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Uses of Nano-materials Against Coronaviruses.

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أشهد ان الطلبة قد قاموا بالتعديلات والتصحيحات المطلوبة من طرف لجنة التقييم / المناقشة، وان المطابقة بين النسخة الورقية والإلكترونية استوفت جميع شروطها.

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ملاحظة :لاتقبل أي شهادة بدون التوقيع والمصادقة.

Dedication

To my dear Mum

The one who gave me life, who supported me in joys and sorrows

To my dear daddy,

To my husband and his family,

To my dear brothers and sisters.

I dedicate this modest work.

Acknowledgments

My gratitude is extended to my thesis chair, **Dr. Elfahem Sakher**, who offered a lot of encouragement, patience, and invaluable support through every stage of this process. I also extend my thanks to Pr. **Stefano BELLUCCI**, who accepted to participate in this work despite the difficult circumstances in the world, and I hope that future research relations will continue to benefit from his great experience as a scientist in the field of physics. His expertise has greatly influenced me as a learner, a teacher, and a researcher. I would also like to thank Head of the department and deputy head of the department **Dr. Goumni** Additionally, I would like to **Rector of the University** and the Faculty of Material Sciences, including students and teachers, without all these wonderful people this work would not have been possible.

Abstract

Coronaviruses are a large family of viruses that can infect humans or animals. The animal corona virus can sometimes mutate so that it can infect humans and become the human corona virus. There are seven known types of human coronavirus that cause mild to moderate respiratory infections, such as the common cold. Two types, Severe Acute Respiratory Syndrome (CoV-SARS) and Middle East Respiratory Coronavirus Syndrome (CoV-MERS), can cause acute respiratory infections. Type VII (2019-nCoV) is a new coronavirus recently discovered in China. In this note, I will present the types of this virus in addition to its symptoms, how to diagnose it, and the latest treatment methods.

Key words: *Covid-2019, SARS-CoV, MERS-CoV, HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, Nano-materials particle and coronavirus.*

French Abstract:

Les coronavirus sont une grande famille de virus qui peuvent infecter les humains ou les animaux. Le virus corona animal peut parfois muter pour infecter les humains et devenir le virus corona humain. Il existe sept types connus de coronavirus humain qui provoquent des infections respiratoires légères à modérées, telles que le rhume. Deux types, le syndrome respiratoire aigu sévère (CoV-SRAS) et le syndrome respiratoire du coronavirus du Moyen-Orient (CoV-MERS), peuvent provoquer des infections respiratoires aiguës. Le type VII (2019-nCoV) est un nouveau coronavirus récemment découvert en Chine. Dans cette note, je présenterai les types de ce virus en plus de ses symptômes, comment le diagnostiquer et les dernières méthodes de traitement.

Mots clés: Covid-2019, SARS-CoV, MERS-CoV, HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, Particule de nano-matériaux et coronavirus.

الملخص:

إن فيروسات كورونا عبارة عن عائلة كبيرة من الفيروسات التي يمكنها إصابة البشر أو الحيوانات. يمكن أن يتغير أحيانًا فيروس الكورونا لدى الحيوان بحيث يمكنه إصابة البشر ويصبح فيروس كورونا البشري. هناك سبعة أنواع معروفة لفيروس كورونا البشري تسبب عدوى الجهاز التنفسي الخفيفة إلى المتوسطة، مثل االصابة بنزالت البرد العادية. وهناك نوعان، هما المتالزمة التنفسية الحادة الوخيمة لفيروس كورونا(CoV-SARS)ومتالزمة فيروس كورونا التنفسية الشرق أوسطية (CoV-MERS)،يمكنهما أن تتسببا في حالات العدوى التنفسية الحادة. النوع السابع (2019 -nCoV)هو فيروس كورونا الجديد المكتشف مؤخرا في الصين. سأقدم في هذه المذكرة أنواع هذا الفيروس بالاضافة الى اعراضه وكيفية تشخيصه وأحدث طرق العلاج.

الكلمات المفتاحية:

فيروس كورونا. SARS-CoV, MERS-CoV, HCoV-229E, HCoV-NL63, HCoV-OC43,. جسيمات المواد النانوية ,HCoV-HKU1.

List of Terms

CoV: Coronavirus.

HIV: Human Immunodeficiency Virus.

MERS-CoV: Middle East Respiratory Syndrome Coronavirus.

RBD: Receptor Binding Domain.

RdRp: RNA-dependant RNA polymerase.

RNA: Ribonucleic Acid.

RT-PCR: Reverse transcriptase –Polymerase Chain Reaction.

SARS: Severe Acute Respiratory Syndrome.

TGEV: Transmissible Gastroenteritis Virus.

WHO: World Health Organisation.

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General introduction

General introduction:

Coronaviruses (CoVs) were first identified during the 1960s by using electron microscopy to visualize the distinctive spike glycoprotein projections on the surface of enveloped virus particles. It was quickly recognized that CoV infections are quite common, and that they are responsible for seasonal or local epidemics of respiratory and gastrointestinal disease in a variety of animals. CoVs have been named according to the species from which they were isolated and the disease associated with the viral infection. Avian infectious bronchitis virus (IBV) infects chickens, causing respiratory infection, decreased egg production, and mortality in young birds. Bovine coronavirus (BCoV) causes respiratory and gastrointestinal disease in cattle. Porcine transmissible gastroenteritis virus (TGEV) and porcine epidemic diarrhea virus (PEDV) cause gastroenteritis in pigs. These CoV infections can be fatal in young animals. Feline infectious peritonitis virus (FIPV) and canine coronavirus (CCoV) can cause severe disease in cats and dogs. Depending on the strain of the virus and the site of infection, the murine CoV mouse hepatitis virus (MHV) can cause hepatitis or a demyelinating disease similar to multiple sclerosis. CoVs also infect humans.

Human history is marked by epidemic diseases. They have always followed movements, linked to trade or wars. These epidemics, defined as plagues before modern times, could be caused by different diseases (typhoid, smallpox, bubonic or pulmonary plague, yellow fever). Recent acceleration in travel, along with the development of air travel, has increased the speed of spread of new epidemics. However, progress in detecting cases and the speed with which treatments have been implemented most often have made it possible to limit their health consequences. From the plagues of Antiquity to the current Covid-19 pandemic, including the Black Death and the Spanish flu.

The main objective of this work was to conduct a general study on the Corona virus, as this note included three chapters in which I will present the latest findings of the studies:
Chapter One: I will discuss the types of coronavirus, their characteristics, symptoms, how to diagnose them, and the latest treatment methods.

Chapter Two: In it, I will present the impact of nanomaterials on the Corona virus.

The third chapter: statistics of the number of cases of infection and the number of deaths since the beginning of the infection to the present day.

Chapter 01: Effect and characteristics of covid-19.

I.1. Introduction:

Viral diseases are widespread throughout the world and can range from minor infections to plagues that alter the course of history. The burden of diseases induced by viral infections is enormous, with most of the deadly infectious diseases being caused by viral infections. Among the viruses, coronaviruses (CoVs; subfamily *Coronavirinae*, family *Coronaviridae*, order *Nidovirales*) represent a major group of viruses known to be responsible for respiratory, enteric, hepatic, and neurological diseases in multiple species. The CoVs affecting human population are referred to as human coronaviruses (HCoVs). They lead to multiple respiratory diseases, such as common cold, pneumonia, and bronchitis. This century has seen rapid evolution of HCoVs, the contributory factors being urbanization and poultry farming. These factors allowed crossing of species barrier and genomic recombination of these viruses. Six HCoVs have been identified so far, namely severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1. The latter four viruses (HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1) are mainly responsible for one-third of common cold infections in human, which in severe cases can lead to life-threatening pneumonia and bronchitis.

I.2. Corona description:

Coronaviruses are large (120- to 160-nm), roughly spherical particles with a linear, non-segmented, capped, and poly adenylated positive-sense single-stranded RNA genome that is encapsidated in a helical nucleocapsid. The envelope is derived from intracellular membranes and contains a characteristic crown of widely spaced club-shaped spikes that are 12 to 24 nm long. The genus Coronavirus (International Committee on the Taxonomy of Viruses database [ICTVdb], virus code 03.019.0.1) belongs to the family Coronaviridae in the order Nidovirales (7, 8).

I.3. History:

In 1965, Tyrell and Bynoe isolated the first coronavirus from the respiratory tract of a patient complaining of colds [1], The virus was named B814, In a similar study conducted by Hamre and Procknow, the researchers reported a similar kind of virus isolated from the samples obtained from medical students with cold which they named 229E [2].

In another study by McIntosh et al. ether sensitive agents of multiple strains were isolated from human respiratory tract [3].
In about the same period of time, by electronic microscopy, Almeida and Tyrell [4] studied organ cultures infected with B814, and reported particulates of size 80-150 nm resembling infectious bronchitis virus of chickens, Astonishingly both 229E agent identified by Hamre and Procknow and OC virus reported by McIntosh et al [5].
In the later part of 1960, a group of virologists under the leadership of Tyrell studied different strains of human and animal viruses, Thus, a new genus of viruses was found which was named CORONA, where the term corona denoted the crown like appearance of the surface in the morphological structure of viruses, These viruses occur more in the rainy, winter and spring seasons compared to the summer season [6].
During the summer of 2003, an outbreak of respiratory disorders was studied in British Columbia, during which nucleic acid testing and serology unexpectedly indicated reactivity to severe acute respiratory syndrome coronavirus (SARS-CoV) [7].
Subgenus Merbecovirus comprises the Middle East respiratory syndrome (MERS)-related coronaviruses, including the MERS-CoV responsible for the 2012 MERS outbreak, as well as two additional species of bat coronaviruses isolated from Tylonycteris and Pipistrellus bats [8].
In December 2019, a new coronavirus was identified in the city of Wuhan, Hubei province in China, in patients who presented with severe unexplained pneumonia, In February 2020, the World Health Organization (WHO) assigned the name of COVID-19 to designate the disease caused by this virus, initially called nCoV-2019, then SARS-CoV-2 by the International Committee on Taxonomy of Viruses. After SARS-CoV-1 in 2002 in China, then MERS-CoV in 2012 in the Arabian Peninsula responsible for often fatal respiratory distress syndromes, it is the third global health threat linked to a coronavirus in less than twenty years [9].

I.4. Coronavirus types:

Corona virus comprises of a large family of viruses that are common in human beings as well animals (camels, cattle, cats, and bats). There are seven different strains of corona virus [10].

- 229E (alpha coronavirus).
- NL63 (alpha coronavirus).
- OC43 (beta coronavirus).
- HKU1 (beta coronavirus).
- MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS).
- SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS).
- SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19).

I.4.1. 229E and OC43:

The HCoV 229E and the HCoV OC43, now called betacoronavirus 1 were the first human coronaviruses to be identified. Since the late sixties, they were recognized as being responsible for upper and mild respiratory tract infections such as the common cold.

Following the identification of new members of coronaviruses that infect humans, the NL63 in 2004 and the HKU1 in 2005 and, of course, the SARS-CoV in 2003, new studies have been conducted on the clinical features of HCoVs infections. Indeed, before 2003, very few studies and routine monitoring dealt with the role of coronaviruses in humans. Thus, epidemiological data were rare and it is likely that, as a result, the precise role that HCoVs played in respiratory tract infections was greatly underestimated.

It is important to note that these viruses have been identified worldwide.

Human coronavirus infections occur mainly in winter, with a short incubation time. They are recovered in 3 to 11%, of patients sampled with a respiratory tract infection, depending on the studied population and the HCoV strain.

Coronaviruses occupy the fourth or fifth place, behind influenza viruses, respiratory syncytial virus, adenoviruses and rhinoviruses and their proportion is generally equivalent to the ones of metapneumo virus and parainfluenza viruses.

They have since been implicated in more serious diseases of the lower respiratory tract as bronchitis, bronchiolitis or pneumonia or croup in the case of the HCoV NL63. These infections concern predominantly weak patients such as newborns or infants, elderly people or

immunosuppressed patients .They have also been implicated in nosocomial infections notably in neonatal care unit.
Furthermore, some studies reported also some heart troubles associated with HCoVs infections [11].

I.4.2. Sars-cov:

From November 2002 to February 2003, in the province of Guangdong (southern China), 305 cases of pneumonia were reported. This highly contagious pathology responsible for an aspecific symptomatology which brought it closer to so-called atypical pneumonia was initially attributed to Chlamydia pneumoniae. This pathogen will be ruled out quickly, but the responsibility for a new coronavirus will only recently be raised. At the end of February, an epidemic of pneumonia affected Hanoi and Hong Kong. The relationship with the Guangdong epidemic will not be formalized until March 17. The epidemic will spread rapidly, justifying, on March 12, 2003, the publication of a global alert by the World Health Organization (WHO) (1). WHO is proposing the acronym "SARS" and case definition criteria on March 15 (2). The epidemic will quickly spread around the world from this initial Chinese focus. As of April 18, 2003, 3,744 cases have been reported in 26 countries, the most affected sites being China, Hong Kong, Singapore, Canada and the USA [12].

I.4.3. NL63:

Even though coronavirus infection of humans is not normally associated with severe diseases, the identification of the coronavirus responsible for the outbreak of severe acute respiratory syndrome showed that highly pathogenic coronaviruses can enter the human population. Shortly thereafter, in Holland in 2004, another novel human coronavirus (HCoV-NL63) was isolated from a seven-month old infant suffering from respiratory symptoms. This virus has subsequently been identified in various countries, indicating a worldwide distribution. HCoV-NL63 has been shown to infect mainly children and the immunocompromised, who presented with either mild upper respiratory symptoms (cough, fever and rhinorrhea) or more serious lower respiratory tract involvement such as bronchiolitis and croup, which was observed mainly in younger children. In fact, HCoV-NL63 is the etiological agent for up to 10% of all respiratory diseases. This review summarizes recent findings of human

coronavirus HCoV-NL63 infections, including isolation and identification, phylogeny and taxonomy, genome structure and transcriptional regulation, transmission and pathogenesis, and detection and diagnosis [13].

I.4.4. HKU1:

71-year-old Chinese man was admitted to hospital in January 2004 because of fever and productive cough with purulent sputum for 2 days. He had a history of pulmonary tuberculosis more than 40 years ago complicated by cicatrization of the right upper lobe and bronchiectasis with chronic *Pseudomonas aeruginosa* colonization of airways. He was a chronic smoker and also had chronic obstructive airway disease, hyperlipidemia, and asymptomatic abdominal aortic aneurysm. He had just returned from Shenzhen, China, 3 days before admission. A chest radiograph showed patchy infiltrates over the left lower zone. NPA for direct antigen detection of respiratory viruses, RT-PCR of influenza A virus, human metapneumovirus, and SARS-CoV, and viral cultures were negative. After the virus was determined to be a coronavirus, the NPAs were inoculated into RD (human rhabdomyosarcoma), I13.35 (murine macrophage), L929 (murine fibroblast), HRT-18 (colorectal adenocarcinoma), and B95a (marmoset B-lymblastoid) cell lines and mixed neuron-glia culture. No cytopathic effect was observed. Quantitative RT-PCR, using the culture supernatants and cell lysates to monitor the presence of viral replication, also showed negative results. Moreover, intracerebral inoculated suckling mice remained healthy after 14 days. Sputum was negative for bacterial and mycobacterial pathogens. Paired sera for antibodies against *Mycoplasma*, *Chlamydia*, *Legionella*, and SARS-CoV were negative. His symptoms improved, and he was discharged after 5 days of hospitalization. Here we report the discovery of another novel coronavirus, coronavirus HKU1 (CoV-HKU1) [14].

I.4.5. Mers-cov:

Ten years after the SARS-CoV pandemic, a new coronavirus has emerged in the Arabian Peninsula.

MERS-CoV is responsible for severe respiratory syndrome, especially in people with co-morbidities. Kidney or multiorgan impairment accompanying respiratory disease is often the cause of death.

Because of the health threat it represents, MERS-CoV has been classified as a highly pathogenic microorganism and toxin (MOT) since December 2014. Therefore, special regulations must be applied for the diagnosis of infection, management of probable cases and research activities.
MERS-CoV and anti-MERS-CoV antibodies have been detected in camels from the Arabian Peninsula and eastern Africa, indicating that these animals are likely the reservoir for MERS-CoV. A South African bat coronavirus, named Neo-CoV, appears to be an ancestor of MERS-CoV [15].

I.4.6. Covid-19:

COVID-19: “CO”: for corona, “VI” for virus, “D” for disease and 19 for the year it appeared [16].

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 pandemic. France has been at stage 3 of the epidemic since March 15, 2020. The circulation of the virus is intense in the territory with 7 particularly impacted regions. As of March 23, 2020, 19,856 confirmed cases (38 cases on February 27, 2020) have been identified in France. 2,082 people are hospitalized in intensive care and 860 patients have died. The median age of patients is 60 years. Globally, 392,286 cases have been identified in 196 countries, with Europe currently constituting the epicenter of this epidemic. In France, on March 15, among 6,378 confirmed cases, 285 (4.5%) had been or were being taken in intensive care and 161 (2.5%) had died. The proportion of patients admitted to intensive care was 2.4% in those under 15 years old, 0.9% in 15-44 year olds, 3.9% in 45-64 year olds, 9.2% in 65- 74 years old, and 8.3% from 75 years old. The mortality rate was, for the same age groups, respectively, 0%, 0.1%, 0.5%, 2.4% and 10.3%. Among 5,782 patients

who came to emergency departments with suspicion of COVID-19, those aged 65 and over were hospitalized in 2 out of 3 cases, and those over 75 years of age represent 11.3% of the study population and. 27.3% of hospitalizations [17].

I.4.6.1. symptoms of COVID-19 [18]:

• Symptoms may take between 2 and 14 days to appear. Typically, symptoms appear 4 to 5 days after exposure.
• A person is contagious 2-3 days after exposure, even if they have no symptoms. People are also contagious when they have symptoms.
• Almost everyone with COVID-19 has a fever. If possible, check your temperature twice a day if you experience other symptoms.

FEVER [18]

COUGH [18]

ESSOUFFLEMNT[18]

I.4.6.2. How COVID-19 Spreads:

• COVID-19 is transmitted by respiratory droplets that pass from sick person to sick person by [18]:

- Sneezing and coughing
- Physical touch such as greetings such as shaking hands
- Touch surfaces / objects contaminated with germs and then touch your eyes, nose or mouth before washing your hands.
- Hands touch many surfaces and can come in contact with the virus. Once infected, hands can transmit the virus to the eyes, nose or mouth. From there, the virus can enter the body and make you sick. It is best to avoid physical contact with people or surfaces that may have the virus.
- Covid-19 can spread to any region, regardless of the weather.

I.4.6.3. Transmission:

- **How does Person-to-person transmission occur?**

- **Droplet transmission:**

The virus is released in the respiratory secretions when an infected person coughs, sneezes or talks. These droplets can infect others if they make direct contact with the mucous membranes. Infection can also occur by touching an infected surface and followed by eyes, nose or mouth. Droplets typically do not travel more than six feet (about two meters) and do not linger in the air. However, given the current uncertainty regarding transmission mechanisms, airborne precautions are recommended routinely in some countries and in the setting of specific high risk procedures. Patients are thought to be most contagious when they are symptomatic [19]. Some spread might be possible before symptoms appear, but this is not thought to be a common occurrence [20-22].

- **Other possible modes of transmission:**

It may be possible that a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes, but this is not thought to be the main way the virus spreads. One study suggested that the virus may also be present in feces and could contaminate places like toilet bowls and bathroom sinks [23]. But the researchers noted the possibility of this being a mode of transmission needs more research. In February a Chinese newborn was diagnosed with the new coronavirus just 30 hours after birth. The baby's mother tested positive before she gave birth [24]. It is unclear how the disease was transmitted - in the womb, or after birth. Recently in London another newborn was tested positive for the coronavirus, marking what appears to be the second such case as the pandemic worsens [25].

I.5. Prevention [26]:

- **WHO IS A CONTACT?**

• A contact is a person that is involved in any of the following:

• Providing direct care without proper personal protective equipment (PPE) 2 for COVID-19 patients

• Staying in the same close environment of a COVID-19patient (including workplace, classroom, household, gatherings).

• Traveling together in close proximity (1 m) with a COVID-19 patient in any kind of conveyance within a 14-day period after the onset of symptoms in the case under consideration

• According to a study published in NEJM by Sebastian Hoehl et.al a symptom-based screening process was ineffective in detecting SARS-CoV-2 infection in 2 persons who later were found to have evidence of SARS-CoV-2 in a throat swab and said that shedding of potentially infectious virus may occur in persons who have no fever and no signs or only minor signs of infection.

- **CAN THE VIRUS STAY ON INANIMATE SURFACES?**

• COVID-19 virus can persist on inanimate surfaces like metal, glass or plastic for up to 9 days, but can be efficiently inactivated by surface disinfection procedures with 62–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute.

• Other biocidal agents such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexi dine digluconate are less effective.

• Hence terminal disinfection is important even after the patient getting discharged.

- **WHAT SHOULD INCLUDE IDEAL POST PROTECTIVE EQUIPMENT (PPE)?**
- **PPE for at-risk health facilities:**

Airborne precautions for aerosolized generating procedures:

- **Gloves:**

Gloves nitrile, powder-free, non-sterile. (eg. minimum 230mm total length. Various sizes ranging from small, medium, large.

- **Mask (healthcare worker):**

Medical mask, good breathability, internal and external faces should be clearly identified.

- **Face Shield:**

Made of clear plastic and provides good visibility to both the wearer and the patient, Adjustable band to attach firmly around the head and fit

snuggly against the forehead, Fog resistant (preferable), Completely cover the sides and length of the face, May be re-usable (made of robust material which can be cleaned and disinfected) or disposable.

- **Particulate respirator, grade N95 or higher**

N95 or FFP2 respirator or higher Good breathability with design that does not collapse against the mouth (e.g. duckbill, cup-shaped).

Figure I.1. Mask vs. Respirator [26]

- **N95 vs. FFP3 & FFP2:**

The most commonly discussed respirator type is N95. This is an American standard managed by NIOSH – part of the Center for Disease Control (CDC). Europe uses a "filtering face piece" score (FFP). This comes from EN standard 149:2001 – drafted and maintained by CEN (European Committee for Standardization).

Figure I.2. Different types of Respirators commonly used [26].

I.6. Clinical Characteristic and Diagnosis:

COVID-19 is mainly characterized [27] by high fever, cough, and sore throat, shortness of breath, fatigue, rhinorrhea and dyspnea. Compared with general pneumonia, these symptoms are not specific. The patients of SARSCoV-2 infection had neurologic manifestations [28], such as myalgia, dizziness, anosmia and ageusia [29] .Some had digestive symptoms, such as diarrhea. The majority of patients on admission presented with non-specific symptoms and few patients were asymptomatic [30]. The pregnant women infected SARS-CoV-2 [31] had same symptoms as adult patients and one thirds of their neonates were infected with SARS-CoV-2. Some neonates and children had atypical symptoms. Renal transplantation recipients infected with SARS-CoV-2 had more proportion of moderate and severe disease. Renal transplantation recipients with COVID-19 appeared to have worse clinical outcomes [32].

Current diagnosis of COVID-19 relied on the experience that the patients were at high-risk exposures, repeated positive pathogenic evidence, and clinical manifestations. It is notable that false-negative test of PCR assays results can occur [33]. Pathogenic evidence included the nucleic acid amplifications of SARS-CoV-2, genomic sequencing which is

homologous with SARSCoV-2, and specific IgM or IgG (+) of SARS-CoV-2 in blood. Besides, the differential diagnosis of COVID-19 included upper respiratory infection that caused by other virus, other pneumonia and non-infectious diseases, such as dermatomyositis.

I.7. Treatments:

Except for the general treatment, this section introduced the clinical management of COVID-19 patients according to the manifestations of their illness. Notably, there are no Food and Drug Administration (FDA)-approved drugs for the treatment of COVID-19 [33].

I.7.1. General Considerations:

If patients have comorbidities, the treatments will be given upon the symptoms. Because patients may be facing cases of coinfections with hospital-acquired pneumonia and ventilator-associated pneumonia, NIH suggested routinely using the broad-spectrum empiric antimicrobial therapy [33]. But the Chinese guidelines of COVID-19 think we should not routinely use the broad-spectrum antimicrobial therapy.

I.7.2. Antiviral Treatment:

No proven effective drugs for SARS-COV-2 currently exist. However, there are interferon-α, Remdesivir, Ribavirin, and Oseltamivir, chloroquine, hydroxychloroquine and Lopinavir used in the clinical treatment. It is not recommended to use more than 3 antiviral drugs at the same time [34].

I.7.3. Antithrombotic Treatment:

There are some change of coagulation markers in COVID-19 patients, such as higher D-dimer levels and prolonged prothrombin time. Antithrombotic treatment should not be used to prevent thrombosis. Unfractionated heparin, low molecular weight heparin, and warfarin were frequently-used antithrombotic drugs in clinical treatment [34].

I.7.4. ACE Inhibitors and Angiotensin Receptor Blockers (ARBs):

When patients have comorbidity of cardiovascular disease, the panel recommends using ACE and ARBs drugs. Because ACE2 is the cellular receptor of SARS-COV-2, ACE inhibitors may be wonder drugs for COVID-19. However, no existing evidence shows that ACE inhibitors or ARBs affected the risk of COVID-19 [35].

I.7.5. Renal Failure:

Seeking the reasons of renal failure is urgent for the patients with severe disease. The treatment focus on fluid balance, acid-base balance and water and electrolyte balance. Critical patients could choose the continuous renal replacement therapy [34].

I.7.6. Immune-Based Therapy:

Immune-based therapy includes COVID-19 convalescent plasma, SARS-CoV-2 immune globulins, interleukin-1 and -6 inhibitors. There are no enough scientific data to recommend for or against using this treatment to guide management decisions. Therefore, it is urgent to integrate the clinical data of COVID-19 and perform the clinical trials [34].

I.8. Effect:

HCoVs are suspected to cause digestive dysfunctions. First, they have been associated with necrotizing enterocolitis in newborns, and diarrhea or other gastrointestinal symptoms have been shown to accompany coronavirus infections. Then, other findings such as the detection of viral particles and coronavirus RNA in stool samples, or the presence of HCoV OC43 antibodies in children with gastroenteritis, support this idea. However, despite these arguments, their implication in human intestinal infections is still controversial but should be considered to evaluate the potential routes of HCoVs spread.

Another debate is the potential involvement of HCoVs in central nervous system diseases such as multiple sclerosis. This is supported by a body of evidence, e.g. neurological symptoms in some HCoV OC43 infected patients, experimental infection of neural cells with HCoV 229E and

OC43, detection of HCoV 229E and OC43 RNAs and antigens in brain of multiple sclerosis patients, or, more recently, neuroinvasive properties of HCoV OC43 after intranasal inoculation in mice. However, the precise and real implication of HCoVs in neural diseases has not yet been clearly demonstrated [11].

I.9. Conclusion:

The pandemic of COVID-19 has caused severe health problems all over the world. To slow down the increase of SARS-CoV-2 infected patients, super spreading events are non-negligible. According to a news report in Science, perhaps 10% of infected people caused 80% of the spread.100 Furthermore, it is important to avoid super spreading events by restricting gatherings of people. In addition, strategies including quarantine and personal protective equipment are essential to stop further spread of COVID-19. The rapid development of therapeutic drugs targeting SARS-CoV-2 is urgently needed for the treatment of current COVID-19 patients. For example, based on the highly conserved substrate-binding pocket among coronavirus Mpro (or 3CLpro), the combination of structure-based drug design, virtual screening, and high-throughput screening could help us find more effective anti-SARS-CoV-2 drug leads or treatment strategies.101 In the long-term, it is more important to develop vaccines against COVID-19 and provide active acquired immunity to COVID-19.

Chapter 02
Nano-materials particle and coronavirus.

II.1. Introduction:

The global outbreak of coronavirus disease (COVID-19) has set an alarming message for the research and discovery of new and advance technology. This is possible by either combining the convectional technology with modern discoveries or initiating new avenues of research using nanotechnology. The vast library of nanomaterials and its integration into modern technology can offer various possibilities for discovery of nanomedicines, nano-biosensors, Nano compounds for controlling the sever acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and other similar virus outbreaks. Here we review the ongoing approaches utilized in detection, treatment and prevention of SARS-CoV-2 and describe their advantages and drawbacks. Additionally, we provide the new and innovative technology that are currently being researched or commercialized with the aid of nanomaterials and nanotechnology for disease identification, treatment and control. We further suggest new research area based on natural product research that can provide new opportunities for jobs and economic movements during the post-COVID-19 pandemic.

II.2. Nanomaterials application in COVID-19 pandemic:

SARS-CoV-2 are spherical shaped and Nano dimensional positive-stranded ribonucleic acid (RNA) viruses which are encapsulated inside a helical Nucleocapsid protein shell and enveloped by lipid membrane and three structural protein (membrane glycoprotein, nucleocapside protein and envelop protein) with spike protein on the outer layer . This core-shell nano-structure and the crown-like spike protein outside of the virus surface in SARS-CoV-2 thus provides opportunities in engineering drugs, protective coatings and vaccines against COVID-19. This is because the lipid membrane can be easily destroyed by even soap molecules while the envelop and capsid can be compromised by physical treatments like UV 157 exposure, heating and desiccation as well as by chemical sanitization using acids, oxidants, alcohols or surfactants. Similarly, neutralizing the spike protein outside the virus surface by antibodies and vaccines. The idea of

incorporating multivalent binders with the pathogens, enveloping the host cell and using the ligand scaffolds to prevent the pathogens adhesion are additional Nano/bioengineering research fields that can be considered for prevention of COVID-19 and other potential virus outbreaks as illustrated schematically in Figure I.1. Additionally, the recent development of nanomaterials from Chinese scientists that can absorb and deactivate the virus with 96.5-99.9% efficiency can be another important discovery for the treatment and prevention of SARS-CoV-2 these nano-technological developments and their successful implication in virus identification, COVID-19 cure and preventive measures [35].

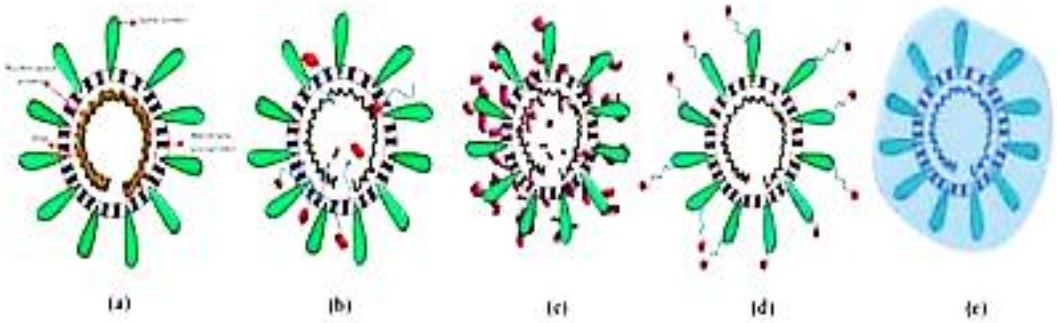

Figure II.1. Nanomaterial for controlling SARS-CoV-2. (a) Schematic showing the SARS-CoV-2 and its constituents. (b) Insertion of nanoparticles into the SARS-CoV-2 for neutralizing the virus. (c) Nanomaterials based passivation of SARSCoV-2 to control the growth and multiplication of virus. (d) Nano chemical functionalization of spike protein in SARS-CoV2. The spike protein are known to be the main component of virus, which allows to virus to interact with the human cells. (e) Encapsulation of SARS-CoV-2 with nanomaterial or Nano compounds which passivates the virus for growth as well as preventing the spike protein to functionalize with human cells [35].

II.3. State-of-the-Art of Antiviral Nanomaterials: From Research to the Clinic:

II.3.1. Nanomaterial Definition:

There are different definitions of the nanomaterial concept. In general, nanomaterials can be described as single-structures—free or in a composite—with

a size within the nanometric range, usually less than 100 nm in at least one of their three dimensions. Within the nanometric range—the nanoscale—the physicochemical properties of materials display significant changes that contrast their counterparts at larger scales, as the quantum effects determine their new properties [36]. There is an increasing interest in nanomaterials, precisely due to their novel or improved physicochemical properties such as endurance, chemical reactivity, biocompatibility, conductivity, or reduced toxicity [37]. The chemical composition of nanomaterials can be organic or inorganic, and they can be found as single structures, composites, embedded in a matrix, etc. Nowadays, nanomaterials are found in a wide range of existing products, such as in electronics, health and fitness, paints and other surface coatings, food, and clothing, among many others [38–40]. Moreover, medicine is among the areas with a growing interest in the use of nanotechnology.

II.3.2. Use in Nanomedicine:

Nanomaterials are widely used in different healthcare-related applications, such as sanitizers, diagnosis, imaging tools, wound dressing, wearable devices, anticancer therapies, pharmaceuticals, drug delivery, vaccines, diagnosis techniques, and implants, among others [41–43]. Nanomaterials have been researched for developing antiviral and antimicrobial drugs, as they display properties for combatting multiple pathogenic microorganisms [44–50]. The global consumption for healthcare-related nanotechnology is expected to be over 50 tons, just for silver nanoparticles, in 2020 [51].

Multiple nanomaterials can display antiviral activity. The chemical composition of these nanomaterials can be either organic or inorganic (metal-based); their typical shape is spheroid or polyandric (aspect ratio close to 1) with a usual size range from 1 to 50 nm, and their active formulation is often as free particles in suspension. Antiviral nanomaterials are typically smaller than most viral particles, such as the SARS-Cov-2 viral particle, which has an average size of 120 nm (Figure II.2.). Therefore, nanomaterials can interact with the whole viral particle or with the surface proteins and other structural components, leading to the inactivation of viruses. The characteristics of antiviral nanomaterials, their potential

mechanisms of action, the ongoing preclinical/clinical research, and the currently approved products for consumer use are discussed below [52].

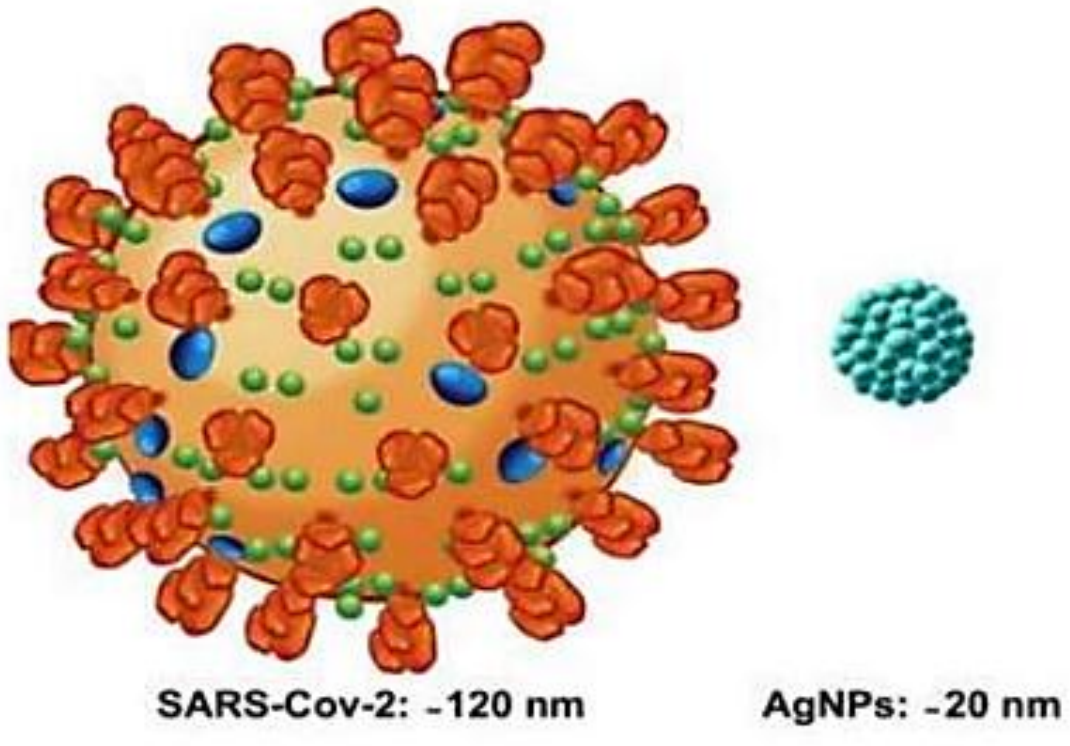

Figure II.2. Size comparison between the average sizes of the SARS-Cov-2 coronavirus and a single silver nanoparticle (AgNPs). Both structures are at a proportiona [52].

II.3.3. Preclinical Studies, In Vitro and In Vivo:

The antiviral activity of nanomaterials against multiple viral families has been studied in a wide diversity of reports (Table 1). Studies in vitro show that silver nanoparticles (AgNPs) inactivate different types of viruses, such as HIV-1 [53], monkeypox virus [54], hepatitis B [55], Tacaribe virus [56], and the Rift Valley fever virus [57]. Also, AgNPs display activity against influenza viruses like H3N2 [58] and H1N1 [59]. Current literature suggests that nanomaterials may also effectively inactivate the SARS-Cov-2 virus particles, as nanomaterials have been used for inhibiting other viruses from the Coronaviridae family [60]. Other nanomaterials also display antiviral activity against viruses that cause respiratory syndromes. Titanium oxide

nanoparticles inhibit the H9N2 [61], carbon fullerene lipidosomes inactivate H1N1 [62], and a peptide–nanoparticle complex is capable of inactivating the influenza A virus [63]. Regarding other viruses, ivermectin-nanoparticles complexes can inactivate the Zika virus [64]. Therefore, nanomaterials can inactivate a wide variety of viruses, regardless of the viral structure and strain [65]. Moreover, several studies report the effectivity of nanomaterials for reducing viral replication, in vivo against viruses from multiple families (Table 2). In murine models, different nanomaterials are effective to inhibit the respiratory syncytial virus [66]; HIV [67], influenza virus [68], herpes simplex virus, human papillomavirus, dengue and lentivirus [69]. Additionally, antiviral nanomaterials display antiviral activity in other in vivo models; such as the canine distemper virus in dogs [70], the Newcastle disease virus in chicken [71], and the white spot syndrome virus in shrimp [72], among others.

II.3.4. Mechanisms of Action of Antiviral Nanomaterials:

Preclinical trials have shown how virus-nanoparticle interactions lead to direct or indirect antiviral activity. Nanomaterials with indirect activity do not inhibit the viruses by themselves; instead, they improve the activity of the antiviral treatments, and are used for transport [73], stability [74], and enhanced bioavailability [75], among others. Moreover, nanomaterials can also induce an immune response for generating short or long-term immunity [76]. In contrast, nanomaterials with direct activity act as the active compound, because they inactivate the viruses by themselves, usually by altering the viral structure or its genetic material. Back in 2005, Lara et al., showed that AgNPs interact with the receptors from HIV, inhibiting its infectivity [77]. They suggested that AgNPs bind to the gp120 glycoprotein knobs, preventing the virus from binding to cells, as observed in their in vivo results. In addition, Morris et al., suggested recently that AgNPs may be attaching to the surface glycoproteins of the virus [66]; which prevents the fusion process by reducing its ability to attach to the cells. Additionally, Cagno et al., showed that gold and iron oxide nanoparticles—coated with organic ligands—disrupt the ultrastructure of multiple viruses [69], breaking the viral particle, leading to virucidal inhibition of enveloped and naked

viruses. Moreover, Kim et al., demonstrated that nanomaterials can silence viral genes, as they observed that in vivo administration of anti-CCR5 siRNA/LFA-1 I-tsNPs exclusively silenced genes in leukocyte for around 10 days, preventing the HIV infection [78]. In a recent review, Cojocaru et al., described the potential mechanisms that allow nanomaterials to inactivate both DNA and RNA viruses [79]. Among the main mechanisms are the viral DNA/RNA synthesis inhibition; viral protein synthesis inhibition; and inhibitors of the entry, fusion, or integration of viruses into the cell. The general mechanisms that nanomaterials display against viruses are exemplified in Figure II.3. [52].

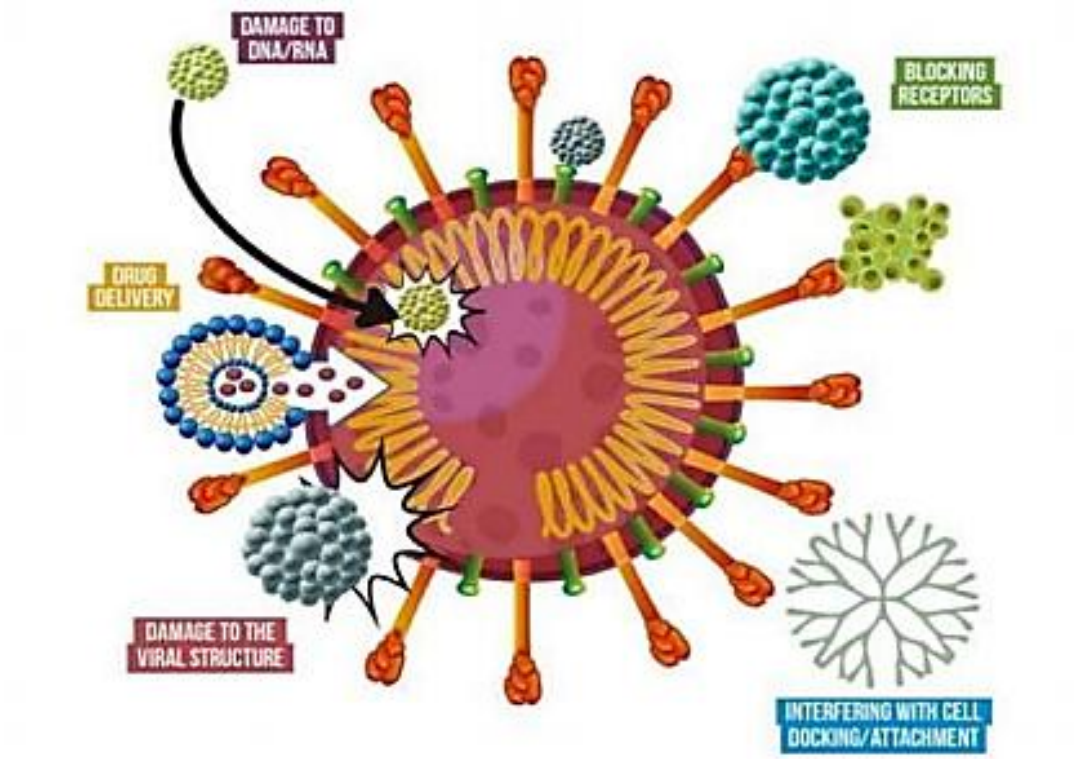

Figure II.3. Proposed antiviral mechanisms that nanoparticles use to deactivate viruses [52].

Moreover, nanomaterials display other properties of clinical interest, such as enhanced chemical reactivity and biocompatibility, controlled drug release, and customizable target specificity [80,81], and may display reduced toxicity when compared to the non-nanostructured materials.

II. 3.5. Clinical Studies and Products in the Market:

Nowadays, multiple antiviral nanomedicines are still under clinical research, whereas others have been approved and are currently commercially available for use. Some recent reviews show the current stage of development of antiviral nanomedicines, from ongoing preclinical and clinical trials to those that are currently approved. Lembo et al., review how nanotechnology-based formulations improve the activity of antiviral drugs, describing the advantages provided by different nanomaterials [82]; whereas Sato et al., provide an insight of the status of several therapeutics anti-HBV undergoing clinical trials in phases 1 and 2 [76]; finally, Singh et al., present an overview of the research of nanomaterials, from preclinical research to clinical assays and commercialization, for the treatment of viral infections [83]. Some examples of FDA-approved, nanotechnology-based products are Inflexal V, a virosomal anti-influenza vaccine, [73], and Pegasys, a pegylated IFN alpha 2a anti-Hepatitis (HBV and HVC) [84].

II.4. Current nanotechnology applications that can be used to combat COVID-19:

As mentioned earlier, nanomaterials are currently used in multiple commercially available products, including cosmetics and healthcare. A detailed, updated list of products can be consulted at the Nanowerk databases [39]. The wide range of physical and chemical properties of nanomaterials provides numerous advantages to combat the SARS-Cov-2; from reducing its spread to future treatments. When antiviral nanomaterials are fixed in support, their stability and reactivity are increased, as well as the surface area of the support. Usually, nanomaterials are adsorbed by textiles [85] and polymers [86] for diverse applications, such as personal protective equipment (PPE), medical textiles, packaging, and filters. Nanomaterials in suspensions can be used for sanitizing, coatings, and therapeutic applications. Finally, multiple nanomaterials can be used for nanocarriers, diagnosis, and detection. Some of the current applications that can be used to prevent and treat the COVID-19 are described below and summarized in Figure II.4. [52].

Figure II.4. Representative uses of nanotechnology to combat viruses and other pathogens [52].

II.4.1. Personal Protective Equipment (PPE):

The application of nanomaterials-embedded textiles has been intensely researched. These textiles may be used for PPE, such as lab coats, and facemasks, as current research shows that they improve the physicochemical properties of textiles [87], such as fire-retardant, self-cleaning, UV protection, antimicrobial, and antiviral, among others. Several patents consider the use of fibers embedded with metallic nanoparticles, such as copper and silver nanoparticles, due to their antimicrobial and antiviral properties [88, 89]. The use of nanoparticles in textiles has been increasing rapidly, with a current global consumption of around 35 tons just for silver nanoparticles [51]. Moreover, wearable smart textiles for sensing have been under study, particularly for health-related applications. One area of interest is the early detection of pathogens [90], which may include viruses, such as the SARS-Cov-2.

II.4.2. Surface coatings:

Nanomaterials-based coatings are currently used for several applications, and different products are now available [88]. Numerous nanomaterials, such as silver, bismuth, or titanium nanoparticles, have been developed for coating surfaces, [87,91,92]. Also, nanostructured surfaces can physically reduce the attachment of pathogens [93] and even disrupt the structure of the pathogens due to the nanoscale topography organization [94]. Nanomaterials can be embedded in paint or coatings for medical instrumentation, gloves, and other highly-touched surfaces, such as doorknobs, handrails, other medical devices, etc. to reduce the viability of viruses and other pathogens [95].

II.4.3. Sanitizers:

Currently, disinfectants with silver salts are already available [96], as silver is deemed safe for sanitizing purposes [97]. In hospitals and other healthcare-related facilities, sanitizing with nanotechnology-based products could inactivate the viruses on surfaces. Moreover, sanitizers with nanomaterials could reduce the presence of the SARS-Cov-2 on surfaces [95].

II.4.4. Other current and potential applications:

Among other uses, nanomaterials can be used to improve the function of air filters in healthcare facilities or in other places that use recirculated air. Nanotechnology-improved air filters can reduce the spread of viral particles [98, 99]. Also, the use of nanotechnology for producing wound dressings has been thoroughly explored [81, 100, 101], due to their ability to protect against infections and increase the healing speed rate. Future applications may include the development of improved detection kits, as it has been one of the major needs for the current strategies to contain and follow the virus spread [95].

II.5. Nanotechnology in SARS-CoV-2 detection:

The current method for the detection of COVID-19 infection is nucleic acid testing by reverse transcription polymerase chain reaction (RT-PCR). There are three main issues with RT-PCR based SARS-CoV-2 detection. First, RT-PCR is unable to detect asymptomatic patients, as it requires the presence of detectable SARS-CoV-2 in collected samples. Second, healthcare centres in non-urban settings lack sufficient PCR infrastructure in order to accommodate high sample throughput. Third, the availability for RT-PCR kits and reagents is unable to meet the increased demand. A recent WHO report, mentions the immediate need for point-of-care diagnostics and the development of protein and nucleic acid detection tests for SARS-CoV-2 [102].

II.6. Nanotechnology in SARS-CoV-2 treatment:

Currently, no SARS-CoV-2 specific antiviral drugs are available in the clinic. The development of anti-viral drugs takes many years before it can be made available for the treatment of patients [103]. The drug has to pass through various regulatory and safety measures before its clinical use [104]. Moreover, the development of viral resistance seen in the case of other viral infections is another challenge of employing drugs for viral infection treatment. In this section, we will explore the potential of nanotechnology in addressing these concerns. We will review some of the previous studies which have successfully demonstrated the application of nano-based therapies in targeting SARS-CoV-2 related viruses, such as SARS-CoV, MERS-CoV, and other members of the coronavirus family [105].

II.6.1. Blocking viral entry into the host cell:

The first step of the viral infection cycle involves the binding of the virus to the host via cell surface receptors. Blocking the entry of viruses has been found to be a successful anti-viral strategy in many viral infections (figure 3). By virtue of their properties, nanostructures are suitable to competitively bind and inhibit viral entry into cells [106]. Some nano-based approaches are targeted to binding the virus particles directly, preventing them from

approaching the host cell in the first place. For instance, carbon quantum dots were found to interact with the S protein of human coronavirus (HCoV-229E strain), preventing the viral protein interaction with the host cells. This reduced viral replication (figure II.5.). When the carbon quantum dots were functionalized with boronic acid, they exhibited even higher antiviral activity [107]. Huang et al demonstrated the benefit of utilizing gold nanorods in developing anti-viral therapy for the Middle East Respiratory Syndrome (MERS) virus, which is also a member of the coronavirus family. MERS virus utilizes its surface spike (S) protein to mediate the fusion of the viral membrane with the host cell membrane in order to facilitate entry of the viral genome into the host cell. However, a small α-helix peptide, pregnancy-induced hypertension or PIH was effective in blocking the membrane fusion mediated by the S protein. Conjugation of the S protein to gold nanorods not only increased the therapeutic potential of PIH but also improved its biocompatibility, biostability and pharmaceutical profiles in vitro and in vivo [108].

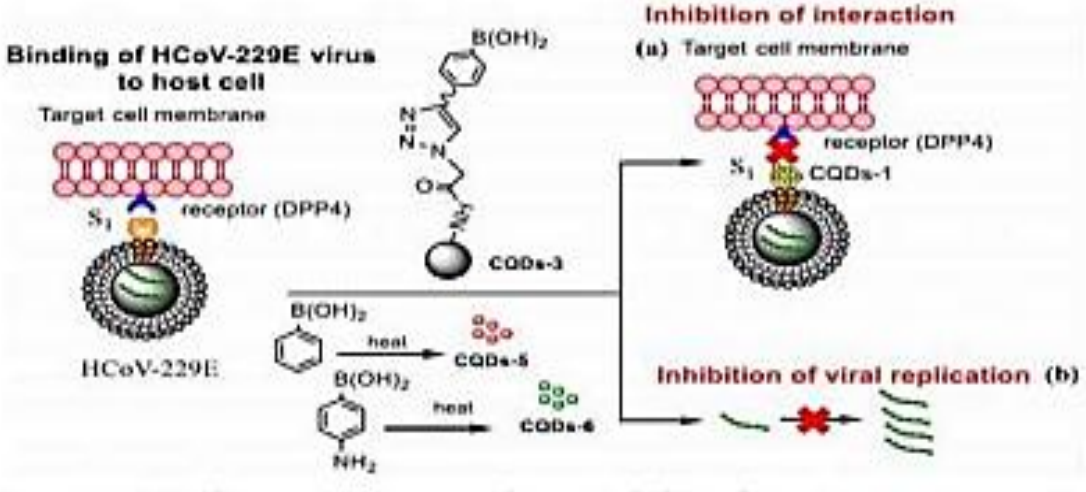

Figure II.5. Carbon quantum dots inhibit human corona virus interaction with its host receptor (a) and also inhibit virus genome replication (b). Reprinted with permission from [107]. Copyright (2019) American Chemical Society [105].

Some natural compounds possessing anti-viral potential can be coupled with nanoparticles for synergistic therapeutic effects. Du et al reported the antiviral potency of hypericin (HY) loaded graphene oxide (GO) complex (GO/HY). Hypericin, which is an anthrone derivative, obtained from

Hypericum perforatum, exerts anti-viral effect against a wide range of viruses. The low cytotoxicity and high loading capacity of GO helped to improve the anti-viral efficacy of hypericin. The GO/HY complex inhibited viral replication, which can be attributed to either suppression of viral attachment to the host cell or due to the inactivation of the virus itself [109]. Not only hypericin but also graphene oxide also possesses intrinsic anti-viral properties [110]. Akhavan et al found that graphene tungsten oxide composite film inactivated viruses when irradiated under visible light. The inactivation of the virus was reported due to photo-degradation of viral capsid protein followed by the subsequent release of viral RNA [111]. Curcumin also possesses broad-spectrum antiviral activity and exerts its viral inhibitory actions by various mechanisms. However, the low water solubility of curcumin limits its application in clinics. Yang et al improved the solubility and biocompatibility issue of curcumin by loading them into graphene oxide nanoparticles (GSCC). Functionalization with sulfonate groups allowed curcumin loaded graphene oxide to mimic cell surface and inhibit viral attachment by a competitive inhibition mechanism. Moreover, the GSCC exhibited antiviral activity, both pre- and post-viral infection of the host cell [112]. Furthermore, carbon quantum dots synthesized from curcumin possess superior anti-viral properties and greater water solubility, compared to natural curcumin. These carbons dots were effective in inhibiting viral binding to the cell surface [113]. Du et al reported that curcumin based cationic carbon dots act as multi-site viral inhibitors [114]. The study involved porcine epidemic diarrhea virus (PEDV), which is a member of the coronavirus family. The curcumin carbon dots altered the structure of the viral surface protein, thereby inhibiting the cell entry of the virus. The carbon dots also suppressed the formation of negative-strand RNA of virus and viral budding. The carbon dots stimulated the production of pro-inflammatory cytokines and interferon-stimulating genes (ISGs) to inhibit viral replication. Yang et al also reported that curcumin modified silver nanoparticles were effective antiviral agents and inhibited the virus prior to cell infection [115]. It has been reported that many viruses, including coronaviruses, utilize HSPG as a receptor to mediate the first step of the virus replication cycle [116]. Therefore, many HSPG mimicking materials, including heparin have been utilized to prevent viral infection

[117, 118]. However, most of these substances exhibit reversible binding with the virus and hence the inhibition is lost upon dilution, exerting virustatic effectsin vitro and no anti-viral effectsin vivo. Cagno et al synthesized heparin sulfate proteoglycan (HSPG) mimicking nanoparticles to irreversibly inhibit viral binding to host cells [119]. Gold nanoparticles coated with mercapto-1- undecanesulfonic acid (MUS-AuNPs) bound irreversibly to the virus, eventually leading to viral deformation. The long backbone of MUS allows flexibility to the terminal sulfonate groups to bind in a multivalent fashion. The MUS-AuNPs were virucidal in vivo in mice infected with the respiratory syncytial virus. Viana et al developed glycodendri nanoparticles to competitively inhibit viral binding to the glycan receptors. Using nested layers of multivalency, highly valent glycodendrimeric constructs were fabricated which mimicked the virus both in size and the high surface glycosylation present on the virus. These nanoparticles were able to successfully block host-pathogen interaction at picomolar concentrations [120].

II.6.1. Inhibiting viral replication:

Once the virus enters the cell, it hijacks the cellular biochemical machinery to produce more copies of itself. If the virus is able to successfully execute the second step of the infection cycle, it is able to spread in the body and cause infection. Thus, therapeutic strategies targeting this step are extremely essential to contain the infection. Nanostructures have mainly been utilized as carriers to deliver the anti-viral molecules. The benefits which the nanoparticles provide in this regard are- higher specificity and bioavailability of the viral drug, combining different drug molecules in a single particle, improved solubility of the drug and decreased toxicity to the host. However, recently a number of nanoparticles are shown to intrinsically inhibit viral replication, such as Ag2S nanoclusters, which were reported to exert an inhibitory effect on coronavirus replication, thereby preventing the budding of new viral particles from the host cell. In addition, Ag2S nanoclusters also enhance the expression of pro-inflammatory cytokines, which might also play a role in combating viral infection. The study was carried out using the porcine epidemic diarrhea virus (PEDV) as a model for

coronavirus infection. Similarly, zinc oxide (ZnO) nanoparticles have also been reported to possess antiviral activity. ZnO nanoparticles have been effective against H1N1 influenza virus infection, and studies have also reported the ability of zinc to inhibit SARS-CoV replication. Zinc modulates host immune response, inducing the production of antiviral cytokines and suppressing inflammation. Other studies have also highlighted the role of antiviral efficacy of zinc oxide nanoparticles, and exploring the anti-SARS-CoV-2 potential of these nanoparticles might provide an early therapeutic solution for COVID-19. RNA dependent RNA polymerase (RdRP) is an important SARSCoV-2 protein, which helps to maintain genome fidelity, together with some other non-structural proteins. Inhibiting viral RdRP enzyme will provide a therapeutic advantage against COVID-19. A similar strategy employed by Shiang et al to inhibit HIV reverse transcriptase may be utilized for inhibiting SARS-CoV-2 RdRP. His research group developed aptamer functionalized gold nanoparticles to inhibit viral reverse transcriptase. The conjugation of aptamers to gold nanoparticles protected them from nuclease degradation and increased theirin vivo lifetime. Also, the conjugation allowed a multivalent display of aptamers, resulting in greater antiviral activity. Two different aptamer-Au nanoparticle conjugates were synthesized, one containing aptamers specific for the polymerase region and other containing aptamers specific for the RNaseH of HIV reverse transcriptase. Silver nanoparticles have also been found to exert anti-viral effects on coronavirus as well. Xiaonan's research group reported that silver nanoparticles and silver nanowires inhibited TGEV (a type of coronavirus) multiplication and also inhibited TGEV-induced host cell infection. These nanomaterials also downregulated host cell apoptosis triggered by TGEV infection [105].

II.6.3. Nano-delivery systems for COVID-19 treatment:

Drug delivery via nanocarriers helps to overcome several challenges associated with the traditional method of antiviral drug administration. Poor bioavailability, susceptibility to in vivo degradation of drug, systemic toxicity, and short half-life in the body are some of the drawbacks associated with antiviral therapeutics. However, nano-delivery systems resolve these

issues and enable higher bioavailability, reduction in effective drug dosage, lower toxicity, protection from degradation, improved half-life in circulation and ability to cross the biological barriers to target viral infection in sheltered body sites. Stealth technology, specific tissue or cell targeting, and desired drug release profiles are some other advantages of nano-delivery systems. Specific targeting of nanocarriers can be achieved by targeting moieties like monoclonal antibodies for cell surface antigens or by employing stimuli-responsive nanoparticles. The stimuli sensitive nano-delivery systems can be triggered by some intrinsic abnormal factors at the viral infected tissue such as temperature values or pH. On the contrary, these smart nanocarriers can also be sensitized to external stimuli like applied magnetic field or ultrasound waves. Liposomes, dendrimers, micelles, microspheres and other organic nanoparticles have been successfully used for improved and targeted delivery of different antivirals such as dapivirine, efavirenz, acyclovir and zidovudine. Given that COVID-19 is a respiratory disease, inhalable nanoparticles can be a non-invasive method of delivering anti-SARS-CoV-2 therapeutics directly to their site of action. This can help in the preferential deposition of nanoparticles in the SARS-CoV-2 infected lung tissues. To administer drugs in respirable form, devices such as nebulizers are used, which deliver the drug as a solid or liquid, suspended in a gaseous medium. It has been reported that many therapeutic molecules, when administered alone, are not stable in aerosolized form. However, when combined with nano-delivery systems, they can be easily administered in inhalable forms with enhanced lung deposition and retention. Nanocarriers are especially important delivery of poorly soluble drugs, which exhibit bolus formation and subsequent lung toxicity when given as free drugs. Both inorganic as well as polymeric nanoparticles have been studied as nanocarriers for drug delivery in the respirable form. Mucociliary clearance and phagocytosis by alveolar macrophages are the physiological barriers that must be taken care of when developing inhalable nanomedicines [105].

II.6.4. Nano-based vaccine:

Conventional vaccines such as live attenuated viruses, inactivated viruses, or subunit vaccines, all have certain limitations. The risk of reversion of

viral virulence (live attenuated vaccines), weak immune response (inactivated viruses), and limited immunogenicity (subunit vaccines) are some of the concerns of conventional vaccines. However, advances in biological and chemical engineering allow designing nano-based vaccines with strong immunogenicity and enhanced antigen presentation. Nanoparticles can serve as platforms for displaying the viral antigen to host immune cells such as the small nanovesicles expressing MERS virus S protein on its surface, mimicking MERS-CoV pathogen. Recombinant viral proteins, namely, Spike (S), Envelope (E), and membrane (M) proteins, were transfected into Bm5 cells, and S-protein displaying nanovesicles were obtained by both surfactant treatment as well as mechanical extrusion method. Raman et al and Pimentelet al reported that peptide nanoparticles could act as potent immunogens and serve as a vaccine for SARS and other enveloped viruses. They designed a polypeptide that self-assembles into icosahedral nanoparticles. The polypeptide sequence corresponded to a C-terminal region of viral S protein which plays an important role in the entry of the viral genome into the host cell. The icosahedral nanoparticle repetitively displayed the B-cell epitope and elicited an adequate antibody response with the use of any adjuvants. The potent immunogenic effect of the vaccine is due to the small size of the immunogen and the repetitive presentation of the epitope, both of which were met by virtue of utilizing nanoparticles. Functionalizing the antigen-loaded nanoparticle with ligands targeting the antigen-presenting cells of the immune system helps to enhance significantly the vaccine potential. For instance, Raghuwanshiet al developed plasmid DNA loaded chitosan nanoparticle formulation as a potential vaccine for immunization against the SARS-CoV virus. The plasmid DNA encoded the nucleocapsid (N) protein of SARS-CoV, as it is highly conserved compared to other SARS-CoV proteins and is also abundantly shed during viral infection. The chitosan nanoparticles surface contained bifunctional fusion protein which specifically recognized the DEC-205 receptor of nasal dendritic cells to elicit an immune response at the site of the viral entry itself. When these nanoparticle vaccines were delivered intranasal along with antiCD40 dendritic cell maturation stimuli, they stimulated mucosal IgA response and systemic IgG response against viral N protein. However, when the naked plasmid DNA was delivered intranasal, it

did not elicit mucosal or systemic immune response. Many studies have reported that, in case of respiratory infections, vaccination via the intranasal route leads to better immune-mediated protection. Intranasal vaccination induces higher levels of antigen-specific IgA antibody, higher cytokine production and a more increased proliferation of antigen-specific lymphocytes. Shim et al developed a SARS vaccine, comprising of DNA encoding for viral spike protein (pci-S), complexed with polyethyleneimine (PEI). Intranasal delivery of the PEI/ pci-S vaccine nanoparticle elicited antigen-specific antibody and cellular immune response. Mice vaccinated with PEI/pci-S had a high number of B220+ cells as well as elevated levels of class II major histocompatibility complex molecules(I-Ad) and costimulatory molecules(CD80 and CD86) on CD11c+ dendritic cells of cervical lymph nodes. Nano-based vaccines allow loading the adjuvant along with the viral antigen, accelerating the development of safe and effective vaccines. Lin et alreported virus-like polymeric nanoparticles as a vaccine for the MERS-CoV. A suitable adjuvant (STING agonist)was encapsulated in a shell layer of poly (lactic-co-glycolic acid (PLGA), and the MERS CoV RBD antigen was displayed on the nanoparticle surface to mimic the viral morphology. The viromimetic nanoparticle vaccine-elicited RBD antigen-specific T-cell and potent neutralization antibody responses in mice. Moreover, the transgenic mice model (permissive for MERS-CoV) immunized with the nanoparticle vaccine was safely protected when challenged with a lethal MERS-CoV infection [105].

II.6.5. Current SARS-CoV-2 nanotherapies under development:

Many therapy candidates currently in development for COVID-19 infection are utilizing nano-based approaches. iBio and Beijing CC-Pharming are developing SARS-CoV-2 virus-like particles using iBio’s FastPharming System (ibioinc; see Related Links). The Virus-like particles (VLPs) will be purified from plants and tested further as vaccine candidates. Moderna has developed a lipid nanoparticles encapsulating mRNA vaccine. The mRNA codes for SARS-CoV-2 spike protein (Moderna, Inc, see Related links). This nanoparticle-based vaccine has already entered the clinical trials.

NanoViricides, Inc. has developed nanoviricides capable of binding and engulfing the SARS-CoV-2 virus particle. The nanoviricides comprise of a nanomicelle conjugated with ligands that can bind to the virus. These ligands are derived from the host receptor angiotensin converting enzyme type 2 (ACE2) of SARS-CoV-2 [105].

II.7.Conclusion:

The current emerging COVID-19 pandemic has caused a global impact on every major aspect of our societies. It is known that SARS-Cov-2 can endure harsh environmental conditions for up to 72 h, which may contribute to its rapid spread. Therefore, effective containment strategies, such as sanitizing, are critical. Nanotechnology can represent an alternative to reduce the COVID-19 spread, particularly in critical areas, such as healthcare facilities and public places. Nanotechnology-based products are effective at inhibiting different pathogens, including viruses, regardless of their drug-resistant profile, biological structure, or physiology. Although there are several approved nanotechnology-based antiviral products, this work aims to highlight the use of nanomaterials as sanitizers for the prevention of the spread of mainly SARS-Cov-2. It has been widely demonstrated that nanomaterials are an alternative for sanitizing surfaces to inactivate the virus.

Chapter 03
Corona stats

III.1. Introduction:

In this chapter, we will present the statistics of the Corona virus, and we will show the factors affecting the increase and decrease in the number of cases and the number of deaths.

III.2. Number of cases in terms of time:

Curve showing the number of corona cases in terms of time.

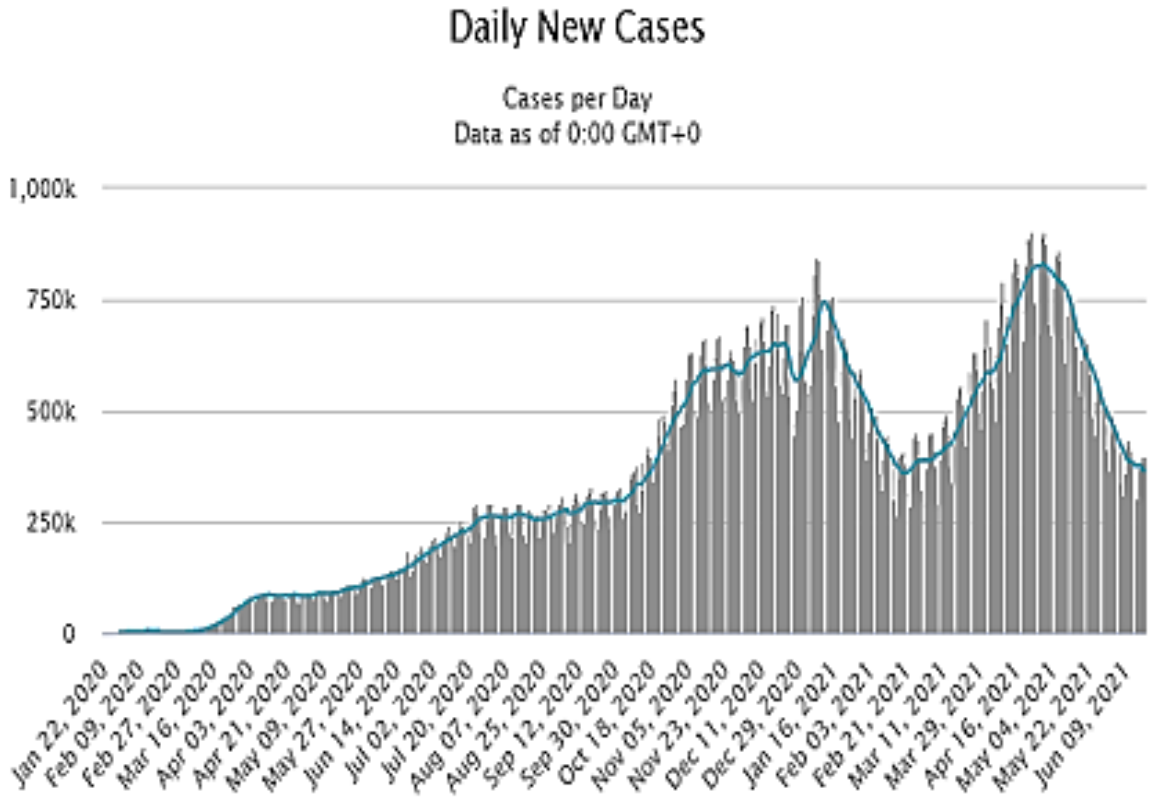

Figure III.1. The number of cases in terms of time [121].

III.1.1. Analysis:

We note that at the beginning of 2020, the number of infections was very small, but starting from March 2020, it began to gradually increase, reaching its peak on 01/11/2021, and the number of cases decreased significantly on February 20, 2021, to increase after that and reach its maximum peak on 29/04/2021. This is for several reasons, including:

1. Low levels of adherence to public health and social measures resulting in increased social mixing.
2. The spread of new mutated variants of corona that are more transmissible and contagious.
3. Uneven or uneven distribution of COVID-19 vaccines.

Then it decreases these days.

III.2. Number of deaths in terms of time:

A curve showing the number of deaths in terms of time.

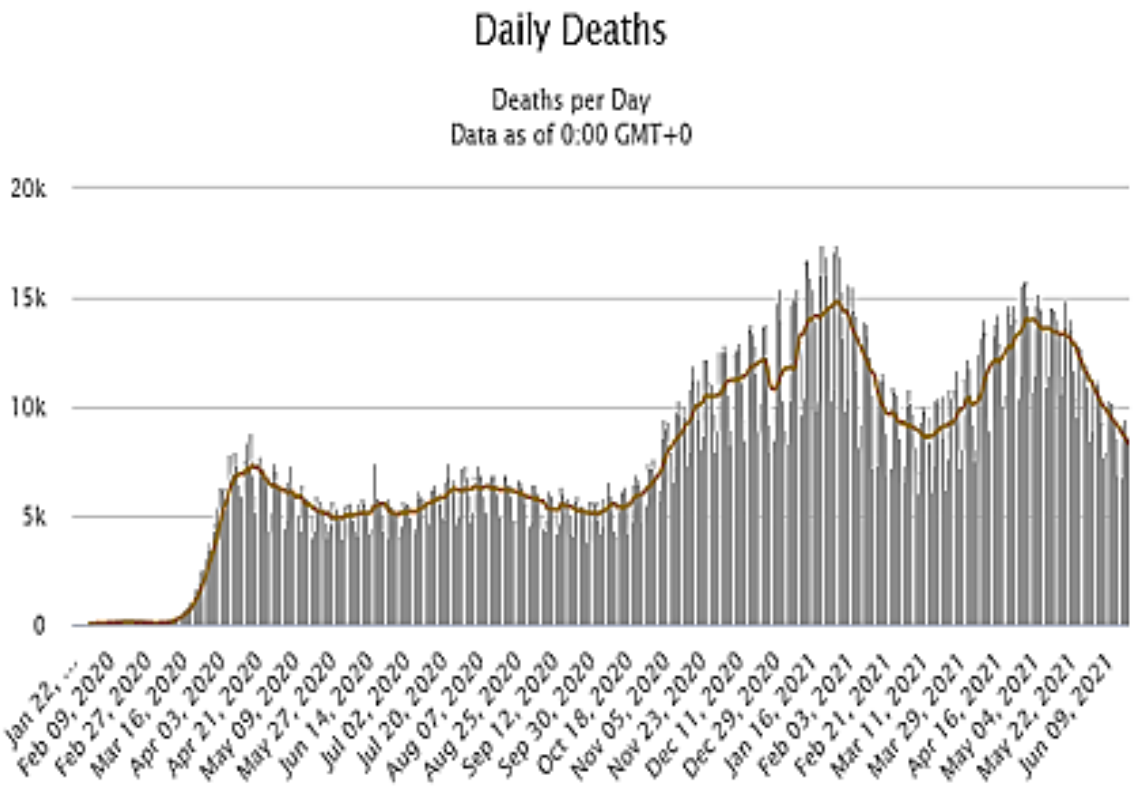

Figure III.2. The number of deaths in terms of time [121].

III.2.1. Analysis:

We note that the number of deaths fluctuates increasing and decreasing due to several factors, including: the sharp increase in the number of injuries, but

in recent times the number of deaths has decreased significantly, due to the development of treatment and the emergence of several new vaccines.

III.3. Conclusion:

The reason for the decrease in the number of cases and the number of deaths is due to the development of methods of prevention and treatment.

General Conclusion

Conclusion General:

The novel coronavirus pneumonia pandemic was declared as‘public-health emergency of international concern’ by the World Health Organization on 30 January 2020. The sudden emergence of the viral pathogen responsible for this outbreak, the novel coronavirus, SARS-CoV-2, has triggered alarm for their instant management using anti-viral measures and diagnostic tools. Early diagnosis will enable containment of COVID-19 (coronavirus disease 2019), allowing quick implementation of control measures for limiting the spread of this disease. Due to high human to human transmission, the development of effective anti-SARS-CoV-2 therapeutics for treating affected patients will help to slow down the transfer of viruses from patients to healthy individuals. However, till the time any effective therapeutic or vaccine is developed, preventing exposure to SARS- CoV-2 virus is the best way out. The development of more effective personal protective equipments (PPEs) is essential to maintain the safety of healthcare professionals and the public at large. Taking into consideration the current severity of this disease and the imperative need of SARS-CoV-2 specific treatment and diagnostic tools, nanotechnology-based approaches can provide promising alternatives to conventional ways of disease diagnosis, treatment, and preventing exposure to SARS-CoV-2. In this review, we inform about the different ways in which nanotechnology can help in the detection and treatment of prevailing SARS-CoV-2 infection as well as help to improve the PPE devices.

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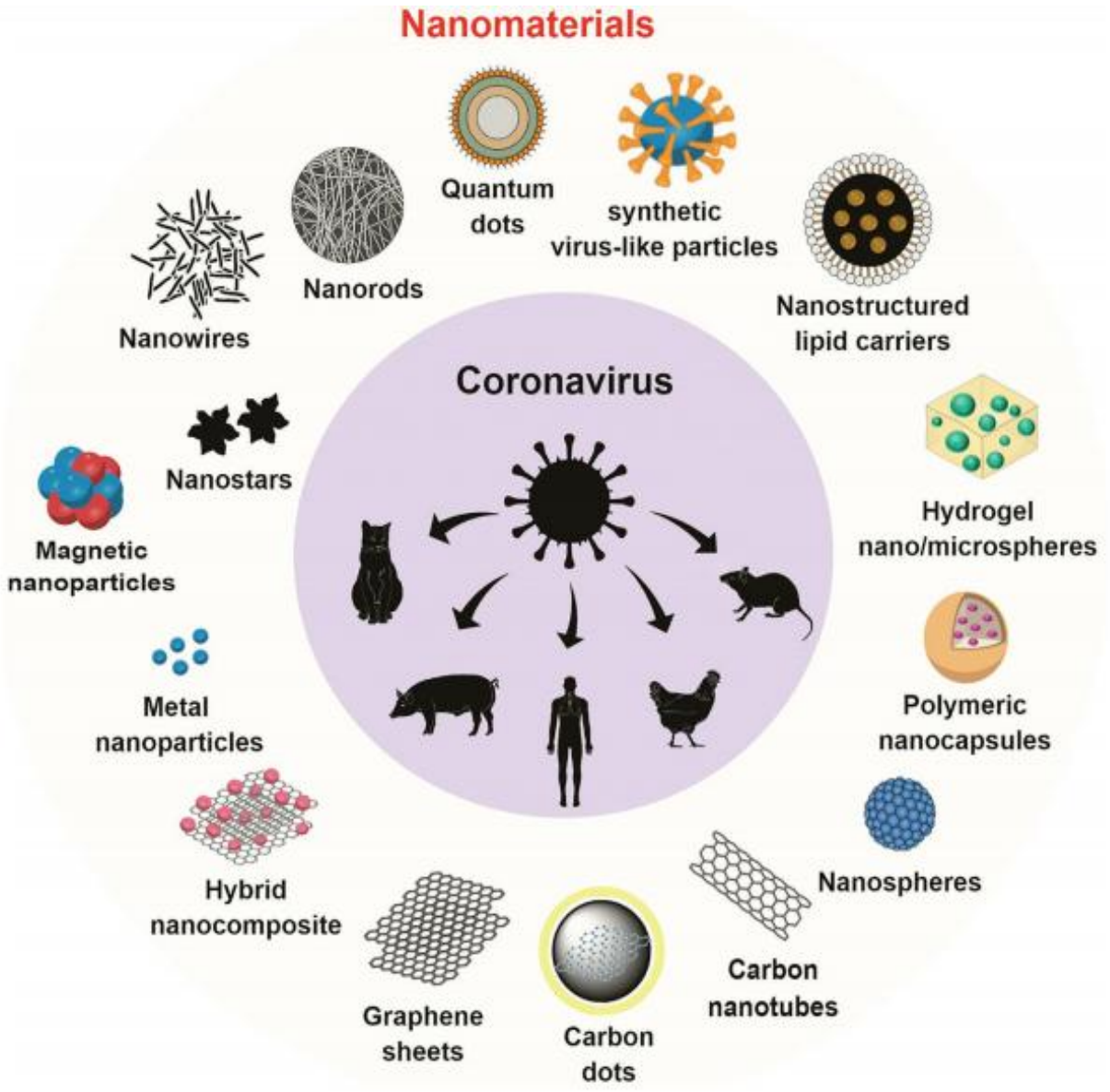
Appendices

Appendices


Nanomaterials
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synthetic virus-like particles
Nanorods
Nanowires
Nanostructured lipid carriers
Coronavirus
Nanostars
Magnetic nanoparticles
Hydrogel nano/microspheres
Metal nanoparticles
Polymeric nanocapsules
Hybrid nanocomposite
Nanospheres
Graphene sheets
Carbon dots
Carbon nanotubes