.4. Ultrasound investigation

The investigation of the lungs using ultrasound is an important technique that is found to be precise for the visualization of pulmonary and pleural conditions in patients with suspected COVID-19 [22].
2.5. General and biochemical blood test

Viral infections are accompanied by dynamic changes in routine blood indices, such as white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, red blood cells, hemoglobin, neutrophil-lymphocyte ratio, platelets and platelet lymphocyte ratio [23]. Lymphocytes and platelet count have indicated significantly lower levels in severe infections compared to non-severe patients [24].

2.6. Immunoassays

These methods are based on the antigen–antibody reaction which reveals the substances of protein nature, including viruses. In laboratory diagnostics, items of interest are most often antibodies such as IgM, IgG, and IgA; by their concentration, the stage of the infection can be assessed and the ‘track record’ of previous diseases be retrieved [25]. For instance, Demey et al. [26] reported the results of four immune-chromatographic tests for the detection of antibodies against SARS-CoV-2 and assessed the antibodies’ emergence kinetics using these analyses in patients with positive PCR. The efficiency of the immuno-chromatographic analysis of IgM/IgG antibodies for the severe acute respiratory syndrome of coronavirus 2 (SARS-CoV2) was also presented by Imai et al. [27]. Table 1 summarizes some important conventional methods available for the detection of COVID-19 with their advantages and limitations [7].

2.7. Nano-based detection methods

To date, unique technologies of fabricating nanowire-biosensor chips based on silicon-on-insulator (SOI) structures have been developed. The main advantage of nanowires based on SOI structures as compared with nanowires from other materials and individually grown cylindrical nanowires is that the methods of their fabrication are compatible with complementary metal–oxide–semiconductor (CMOS) technology. This determines the potential of the entire system of the biosensor with SOI chips, i.e., of the SOI biosensor, as a universal platform for a wide-scale production of portable highly sensitive diagnostic system affordable for personal use [28]. In the case of the detection of COVID-19 antibody, an antigen–antibody complex should be formed as the detecting element, with IgM or IgG used as the antigen. The time required for assay is 5–15 min at an expected sensitivity of $10^{-12}$–$10^{-15}$ M.

Field-effect transistors based on graphene have already been reported for the determination of the viral load of COVID-19 in clinical nasopharyngeal swab specimens using specific antibodies against its protein [29]. The sensor was produced by coating graphene sheets of a field-effect transistor with a specific antibody against SARS-CoV-2 spike protein. SARS-CoV-2 spike antibody was immobilized onto the fabricated device through 1-pyrenebutanoic acid succinimidyl ester, an efficient interface coupling agent used as a probe linker. The detection limit of the SARS-CoV-2 target antigenic protein was 1 fg/ml. Herewith the specificity of the device was sufficiently high – the sensor could distinguish S-CoV-2 antigen protein from MERS-CoV protein.

Moitra et al. [30] devised a colorimetric bioassay based on gold nanoparticles. These gold nanoparticles are capped with thiol-modified antisense oligonucleotides (ASO) specific for N-gene (nucleocapsid phosphoprotein) of SARS-CoV-2 which can be efficiently used for diagnosis of COVID-19 in a time span of a few minutes. In the synthesis process, an all-inclusive targeting approach involving four of the ASO sequences covering two regions of the viral genome along with anisotropic plasmonic properties of gold nanoparticles are employed. The gold nanoparticles capped with thiol modified ASO aggregate can be employed for naked-eye detection within 10 minutes (Figure 2).

Baker et al. [31] reported the synthesis of polymer-stabilized multivalent gold nanoparticles bearing sialic acid derivative and their interaction with spike glycoprotein. It was observed that α, N-acetylenuraminic acid binds strongly

| Table 1. Conventional methods available for the detection of COVID-19 with their advantages and limitations Rabiee et al. [7]. |
|----------------------------------|-------------|----------------|----------------|
| Methods                        | Sensitivity of Detection | Time required for Analysis | Advantages                          | Limitations                        |
| Culture                        | 30–50%       | 1–3 days        | Appropriated for slow-growing pathogens | Risk of contamination, time-consuming |
| Next-generation sequencing (NGS) | -            | Around 1–2 weeks | Ability to fully recognize the genome, even mutations. Detection based on genes | Time-consuming, short reads, need for technical expertise |
| Immunoassays methods (e.g., ELISA) | 20–80%      | About 2 h with the kit | High sensitivity, ability to detect IgG and IgM antibodies in serum. Detection based on antibodies | Expensive to prepare antibody, limits the amount of antigen in samples, antibody instability Requires expensive instrument, long reaction times Difficult in primer design, false-positive results |
| RT-PCR                          | 95%          | 2 h             | Highly sensitive method                 | Non-specific sometimes imaging of COVID-19 is similar to other lung diseases |
| Loop-mediated isothermal amplification (LAMP) | >95%         | About 30 min | Rapid, simple, high specificity |                           |
| Computed tomography (CT)        | 97%          | Rapid           | Rapid analysis                          |                           |
with the spike glycoprotein and functions as a detection unit in a prototype lateral flow diagnostic device (Figure 3).

Sometimes the conventional detection techniques such as PCR-based methods may give false positive/negative results. The ability of PCR for precise detection of SARS-CoV-2 can be enhanced by using nanoparticles. It can be carried out through the conjugation of fluorescent nanoparticles to a specific probe used for viral RNA, followed by fluorescent detection of conjugated nanoparticles. It was reported that a minute (1 fg/ml) concentration of SARS-CoV-2 can be detected by using an anti-coronavirus antibody conjugated graphene sheet coated field-effect transistor [11]. The fluorescent zirconium quantum dots (Zr QDs) and magnetic nanoparticles in conjugation with the anti-coronavirus antibodies bind to the coronavirus. This complex can be isolated magnetically, and fluorescence can be measured at 412 nm [32]. The difference in the fluorescence of green fluorescence protein complex consisting of gold nanoparticles bound to SARS protein will show altered fluorescence as compared to complex without gold nanoparticles [11].

3. Nano-based vaccines for immunity development

The outbreaks of infectious diseases have generated the need for the development of effective vaccines. Vaccination is a process of introducing antigenic materials to trigger an individual’s immune system for the development of adaptive immunity against a pathogen [33]. However, there are many limitations of conventional vaccines to elicit immune responses effectively for the management of novel emerging pathogens due to drawbacks such as low stability in the bloodstream and inability to provoke prolonged and sufficient immune response [34,35]. As a result, higher titers of vaccines are needed to elicit therapeutic effects. But, the higher doses often lead to a greater risk of side effects [36].

COVID-19 is a global pandemic and hence, there is an urgent need to develop novel vaccines to stimulate a strong humoral and cellular immune response. The use of nanotechnology in vaccine development has lead to the birth of ‘Nanovaccinology’ or ‘Nano-based vaccines’ in therapeutics [37]. Nanoparticle-based vaccines can be an effective alternative to conventional vaccines owing to their strong immunostimulatory effects [38]; nanoparticle-based vaccines offer potential benefits such as high payloads, tunable sizes, tailorable surface properties, controllable drug release kinetics, and improved stability [39]. Vaccines are developed from live-attenuated microorganisms or inactivated/killed pathogens (first-generation vaccines), synthetic peptides (second-generation vaccines), and DNA vaccines (third-generation vaccines) [40]. These three vaccine types eliminate the risk of developing the disease, but they must be used in conjunction with an adequate adjuvant or delivery system. The combination of the vaccine with the adjuvant or delivery system should be safe, stable and have the ability to induce long-lived memory B and T cell responses, preferably with a single dose and a maximum of two doses and without the need of strict storage requirements [41]. DNA and RNA vaccines are
The mechanism of nanoparticles-based vaccine highly supports the utility of nanocarriers for target-specific delivery. Many nanoparticles are able to stimulate different immune cells to boost the host immunity. The size, shape, and surface chemistry of nanoparticles are significant factors that determine their potential to activate immune responses [44]. The size of the nanoparticles determines the cellular uptake mechanism (endocytosis, phagocytosis, macrophagocytosis, clathrin-dependent, and/or caveolae-mediated) [45]. The nanoparticles such as gold, carbon, dendrimers, polymers, and liposomes have the ability to induce cytokine and antibody responses [46,47]. In an interesting study, the administration of empty PEGylated liposomes was able to elicit IgM response in an in vivo model [48,49]. The size of nanoparticles helps to facilitate uptake by APCs, leading to effective antigen recognition and presentation. The modification of the surfaces of nanoparticles with different targeting moieties permit the delivery of antigens to specific receptors on the cell surface, and stimulates selective and specific immune responses [50].

The nanoparticles used for vaccine delivery typically have three different parts: (i) the material(s) that the nanoparticles are composed of natural polymers, synthetic polymers, inorganic substances, lipids, etc. (ii) immunogen or immunomodulatory agents such as antigens, DNA vaccines, siRNA, cytokines, etc. (iii) targeting and immune-stimulatory ligands that are added to the particle surface including immune specific ligands, tissue-specific ligands, and pathogen-associated molecular patterns (PAMPs). The composition of nanomaterial play an important role in transport, cellular uptake, and intracellular trafficking of the nanoparticles, and also, its biodegradability and biocompatibility. Likewise, it plays an important role in pharmacokinetic properties, the discharge rate, biodistribution, and bioavailability of the immunogen. The immunogen, which is a key part of a nano-based vaccine, might be attached to the nanoparticles in three different ways: (i) conjugation (covalent binding), (ii) adsorption (on the surface of the nanoparticles), and (iii) encapsulation (within the nanoparticles). The incorporation of PAMP ligands to the vaccine formulations can provoke inflammatory responses by stimulating pathogen recognition receptors (PRRs). These receptors are mainly expressed on immune cells together with macrophages, dendritic cells, and B cells. Toll-like receptors (TLRs) are a main cluster of PRRs. TLR ligands, such as CpG DNA, lipopolysaccharide (LPS), monophosphoryl lipid A, and muramyl peptides are strong adjuvants that are useful in a variety of vaccine formulations.

Nanoparticles are often classified as organic (e.g. polymeric, liposomes, virus-like particles, etc.) or inorganic (e.g. silver nanoparticles, gold nanoparticles, iron oxide, mesoporous silica nanoparticles, etc.). Such nanoparticles have attracted attention as potential delivery vehicles for vaccine antigens, which can both stabilize vaccine antigens and act as adjuvants [51,52]. Therefore, due to their immunogenic properties, various types of nanoparticles, including gold nanoparticles, spike protein nanoparticles, and hollow polymeric nanoparticles have been reported to have tremendous potential to induce an immune response against coronaviruses in animal models and in vitro [53]. The possible mechanism of nano-based vaccine has been elaborated in Figure 4.

4. Preventions and treatments

4.1. Nanoparticles-based antiviral coatings

SARS-CoV-2 is a gentle but deadly contagious virus capable of spreading from one individual to another around the world. It spreads mainly by two ways: when an infected person sneezes, coughs or a droplet lands on a surface or an object and if the person comes in contact with the contaminated surface and then touches any part of the body such as nose, mouth or eyes, may be infected [54]. Personal hygiene measures are recommended to prevent the spread of coronavirus, especially at places where individuals are in direct contact with patients. Washing hands with soap and water or with alcohol-based hand-rubs are effective for interrupting virus transmission. Recent studies have shown that coronavirus can remain viable or infectious on metal, glass, wood, fabric and plastic surface for many hours to some days [55]. It can be destroyed by ethanol (62–71%), hydrogen peroxide (0.5%) or sodium hypochlorite (0.1%) as these chemicals break the envelope that surrounds the virus [56].

It is practically impossible to sanitize surfaces all the time, and there is no guarantee that the surface will not be contaminated again. Hence, researchers aim to develop surface coating by using active chemicals, that can inactivate the spike glycoproteins as well as viral nucleotides. In the present scenario, nanotechnology can serve as an important tool for the designing of contamination-free equipment. The study revealed that metal-loaded nanocomposites or metal embedded copper nanoparticles in polymer matrices are very effective against viral pathogens. Moreover, the combination of copper nanoparticles with quaternary ammonium shell exhibits potential antiviral activity [57].

The previous studies have shown that various metal and metal oxide nanoparticles such as zinc oxide nanoparticles (ZnONPs) [58], cuprous oxide nanoparticles (CuONPs) [59], silver nanoparticles (AgNPs), nanosized copper (I) iodide particles (CuINPs) [60], gold nanoparticles (AuNPs), silica nanoparticles (SiONPs) [61] and also some quaternary ammonium cations commonly called QUATs [62] are capable of inactivating the virus.

In another study, Bhattacharjee et al. [63] reported that graphene oxide grafted with metal nanoparticles can be used for coating of personal protective equipment (PPE). Incorrect disposal of PPE is also hazardous and can spread the virus. Hence, a combination of graphene oxide with metal nanoparticles such as silver, iron, copper and zinc can prevent the PPE from contamination caused due to such viruses. Silver
and copper nanoparticles loaded on graphene oxide were found to be effective against enveloped and non-enveloped viruses.

Balagna et al. [64] evaluated the antiviral effect of silver nanocluster/silica composite coating deposited on filtering facepiece-3 (FFP3) facial mask toward SARS-CoV-2. The silver nanocluster/silica composite coating was deposited by the co-sputtering process. Silver nanoparticles possess antiviral properties, and hence can be impregnated in facial masks. The authors deposited silver nanocrystal/silica coating on disposable FFP3 masks. The radiofrequency co-sputtering process was used in a pure argon atmosphere. Scanning Electron Microscopy with Energy Dispersive Spectroscopy (EDS) was applied to observe the morphology and to detect the composition of the coating on the mask fibers. The study demonstrated that the silver nanocluster/silica coating deposited on the facial mask possesses virucidal activity. This antiviral coating is able to reduce the SARS-CoV-2 titer, and can be deposited in filtering media and on metallic, polymeric and glasses surfaces. Thus, silver nanocluster coating can provide safety in crowded areas such as hospitals, schools and supermarkets.

Surface-coated copper nanoparticles can also effectively block the virus infection. Polymer-based copper nanoparticles and other metal nanoparticles can be used as an antiviral coating which can be applied or sprayed on the surfaces. These nanoparticles were found to be very effective in the release of metal ions on the coated surface [65]. It was demonstrated that these ions can act as an antiviral, which can kill viruses adhered to various surfaces. The antiviral coating can also be used to minimize the spread of coronavirus [66]. The discovery of new antiviral material is essential because many diseases are caused by viruses. It is known from previous research that silver nanoparticles are broad-spectrum [67,68] and a new generation of antimicrobials [69]. Chen et al. [70] for the first time reported the antiviral activity of graphene-silver nanocomposite against enveloped and non-enveloped viruses. Graphene is a potential antimicrobial material with high carrier mobility and biodegradability. The antiviral activity of graphene oxide sheets along with silver nanoparticles was evaluated against enveloped and non-enveloped viruses, feline coronavirus (FCoV) with an envelope and infectious bursal disease virus (IBDV) without an envelope.

5. Toxicity of nanoparticles

Although nanoparticles can be useful for biomedical applications, they have a reverse side i.e. their toxicity, which needs to be addressed judiciously to optimize their use against COVID-19 treatment. Nanoparticles are being used due to their novel properties, but scientists across the globe have realized the importance of nanotoxicological studies. Taking into consideration the use of nanomaterials for the treatment of COVID-19, it implies that they can be delivered directly in the respiratory system which is the target site for the virus.

During the course of inhalation, nanoparticles can penetrate into the mucosal membrane lining of the respiratory tract. The nanoparticles smaller than 10 µm can easily enter into the respiratory system [71]. The inhaled nanoparticles entering into alveoli, may get accumulated and cause inflammation in the lungs [72]. It was reported that the toxicity of
nanoparticles to the respiratory system depends upon the structure, composition, and function of the mucosal membrane. For instance, bronchi and bronchioles are protected by the mucus layer wherein a single layer of cell separates inhaled air from blood capillaries. For efficient absorption of inhaled air, these cells have a larger surface area, which makes it prone to the damage caused by inhaled nanoparticles. During the normal functioning of lung tissues, all structural cells of the lungs including endothelial cells, alveolar macrophages, lymphocytes, mast cells, etc. form an inflammatory and repair system [73]. The cellular damage by nanoparticles is size-dependent. Smaller nanoparticles are more active and hence they can cause greater damage. The myofibroblast cells are activated and produce a collagen-rich extracellular matrix for keeping the alveolar structure intact [72]. The inhalation of silver nanoparticles of 14–15 nm was reported to induce the increased accumulation of alveolar macrophages and chronic inflammation [74]; 18–19 nm-sized silver nanoparticles caused abnormal cell infiltration, chronic alveolar inflammation, and small granulomatus lesions [75,76]. However, recurrent exposure to nanoparticles causes damage to the alveolar cell, which may further penetrate the blood vessels, and can be translocated from lung tissue to other organs via systemic circulation. Besides size-dependent toxicity, the dissolution of nanoparticle also plays an important role in their toxic effects. Nanoparticles release ions in the medium wherein they remain as suspension. The released ions can induce lung inflammation. However, still it is a matter of debate whether dissolution or non-dissolution contribute to the toxic effect of the nanoparticles [77]. The morphology of nanoparticles also contributes to their toxic effect. Zhu et al. [78] reported that nanofibres showed more toxicity than spherical nanoparticles of the same composition.

Nanoparticles with low solubility or degradation accumulate within the cells and tissues, where they can persist for a longer duration. It is because in the body there is no mechanism available to remove or discard the majority of nanoparticles. For instance, nasal exposure of gold nanoparticles to rat retained for 15 days. Whereas, the aggregates of silver nanoparticles were accumulated in the lungs for seven days [79]. Metal nanoparticles are well known to reduce cell viability and induction of reactive oxygen species leading to cellular stress [68,80]. Such studies suggest that metal-based nanoparticles sustain in the lung for long-duration whereby they can implicate in initiating and developing lung tissue damage. On the contrary, biodegradable nanoparticles (upto 8 nm) can be removed from the body through the renal system [81]. However, it will be difficult to remove the bigger nanoparticles. The nanoparticles can be rapidly cleared out either through the fast mucociliary action of the upper respiratory tract or across the alveolar macrophages [82].

At the cellular level the uptake, type of internalization and involvement of particular organelle results in nanoparticle cytotoxicity. While interacting with the cell membrane, nanoparticles can physically damage it. The nanoparticles entered inside the cell induce the accumulation of reactive oxygen species (ROS) up to a greater extent. The accumulated ROS interacts with the protein machinery of the cell and thus affects all the cell metabolic processes. They also show the toxicity to mitochondria and cause damage to nuclear DNA. In such a situation the exposed cell leads to apoptosis [80]. Consequently, the nanoparticles at higher concentrations or their accumulation result in the disorder of cellular homeostasis.

Considering all of the aforesaid toxic aspects, it can be said that inhalation of metal nanoparticles can manifest injury to lung tissue, resulting in the local and systemic pathophysiological conditions. Hence, there is a necessity to develop a sustainable nanotechnological solution for COVID-19 with least or no toxicity. Therefore, before use, a thorough study concerning nanotoxicity should be made for safety and reliability.

6. Conclusions

The outbreak of the coronavirus began in December 2019 and since then the researchers worldwide are engaged to find out novel solutions for the treatment of SARS-CoV-2. Diagnostics lead a crucial part in the control measures of COVID-19 as it can restrict the spread of the virus by rapid detection of infected patients. Researchers argue that nanotechnology could be the best approach for the control of SARS-CoV-2 in the absence of vaccines. Since the coronavirus has a structure of a similar scale as of the nanoparticles, nanotechnology-related tools can serve efficiently to manage this global pandemic. The authors also ascertain with the above views and consider nanotechnology as an effective tool for the prevention and management of COVID-19. The concerted efforts of researchers worldwide will help in overcoming this global pandemic and also in dealing with future virus outbreaks.

7. Expert opinion

Considerable reports are available demonstrating the antiviral efficacy of different nanomaterials against a variety of viruses including RNA viruses. From these facts, it is believed that nanotechnology will play a crucial role in the effective management of COVID-19 by the use of different nanomaterials. It is well-known that nanomaterials possess remarkable bioactivities including antiviral activity due to their unique physicochemical properties, therefore, it is obvious that nanomaterials having broad-spectrum antiviral activities can be effectively used in the management of SARS-CoV-2. Of course, toxicological concerns of nanomaterials used warrants extensive studies before their application. In addition, due to strong antiviral nature, specific nanoparticles can be used in the preparation of various nano-based disinfectants and sanitizers.

The dreaded disease caused by SARS-CoV-2 has encouraged scientists around the globe to search and develop highly sensitive diagnostic tools for the rapid and precise detection of the disease. It has been observed that different conventional techniques including quantitative real time polymerase chain reaction (qRT-PCR) are mainly used to detect COVID-19, but these approaches are reported to be time-consuming, tedious, and not useful for remote areas. In this context, we believe that the development of nano-based point-of-care (POC) biosensors such as chip-based and paper-based biosensors will be most effective for the rapid diagnosis of the virus and also for blocking the infection in the early stage which is low-cost, rapid and user-
friendly. Similarly, considering the recent therapeutic advancements in the field of nanotechnology for the last few years, it is obvious that this technology has emerged as an advanced tool in drug designing as well as drug targeting. Therefore, efforts should be made to use nanomaterials for targeting viral structures and removing the impact of SARS-CoV-2 infections.

In addition, nanoparticles-mediated drug delivery has enormous potential to overcome the challenges posed by conventional drug therapies; and thus, it has generated huge curiosity in the treatment of viral infections. Nanoparticles can be engineered to incorporate conventional antiviral drugs with enhanced stability at appropriate site of infection. The development of a reliable, safe, and effective vaccine against the SARS-CoV-2 is still under investigation. Several candidates have been either proposed or claimed for it, but till the time of writing this review, there is no licensed vaccine available that can be used against this dreaded virus.

As far as effective management strategies for COVID-19 are concerned, there is tremendous scope for nanotechnology as compared to conventional therapeutic and vaccine designs. It will not be an exaggeration if it is envisaged that the practice of innovative nanomedicine will have a huge positive impact on the treatment of dreaded infectious diseases like COVID-19. It will act as a promising therapeutic strategy against viral diseases and for improving treatment success rates. However, further thorough studies needed before the real potential of nanotechnology can be harnessed into safe and effective antiviral formulations for clinical use. It is necessary that scientists from various disciplines should work together to find effective solutions for the treatment of COVID-19 and provide some convincing strategies to manage the pandemic.

Perceiving nanoparticles as a promising tool for diagnosis, prevention, antiviral drug delivery, and therapeutics, the novel innovations are expected in the next 5 years that will revolutionize the treatment of viruses. It is hoped that the global scientific community will emphasize their research on the search for new nanosensor-based diagnostics, antiviral treatment strategies and vaccine development. Nanoparticles will be used worldwide in biomedical and clinical research to combat emerging and difficult-to-treat infections like COVID-19. However, more thorough research could improve the efficacy of antiviral drugs and reduce their side effects. The novel antiviral therapies using nanoparticles method unlocks new therapeutic approaches to combat aggressive viral diseases. Innovative nanomedicine can play a vital role in prevention, early diagnosis, and personalized therapy. It is expected that the main focus of future research will be the development of biocompatible and biodegradable nanocarrier systems that have no cytotoxicity, efficiently target specific sites of viral infection, and have reduced drug toxicity to other tissues.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments
MR and PG would like to thank NAWA Programme, Poland for financial support under the grant PPN/ULM/2019/1/00117/DEC/1 2019-10-02.

ORCID
Mahendra Rai http://orcid.org/0000-0003-0291-0422

References
Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.
1. Itani R, Tobaigy M, Al Faraj A. Optimizing use of theranostic nanoparticles as a life-saving strategy for treating COVID19 patients. Theranostics. 2020;10(13):5932–5942.
• The article focused on the role of nanoparticles in the treatment of COVID-19.
2. Sivansankarapillai VS, Pillai AM, Rahdar A, et al. On facing the SARS-CoV-2 (COVID-19) with combination of nanomaterials and medicine: possible strategies and first challenges. Nanomaterials. 2020;10(5):E852. DOI:10.3390/nano10050852.
• The article demonstrated the role of magnetic nanoparticles in RNA extraction of SARS-CoV-2.
3. Somvanshi S, Khatar PB, Saraf TS, et al. Multiphunctional nano-magnetic particles assisted viral RNA-extraction protocol for potential detection of COVID-19. Mat Res Inn. 2020;DOI:10.1080/14328917.2020.1769350.
• The article discussed about pandemic situation of COVID-19 and different opportunities for its treatment.
4. Uskokovic V. Why have nanotechnologies been underutilized in the global uprising against the coronavirus pandemic? Nanomedicine (Lond). 2020;15:1719–1734.
5. Rabiee N, Rabiee M, Bagherzadeh M, et al. COVID-19 and piocotechnology: potential opportunities. Med Hypotheses. 2020a;144:109917.
• The article discussed about pandemic situation of COVID-19 and different opportunities for its treatment.
6. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. J Microbial Immunol Infect. 2020. DOI:10.1016/j.mii.2020.03.022.
7. Rabiee N, Bagherzadeh M, Ghasemi A, et al. Point-of-use rapid detection of SARS-CoV-2: nanotechnology-enabled solutions for the covid-19 pandemic. Int J Mol Sci. 2020b;21:5126.
8. Sereen MA, Khan S, Kazmi A, et al. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;20:24:91–98.
9. Micah AE, Su Y, Bachmeier SD, et al. Health sector spending and spending on HIV/AIDS, tuberculosis, and malaria, and development assistance for health: progress towards sustainable development goal 3. Lancet. 2020;396:693–724.
10. Sarkar S. Silver nanoparticles with bronchodilators through nebulisation to treat COVID 19 patients. J Curr Med Res Opin. 2020;3(4):449–450.
11. Alphandéry E. The potential of various nanotechnologies for coronavirus diagnosis/treatment highlighted through a literature analysis. Bioconjugate Chem. 2020;31:1873–1882. • This article is very interesting focused particularly on possibilities of nanotechnology in the diagnosis and treatment of COVID-19.
12. Ahmadi S, Rabiee N, Bagherzadeh M, et al. Stimulus-responsive sequential release systems for drug and gene delivery. Nano Today. 2020;34:100914.

13. Rabiee N, Bagherzadeh M, Ghadir AM, et al. Green synthesis of ZnO NPs via Salvia hispanica: investigation of potential antioxidant, antibacterial, mammalian cell viability, H1N1 influenza virus inhibition and photocatalytic activities. J Biomed Nanotechnol. 2020;16(4):456–466.

14. Shen M, Zhou Y, Ye J, et al. Recent advances and perspectives of nucleic acid detection for coronavirus. J Pharm Anal. 2020;10:97–101.

15. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020;25(3):2000045.

16. Chu DKW, Pan Y, Cheng SMS, et al. Molecular diagnosis of a novel coronavirus (2019-nCoV) causing an outbreak of pneumonia. Clin Chem. 2020;66:549–555.

17. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–1069.

18. Ardakani AA, Kanafi AR, Acharya UR, et al. Application of deep learning technique to manage COVID-19 in routine clinical practice using CT images: results of 10 convolutional neural networks. Comp Bio Med. 2020;121:103795.

19. Lei DP. The progression of computed tomographic (CT) images in patients with coronavirus disease (COVID-19) pneumonia. J Infect. 2020;80:e30–e31.

20. Ucar F, Korkmaz D. COVID diagnosis-net: deep bayes-squeeze net based diagnostic of the coronavirus disease 2019 (COVID-19) from X-ray images. Med Hypoth. 2020;140:109761. DOI: 10.1016/j.mehy.2020.109761.

21. Panwar H, Gupta PK, Siddiqui MK, et al. Application of deep learning for fast detection of COVID-19 in X-rays using nCOVnet. Chaos, Solitons Fractal. 2020;138:109944.

22. Inchingolo R, Smargiassi A, Moro F, et al. The diagnosis of pneumonia in a pregnant woman with COVID-19 using maternal lung ultrasound. Am J Obstetrics Gynecol. 2020;223:9–11.

23. He R, Lu Z, Zhang L, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol. 2020;127:104361. DOI: 10.1016/j.jcv.2020.104361.

24. Kermali M, Khalsa RK, Pillai K, et al. The role of biomarkers in diagnosis of COVID-19 – A systematic review. Life Sci. 2020;254:117788.

25. Vogel G. New blood tests for antibiotics could show true scale of coronavirus pandemic. Science Mag. 2020. DOI:10.1126/science.abbb0828.

26. Demey B, Daher N, François C, et al. Dynamic profile for the detection of anti-SARS-CoV-2 antibodies using four immunochromatographic assays. J Infect. 2020;81:e6–e10.

27. Imai K, Tabata S, Ikeda M, et al. Clinical evaluation of an immunochromatographic IgM/IgG antibody assay and chest computed tomography for the diagnosis of COVID-19. J Clin Virol. 2020;128:104393.

28. Ivanov YD, Malsagova KA, Pleshakova TO, et al. Ultrasensitive detection of 2,4-dinitrophenol using nanowire biosensor. J Nanotech. 2018;2018:9549853. DOI:10.1155/2018/9549853.

• This article is about the application of nanowires in the develo- pment of nanosensors for effective detection of SARS-CoV-2.

29. Seo G, Lee G, Kim M, et al. Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor. ACS Nano. 2020;14(4):5135–5142.

30. Moitra P, Alafaeef M, Dighe K, et al. Selective naked eye detection of SARS-CoV-2 mediated by N gene targeted antisense oligonucleotide capped plasmiconic nanoparticles. ACS Nano. 2020;14(7):7617–7627.

31. Baker AN, Richards SJ, Guy CS, et al. The SARS-CoV-2 spike protein binds sialic acids and enables rapid detection in a lateral flow point of care diagnostic device. Chem Rev. 2020;DOI:10.1021/acscentsci.0c00855.

32. Ahmed SR, Kang SW, Oh S, et al. Chiral zirconium quantum dots: A new class of nanocrystals for optical detection of coronavirus. Heliyon. 2018;4:e00766.

• This article is focused on the application of nanoparticles in fluorescence-based detection of SARS-CoV-2.

33. Chattopadhyay S, Chen JY, Hu CMJ, et al. Nanoparticle vaccines adopting virus-like features for enhanced immune potentiation. Nanotheranostics, 2017;1244–260.

34. Arnon R, Ben-Yedidia T, Old and new vaccine approaches. Int Immunopharmacol. 2003;3:1195–1204.

35. Kim M, Park J, Shon Y, et al. Nanotechnology and vaccine develop- ment: A review. Asian J Pharm Sci. 2014;9(5):227–235.

36. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200–1205.

37. Mamo T, Poland GA. Nanovaccination: the next generation of vaccines meets 21st century materials science and engineering. Vaccine. 2012;30:6609–6611.

38. Zaman M, Good MF, Toth I. Nanovaccines and their mode of action. Methods. 2013;60(3):226–231.

39. Zhao L, Seth A, Bibow N, et al. Nanoparticle vaccines. Vaccine. 2014;32:327–337.

40. Lugade AA, Bharali DJ, Pradhan V, et al. Single low-dose un-adjuvanted HBsAg nanoparticle vaccine elicits robust, durable immunity. Nanomed Nanotechnol Biol Med. 2013;9(7):923–934.

41. Salvador A, Sandgren KJ, Liang F, et al. Design and evaluation of surface and adjuvant modified PLGA microspheres for uptake by dendritic cells to improve vaccine responses. Int J Pharm. 2015;496(2):371–381.

42. Eidi H, Joubert O, Attik G, et al. Cytotoxicity assessment of heparin nanoparticles in NR8383 macrophages. Int J Pharm. 2010;396(1–2):156–165.

43. Diaz-Arévalo D, Zeng M. Nanoparticle-based vaccines opportunities and limitations. In: Shengka R, editor. Nanopharmaceuticals. UK: Esvlier; 2020. p. 135–150.

44. Smith DM, Simon JK, Baker JR. Applications of nanotechnology for immunology. Nature Rev Immunol. 2013;13:592–605.

45. Foged C, Brodin B, Frokjaer S, et al. Article size and surface charge affect particle uptake by human dendritic cells in an in vitro model. Int J Pharm. 2005;298:315–322.

46. Vallihov H, Qin J, Johansson SM, et al. The importance of an endotoxin-free environment during the production of nanoparticles used in medical applications. Nano Lett. 2006;6:1682–1686.

47. Mottram PL, Leong D, Crimen-Irwin B, et al. Type 1 and 2 immu- nity following vaccination is influenced by nanoparticle size: formulation of a model vaccine for respiratory syncytial virus. Mol Pharm. 2007;4:73–84.

48. Wang X, Ishida T, Kowa H. Anti-PEG IgM elicited by injection of liposomes is involved in the enhanced blood clearance of a subsequent dose of PEGylated liposomes. J Control Release. 2007;119:236–244.

49. Ishida T, Wang X, Shimizu T, et al. PEGylated liposomes elicit an anti-PEG IgM response in a T cell-independent manner. J Control Release. 2007;122:349–355.

50. Kheirrollahpour M, Mehrabi M, Dounighi N, et al. Nanoparticles and vaccine development. Pharm Nanotech. 2020;8:6–21.

51. Hajizade A, Ebrahim F, Salmanian A, et al. Nanoparticles in vaccine development. J App Biotech Report. 2014;4(4):125–134.

52. Poon C, Patel A. Organic and inorganic nanoparticle vaccines for prevention of infectious diseases. Nano Express. 2020;1:012001.

53. Nikkaen G, Abbaszadeh S, Yousefnejad S. Application of nanomate- rials in treatment, anti-infection and detection of coronaviruses. Future Med. 2020;15:1743–5889.

54. Tong Y, Ruiqi RM, Leung D, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199–1207.

55. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418–423.
56. Kampf G, Todt D, Pfaender S, et al. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. J Hosp Infect. 2020;104(3):246–251.

57. Sportelli MC, Longano D, Bonerba E, et al. Electrochemical preparation of synergistic nanoantimicrobials. Molecules. 2020;25:49.

58. Tavakoli A, Ateai-Pirkooh A, Mm Sadeghi G, et al. Polyethylene glycol-coated zinc oxide nanoparticle: an efficient nano weapon to fight against herpes simplex virus type 1. Nanomedicine (Lond). 2018;13(21):2675–2690.

59. Hang X, Peng H, Song H, et al. Antiviral activity of cuprous oxide nanoparticles against hepatitis C virus in vitro. J Virol Methods. 2015;222:150–157.

60. Fujimori Y, Sato T, Hayata T, et al. Novel antiviral characteristics of nanosized copper(I) iodide particles showing inactivation activity against 2009 pandemic H1N1 influenza virus. Appl Environ Microbiol. 2011;78(4):951–955.

61. Lysenko V, Lozovski V, Lokshyn M, et al. Nanoparticles as antiviral agents against adenoviruses. Adv Nat Sci: Nanosci Nanotechnol. 2018;9:025021.

62. Torkelson A, da Silva AK, Love DC, et al. Investigation of quaternary ammonium silane-coated sand filter for the removal of bacteria and viruses from drinking water. J Appl Microbiol. 2016;113:196–207.

63. Bhattacharjee S, Joshi R, Chughtai AA. Graphene modified multifunctional personal protective clothing. Adv Mater Interfaces. 2019;6:1900622.

64. Balagna C, Perero S, Percivalle E, et al. Virucidal effect against coronavirus SARS-CoV-2 of a silver nanocluster/silica composite sputtered coating. Ceramics. 2020;1:100006.

**Interesting article focusing virucidal efficacy of nanomaterials in the management of SARS-CoV-2.**

65. Rai M, Deshmukh SD, Ingle AP, et al. Metal nanoparticles: the protective nanoshield against virus infection. Crit Rev Microbiol. 2016;42:46–56.

66. Dicastillo CL, Vidal CP, Falco I, et al. Antimicrobial bilayer nanocomposites based on the incorporation of as-synthesized hollow zinc oxide nanotubes. Nanomaterials (Basel). 2019;10(3):503.

67. Gaikwad S, Ingle A, Gade A, et al. Antiviral activity of mycosynthesized silver nanoparticles against herpes simplex virus and human parainfluenza virus type 3. Int J Nanomed. 2013;8:4303–4314.

68. Rai M, Birla S, Ingle AP, et al. Nanosilver: an inorganic nanoparticle with myriad potential applications. Nanotechnol Rev. 2014;3(3):281–309.

69. Rai MK, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotech Adv. 2009;27:76–83.

**The article focused on the antiviral efficacy of silver nanoparticles.**

70. Chen YN, Hsieh CT, et al. Antiviral activity of graphene–silver nanocomposites against non-enveloped and enveloped viruses. Int J Environ Res Public Health. 2016;13:430.

71. Kumar S, Khilnani A, Sharma SK. Predictors of requirement of mechanical ventilation in patients with chronic obstructive pulmonary disease with acute respiratory failure. Lung India. 2013;30(3):172–182.

72. Nho R. Pathological effects of nano-sized particles on the respiratory system. Nanomed Nanotechnol Bio Med. 2020;29:102242.

73. Kasper M, Barth K. Potential contribution of alveolar epithelial type I cells to pulmonary fibrosis. Biosci Rep. 2017;37(6):BSR20171301.

74. Song KS, Sung JH, Ji JH, et al. Recovery from silver-nanoparticle-exposure-induced lung inflammation and lung function changes in Sprague Dawley rats. Nanotoxicology. 2013;7:169–180.

75. Sung JH, Ji JH, Park JD, et al. Subchronic inhalation toxicity of silver nanoparticles. Toxicol Sci. 2009;108(2):452–461.

76. Hadrup N, Sharma AK, Loeschner K, et al. Pulmonary toxicity of silver vapours, nanoparticles and fine dusts: A review. Regulatory Toxicol Pharmacol. 2020;115:104690.

77. Buzea C, Pacheco I. Toxicity of nanoparticles. Nanotech Eco-Efficient Const. 2019;705–754. DOI:10.1016/b978-0-08-102641-0.00028

78. Zhu M, Nie G, Meng H, et al. Physicochemical properties determine nanomaterial cellular uptake, transport, and fate. Acc Chem Res. 2013;46(3):622–631.

79. Yu LE, Yung LYL, Ong CN, et al. Translocation of gold nanoparticles after inhalation exposure in rats was observed. Nanotoxicology. 2007;1:235–242.

80. Gupta I, Duran N, Rai M. Nano-silver toxicity: emerging concerns and consequences in human health. In: Rai M, Cioffi N, editors. Nano-antimicrobials: progress and Prospects. Verlag Germany: Springer; 2012. p. 525–548.

81. Longmire M, Choyke PL, Kobayashi H. Clearance properties of nano-sized particles and molecules as imaging agents: considerations and caveats. Nanomedicine (Lond). 2008;3(5):703–717.

82. Osman N, Sexton D, Saleem I. Toxicological assessment of nanoparticle interactions with the pulmonary system. Nanotoxicology. 2020;14(1):21–58.

**This article is focused on possible toxicological concerns of nanoparticles particularly with pulmonary systems.**