



Nanomaterials and metal-organic frameworks for biosensing applications of mutations of the emerging viruses

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ABSTRACT

The world today lives in a state of terrible fear due to the mutation of the emerging COVID-19. With the continuation of this pandemic, there is an urgent need for fast, accurate testing devices to detect the emerging SARS-CoV-2 pandemic in terms of biosensors and point-of-care testing. Besides, the urgent development in personal defense tools, anti-viral surfaces and wearables, and smartphones open the door for simplifying the self-diagnosis process everywhere. This review introduces a quick COVID-19 overview: definition, transmission, pathophysiology, the identification and diagnosis, mutation and transformation, and the global situation. It also focuses on an overview of the rapidly advanced technologies based on nanomaterials and MOFs for biosensing, diagnosing, and viral control of the SARS-CoV-2 pandemic. Finally, highlight the latest technologies, applications, existing achievements, and preventive diagnostic strategies to control this epidemic and combat the emerging coronavirus. This humble effort aims to provide a helpful survey that can be used to develop a creative solution and to lay down the future vision of diagnosis against COVID-19.

1. Introduction

Coronavirus (COVID-19); “a global pandemic requires a global response”. In Dec. 2019, pneumonia outbreak cases appeared for several unknown reasons in “Wuhan city, the capital of Hubei Province in China”. The clinical symptoms closely resemble viral pneumonia [1–6]. After conducting medical, clinical, and laboratory examinations, it was confirmed that the pathogenic gene causing the viral pneumonia is caused due to a new mutated strain closely like the SARS-CoV virus [7, 8]. The new virus is known as a coronavirus (COVID-19) due to the analogy of the “ β -coronavirus, SARS-CoV” [9], and the “Middle East Respiratory Syndrome” (MERS), appeared in 2003 and 2012, respectively [10,11]. In a very short time, the situation evolved and quickly developed then this virus turned into an epidemic like wildfire, and it spread rapidly throughout China. Soon after, it moved to all parts of the world [12,13]. The “World Health Organization (WHO)” declared on March 11, 2020, the outbreak of the epidemic and called it the “COVID-19 Pandemic” [14–16]. The disease was declared as a public health emergency of international concern. As a result of the outbreak of this epidemic disease has caused all the governments to resort to international measures to contain the spread of the disease. For example,

the Chinese government initially resorted to imposing a quarantine on Wuhan and other affected cities, preventing mixing at the state level and encouraging citizens to stay/work from home, and the obligation to wear personal protection methods such as face masks, etc. and so on. However, these efforts have been limited to this challenging problem.

The challenge was distinguishing between confirmed cases of the coronavirus and healthy people. Clinical symptoms such as fever, cough, muscle pain, or fatigue [17] are not unique and distinctive symptoms of the new SARS-CoV-2. On the other hand, the symptoms are identical to other virus-infected diseases such as influenza [18]. The international standard diagnosing of new cases of COVID-19 is the nucleic acid (NA) Real Time-PCR (RT-PCR) of the virus. Additionally a CT scan on the chest, some hematology, and medical investigations such as complete blood picture, sedimentation rate, liver function, etc. [19]. The previous analysis is the standard method for the detection of COVID-19 infection, besides, some analytical methods and reagents that some companies have developed. Although RT-PCR-NA kits are currently the leading international standard for COVID-19 disease diagnosis, it has some flaws and many limitations: (a) these tests have long and complex periods; usually take between two to 3 h to achieve the results; (b) RT-PCR tests require laboratory accreditation, unique instruments, and professional technicians trained to work; (c) a disadvantage of this method is also

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List of abbreviation

ACE2	Angiotensin-converting enzyme 2	MIP	Molecularly imprinted polymer
Ag NPs	Silver nanoparticles	MNPs	Metallic nanoparticles
AIV	Avian Influenza virus	MONPs	Metal oxide nanoparticles
Au-NPs	Gold nanoparticles	MOF-NPs	Metal-organic framework nanoparticles
Au-NS	Gold nanostars	MOFs	Metal-organic frameworks
H7N9/H5N1	Avian influenza virus subtypes strains	M protein	Membrane glycoprotein
CBC	Complete blood picture	MTB	<i>Mycobacterium tuberculosis</i>
CDC	Centers for Disease Control and Prevention	NA	Nucleic acid
C60	Fullerenes	NASBA	Nucleic acid sequence-based amplification
C-dots	Carbon dots	NB	Nano-biosensors
C-QDs	Carbon quantum dots	NFMs	nano-functionalized materials
CNTs	Carbon nanotubes	NLRP3	Nod-like receptor family, pyrin domain containing 3
COFs	Covalent organic frameworks	NMs	Nanomaterials
COVID-19	2019 novel coronavirus disease	NMOFs	Nanomaterials-based metal-organic frameworks
CRP	C-reactive protein	N protein	Nucleocapsid protein
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats -associated protein 9	NPs	Nanoparticles
CT scan	Computerized tomography scan	NTS	Nanopore targeted sequencing
C2CA	Circle-to-circle amplification	ORF1	Open reading frame-1
DENV	Dengue virus	PAN	Polyaniline
DNA	Deoxyribonucleic acid	PCR	Polymerase Chain Reaction
EBOV	Ebola virus	PNA	Peptide nucleic acid
ECDC	European Centre for Disease Prevention and Control	PPTs	Personal protective tools
ELISA	Enzyme-linked immunosorbent assay	PDTs	Personal defense tools
E protein	Envelope glycoprotein	POCT	Point-of-care testing
ESR	Sedimentation rate	PU	polyurethane
FAM	Carboxyfluorescein	QCM	Quartz crystal microbalance
FET	Field-effect transistor	QDs	Quantum dots
Fe₃O₄-NPs	iron oxide magnetic nanoparticle	qRT-PCR	Real-time quantitative reverse transcription-polymerase chain reaction
FIPV	Feline infectious peritonitis virus	RBD	Receptor-binding domain
G	Graphene	RCA	Rolling circle amplification
GO	Graphene oxide	RdRp	RNA-dependent RNA polymerase
Gr	Graphite	RNA	Ribonucleic acid
HAdV	Human adenovirus	ROS	Reactive oxygen species
HAV	Hepatitis A virus	RT-PCR	Real Time Polymerase Chain Reaction
HBV	Hepatitis B virus	RT-qPCR	Real-time quantitative reverse transcription-polymerase chain reaction
HCV	Hepatitis C virus	RV	Rubella virus
HIV	Human immunodeficiency virus	SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
HIV-1	1Human immunodeficiency virus-1	SARS	Severe acute respiratory syndrome
H. influenzae	Haemophilus influenzae	SAM	Self-assembled monolayers
HLE	Hemagglutinin-esterase	SAW	surface acoustic wave
HSV	Herpes simplex viruses	SERS	Surface-enhanced Raman scattering
HTV	hantavirus	S protein	Spike glycoprotein
HRPs	Horseradish peroxidases	SPR	Surface plasmon resonance
IgG	Immunoglobulin antibody γ -type	ssDNA	Single-stranded DNA
IgM	Immunoglobulin antibody μ -type	SUDV	Sudan virus
IL-6	Interleukin 6 test	TMA	Transcription-mediated amplification
JEV	Japanese encephalitis virus	TMPRSS2	Transmembrane protease/serine subfamily member 2
LSPR	Localized surface plasmon resonance	TMV	Tobacco mosaic virus
LAMP	Loop-mediated isothermal amplification	US-EPA	United states Environmental Protection Agency
LFDA	Laminar flow assisted dendritic amplification	VOC	Variants of concern
LFT	lateral flow test	VOI	Variants of interest
LNPs	Lipid nanoparticles	WHO	World Health Organization
LOC	lab-on-chip	YFV	Yellow Fever virus
LOD	Limit of detection	ZIKV	Zika virus
LOQ	Limit of quantification	0D	Zero-dimensional
LV	Leprosy virus	1D	1-dimensional
MERS	Middle East Respiratory Syndrome	2D	2-dimensional
		3D	3-dimensional

obtaining false-negative results, which could lead to a disaster. These flaws and limitations make RT-PCR testing unsuitable for rapid and straightforward diagnostic for examination of patients [20–23]. Further, alternative techniques were suggested diagnosing the COVID-19 infection as immunoglobulin antibodies [24]. It is known that the immunoglobulin antibody test (IgM/IgG) is considered a specific test for any type of viral infection. For example, in the patient's blood, one of the simple, fast, and sensitive options for the clinical diagnosis of viral infection is the μ -type (IgM) antibodies. IgM-antibodies provide the first line of defense during viral infection and the largest antibody in blood and lymphatic fluid, and the γ -type (IgG) antibodies represent the second line of defense for a viral infection or so-called on its long-term immune memory or immunity. It is the most abundant in the body, as it is found in all body fluids, which are the bodies that defend the body against invading bacteria and viruses. In addition to being the smallest antibody in the body, and for this reason, they move quickly through the cell membranes [25]. For example, after infection with the SARS virus, IgM antibodies can be detected in the patient's blood from the third day of infection, IgG can be detected from the eighth day of infection [26]. Hence, the COVID-19 virus belongs to the same large group of viruses (as SARS), it is assumed that the process of antibody generation is done similarly, and based on that we will create analytical methods and techniques to detect both the IgM and IgG of the new COVID-19 virus that will enable to provide information about the virus infection or not. However, these serological techniques have many disadvantages. These types of testing do not introduce an accurate interpretation of the patient's immune status. In addition, these tests commonly occur cross-reactivity with other coronaviruses types [24,27].

This review will focus on and summarize the three main hot topics up to date: i) What is the "SARS-CoV-2" virus? (the definition of the virus and its structure, the transmission of viral infections and pathophysiology, the identification and diagnosis of the mechanism of host and receptor interaction on the spread of viral infection, mutation, and genomes transformation.); ii) Global situation (Where the world from COVID-19 now?); iii) The role of nanomaterials and metal-organic frameworks (MOFs) for SARS-CoV-2 biosensing techniques, diagnosis, and development of personal defense tools, anti-viral surfaces and wearables, and smartphones base-nanotechnologies. Different types of nanomaterials such as metallic nanoparticles (M-NPs) like (gold and silver); magnetic metal oxide nanoparticles (MO-NPS) like (Fe_3O_4 -NPs); carbon nanomaterials like (C60, C-dots, CNTs, G, GO and Gr); QDs like (CdS-QDs, CdTe- QDs, and C-QDs), nano-polymers like (cellulose and chitosan); etc. In addition to (MOFs) like (ZIF-8, MIL-101 (Cr), etc.) which have been used to improve a new technique to diagnose COVID-19". With the help of different biosensing techniques such optical magnetometry, chromatography, current, impedance, and fluorescence. The associated mechanisms for the detection of "SARS-CoV-2", will be also discussed in detail in this review. The emphasis has been made on the different methods for biosensing using a variety of nanomaterials/MOFs and the associated mechanisms detecting "SARS-CoV-2" infection. Besides, the urgent development in personal defense tools, anti-viral surfaces and wearables, and smartphones open the door for simplifying the self-diagnosis process everywhere based on advanced nanotechnologies. Furthermore, highlight the latest technologies, applications, existing achievements, and preventive diagnostic strategies to control this epidemic and combat the emerging coronavirus. Moreover, future perspectives for implementing biosensing techniques based on nanomaterials/MOFs for detection of COVID-19 will be highlighted, and finally, closing remarks.

2. Global situation (where is the world from COVID-19 now?)

A great effort was made by governments, relevant bodies, and organizations worldwide, to contain the spread of the disease. Although, scientists have made great significant efforts to develop safe vaccines [28] or limit virus spread. Through, innovative new fast detection

methods and prepare new materials [12,29–33]. The numbers of confirmed cases globally pass 440 million according to the last report updated by WHO "Globally recognized, on March 04, 2022, 5.18 p.m., and as represented in (Fig. 1) the confirmed cases of COVID-19 reach 440,807,756, and 5,978,096 deaths [34]. Meanwhile, catastrophic and tragic events occurred in India, the number of deaths exceeded 200,000 in a few days" [35]. In this context, our country Egypt is classified as "Very High Level of COVID-19" according to the report edited by "Centers for Disease Control and Prevention (CDC)" [36].

More detailed information about the world situation weekly can be found from the link titled "COVID-19 Weekly Epidemiological Update" report by WHO (pdf) file and it is available at [37]. This pdf file is also a website that includes data about SARS-CoV-2 VOC and VOI, published and updated by ECDC to follow the transmission of the virus variants globally elsewhere [38].

3. COVID-19: identification, diagnosis, host-interaction mechanism, and prospective

COVID-19, a global pandemic requires a global response. To overcome and solve any problem, especially the "SARS-CoV-2" virus, the following questions must be answered. What is the "SARS-CoV-2" virus? What is the mechanism of transmission, pathophysiology, and interaction with human organs? Why is the Coronavirus spreading more dreadfully than the other virus? What are the types of mutation and genomes transformation? Finally, what are the suggested solutions?

3.1. COVID-19: virus identification, and structure

"SARS-CoV-2", (Fig. 2): It is a β -corona single-stranded ribonucleic acid (RNA) enveloped virus (positive-stranded RNA genome/RNA-enveloped positive sense) [39–41]. β -coronavirus belongs to the order Nidovirales family. The SARS-CoV-2 virus structure is composed of 4-main proteins "(spike glycoprotein (S protein), envelope glycoprotein (E protein), membrane glycoprotein (M protein) and nucleocapsid protein (N protein)), in addition, envelope, genomic RNA, and hemagglutinin-esterase (HLE)" [12,27].

The functionals of coronavirus portions can be concluded as follows: S protein, which binds to the host receptor through "angiotensin-converting enzyme 2 (ACE2)" and is responsible for viral entry into the cell [42]. Furthermore, it has two functional subunits; S1, and S2, which facilitate the cell attachment process and enable membrane-binding [43]. Although it's the smallest component in the SARS-CoV-2 virion envelope (present in minor amounts), E protein plays a major role in the virus's maturation and replication [43]. M protein is defined as the virus envelope (the most abundant component present in the virus structure) [44]. Finally, the N protein is a structural protein, responsible for binding the single-stranded RNA genome to form a shell around the enclosed nucleic acid [45]. It plays a vital role in the cycle of viral replication and host cell response to viral infection [46]. The original virus family name is due to the S protein assembles into trimers on the surface of the virion, forming peplomers-embedded in the envelope to form a crown-like appearance (distinctive "corona") which gave the name to the whole family [47,48] as shown in Fig. 2. Virions "the complete, infective form of a virus outside a host-cell, with a core of RNA/DNA and a capsid" of the coronavirus family, is roughly spherical, its diameter about 118–140 nm [47].

A comparison between SARS-CoV and MERS-CoV mortality against SARS-CoV-2 is discussed in the next paragraph. The SARS-CoV disclosed a 9.7% fatality rate with a total number of confirmed cases globally about 8098 and 774 deaths [49]. Whereas, MERS-CoV disclosed in 27 countries a 34% fatality rate with a total number of confirmed cases globally about 2494 and 858 deaths [49]. Whereas SARS-CoV-2 was just the first pandemic wave, the number of confirmed cases globally, rapidly reached 10 million and around 500000 deaths. It was continued until reached over 440 million confirmed cases and over 5.97 million

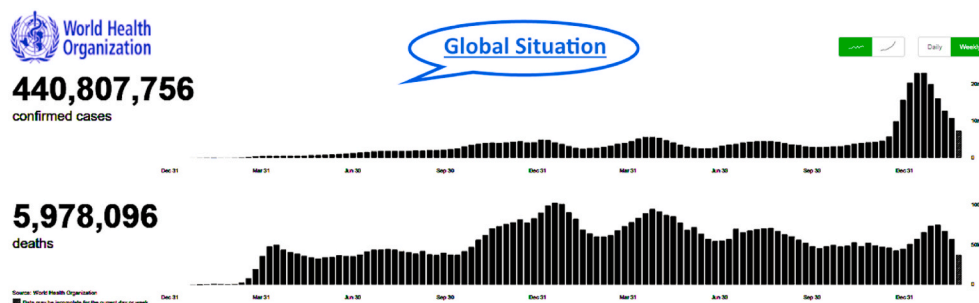


Fig. 1. Global situation of COVID-19 updated by the World Health Organization.

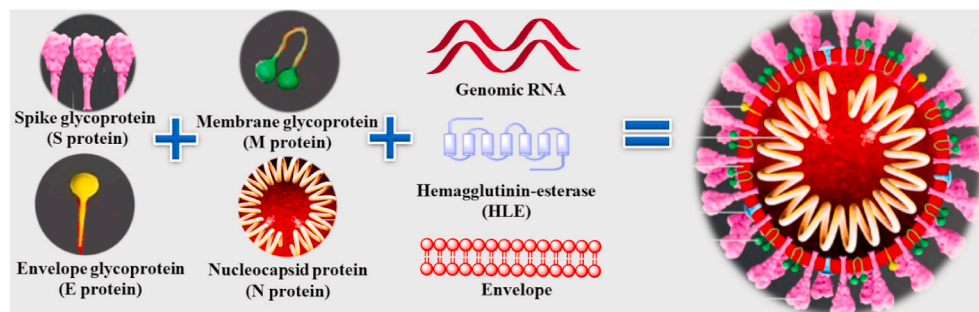


Fig. 2. Showed a schematic of COVID-19 components viral structure, proteins, and a cross-sectional representation. [modified from Ref. (29)].

deaths in March 2022 [34,49]. The “SARS-CoV-2” genomic phylogenetic analysis is quite similar to “SARS-CoV” by about 82% and to MERS-CoV by about 50% [50,51]. Moreover, the “SARS-CoV-2” genomic expression is 89–96% identical with the bat coronavirus RaTG13, so “COVID-19” may have originated and mutated from the bat [50,51]. SARS-CoV differs from “SARS-CoV-2” in pathogenesis, in that it induces inflammation of both upper and lower respiratory tract [12,27]. Both SARS-CoV and COVID-19 need ACE2-receptor to enter into cells for human infection and replicate inside them [52]. The “SARS-CoV-2” genomic organization of non-structural and structural proteins can be targeted for antibody-neutralization for vaccine development and as biological receptors for diagnostic applications as shown in Fig. 3 [12].

3.2. SARS-CoV-2 viral infection: virus-host interaction mechanism

The interaction of the “SARS-CoV-2” cell-entry mechanism and the associated immune responses are represented in Fig. 4. In the upper

section, we mention that the SARS-CoV virus has a genomic phylogenetic sequence similar to its predecessor viruses responsible for “severe acute respiratory syndrome” (SARS-CoV/MERS-CoV) [39,50,53]. Moreover, the S protein of SARS-CoV has a “Receptor-Binding Domain (RBD)” (ACE2-receptor) that intensely identifies ACE2 and binding to the cellular-uptake [54]. Through the binding process, the virus enters inside an endosome and is ingested into the cell (cell penetration). Inside the endosome cathepsin L “a lysosomal endopeptidase enzyme starts digesting the S proteins of the SARS-CoV virus (initiation of COVID-19 S protein degradation)”, this process allowed the viral RNA to complete the replication. “ACE2 surface proteins are mainly present in the nose, lungs, blood vessels, kidneys, and gastrointestinal tract, the ACE2 receptors responsible about the converting (catalyzing) the angiotensin II peptides to angiotensin this molecule capable of vasodilation in decreasing blood pressure and vice-versa (a vasoconstrictor peptide) [55,56], it also plays a master key in physiological functions, which regulated the blood pressure level, sodium, and potassium balance,

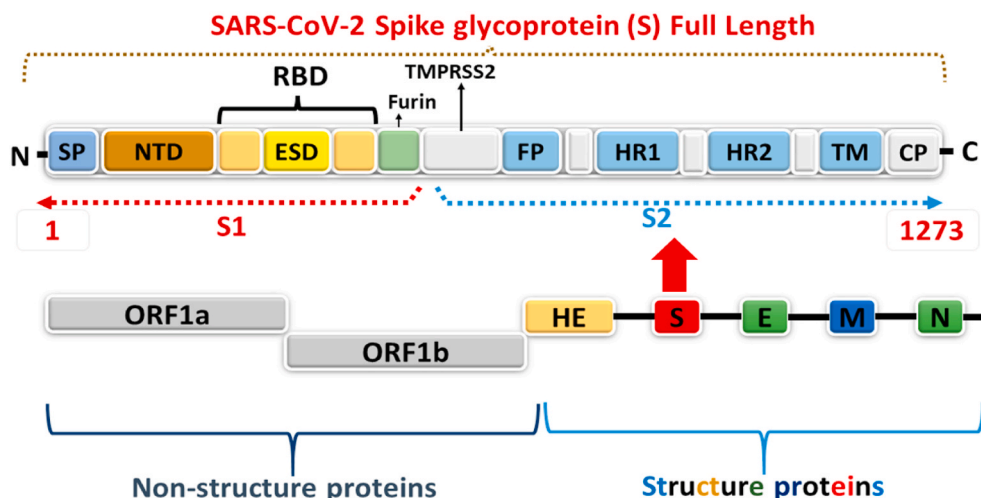


Fig. 3. Representing the non-structural and structural proteins of SARS-CoV-2 genome organization. “(N, Nucleocapsid; M, Membrane; E, Envelope; S, Spike; HE, Hemagglutinin Esterase; ORF, Open Reading Frame; CP, Cytoplasm Domain; TM, Transmembrane Domain; HR1, Heptad Repeat 1; HR2, Heptad Repeat 2; FP, Fusion Peptide; ESD, External Subdomain; NTD, N-Terminal Domain; SP, Signal Peptide; S1, Subunit 1 (Receptor attachment); S2, Subunit 2 (Fusion); TMPRSS2, Transmembrane Protease/Serine Subfamily Member 2; and RBD, Receptor Binding Domain). [modified from Ref. (12)]”.

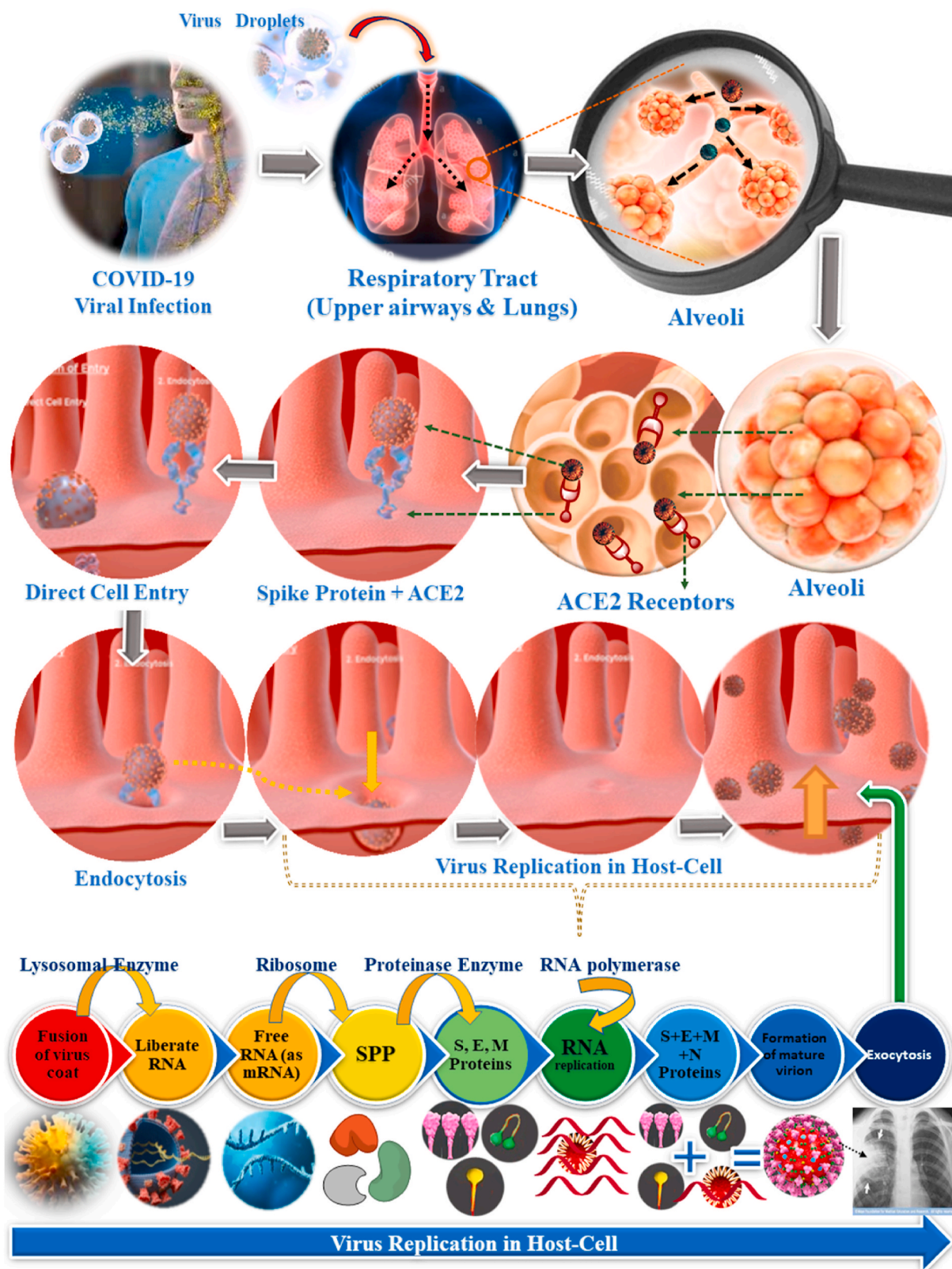


Fig. 4. Schematics showing the mechanism of SARS-CoV-2 virus toward the host cell: Entry, replication, transmission, and the associated immune response. “[3D images adapted from: <https://en.wikipedia.org/wiki/Coronavirus>, CC BY-SA 4.0]”.

preserve the fluid volume, and inflammatory response” [55–57]. Besides the RBD, many reports showed that some of the protease activators like “transmembrane protease/serine subfamily member 2 (TMPRSS2)” play a major role in the combining of “SARS-CoV-2” to surface of the cell

through cleave the viral S protein, lead to releasing the viral-RNA into the host-cell for successive virus replication Fig. 4 [54,58,59]. In brief, as represented in Fig. 4 the mechanism done as follows: COVID-19 is transmitted through respiratory droplets of infected subjects to mucosal

cells in the oral and respiratory systems. SARS-CoV-2 binds to the ACE2 receptor after activating the spike protein by transmembrane protease serine 2 (TMPRSS2).

Lysosomal enzymes make and liberate RNA. Free RNA (+V sense) goes to Ribosome as mRNA to produce specific polyproteins (SPP). The proteinase enzyme converts SPP to COVID-like proteins (coat, S protein). RNA is replicated by RNA-dependent RNA polymerase. The copies of RNA, coat, and S protein formed replication on viruses and were subsequently released. After release, the virus causes destruction for the cell and subsequently releases the inflammatory mediator and activates Macrophages to the secretion of Cytokines in the bloodstream. Cytokines make three functions: a) Going to Hypothalamus and secreting PGE2 which causes fever, b) Making vasodilation and capillary permeability in salt (Na, K, ...) causing Alveoli edema, and c) Stimulate the neutrophils to secrete the usual defense (Oxygen superoxidase protease enzyme) to kill the virus, but itself is dying and lung cells are destroyed.

3.3. COVID-19: transmission and pathophysiology of viral infection

COVID-19 is transmissible from one to one at the rate of more than three people per confirmed infected patient. Furthermore, many reports have demonstrated that the S protein of "SARS-CoV-2" exhibits a higher affinity 10 to 20 times for ACE2 than SARS-CoV, which proves the increase in the number of human infections. Besides the nano size, the shape of the "COVID-19" virus (about 140 nm), allowed its penetration through surgical masks and increased the possibility of infections as shown in Fig. 5. Moreover, the trait proves the virus's ability to live in aerosols with a size of $<5 \mu\text{m}$ for $>3 \text{ h}$. In addition to the possibility of viruses in aerosols to movement in the cloud, up to 8 m [60–62], and limitation of home-based virus diagnosis and detection methods increased the infection globally.

The "SARS-CoV-2" main target organ is the respiratory tract, especially the upper airways and lungs [63]. Once COVID-19 enters the cell,

the symptoms differ from patient to one between simple (asymptomatic), acute, and very acute cases. No specific indications or symptoms have been recognized in asymptomatic cases, that can transmit the infection. So, technically, the major problem in these individuals who carry the disease and did not show symptoms indicative of it and the extent of what they represent is the danger of transmitting it in societies without paying attention to this. The patients generally show the symptoms of fever/headache/dry-cough and/or myalgia at the incubation period such as influenza. In acute cases a slowly develops pneumonia within 7-days from the onset of infection with SARS-CoV-2, which finally gets worsened into acute respiratory suffering syndrome and is fatal at the convalescence phase. In most cases, the virus diagnosis is detected in the upper respiratory tract, in the nasopharynx as the core replication site. However, some gastrointestinal symptoms have been noticed in many COVID-19 patients [64]. At any stage of the infection, significant biomarkers like (CBC, serum ferritin, amyloid-A, CRP, D-Dimer, etc.) will be released on the host system. So, the follow-up of biomarkers is very crucial for diagnosing COVID-19 patients and the pathogenesis of the disease. After 7- days of the onset of infection, the immune system produces IgG and IgM antibodies, which could be analyzed by sampling blood samples [65,66].

3.4. "SARS-CoV-2" mutation and genomes transformation

"COVID-19" death rate and genome mutation can change entirely from one geographic region to another [53]. Reports issued by the World Health Organization indicate that patients are spreading quickly from one country to another despite the imposition of a total ban in many places and lack of travel and that the nature of the virus mutates from one country to another in various forms and with terrible mutations as the new mutation that appeared recently in India [35]. In "COVID-19" open reading frame-1 (ORF1) about thirteen variation sites were depicted recently In some places, a mutation rate of about 30% has been

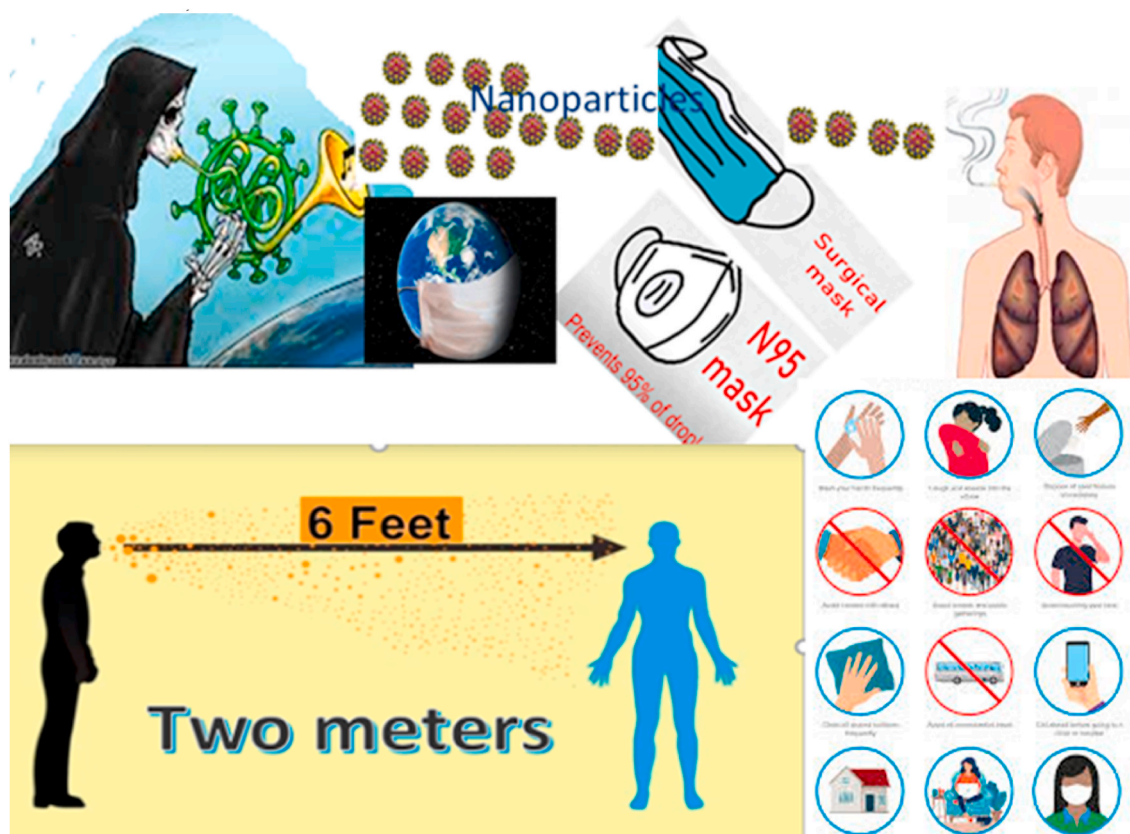


Fig. 5. The schematic shows the precautions that the person should take to avoid the infection with SARS-CoV-2.

identified for this virus [67]. Commonly, the mutagenic process of any viral genome depends on the viral enzymes that are responsible for the nucleic-acid replication and is slightly affected by post replicative nucleic-acid repair and/or proofreading capacity [47]. In most viruses' families like "Nidovirales, the RNA-polymerase lacks proofreading capability, with some exceptions". For example, in "COVID-19", Pachetti et al. [68], reported 8- new mutations were characterized with different causes of occurrence in North America, Asia, and Europe.

Recently, specific combinations of mutations and deletions of "SARS-CoV-2" variants are recognized and still circulating on a huge scale globally. The most common mutations are the Delta and Omicron variants. In comparison between the two variants, they demonstrated the two main and exotic molecular characteristics and features with slight mutations [69,70]. Before the two Delta and Omicron variants, Alph, Beta, and Gamma variants have appeared. In between (in the interim) them (Delta and Omicron) many other variants already have been detected like "Epsilon, Zeta, Eta, Theta, Iota, Kappa, and Lambda, respectively, and the then Omicron (as a variant of concern of "B.1.1529 variant")". This variant was declared by WHO at the end of November 2021 and spread quickly with high transmissibility and led to increased infectivity and the rates of re-infection even between vaccinated cases. However, the mortality rate is still under investigation and maybe will dramatically increase [69,70].

Due to the mutations mentioned above, the early monitoring and detection of spread and disease development with a technique like standard RT-PCR is complicated due to the possible mismatching of the primer with targets [71]. Consequently, focusing on the mutation and the genomes transformation of endemic regions is recommended and considered a vital task to decrease the probability of false-negative results [72].

3.5. A vision of pandemic management and suggested solutions

Until now, no specific drug has been developed as a treatment for "SARS-CoV-2" infections. The approved vaccines are very limited, besides the clinical studies for the approved vaccines, not enough. Therefore, in our opinion the global responses or the suggested solutions should be directed in four aspects or actions as represented in Fig. 6:

- 1) Beware of getting sick with "COVID-19", through taking different announced precautions in different social media.
- 2) Prompt and rapid diagnosis is the "key to controlling the COVID-19 pandemic". At present, it is necessary to rely on home techniques for diagnosis, what can be available in this area inside the home is a fundamental matter and a magical solution for not going out and then helping the spread of the disease. Now, the world is heading and considers it a top priority to search for a fast, reliable, and inexpensive way to test the point of care. Moving towards this vital trend for quick and simple solutions such as a wristwatch, mobile phone, or other easy-to-use technologies in critical areas and situations, the role of biosensor technology based on nanotechnology, nano-materials, and enabling organometallic frameworks may be the hope of introducing new technologies that may meet the current demand. Provides early and rapid diagnosis of SARS-CoV-2 infection. Hence, such advanced and affordable technologies in developing point-of-care devices at the point of care and diagnostic platform, as well as homes, can limit the spread of this disease.
- 3) Working with the current approved COVID-19 medical approaches in four aspects:
 - i) Administration of available vaccines, and at the same time, working in the development of several safer vaccines and innovative drugs for "SARS-CoV-2" infection treatment using nano-technologies and nano-solutions
 - ii) Targeting the life-cycle of the "SARS-CoV-2" virus by preventing cell entry or inhibiting the cell cycle in the host cell.
 - iii) Targeting immune response by Interferon-beta or purified patient plasma.
 - iv) Prophylactic treatment: tenofovir-mefloquine, prevention of long-term injuries, and other like-treatment.
- 4) Eye on the future in COVID-19 mutagenic process and follow up the virus mutation in different regions (follow "SARS-CoV-2" genomes with new mutation hotspots are emerging).

4. COVID-19 surveillance and biosensors types

Recently sensors, biosensors, nanotechnology, and near-patient testing applications have been developed rapidly and have been



Fig. 6. The authors' vision for pandemic management and suggested solutions.

increasingly used for clinical analysis, and diagnostic tools [73–75], which can offer fast test results with minimal or without pre-analytical preparations and interference. As well as the near-patient diagnostics are commonly used increasingly in limited-resource countries, because of the very limited of inadequate health care services in resource-constrained settings. In addition, these applications provide an unprecedented opportunity to improve the treatment of many diseases and discover many diseases early and allow the construction of diagnostic devices for cancer, biomolecules, bacteria, virus, etc., and point-of-care testing [76]. Moreover, the classification of sensors and biosensors is based on the recognition principle of the analyte of interest as examples: immunosensors (antibody-antigen interaction), enzymatic biosensors (enzyme–target analyte interaction), non-enzymatic receptor, molecularly imprinted polymer (MIP), deoxyribonucleic acid (DNA) elements and whole-cell, etc.). The recent classical recognition elements (enzymes and antibodies) play a major role in chemical sensors and biosensors by recognizing the target analytes of interest [77]. Likewise, individuals can be monitored periodically and continuously in vivo and made in-person diagnostics, using biosensors such as “Point of Care Testing” (POCT) devices, where many functions are integrated into individual microchips [78–81]. POCT devices facilitate the process of quick diagnosis for these viruses like COVID-19 [12,31,39,82–85].

The biosensors for detection of COVID-19 and different types of viruses can also be classified according to the technology used to 1) Biochemical technologies; 2) Immune technologies, and 3) Molecular technologies as well the main biosensor components were represented in Fig. 7. However, most of the above technologies have exceptional performance in terms of the time of detection, sensitivity, specificity, flexible portability, etc., but at the same time have many limitations for the requirements of detection of some viruses and microorganisms [83,86]. In this context, based on the specific antibody/antigen combination, the immune technologies introduced many biosensors. For example, Mavrikou et al. [87]; reported an immunosensor for the detection of the “SARS-CoV-2” S1 spike protein antigen. In addition, Seo et al. [88]; reported a fast detection method for “SARS-CoV-2” using field-effect transistor-based biosensors with good results. Moreover, as a recent technology, molecular technologies can be improved biosensors. It is primarily used for the component’s identification and amplification of biosensors signal [89]. For example, Zhang et al. [90] reported a nano-biosensor combined with RT-PCR amplification of dengue virus rapid detection using a peptide nucleic acid (PNA) probe binding on

silicon nanowire surface.

As we mentioned in the above section, the biosensor’s basic essential composition components were represented in Fig. 7. However, one of the most important priorities in designing biosensors is signal amplification. This is due to the difficulty to receive a signal of extremely low magnitude between biological species (bio-receptors and analysts). To get rid of this problem, there are three common signal amplification strategies: i) Nanomaterial amplification strategy [91], ii) Enzyme catalysis amplification strategy [92], and iii) Nucleic acid-based amplification strategy [93].

Today, nanomaterials (NMs) and nanomaterials-based metal-organic frameworks (MOFs) have a critical role in SARS-CoV-2 and other related virus diagnosis and viral control applications [94–97]. These applications differentiate between biosensing, bio-composites, bio-barriers, etc. For example, nanomaterials and nanomaterials-based metal-organic frameworks (NMOFs) in the biosensing field beside the signal’s amplification features, have been found to used improve the sensitivity and the stability of the analytical response of biosensors either in the transduction substrate or in association with metal nanoparticles or polymers and the following sections will discuss these hot topics in details.

5. Nano-materials for biosensing and viral control applications: COVID-19 and other related viruses

5.1. Nanotechnology-based nano-materials: quick overview

Nanotechnology is an interdisciplinary science ranging from 1 to 100 nm with many applications. One of the most applications is nanomaterials which possess a distinct property and unique structure. Nanomaterials can be classified depending on the shape of metallic nanoparticles (MNPs) like noble metal nanoparticles (Au/Ag-NPs); metal oxide nanoparticles (MO-NPs) like (magnetic Fe₃O₄-NPs); carbon nanomaterials with different dimensional nanomaterials 0D like (C60, C-dots), 1D like (CNTs), 2D like (G, GO), and 3D like (Gr); and quantum dots (QDs) like (CdS QDs, CdTe QDs, carbon QDs). Another branch of nanomaterials depends on the properties to porous materials like (NMOFs, NCOFs, N-silica); natural and synthetic polymers like (cellulose, chitosan; and polypyrrole, polythiophene); and lipid nanoparticles (LNPs) like (fatty acids, triglycerides, waxes, and steroids).

Nanomaterials/nanoparticles exhibit several exceptional properties

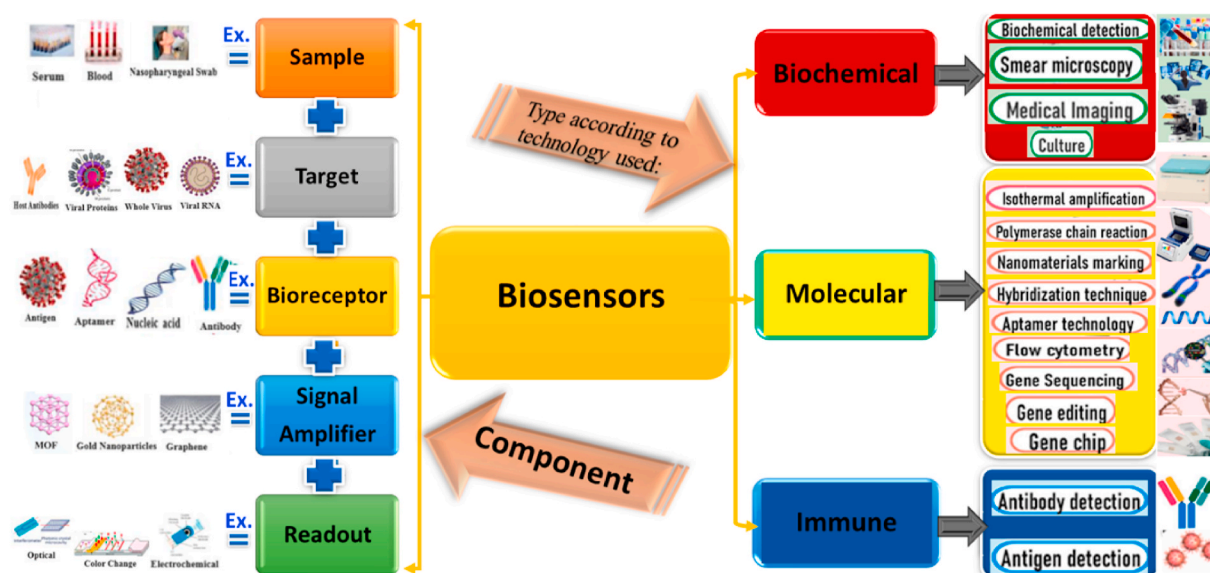


Fig. 7. COVID-19 and different types of viruses’ detection using biosensors based on different technologies flowchart (at right), and biosensor main components flow chart (at left).

such as i) large surface area; ii) can simply functionalize via in-situ addition or post-synthesis with inorganic/organic/biomolecules (as enzymes, protein, etc.); iii) high catalytic activity; iv) high antimicrobial, antifungal, antiviral activities; v) unique properties in electricity, optics, biology, magnetism, and other aspects [29,32,39]. Based on the exceptional properties of nanomaterials, it can offer a different promising application in many fields. For example, MNPs, such as Au/Ag-NPs, provide exceptional electronic and optical properties such as “surface plasmonic resonance (SPR)” and “localized surface plasmon resonance (LSPR)” which led to application in many vital applications such as nano-plasmonic sensors, plasmonic-enhanced fluorescence, surface-enhanced Raman spectroscopy (SERS), colorimetric sensors, etc. [98–100]. And CNPs, such as graphene revealed unique optical, electronic, and electrochemical properties which were used in a promising “point-of-care tests (POCT)” application [101]. Moreover, functionalized nanomaterials (NFM) can be used in signal amplification progress [92], signal carriers [102], enrichment materials [103] and electro-active markers [91].

Recently, different nanomaterials such as (QD, CNTs, GO, MNPs, MONPs, etc.), were used to increase the efficient biosensors. Additionally, it can be used to manufacture many ultra-high sensitive biosensing systems with excellent performances and long-term stabilities for the diagnosis and detection of different pathogenic viruses like HTNV, RVFV, HCV, HBV, HAV, HIV, etc., [102,104,105]. Moreover, a hybridization offers nanomaterials like silicon nanowires with biosensors afforded extra real-time and fast aerosol biosensing systems to detect H3N2 viruses as reported by Shen et al. [106]. In this context, a nano-sheet biosensor resulting from hybridization of Au-NPs with fullerene nanoparticle/nitrogen@ doped graphene showed a high sensitivity reach to 3 fM when detecting MTB [107].

5.2. Role of nanomaterials in COVID-19 diagnosis and viral infection control

Nowadays, nanomaterials play a vital role in diagnosing, protecting, and preventing the COVID-19 crisis. Using nanomaterials in new nanomedicines, therapeutics, vaccines, and diagnostic tools to overcome the COVID-19 pandemic can be given [27,108]. For example, biosensing-based nanomaterials can detect extremely deficient viral load. Therefore, these new biosensing-based nanomaterials can be employed for an affordable cost, accurate, and rapid detection of COVID-19 in low-volume samples/low-viral load [109]. Nanomaterials are also used as labels to achieve considerable signal amplification to be high enough to detect easily. The labeling progress was performed using nanoparticles such as (Au-NPs, Ag-NPs, Cd/Pb-QD, etc.) via attaching on

the targeted probe (DNA/bio-recognizing elements) [110,111]. Significant signal amplification was obtained due to the synergic effect of nano-labeling. Consequently, it is conceivable to develop labeled-biosensing techniques with high selectivity and sensitivity [111]. Biosensors are classified into four main categories nucleic acid, anti-body, antigen-dependent, and aptamer for detection of mediated viruses [112]. In this regard, recently many nano-enabled biosensing platforms for the detection of the SARS-CoV-2 virus were developed. Besides the biosensing applications, many other applications like personal defense tools (as face mask-based nanomaterials), air filters, surface coating, etc. against COVID-19 were included. Fig. 8 shows a schematic classification of nanomaterials and examples for their different applications. Herein, a summarized nearly most published reports in this context are included in the following subsections.

5.3. Biosensors based on nanomaterials for COVID-19 detection and point of care application

Recently, biosensing platforms and techniques based on nanomaterials and POCT applications for different types of respiratory infections, especially SARS-CoV-2 have been gaining great attention. The challenge and demand for fast, highly sensitive, selective diagnostics tools are increasing. Moreover, exceptional progress in the performance and design of different devices based on nanomaterials. Nanoparticles gain much significance in developing POC diagnostic platforms; this is due to they have offered a tool that can be used by patients directly (self-devices). In addition, it is not required to treat the samples in the central hospitals, cost-efficient, robust, ease in bio-conjugation, biocompatibility, rapid and ultrasensitive diagnosis with less sample volume. Today, POCT is required urgently to an early detection tool for COVID-19 at home which will decrease the limitation of the virus. Different types of nanomaterials are reported in significant number of articles that have been devoted to developing the different molecular and serological assay for COVID-19 detection with the help of fluorescence, colorimetric, impedimetric, amperometric, Opto-magnetic, etc.

The biosensors can be classified into four main categories based on nucleic acid, anti-body, antigen-dependent, and aptamer [112]. Nucleic acid-based biosensors (Genetic biosensors/Viral nucleic acid tests) analysis depends on the viral genome using several techniques such as RT-qPCR, LAMP, NASBA, TMA, RCA, CRISPR, and NTS. The analysis carried out using antigen-based biosensors depends on the viral proteins (M, S, and N proteins) using several techniques such as (colorimetric, fluorescence, FET, ELISA, and MS. antibodies-based biosensors (serological tests) the analysis based on the antibodies (IgM and IgG) against the whole virus using several methods such as LSPR, SERS, QCM, ELISA,

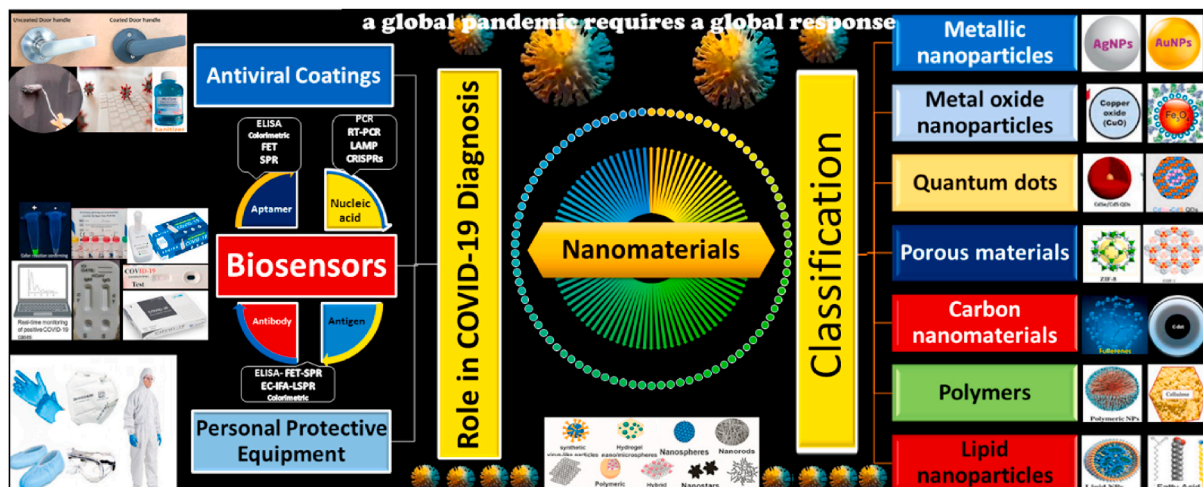


Fig. 8. A schematic representation for the classification of nano-materials and examples for their different applications.

fluorescence, colorimetric, chemiluminescence immunoassay, gold immunochromatography, electrical and piezoelectric. Aptamer-based biosensors analysis depends on a synthesized single-stranded nucleic acid and acts as label-free bioassays by using several techniques such as

SPR, QCM, and SAW. In this subsection, we summarized in Table 1 the most published studies based on nanomaterials related to the different development techniques, methodologies, and biosensing platforms for the detection of COVID-19 nanomaterials.

Table 1

Some of the different techniques, methodologies, and biosensing platforms for the detection of COVID-19 based on nanomaterials.

Method of detection/Technique/ Diagnostic Platforms	Sensitive materials	Analyte	LOD of detection/Sensitivity	Ref.
qRT-PCR/RT-PCR	Au-NPs	NA/(E & RdRp genes) of SARS-CoV-2	E-gene:3.9Copies/reaction; RdRp-gene:3.6Copies/reaction	[113]
	Nano-Chip400 system gold	OC43/229E/HKU1	OC43: 760 ng/μL 229E: 128 ng/μL HKU1: 1×10^5 copies/mL	[113]
	Au-NPs	SARS-CoV-2 RdRp coding gene	0.4 fM	[114]
	Magnetic NP-based RNA	ORF1b gene, N gene	10 Copies of pseudovirus	[30, 110]
RT-LAMP	Nanoparticle-based lateral flow biosensor	ORF1ab, N gene	12 Copies/reaction	[116, 117]
	Coated polymer NPs	SARS-CoV-2	12 Copies/reaction	[116, 118]
	–	SARS-CoV-2	100 Copies/reaction	[114, 115]
	–	–	–	[15]
LFIA	AuNPs	IgM and IgG antibodies	–	[121]
	Lanthanide-doped NPs	IgM and IgG antibodies	–	[122]
	Gold receptor ACE2	Spike 1-protein antigen	1.86×10^5 Copies/mL	[123]
	Lanthanide-Doped Nps	anti-SARV-CoV-2 IgG in human serum.	–	[124]
	400 nm carboxylic-red latex beads	N-protein antigen	0.65 ng/mL	[125]
	Au-NPs	IgM/IgG/IgA	Sensitivity, 95%	[126]
	Colloidal- Au-NPs	IgG antibody	Sensitivity 69%	[127]
	Colloidal- Au-NPs	IgM antibody	Sensitivity 100%	[15]
	Colloidal- Au-NPs	IgM/IgG antibody	N/A	[128]
	Thiol-modified antisense oligonucleotides (ASOs) [AuNPs-ASOs]	SARS-CoV-2	0.18 ng/μL	[129]
Colorimetric biosensing approach	Colloidal- Au-NPs	SARS-CoV-2 detect RdRp gene	0.5 ng of SARS-CoV-2-RNA	[130]
	Au-NPs	Nucleic acid	–	[131]
	Au-NPs nanoplasmonic	SARS-CoV-2	370 p/mL	[88]
	Si/SiO ₂ /graphene/PBASE/anti-SARS-CoV-2	SARS-CoV-2	2.4×10^2 copies/ml	[132]
	Graphene/CSAb	S1 protein	0.1×10^{-12} M	[88]
	–	SARS-CoV-2 antigen protein,	2.4×10^2 Copies/ml	[88]
	SpAb-PBASE/Graphene	S protein	2.4×10^2 Copies/ml	[88]
	Graphene sheets	Ab against SARS-CoV-2 S protein	2.4×10^2 Copies/ml	[88]
	PBASE Graphene sheets Layers	S protein antibody	2.4×10^2 Copies/ml	[133]
	Au-NPs	(spike S1 protein) antigen	10 fM& 90 fM& 120 fM	[134]
Electrochemical biosensor	Silicon-based TriSilix	cDNA fragment	20 fg Equivalent	[135]
	GO@Au-NS	SARS-CoV-2	1.68×10^{-22} mg/mL	[136]
	Calixarene-functionalized (GO)	RNA of SARS-CoV-2 without nucleic acid	200 copies/mL	[133]
	SpAb/AuNPs/FDIO	S protein	90 fM	[133]
	Au-NPs	(S1 protein) antigen	...	[133]
	MONPs semiconductor	Nucleic acid	...	[137]
	SPCE@NPs@nano-Dendroids@GO@Ab	S Protein	...	[138]
	Magnetic beads mutual with carbon black nano-materials	S Protein or N protein IgG-MB/MAB anti-S or MAB Anti-N/PAB anti-S or PAB anti-rabbit-AP	19 ng/mL & 8 ng/mL in untreated saliva	[139]
	FTO/AuNPs/nCOVID-19 Ab	(N protein) antigen	10^{-14} M	[133]
	SiO ₂ /Ti/AuNPs/Thiolated ssDNA	viral RNA, or c-DNA	...	[140]
ELISA	SPCE/Au@SCX8-RGO-TB/CP/Au@Fe ₃ O ₄ /Probe	viral RNA	200 copies/mL	[136]
	Colloidal- Au-NPs	IgM antibody	100%	[141]
	Colloidal gold	(SARS-Cov-2)	IgM/IgG 87.3%	[142]
	Nanogold-labeled anti-human IgA	IgA in serum and saliva	...	[143]
	Dual optical/chemiluminescence LFIA immunosensor	IgM/IgG antibody	IgM: 1.0 AU/mL; IgG: 1.1 AU/mL	[144]
	Chemiluminescent Method	N protein	...	[145]
	Plasmonic fiber-optic absorbance biosensor	–	–	–
	EWA-and LSPR	AuNPs @ PANI/anti-IgG or anti- IgM	100 units/ml	[146]
	SERS	Silver-nanorod	SARS-CoV-2	[147]
	Dual-functional plasmonic photothermal biosensors	Au-NPs	SARS-CoV-2	0.22 pM
Fluorescent microspheres	Immunochromatographic Method	IgG and IgM	Sensitivity100% (IgG), 98.68% (IgM)	[148]
	Fluorescent microspheres	DNAs	0.22 fM	[149]
	Immunochromatographic Method	CS-Ab, ACE2	0.1 pM	[118, 132]
	Ultrasensitive fluorescent detection	–	–	[150]
	Gr-FET- PCR	Steel tips modified with MWCNTs	level of SARS-CoV-2-ROS	[151]
	Electrical	–	–	–
	ROS-sensor	–	–	–
	–	–	–	–
	–	–	–	–
	–	–	–	–

Generally, the Table data elucidate the efforts done by the Scientists based on the nanomaterials for the development of several types of sensing platforms, diagnostic kits, and POCT. If we take the Au-NPs as an example. Au-NPs used for SARS-CoV-2 detection in different applications based on plasmonic effects to achieve an excellent dual-functional biosensing platform have been reported by Qiu et al. [5]. A colorimetric biosensing approach specific for N protein from the oropharyngeal swab RNA sample using “Au-NPs capped with thiol-modified antisense oligonucleotides (ASOs)-(AuNPs-ASOs)” within 10 min has been reported by Moitra et al., [128]. In addition, Kumar et al. [129], reported colorimetric dependent biosensing to detect the RdRp gene of SARS-CoV-2 using Au-NPs within 30 min. Moreover, in a lateral flow immunoassay (LFIA) based on AuNPs direct detection of immunoglobulin M/G (IgM and IgG antibodies) of SARS-CoV-2 in real human samples within 15 min has been reported by Li et al., [15]. The LIFA based Au-NPs exhibited a good clinical detection sensitivity of 88.66%, with specificity reaching 90.63% [15].

Besides viral proteins/genes, antibodies, etc., as biological elements for COVID-19 diagnosis, there are many clinical importance supplementary biomarkers like reactive oxygen species (ROS), cytokines, C-reactive protein, etc. Such biomarkers are considered a confirmatory test for COVID-19 diagnosis and provide supplementary clinical significance data. For example ROS; one of the stimulating side effects of COVID-19 virus in lung host-cells is the progress of inducing mitochondrial ROS functions to stimulate the virus replications [152]. Upon the infection with COVID-19, ROS are released from the mitochondria damaged cells followed by stimulating the SARS-CoV-3a-NLRP3 which is responsible for inducing viral replication [151]. Correspondingly, as far it has been reported that cellular ROS have increased markedly in SARS-CoV-3L pre-pressing cells [153]. In this regard, Miripour et al. [151], reported an electrochemical sensor based on growing multi-walled carbon nanotubes (MWCNTs) on steel electrode tip needles to detect mitochondrial ROS levels in patients' sputum samples. The signal was detected via cyclic voltammetry as a function of the ROS amount released from the viral-infected lung epithelial host cells.

5.4. Nanomaterials for personal defense tools and anti-viral surfaces

The current global situation has shown how the ongoing development of nanomedicine and nanotechnology can accelerate the fight against the COVID-19 virus as shown in Fig. 8. As we mention in the introduction section one of the suggested solutions preventing/limiting the spread of viruses is the use of anti-viral personal protective tools (PPTs) and antiviral surfaces. According to the guidance issued by WHO, the virus is mostly transmission, from one to one via respiratory droplets through sneezing, coughing, or in close contact with an infected person [60–62]. Therefore, PPTs (as masks, gloves, gowns, and eye protection) make a barrier preventing the virus transmitted especially if the PPTs are developed based on nanomaterials and nanotechnology guidelines. In this context, Aydemir et al. [154] reported synthesizing ACE2 coated with nanoflowers/quantum dots to manufacture nose filters, chewing gums, and PTTs as long-permanent protective equipment to limit the infections. This concept is based on holding or masking coronaviruses to enter the host cells by making a barrier between ACE2 and S protein. Another long-permanent protective way to avoid the transmission of the virus is through surface protective coatings with antiviral nanomaterials. Subsequently, COVID-19 aerosol stability studies on diverse surfaces showed that the SARS-CoV-2 is relatively stable on stainless and steel plastic surfaces (remaining viable up to 72 h) [155]. To reduce and limit transmission of the virus via self-disinfecting surfaces with antiviral coatings nanomaterials such as (zinc oxide tetrapod NPs, tin oxide nanowires, polysaccharide-coated NPs, hybrid coating, etc. are used. These materials act as barriers and gain a vital role in reducing human exposure to COVID-19 infections. Recently, many efficacious coating strategies were developed. For instance, Behzadinasab et al. [156] developed a coating material based on Cu₂O@polyurethane and tested it

as antiSARS-CoV-2 on the stainless steel surface. The results showed that within 10 min >90% of the coronavirus was reduced and after 2 h > 99.9%. Some published reports for personal defense tools and antiviral surfaces against COVID-19 are summarized in Table 2.

5.5. Eye on the future of POCT and nano-sensors based on developed nano-technologies for simplifying the self-diagnosis process everywhere

Nanotechnology provides exceptional benefits with the use of new nano-systems, and nano-sensors to produce new wearable electronic devices. Through that, it can translate the physiological signals to readout which can be monitored, and subsequently used as early diagnostic tools for pre-symptomatic and asymptomatic cases of COVID-19. Nowadays, smartwatches offer information such as sleep time, heart rate, phone cell, and activity patterns. Moreover, a new generation of developed nano-sensors for body temperature, etc. Shortly, with the increasing rate of nanotechnologies developing, new classes of wearable devices will be presented in Ref. [79].

These wearable devices could monitor, for example, cortisol concentrations for tracking stress “using electronic epidermal tattoos”, inflammation biomarkers and blood gases as O₂ “using microneedle patches”, blood pressure “smart rings”, intraocular pressure “smart contact lenses”, skin temperature “electronic textiles”, the concentration of ions in blood steam “wristbands”, the presence of airborne pathogens and breathing anomalies “face masks”, and the concentration of therapeutic drugs “on-teeth sensors”. Such emerging low-cost wearable sensing technologies could also be used to remotely monitor the recovery of individuals undergoing treatment or self-isolating at home [79].

6. Metal-organic frameworks (MOFs) nanomaterials matrix for biosensing and viral control applications: COVID-19 and other related viruses

6.1. Metal-organic frameworks: quick overview

MOFs (hybrid porous coordination polymers) were first reported by “Hoskins and Robso” in the 1980s [165]. After that, research on MOFs became more popularized. This domain started to develop and expand

Table 2

Some pick out published reports for personal defense tools and antiviral surfaces against COVID-19.

Fabrication method	Composition	Application	Inhibition Efficiency %	Ref.
Radiofrequency co-sputtering	Ag nanocluster/silica composite	Facial FFP3 mask	100	[157]
Pad-dry-cure	Ag NPs	Polycotton fabrics	Almost 100	[158]
Aerosolized coating	SiO ₂ -Ag nanoparticles	Air filter	92	[159]
Fused deposition modeling (FDM)	NPs combined with standard polylactic acid	Powered air-purifying respirators	N/A	[160]
N/A	Graphene and its derivatives	Filters	Ideation	[161]
Dual-channel spray-assisted	Shellac/CuNPs nanohybrid nanocoating	Mask (self-cleaning) Photoactive antiviral		[162]
Colloidal coating: Ag-NPs dispersed in PVP	Silver nanoparticles	Virucide-coating	Block viral	[163]
Alloy surface by wet-etching	Aluminum nanofibers	Antiviral-surfaces	Inactivated after 6h from the exposure	[164]

continuously after the synthesis of MOF-5 by “Omar Yaghi” in 1995 [166,167]. The composition and structure of MOFs can easily be tuned through different methodologies by combining organic ligands/linkers (as phosphonates, carboxylates, etc.) with metal ions/subunits/nodes/clusters via coordination bonding [168–170]. The variations of used metals (transition metals, lanthanides, etc.) and different organic ligands led to producing thousands of novel MOFs with exceptional features [171–174]. For example, MOFs have auspicious properties as its highly porous structures (as well as it can control in the pore size micropores or mesopores, etc.); some have shaped-pore in the form of channels, cages, etc.; possess whichever flexible or rigid frameworks; have a large surface area reached to $1 \times 10^4 \text{ m}^2/\text{g}$; can control in MOF polarity (polar or nonpolar character) based on the polarity of organic functionalities; have excellent thermal, chemical and mechanical stability; have a high adsorption affinity, and many other. Consequently, these exceptional properties make MOFs have a large number of promising and potential applications in distinct life science fields [175–178]. A flow chart summarized the MOF's main common synthetic methodologies, properties, and miscellaneous applications as shown in Fig. 9.

On the other hand, metal-organic frameworks nanoparticles (MOF-NPs/NMOF) are a hot topic area and have been demonstrated in numerous studies [179,180]. The downsize of the materials to the nanoscale compared to it in analogs bulk is of great potential. It is considered an exciting topic rapidly developed [171,181]. Generally, nanomaterials have a small size particle, which can improve their properties by accelerating the adsorption\desorption kinetics and improving bioavailability. So, the metal-organic framework nanomaterials were assembled and conceived in different applications and fields like biosensing, biomedicine, anticancer, theragnostic, etc. Indeed, the preparation of uniform MOF-NPs is used in vital applications based upon the extraordinary features of such structures. As a potential example, drug delivery applications for the treatment process of numerous diseases and the evolution of the performance of materials used in this critical field.

Taking into our consideration the requirements for drug delivery that the material (nanocarriers) should: i) have high entrapment for drug, ii) the drug release can be controlled without burst effecting, iii) have high selectivity and ability to target the diseased tissues or cells, iv) through the progressive degradation should lack toxicity, v) be not accumulated

in the body, vi) can be detected by imaging techniques. Therefore, the high porosity, regular structures, and the exceptional arrangement and well-dispersed of organic groups and metal sites within the framework beside the smaller particle size in the nanoscale (MOFs-NPs), in combination with the low toxicity of poly-carboxylic acids and selected metals (Fe, Zn, Ca, etc.), make these porous materials attractive as nanocarriers and have high performances in wide application [171].

6.2. Application of MOFs in viral biosensors

Given the above section, exciting progress resulting from combining MOFs/MOFs-NPs with different functional components is achieved. A thousand novel structures with new different skeletal properties and features such as high stability, specificity, sensitivity, flexibility, etc., make hot opportunities for using these materials in various biosensing applications. Moreover, the MOFs can be conjugated with bioactive molecules (recognition elements) via in-situ addition of the molecules during the synthesis stage or modifying the MOFs with the bioactive molecules which call the post-synthesis method. The MOFs/MOFs-NPs play vital central roles in biosensors mechanism, for example, it's used as i) enzyme-mimic element, ii) carriers of sensitive elements, iii) gas sensing, iv) transducer or signal amplifier “electrochemical signaling, optical signaling, etc.” [182].

Comparing the performance of the biosensor based on using materials such as “graphene, graphene oxide, and gold nanoparticles, etc.,” with MOFs-/MOFs-NPs based biosensors for nucleic acid and immunological detection. MOFs-/MOFs-NPs possess significant advantages, like have: 1) Conjugated π electron system; 2) Flexible and high porosity reached to 90%; 3) High loading capacity; 4) Open metal sites; 5) Large surface area reach to $1 \times 10^4 \text{ m}^2/\text{g}$; 6) Tunable pore sizes; 7) Easy post-synthetic modification and functionalization; 8) Biodegradable and biocompatible; 9) Fast detection tools; 10) Adsorption and quenching the fluorophore-labeled probes; 11) The ability of fluorescence quenching can adjust via functional groups or ligands; 12) Selectivity options can be established based on size discrimination capacity; 13) Specific molecular recognition and facile molecular enrichment; 14) Efficient molecular immobilization; 15) Low cost, and 16) Excellent adsorption performance [183–186]. These tremendous advantages facilitate their biosensing applications especially in detecting bacteria, viruses' biomolecules, and cells. For example, Sohrabi et al. reported a

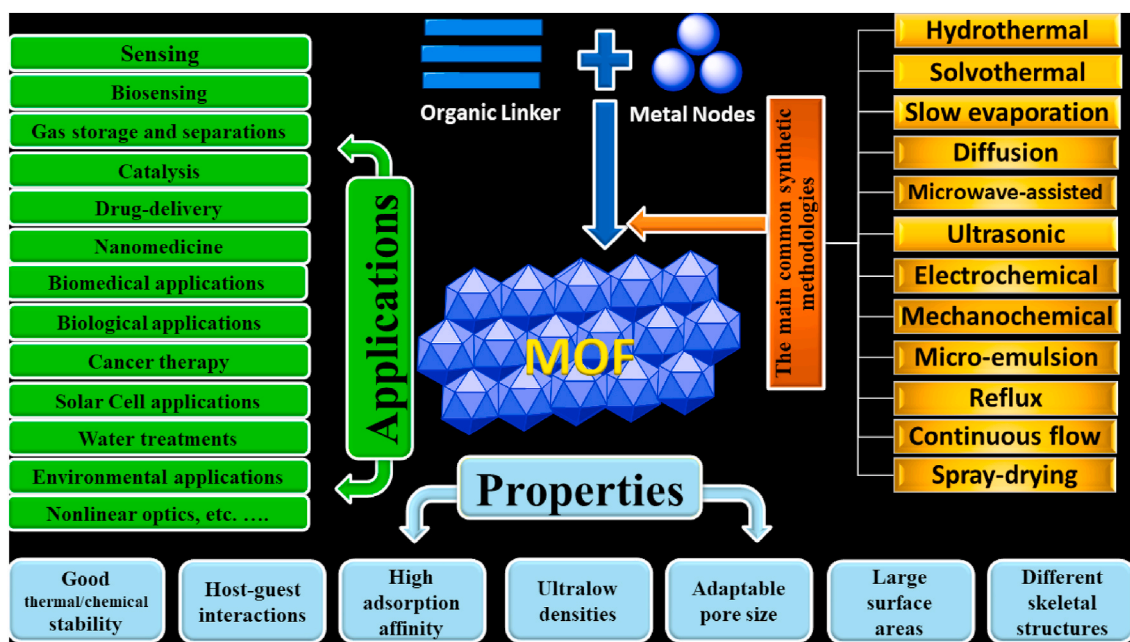


Fig. 9. Systematic representation for the MOFs common: main synthetic methodologies, properties, and applications.

susceptible detection method for Haemophilus influenza via improving the sensitivity of Au-electrode surface with a solution of Zn-MOF@CMC [187]. Yiwei et al., reported an electrochemical biosensor for the detection of hantavirus (HTV) using AuNPs-RGO/GCE@Cu-MOF [188]. Herein, in this review, a summary of the most recent reports concerned by the biosensing based- MOFs COVID-19 and other related viruses are represented in (Table 3).

6.3. Role of nanomaterial-based MOFs in COVID-19 diagnosis and viral infection control

Recently, a few numbers of studies on the application of MOFs in COVID-19 diagnosis and viral infection control have been reported. The related research articles exponentially increased in the last and the current year, demonstrating the important effects of MOFs/MOF-NPs in this field. For example, in recent studies on glycoproteomic, many MOFs were used to enrich glycopeptide of SARS CoV-2 glycosylation [203]. Li et al., [204] reported sensitive fast detection CRP as one of the crucial clinical laboratory tests for follow-up COVID-patients using a novel sandwich immunosensor based on Au-NPs@Cu(II)-HKUST-1@Tb and CoFe@N-GCT.

Another vital application of MOFs in the fabrication and development of face masks and fabric having MOFs nanomaterials. Face masks treated with MOFs nanomaterials are one of the most important self-protection tools and recommended by WHO as a vital way should be taken into consideration precautions to avoid the infection with SARS-

CoV-2. The question arises here, why masks are treated with MOF nanomaterials. This is because traditional masks such as disposable protective masks or surgical masks cannot prevent the infection of SARS-CoV-2. They even mask N95 can prevent less than 90%. The droplets coming out of the patient's mouth are within the range of 60–140 nm [61,62]. So, the use of commonly traditional masks usually allows the penetration of COVID-19 through it and increases the infection cases. Consequently, the emergence of the pandemic in this form is terrible, although people say that they have seen masks.

The development of MOF nanomaterials masks with advanced features could be vital for precautions and early diagnosis. In this context, Rabiee et al. [82], developed visual color changes coated wearable-based MOF for real-time diagnosis of COVID-19 virus. In this work, virus detection and diagnosis capability are based on the "Surface-Enhanced Raman Scattering (SERS) mechanism". Therefore, this work is based on doped Au-NPs @ nano-MOF onto the mask surface and subsequently used to detect viruses based on the changes in the optical properties utilizing physisorption or chemisorption. Moreover, the new smartphone technologies could be exploited for imaging and color map analysis to stimulate quantitative selective detection tools [82]. Despite the easy detection process, this opens the door for more clinical trials to commercialize the MOFs, and MOF-NPs are treated masks and fabric for COVID-19 diagnosis.

Moreover, using new technologies to prepare new bio-composites/nanocomposites-based MOFs is one of the vital targets. In the interaction mechanism, the pathogen/analyte/biological target does not need to be absorbed by the porous bio-composites/nanocomposites. In such cases nevertheless, the pathogen/analyte/biological target just needs to interact with the MOF surface that is modified by different NPs [179, 205]. In this regard, Kumar et al., [206] reported an inexpensive and effective preparation method for suitable chemical thermal, stable copper/ZIF-8-MOF nanocomposites, these nanocomposites are used in face-masks fibers in the application of reusable antibacterial/antiviral masks. These nanocomposites examined the antibacterial activity toward *E. coli* and *S. mutans*; whereas, the antiviral activity was examined against SARS-CoV-2. The results demonstrated a good antibacterial and anti-SARS-CoV-2 performance besides the low toxicity and good biocompatibility [206,207].

Finally, there are a new trend in using MOFs for killing the COVID-19 virus in the last few months based on the concept of "Radical Chemistry". Generally, the direct use of UV-light only can target the virus-RNA in the nucleocapsid and create enough energy to destroy the virus [208, 209]. However, In the present case of MOF-based, a huge quantity of hydroxyl radicals is released. These radicals by applying the UV light can damage the virus's outside organic materials, including the S protein, even inside human lungs [208,209].

7. Challenges and perspectives of nanomaterials and MOFs for biosensing applications

Several challenges and disadvantages disrupt the application of nanomaterials and MOFs in general and in particular in biosensors applications. For example, insufficient selectivity, sustainability, fabrication, toxicity, pore size limitation, cost, large-scale production, structure-activity relationship, sustainable innovations, and hazardous effects on human health. As well a few biosensors have been commercially successful at the global level. On the other hand, biomedical applications require a large sample to be detected which may lead to uncertain results. Moreover, in electrochemical enzyme biosensors setups, the detectable molecules have to diffuse to the electrode which leads to an efficiency decrease. In physical or reversible immobilization enzyme biosensors susceptible to changes in the pH, temperature, and ionic strength are occurring. Moreover, in the case of the covalent binding immobilization a harsh chemical and the upgraded matrix cannot be regenerated once used. In general, the electrochemical biosensors have poor selectivity, pore diffusion limitation, and interference

Table 3
Summary of viral biosensor-based-MOFs applications.

Method/Technique	Sensitive materials	Analyte	LOD	Ref.
Electrochemical genosensor	Zn-based MOF/CMC/AuNPs	H. influenza	1.48 fM	[187]
Electrochemical biosensor	AuNPs-RGO/GCE@Cu-MOF	HTV	740 fM	[188]
Electrochemical biosensor	Bimetallic NiCo-based MOF	HIV-1	16.7 fM	[189]
Electrochemical biosensor	Polyaniline@Ni-MOF nanocomposite	HCV-RNA	0.75 fM	[190]
Fluorescent biosensor	MIL-88B (Fe) nanorods	HIV	10 pM	[191]
Fluorescent biosensor	MIL-101 (Cr)	HIV-1 U5	73 pM	[192]
Fluorescent biosensor	MIL-101 (Cr)	HIV-1 U5	200 pM	[193]
Fluorescent biosensor	UiO-66-NH2	HIV		[194]
Fluorescent biosensor	[Cu3(cmdcp)2(dps)4(H2O)4(SO4)]n	HIV-1/SUDV	73 pM	[195]
Fluorescent biosensor	DTMA-Cu	HIV-1 U5	3000 pM	[196]
Fluorescent biosensor	[Cu(dcbcp)(bpe)]n	DENV/ZIKV	184/121 pM	[197]
Fluorescent biosensor	[Cu(dcbp)(bipy)(OH)]n	ZIKV	190 pM	[198]
Fluorescent biosensor	{[La4(cmdcp)6(H2O)9]}n	SUDV	112 pM	[199]
Fluorescent biosensor	{[La2(cbdcp)3(H2O)10]}n	SUDV	67 pM	[199]
Fluorescent biosensor	MIL-88B-NH2(Fe)	ZIKV	100 pM	[200]
Fluorescent biosensor	MIL-101(Cr)	JEV	13 pM	[201]
Fluorescent biosensor	Cu-based MOF	H1N1	1.6 nM	[185]
Fluorescence anisotropy	MIL-101 (Cr)	RSV	...	[202]

"N-carboxymethyl-3,5-di-carboxyl pyridinium bromide (H3cmdcpBr); 4,4'-dipyridyl sulfide (dps); N-(3,5-dicarboxylbenzyl)-(3-carboxyl) pyridinium (dcbcp); 1,2-bis(4-pyridyl)ethylene (bpe); 1-(3,5-dicarboxylbenzyl)-4'-bipyridiniumbromide (H2dcbpBr), 4,4'-bipyridine (bipy); N,N'-bis(2-hydroxyethyl)dithiooxamidatocopper(II) (DTMA-Cu)."

from other electroactive materials and microbial contamination. When synthesis and stabilization in enzyme-MOF biosensors occur concurrently, enzyme clusters may form, thus reducing the stabilization yield. Finally, specific hybridization of probe DNA with virus-related target nucleic acids can form stable DNA structures, which can be released from the surface of MOFs due to their low affinity towards nanomaterials.

Possible ways for overcoming such challenges and disadvantages are:

- i. A deep study of nanotoxicity and its interaction with biomolecules is essential.
- ii. The sustainability of nanomaterials and MOFs in biosensing applications must be addressed.
- iii. There is also a need for affordable cost nanostructure-based biosensors that give fast, accurate, and easy-to-use results.
- iv. Need to improve sensor performance in terms of sensitivity, selectivity, and stability.
- v. More opportunities in sensor design and integration.
- vi. Structure-activity relationship of nanomaterials and MOFs needs more study.

8. Conclusions and closing remarks

Since the new pandemic Coronavirus (COVID-19) outbreak in December 2019, the world still fights against the virus. The fast mutation of the COVID-19 genome in a close period may also continue for some time to its transmission. The global pandemic requires (necessitates) a global response and tremendous attention. With the continuation of this pandemic, an urgent need for fast, and accurate testing in terms of POCT for detection and diagnosis besides the personal defense tools, anti-viral surfaces, wearables, and smartphones that open the door for simplifying the self-diagnosis process everywhere and various ways to manage the spread of COVID-19. With the help of advanced nanotechnologies, nanomaterials, and MOFs (due to the unique characteristics), it is possible to increase the rate of development diagnostics and personal defense tools, anti-viral surfaces, and wearables and improve the sensitivity and reduce the cost to cover the global demand for rapid and efficient diagnostics and protective tools for enable manufacturing. In this context, we highlighted the latest technologies, applications, existing achievements, and preventive diagnostic strategies to control this epidemic and combat the emerging coronavirus. Finally, to our best knowledge the authors herein refer to closing remarks as follow:

- 1) MOF-based biosensing technologies for diagnosing COVID-19, ranging for virus detection are rarely summarized
- 2) Some reference factors used MOFs for virus detection with impressive results. Due to the unique characteristics of MOFs, these materials have been widely used to prepare biosensors platforms, and various immune sensors, besides self-protective tools like anti-virus masks, coatings, barriers, and bio-composites of viruses to manage COVID-19 with remarkable features. MOFs commonly exhibit functional groups, aromatic rings that promote π - π stacking, hydrogen-bonding, and electrostatic interactions with virus genetic material "negatively charged nucleic acids". Furthermore, MOFs have considerable fluorescence properties underling the fluorophore-linked with biomolecules. Also, in the case of barriers and bio-composites, overall, as reference factors, refer to the pores-sizes of the MOFs very close to the size of the virus's diameter and compatible with different biomolecules which facilitate the interactions. Many events remarks, referred to the use of nanoporous materials (both MOFs and zeolites and other related materials like ordered mesoporous silicas and pseudo-zeolites).
- 3) Dynamic simulations and molecular docking are powerful theoretical tools for studying the relationship between the ligand and receptor binding affinity in drug discovery and other interaction

mechanisms based on nanomaterials. Therefore, most of the nanotechnologies investigated by computational tools were predicted to include the pandemic like interpreting the interfering with the adhesion of the SARS-CoV-2 to the receptors of the human host cell and interpreting the virus replication mechanism, thus inhibiting the viral infection.

- 4) There is a tremendous demand to develop commercially diagnostic and point-of-care kits for COVID-19 detection and removal, which will ultimately lead to the realization and actual advancement in medicine and healthcare benefits. Only then, able to enjoy its benefits in medical and other related areas.
- 5) Increasing the tremendous attention of the biosensing-based technologies for COVID-19 diagnosing, ranging between the research developments and commercial achievements.
- 6) It can be expected that the COVID-19 pandemic will accelerate the transformation of many analytical approaches from lab to manufacturers "from proof-of-concept status to applied technologies".
- 7) The development of new diagnostic methodologies focusing on shortening the sample treatments and processing time and replacing the time-consuming ones is an essential solution to limit the spread of diseases.
- 8) Different COVID-19 diagnostic kits before they enter the commercial market to operate in decentralized settings should check some urgent parameters like limited sensitivity, reproducibility, multiplexing, miniaturization, real-time operability, stability, sampling treatment requirements, and patient motivation and willingness through the validation process and before FDA approval.
- 9) Further work must be done to determine the efficiency of electrochemical platforms for "the detection of SARS-CoV-2", in particular. Additionally, the diversity of analytes, pathogens, and detection mechanisms studied makes it challenging to compare the results within the field of electrochemical sensing directly and between the novel and traditional diagnostic methods. The continual efflux of studies and an ever-growing understanding of the pandemic must be monitored and applied to existing electrochemical concepts to develop and commercialize alternative electrochemical-based SARS-CoV-2 diagnostic tests.
- 10) Future of nanomaterials usage in the targeting novel prophylaxis/therapies ways to COVID-19 management and future outbreaks solutions. Using nanomaterials like nanocellulose may fill in the gaps. Despite nanocellulose being considered one of eco-friendly, biocompatible, non-toxic, sustainable, antimicrobial, antiviral, relatively cheap, and suitable nanocarrier "due to its non-spherical shape in the nanofibrous" and used in many biomedical/pharmaceutical industries, no study based on nanocellulose was retrieved in SARS-CoV-2 virus control-related researches.
- 11) Trends in toxicology research especially in nanomaterials and safety examinations can be helped to fill the principal gaps in the literature and overcome health surveillance's challenges. For example, in the drug delivery field, phytochemicals delivery using nanocarriers is considered a vital candidate for targeting and one of the biofriendly therapy and treatment strategies.
- 12) Some of the major barriers in nanomedicine development are long-term toxicity, fabrication and characterization complexities, and large-scale production difficulties. Moreover, tissue engineering approaches in respiratory injury treatment are still limited and far from clinical use. Therefore, future perspectives should focus on addressing and solving the current drawbacks of polymeric nano-therapies to develop a revolutionary solution for the treatment of COVID-19 and other viral infections.
- 13) The future and prospective of vaccine-based VLPs, nanomedicine, and nano treatment-based new nanotechnologies should be considered.

- 14) Advanced nano-systems for the avoidance, prevention, diagnosis, treatment, and significantly reducing the spread of the disease are still challenges.
- 15) Coronavirus global pandemic requires specialized efforts, and the collaboration of researchers, medical fraternity, clinicians, biologists, engineers, universities, funding agents, companies, and government in meaning need “a global response”.

Declaration of competing interest

There are no conflicts of interest.

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