



# Engineered nanomaterials as fighters against SARS-CoV-2: The way to control and treat pandemics

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## Abstract

In this editorial trend, we aim to collect and present recently available data about the characteristics of SARS-CoV-2 virus, severity, infection, replication, diagnosis, and current medications. In addition, we propose the role of nanomaterials in controlling and treating COVID-19 through their antiviral and antibacterial potential with suggested action mechanisms indicating the capability of interaction between these nanomaterials and SARS-CoV-2. These nanomaterials might be among the possible and most effective cures against coronavirus.

**Keywords** Corona viruses · Nanomaterials · COVID-19 · Nano-vaccines · Nanodrugs

## Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a lethal beta-type virus belonging to a related group of viruses known as coronaviruses, leading to serious infections in the respiratory tract of humans (Fan et al. 2019; Sivakumar 2020; Yang and Wang 2020). Many human coronaviruses have been discovered such as SARS-CoV, HCoV NL63, HKU1, MERS-CoV, and SARS-CoV-2 causing COVID-19 disease (Su et al. 2016; Zhu et al. 2020). The name of coronaviruses was derived from Latin corona meaning crown, the name corresponds to their unique morphology due to the presence of viral spike proteins (Chafekar 2012; Lopez 2007).

Coronaviruses have large spherical structures with an average diameter of 120 nm, and they have a lipid bilayer envelope of about 80 nm and 20 nm long spikes (Buzon et al. 2011; Fehr and Perlman 2015; Goldsmith et al. 2004; Yang and Wang 2020). The members of beta-coronavirus possess additional short-like protein called hemagglutinin esterase (HE) on their surfaces (Fehr and Perlman 2015). Interestingly, the structural proteins of the membrane, envelope, and the spike are anchored. In December 2019, COVID-19 emerged for the first time in China and has quickly-transmitted in the world (Angel-Korman et al. 2020). Recently, COVID-19 pandemic outbreak was recently-declared by the World Health Organization (WHO) (Angel-Korman et al. 2020).

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## Severity of COVID-19

Unlike SARS-CoV, COVID-19 transmission takes place during the prodromal period when the infected persons are mildly ill and carrying on with their common activities, facilitating spread of infection (Liu et al. 2020). Direct contact with infected individuals and sneezing or coughing (droplets spread) are the main causes of person-to-person transmission (Chan et al. 2020; Thompson 2020). According to WHO, individuals at risk include elderly (> 60 years old); cardiac, diabetic, chronic respiratory, cancer patients, and individuals in long-term care facilities (Kabir et al. 2020).

## SARS-CoV-2 infection and replication

The virus relies on the ACE2 receptor not only for host cell entry but also for subsequent viral replication (Zhang et al. 2020b). High viral loads have been observed in the lower respiratory tract, proposing that the virus might have a higher affinity for the epithelium of the lower respiratory tract and indicating a need for repeat testing of the upper or lower respiratory tract samples in the setting of an initial negative result of nasopharyngeal or throat swab in a suspected case (Jansen et al. 2011; McCullough et al. 2013; Rai et al. 2020). ACE2 receptors' presence in the extrapulmonary tissues (heart, kidney, endothelium, and intestine) could also explain the multiorgan dysfunction observed in patients (Zhang et al. 2020a). SARS-CoV-2 is known to cause a delayed type I interferon response during the initial phases of infection (Frieman and Baric 2008). Infection and viral replication lead to activation of neutrophils, macrophages, and monocytes (Nikitina et al. 2018). Th1/Th17-induced specific antibodies are produced (Mitsdoerffer et al. 2010). RNA viruses such as SARS-CoV and MERS are recognized pathogen associated molecular patterns by endosomal RNA receptors, TLR7 and TLR3, and the cytosolic RNA sensor, RIG-I/MDA5 (Kell and Gale Jr 2015; Poeck et al. 2010; Takeuchi and Akira 2008).

## Diagnosis of COVID-19

WHO has published diagnostic criteria that help identify patients requiring confirmation of COVID-19 through either PCR or antibody detection tests (Vos et al. 2019). These criteria include several epidemiological and clinical criteria that the patient has to fulfill in order to be either COVID-19 suspected or confirmed case (<https://www.cdc.gov/coronavirus/2019-ncov/community/correction-detention/guidance-correctional-detention.html>). History of patients infected with coronavirus disease 2019 (COVID-19) can include international travel to where COVID-19 is highly-prevalent. Fever, fatigue, cough, and breath shortness are the most

common symptoms that can appear 2–14 days after exposure (Casella et al. 2020).

Coronaviruses-derived illness can be investigated through many laboratory tests. Specific laboratory tests include serology for viral antigen, molecular testing, and viral culture (Kabir et al. 2020; Storch 2000). All these tests can be used to confirm infection with coronavirus. Non-specific laboratory findings in COVID-19 include lymphocytopenia, thrombocytopenia, elevated CRP, elevated ALT, AST, creatine kinase, D-dimer, and markers of cell damage, e.g., troponin, lactate dehydrogenase, interleukin-4, and procalcitonin (Lippi and Plebani 2020).

The chest x-ray remarks of a suspected coronavirus case can be similar to pneumonia (Jacobi et al. 2020). Severe cases of COVID-19 progressing to acute respiratory distress syndrome (ARDS) can show a typical “white-out” on chest x-ray (Venugopal et al. 2020). There are no specific echocardiography/ultrasound findings associated with coronavirus infection (Zheng et al. 2020). Non-specific echocardiographic findings can include left ventricular systolic dysfunction and pericardial effusion (Pérez-Casares et al. 2017). Chest CT scan findings in patients infected with coronavirus can include unilateral or bilateral pneumonia, mottling and ground glass opacity, focal or multifocal opacities, consolidation, and septal thickening with sub-pleural and lower lobe involvement more likely (Wu et al. 2020).

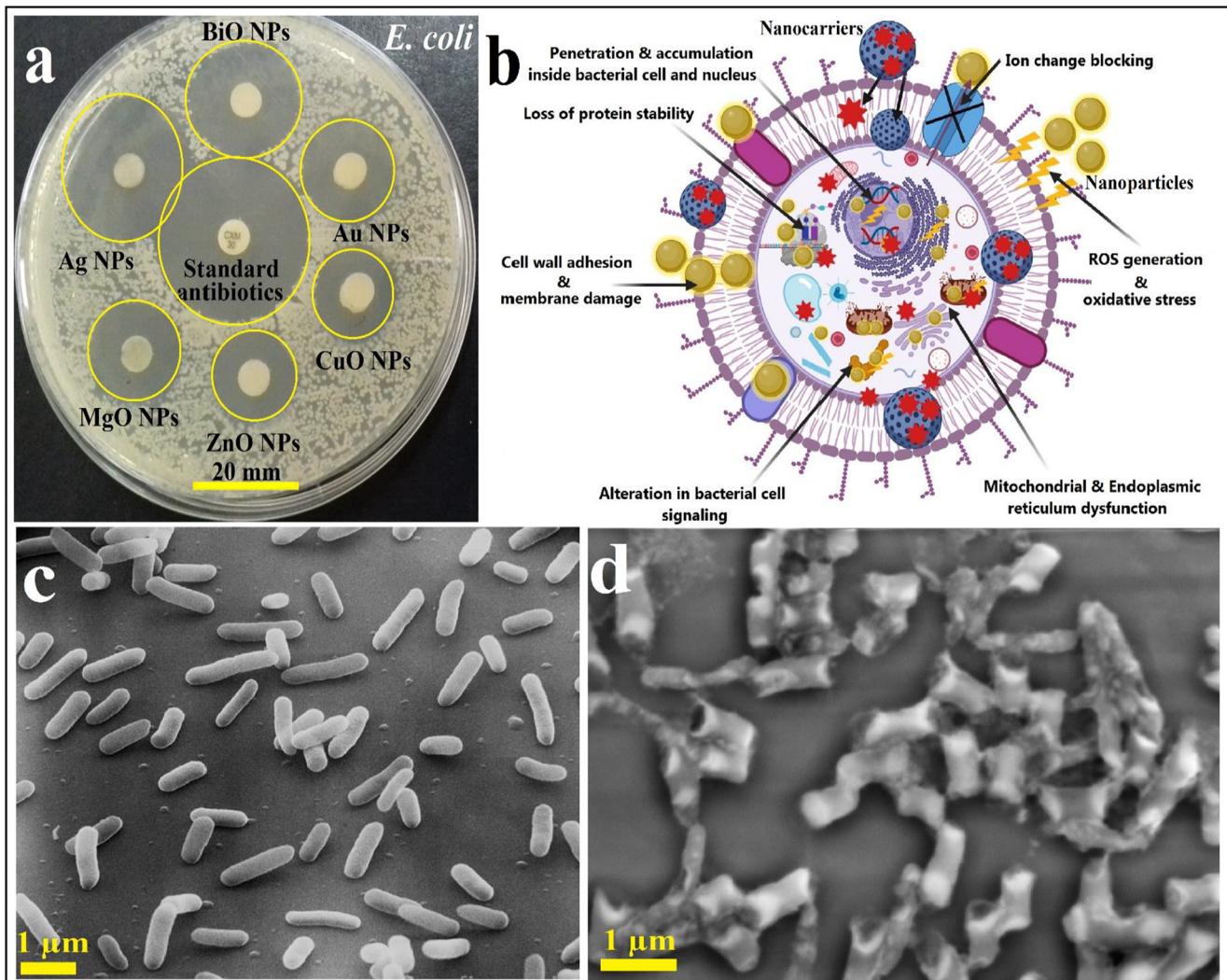
## COVID-19 current medications

Treatment of coronavirus infection includes supportive measures and symptomatic management. No specific treatment is available. Given the emergence of the cases during the influenza season, all patients presenting with COVID-19 were given oral and intravenous antibiotics and oseltamivir (75 mg twice daily via oral route) empirically (Control and Prevention 2014).

Corticosteroids (methyl prednisolone 40–120 mg/day) were given as a combined regimen if severe community-acquired pneumonia was diagnosed (Chen et al. 2011). Oxygen support (e.g., via nasal cannula and invasive mechanical ventilation) was given to patients indicated by the severity of hypoxemia (Curley et al. 2015). Surgery is not indicated in the management of COVID-19. Investigational therapies include hydroxychloroquine alone or in combination with azithromycin, remdesivir, and lopinavir/ritonavir. Currently, avoiding virus exposure is the best way to prevent the infection (Organization 2020).

## Nanomaterials as promising nano-vaccines and nano-drug

Nanotechnology through a large variety of nanomaterials (NMs) possessing multiple structures, properties, and



**Fig. 1** Antimicrobial potential of different synthesized NPs where (a) measuring the activity of different NPs by zone of inhibition (ZOI) method against *E. coli* bacterial cells, (b) suggested reaction mechanism of some nanoparticles (Ag and Au NPs) and drugs nanocarriers against bacterial cells (I): NPs are firstly-interact with the external part of the pathogenic bacteria and change their membrane composition, and then they easily-enter bacterial cells because of their small nano-size; (II) NPs are quickly-diffused across bacterial cells and interacted with the main bacterial organelles and bio-molecules and increased cellular toxicity, loss of protein stability, and finally genotoxicity; (III) NPs generated

active ROS inside bacterial cells and initiated bacterial cell disruption; and (VI) NPs have alternated the cellular sign system causing cell disorder. Also, NPs might serve as a vehicle to deliver their ions to the bacterial cytoplasm leading to a reduction in the proton motive force (PMF) which might decrease the bacterial cell pH to less than 3.5, and promoting the liberations of their ions), (c) normal *E. coli* growth without the effect of any synthesized NPs which appears as normal cell with a rigid cell wall and high cell count, and (d) malformed and distorted bacterial cell (*E. coli*) following the treatment of NPs suggesting the usage of NPs in fighting the secondary bacterial infection associated with viral diseases

characteristics can offer a revolutionary solution for the control and treatment of this disease. Many types of NMs showed very promising antiviral and antimicrobial activities which could be used as nano-vaccines to prevent microbial biofilm formation and the adsorption of microbes onto the surfaces and to control their transmission as shown in Fig. 1 (Abd Elkodous et al. 2019a, b; 2020; Chen and Liang 2020; El-Sayyad et al. 2020; Kim et al. 2020; Mohamed et al. 2020; Tran et al. 2020; Wong et al. 2020).

The antimicrobial activity results of some green synthesized metal NPs (such as Ag NPs, and Au NPs) should be

considered. The biogenic Au NPs mostly-displayed mild antibacterial activities against the highly-pathogenic bacteria (Aina et al. 2019; Elegbede et al. 2020). Sunday A. Ojo et al. (Ojo et al. 2016) investigated the antimicrobial potential of the green synthesized Au and Ag-Au alloy NPs, and the results indicated that they displayed growth inhibitions of 66.67–90.78% against strains of *Aspergillus fumigatus* and *Aspergillus niger* at a concentration of 200 µg/ml. In addition, Ag-Au NPs exhibited tremendous antifungal activities. An interesting result of nearly 100% inhibition of *A. flavus* growth after the treatment with Ag-Au NPs at a concentration of

150 µg/ml was reported (Lateef et al. 2016). The strong anti-fungal potential of Ag-Au NPs can be attributed to the adhesion on the microbial cell wall, subsequent suppression of fungal spores, then cytoplasmic content leakage, and finally microbial cell death (Elegbede et al. 2019).

The antimicrobial characteristics of some nanomaterials depend on their size, shape, surface features, and surface charge. As a result, their toxicological effects are controllable by the employed concentration (Sportelli et al. 2020). The toxic levels of NPs must be taken into consideration before designing any nano-drug, and the antimicrobial minimum inhibitory concentration (MIC) should be measured (Abdel Maksoud et al. 2020; El-Batal et al. 2020).

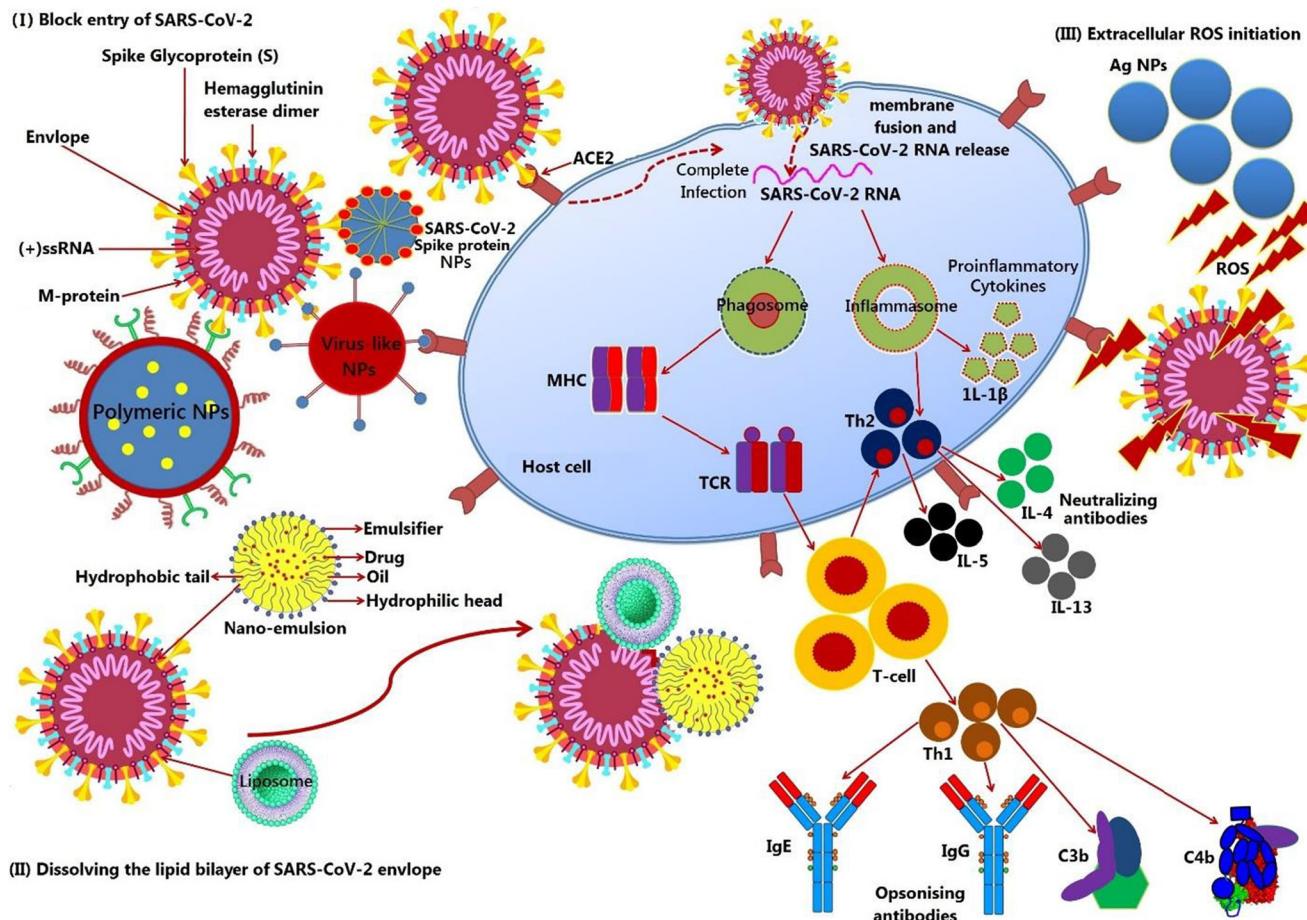
Many studies focusing on reaction mechanisms and cytotoxicity are needed before the development of reliable nano-vaccines and nano-drug (Abd Ellah et al. 2020).

Immune system-stimulating nano-vaccines could be easily-assembled through either encapsulation of viral parts

within NMs or via decoration (covalent functionalization) on the surface of many suitable NMs such as virus-like nanoparticles (NPs), solid-lipid NPs, liposome-based NPs, and biodegradable polymer-based NPs (Dhakal and Renukaradhy 2019; Xu et al. 2020).

In addition, many types of NMs such as TiO<sub>2</sub> NPs, ZnO NPs, and Cu NPs with very small concentrations could be employed to control the disease via surfaces' coating and disinfection at hospitals and public places (Akinola et al. 2020; Xu et al. 2020). Moreover, self-assembled protein NPs obtained through recombinant technologies are considered on the most promising nano-vaccines against respiratory viruses (Scheerlinck and Greenwood 2008; Schneider-Ohrum and Ross 2012).

Christopher M. Coleman et al. reported a unique nano-vaccine based on lipid nanoparticles carrying SARS-CoV and MERS-CoV spike proteins without any viral proteins which effectively-induced antibody responses in mice (Coleman et al.



**Fig. 2** Proposed reaction mechanisms of various engineered NMs against SARS-CoV-2, action mechanisms outside host cell (I) blocking of virus entry through either binding with the virus spike protein or blocking its cell receptor (ACE2) by virus-like NPs, polymeric NPs, and SARS-CoV-2 spike protein NPs (has not been prepared yet); (II) dissolving the lipid bilayer of SARS-CoV-2 envelope by nano-emulsion, liposomes, and solid-lipid NPs; and (III) initiation of extracellular ROS by Ag NPs.

Actions inside host cell include activation of transcription factors by receptor signaling as a response of viral RNA and either the formation of pro-inflammatory cytokines (IL-1B) and activation of Th2 pathway ending with the formation of neutralizing antibodies (IL-4, IL-5, and IL-13) or Th1 pathway activation and the formation of opsonizing antibodies (IgE, C4b, C3b, and IgG)

2014). Similarly, Hyo-Jung Park et al. developed two MERS-CoV vaccines from spike nanoparticles and spike protein-expressing recombinant adenovirus 5 (Park et al. 2017). Both vaccines triggered immune responses of Th1 and Th2.

Choi et al. (2017) reported another nano-vaccine for MERS-CoV in mice; the vaccine was developed from human Fc4-fused eS1–770 spike protein of the virus. After 10 days, they discovered large quantity of antibodies against MERS-CoV, while Ye V. Liu et al. tested vaccines based on virus-like particles (VLPs) similar in morphology and size to the wild SARS-CoV, comprising SARS spike protein conjugated with influenza M1 protein (Liu et al. 2011). Upon treatment, mice protection from death, reducing the lung infection and antibodies against the virus, were achieved.

Another study which showed the great promise of zirconia ( $\text{ZrO}_2$ ) NPs as antiviral candidates against H5N1 pathogenic influenza virus in mice was reported by Huo et al. (Huo et al. 2020). Their results revealed that  $\text{ZrO}_2$  NPs treatment resulted in a reduction in the virus replication, pro-inflammatory cytokines' over expression, and less lung injury.

## Reaction mechanisms of NMs against SARS-CoV-2

Indeed, NMs can be employed as either nano-vaccines to prevent viral infection and to control its spread or as nano-drugs for the treatment (Panda et al. 2020). Nano-vaccines are more effective than traditional vaccines because they are capable of stimulating the immune response (cell-mediated and humoral) of the body to form antibodies and to prevent it from spreading by blocking its entry to the host cell (Sekhon and Saluja 2011). In addition, nano-drugs can be used as nasal drops and can achieve effective targeting of a particular antigen for more effective treatment (Mehrabi et al. 2020).

The action mechanisms start when the NMs react with the virus through hydrogen bonding interactions and electrostatic attractions or when NMs enter the host cell through transient pores in its cell membrane to fight the virus inside (Verma et al. 2008).

The proposed action mechanisms of nano-vaccines and nano-drugs against SARS-CoV-2 can be classified into two categories, the action before virus entering to the host cell (nano-vaccines) and after entering it (nano-drugs). Firstly, several types of nano-vaccines such as virus-like NPs and polymeric NPs can effectively-block virus entry through blocking ACE2 cell receptor or virus spike protein through which it enters the host cell through endocytosis mediated by clathrin (Zhou et al. 2020).

SARS-CoV-2 spike protein-loaded NPs can be prepared to either block virus entry or activate the immune system to form antibodies against the virus. In addition, liposomes and nano-emulsion can dissolve the lipid bilayer envelope of the virus and destroy its structure, and inorganic NPs (Ag NPs) can

effectively-initiate extracellular reactive-oxygen species (ROS) to kill the virus (El-Batal et al. 2018).

Secondly, after virus entry to the host cell, NMs can stimulate ROS and enhance lymphocyte proliferation, over expression of cytokines, and the formation of either neutralizing antibodies or opsonizing antibodies through Th1 or Th2 immune responses as shown in Fig. 2.

In addition, NPs such as  $\text{TiO}_2$ , Ag, and Au can reduce the risk of high mortality among patients with COVID-19 due to hyperactivity of blood platelets which can lead to the formation of deadly blood clots (Akinola et al. 2020; Ojo et al. 2016). Moreover, serious complications such as heart attacks and strokes can be also suppressed (Elegbede et al. 2020). Coagulation of blood through lysis of blood clots can significantly-reduce the severity of COVID-19.

## Conclusion

In this editorial trend, we covered most known data about coronavirus, properties, family identification, its severity, method of infection, and replication. In addition, we discussed its diagnosis and highlighted the currently-available medications to deal with its driven symptoms and effects. Finally, we proposed multiple nanomaterials that can be used as fighters against this disease, and we have classified them according to the mode of action into nano-vaccines and nano-drugs and revealed the way by which they can resist the virus. However, intensive efforts should be devoted for investigating the efficiency of these nanomaterials against viral samples as a step towards cure development. Importantly, with this high rate of dissemination of viruses and the frustrating slow drug development, there is an urgent need for developing new nanomedicines of high quality, safety, and availability to all countries at a reasonable cost.

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**Authors' contributions** (MAE, and GSE manuscript writing, draw figures and revision. MMA conducted manuscript moderation and revision).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** Not required.

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