Review Article

Beibei Zhang#, Qiulan Wu#, Liping Yin, Jialiu Zhang, Wei Gao, Hao Chen, and Haibin Ni*

# Current diagnostic and therapeutic approaches for severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) and the role of nanomaterial-based theragnosis in combating the pandemic

https://doi.org/10.1515/ntrev-2023-0155
received June 20, 2023; accepted November 1, 2023

**Abstract:** COVID-19 was the most devastating pandemic since the Spanish Flu of 1918, affecting 700 million individuals and causing 6.8 million fatalities globally. COVID-19 vaccines are currently in the research and development phase. There is a need to investigate strategies pertaining to expanding the testing capacity, developing effective medicines, and creating safer vaccinations for long-lasting protection. Nanoparticles are frequently employed in a variety of medicine-oriented applications. The employment of nanotechnology in the development of novel medications has improved the treatment outcomes for several illnesses. The discovery of novel nanomaterials and the elucidation of their physicochemical features in connection to their cellular destiny and the relevant biological activities have received considerable attention. Hence, this review gives an updated analysis and data on clinical trials that are currently on-going for the development of drugs and the existing ones that are in use to combat the COVID-19 virus. This article also discusses the clinical management of COVID-19 at this juncture and highlights the influence of nanotechnology on the improvement of conventional COVID-19 treatments in the way of diagnosis and integrated therapy with pharmacology and advanced science. This review also brings to light on the limitations of nanotechnological strategies in combating viral diseases.

**Keywords:** nanomaterials, COVID-19, pharmacology

## 1 Introduction

### 1.1 Origin, epidemiology, and global current status of COVID-19

One of the most devastating pandemics since the flu of 1918 [1,2], with its local center in Wuhan, China, was caused by coronavirus in 2019 and designated COVID-19 [3,4]. As per the World Health Organisation's (WHO) declaration on February 3, 2023, the disease was responsible for causing illnesses in approximately 700 million individuals and leading to 6.8 million fatalities globally. In December of 2019, a cluster of pneumonia cases of mysterious origin was observed in Wuhan, China. Later on January 12, 2020, the sequencing of a novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) found from clustered cases of respiratory contagion was announced and publicized as the etiological agent for an unknown Pneumonia [5]. Due to the lack of rigorous epidemiological investigations, evaluating the risk of this occurrence was apprehensive with great uncertainty, despite a

# These authors contributed equally to this work and should be considered first co-authors.

* **Corresponding author: Haibin Ni,** Department of Emergency and Critical Care Medicine, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, 210028, China; Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, 210028, China, e-mail: nhb_2002@126.com, tel: +86-025-85637880
**Beibei Zhang**, **Liping Yin**, **Jialiu Zhang**, **Wei Gao**, **Hao Chen:** Department of Emergency and Critical Care Medicine, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, 210028, China; Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, 210028, China
**Qiulan Wu:** Department of Oncology, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, 210028, China; Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, 210028, China

Open Access. © 2023 the author(s), published by De Gruyter. This work is licensed under the Creative Commons Attribution 4.0 International License.

common link to a wet market in Wuhan's Huanan Seafood Wholesale Market was reported [6]. As a result of the increasing number of fatalities, irrespective of age and the uncertainty encompassing the antidote discovery, the WHO labeled the COVID-19 outbreak a public health emergency of worldwide alarm on January 30, 2020, and a pandemic on March 11, 2020 [7].

The high pathogenicity of human coronavirus (HCoV) has put forward this specific respiratory infection causing pathogen to the spotlight of research community[8]. Pertaining to this concern, coronaviruses are positive-sense, single-stranded, enclosed RNA viruses of 60–140 nm in diameter [9]. Among the six human betacoronaviruses species, four species including HCoV-229E, OC43, NL63, and HKU1 can cause upper respiratory tract infections like the common cold similar to the symptoms caused by rhinoviruses [10]. Other two coronaviruses species include severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV), with fatality rates 9.6 and 35%, respectively [11]. Among the outbreaks of these two viruses, SARS-CoV outbreak of 2002–2004 was believed to have its primary host as bat, mutating to infect the transitional host Civet cats, and finally spreading to humans [12]. The pathogenesis was better understood through host-pathogen interaction, in which case the virus was found to infect and cause a range of respiratory ailments eventually leading to death [13]. Originating in the primary reservoir (horse shoe bats), the virus typically transmitted to humans. Furthermore, it did spread among humans, through infected body fluids including respiratory droplets (saliva, breathing, coughing, sneezing, and talking) [14–16].

Benign coronavirus has been reported to be harmless, being the reason for common cold alone. But the species that mutated and transitioned from their natural reservoirs have been declared virulent, inflicting excessive infection and mortality in the affected individuals [17]. Despite the majority of cases being asymptomatic or self-recovering, the disease's clinical spectrum includes chronic pneumonia with acute respiratory distress syndrome (ARDS), a deadly illness which demands mechanical ventilation and treatment with critical care [18]. This has caused a severe impact on the human population with severe mortality around the globe. The lack of specific regimen for this disease has provoked or steered the research and medical community toward a necessity in identifying solutions that can be taken to stay healthy [18,19]. Real-time mapping has demonstrated that differential transmission prototypes and infectivity are related to alteration in lineages, clades, and strains of COVID-19 virus. This is despite the fact that the community spread studies of SARS-COV-2 exposed implausible transmission patterns between places which are not even connected geographically [13,20].

According to the WHO's Weekly Epidemiological Update on the survey of COVID-19 pathogenicity, along with other relevant infectious disease information, over 4.8 million fresh cases and 39,000 deaths were announced globally over the duration of January and February months of the year 2023. This has demonstrated a reduction in the number of reported new cases and deaths (at 76% of new cases and 66% of deaths, respectively) compared to the preceding 28 days. At the end of February 2023, a total of approximately 758 million confirmed infections and 6.8 million fatalities had been documented throughout the world [21]. A glimpse at the global status of SARS-COV-2 infection among the affected countries governed by WHO, as on March 22, 2023, Europe had 274,391,717 confirmed cases, 282,646 new cases, and 2,203,052 fatalities. Western Pacific was reported to be affected with statistics showing 201,913,013 confirmed cases, 165,547 new cases, and 408,070 fatalities. Whereas, in Americas, 191,185,511 confirmed cases, 189,265 new cases, and 2,939,388 fatalities have been reported. In this regard, Southeast Asia reported 60,784,561 confirmed cases, 8,336 new cases, and 803,971 fatalities. As the continent considered to be least affected, Africa did report 9,509,869 confirmed cases, 114 new cases, and 175,315 fatalities. The worst affected countries include the United States, China, and India as per the number of cases affected. In the United States alone, 103,436,829 confirmed cases and 1,127,152 deaths were reported on September 21, 2023. As on the same date in China, 99,309,232 confirmed cases and 121,679 fatalities were reported, whereas 44,998,162 confirmed cases and 532,030 deaths were reported in India. As per the number of deaths, Brazil ranks the second with 704,659 deaths after the United States, whereas India ranks the third [22].

Even though personal cleanliness, maintaining social distance, regular hand washing, and avoiding contact with infected individuals are recommended practices, there are evidences suggesting that adequate food, nutrition, and other lifestyle factors increase the immune strength and minimize susceptibility to infectious illnesses. Hence, this review provides detailed insights into the medical management of COVID-19 and the role of nanotechnology in improving conventional treatment modalities for the disease. It also emphasizes the importance of understanding the underlying health conditions (comorbidities) in the context of COVID-19 and the role of biomarkers in disease management. Additionally, it discusses the extensive research and clinical trials aimed at finding effective treatments for COVID-19, which range from antiviral medications to therapies that modulate the immune system, as well as the development of vaccines. Moreover, updated information of currently employed vaccines has been listed. Moreover,

the review highlights the diagnostic advancements made possible by nanotechnology in the fight against COVID-19. These innovations include NanoBeads, Protein Aptamer Sensors, and magnetic levitation, which can enhance the accuracy and efficiency of COVID-19 diagnosis. It also explores therapeutic approaches that employ nanotechnology-based drugs to treat COVID-19.

### 1.2 Comorbid conditions and their relation with COVID-19

Comorbidity is defined as the epidemiologic phenomenon of a population or an individual exhibiting the simultaneous occurrence of two or more disorders or conditions [23]. Understanding the co-occurrence is critical and beneficial in developing effective treatment protocols. The COVID-19 pathogen, the SARS-CoV-2, has rapidly expanded and infected over 180 countries [3]. As the novel coronavirus continually develops, it is only possible to hypothesize as to who will become infected. COVID-19 is a relatively newer and understudied disease, limiting the availability of such data on infection symptoms [24]. Studies have demonstrated that the general symptoms vary from acute common cold [25] to chronic lung infections such as bronchitis, acute respiratory syndrome, and pneumonia, as well as various organ failures, systemic dysfunctions, and eventual death [26,27].

According to the current statistics and clinical expertise, irrespective of age, individuals with substantial pre-existing clinical disorders are at a significant risk of contracting COVID-19, particularly those obtaining long-term medical treatment [3]. However, a meta-analysis of middle-aged and elderly COVID-infected individuals revealed that the geriatric population is more susceptible and pose a significant death rate. This could be attributed to the alterations in the structure and muscular atrophy of the lungs, which can result in changes and a reduction in physiological processes such as lung reserve, airway clearance, and immune barrier functions [28].

In a retrospective review of 1590 laboratory-confirmed Chinese hospitalized patients, 25% were found to have at least one comorbid condition. This statistical information was derived by evaluating the number of documented comorbidities in connection to composite outcomes such as Intensive Care Units, ventilation, and mortality. Included among these conditions were hypertension and diabetes. The most prevalent comorbidity found was that of hypertension with a percentage of around 17. Additionally, smoking, diabetes, and cancer were found to increase the probability toward a life-threatening stage. The number of comorbidities was found to be directly proportional in reaching the composite endpoints [29]. In yet another research done in India on COVID patients, the same prevalence of hypertension was seen, followed by diabetes, bronchial asthma, renal, and heart illnesses, in the order as so mentioned. Additionally, it was noticed that males were more prone in comparison to females in acquiring symptomatology complexes. Males have a higher prevalence of hypertension than females, which could explain why this pattern of death happened across gender [30].

Hypertension, obesity, and diabetes mellitus were the most frequent comorbidities among COVID-19 patients with fatal endpoints, according to another meta-analysis study on the connection between comorbidities and fatal endpoints among 14 countries around the globe. Even though cancer, chronic renal disease, and chronic heart failure were independently related to death in these individuals, obesity was not reported as a factor in the associated mortality [31]. However, the precise processes through which pre-existing diseases influence the vulnerability of the illness and its severity are unknown. Inflammatory and hormonal pathways, and also social variables such as living in a populated or regimented environment, are hypothesized to have a role [32].

## 2 Combating SARS-COV-2

### 2.1 Biomarkers of COVID-19

A biomarker is a trait which is used to track changes in regular or dysfunctional biological processes, or in pharmacological responses to a treatment which provide objective values during the progression or course of a disease [33,34]. Depending on the severity of a disorder, the symptoms or clinical presentation can provide clinicians with a method for precise categorizing of patients as mild, severe, and being critical, thereby predicting the outcome and mortality on the basis of spectrum of the ailment. This can enable early treatment [35]. In addition, this can assist in identification of populations at high risk, justifying therapeutics, assessing treatment response, developing criteria for hospital ICU admission, and discharge [36].

Most of these biomarkers fall into four main groups: immunological and inflammatory host immune response indicators, hematological markers/coagulation factors, organ damage markers (cardiac enzymes, liver markers, and renal function markers), and general response markers (electrolytes). The commonly employed biomarkers for COVID-19 with its identification levels in human body are listed in Table 1.

**Table 1:** List of biomarkers for screening COVID-19

| Biochemical component | Biomarkers | Changes in COVID-19 patients | Ref. |
|---|---|---|---|
| **Blood** | | | |
| Hematological | Hemoglobin | Reduced | [37] |
| | Ferritin | Elevated | [38] |
| | Lymphocytes | Reduced | [37] |
| | Neutrophil: RETN, LCN2, HGF, IL-8, G-CSF | Elevated | [39] |
| | CD4+ and CD8+ | Reduced | [40,41] |
| | Neutrophil–lymphocyte ratio | Elevated | [42] |
| | Platelets | Reduced | [37] |
| | B cells, natural killer cells | Reduced | [37] |
| | Eosinophil-derived neurotoxin | Reduced | [43] |
| Coagulation | D-dimer levels | Elevated | [44] |
| | Fibrinogen | Elevated | [45] |
| | Fibrin degradation products | Elevated | [46] |
| | Prothrombin time | Elevated | [44] |
| | Activated partial thromboplastin time | Elevated | [44] |
| **Inflammatory markers** | | | |
| Inflammation | Cytokines: IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, and TGF-β | Elevated | [33] |
| | Chemokines: CCL2, CCL3, CCL4, CXCL6, CCL7, CCL8, CCL11, CCL17, CCL20, CCL24, CCL27, and CXCL11 [47] | Elevated | [48] |
| | Growth factors | Reduced | [49] |
| | C reactive protein | Elevated | [33] |
| | Procalcitonin | Elevated | [37] |
| | Lactate dehydrogenase | Elevated | [33] |
| **Immunity markers** | | | |
| Antigen | Spike protein | Elevated | [50] |
| | Nucleocapsid protein | Elevated | [51] |
| | Receptor-binding protein | Elevated | [37] |
| Antibody | IgG | Elevated | [52,53] |
| | IgM | | |
| | SigA | | |
| Receptor | ACE2 | Elevated | [54] |
| | IL2R | Elevated | [55] |
| **Organs failure markers** | | | |
| Cardiac | Cardiac troponin brain natriuretic peptide (BNP)/NT-proBNP myoglobin | Elevated | [56] |
| Hepatic | Aspartate aminotransferase | Elevated | [57] |
| | Alanine aminotransferase | Elevated | [57] |
| | Bilirubin | Elevated | [58] |
| | Albumin | Elevated | [59] |
| | Gamma-glutamyl transpeptidase | Elevated | [60] |
| Muscle | Creatine-kinase-myocardial band Myoglobin | Elevated | [61] |
| Renal | Serum creatinine | Elevated | [59] |
| | Urea | Elevated | |
| | Cystatin C | Elevated | [50] |
| **General response** | | | |
| Electrolytes | Sodium | Reduced Na | [62] |
| | Potassium | Reduced K | |
| | Calcium | Reduced Ca | |

## 2.2 Clinical management of COVID-19

In the months following the emergence of the new coronavirus, pharmaceutical corporations and researchers of all sizes endeavoured to combat the pandemic. This comprised of innovative regimens and medicaments to treat COVID-19, such as vaccines based on existing antiviral medications, expediting development of new drug, plasma treatment, and cell-based and monoclonal antibody convalescent therapeutics [63]. During the epidemic, the FDA's programs

enabling doctor's access to experimental treatments were indispensable. The expanded access and emergency use authorization (EUA) initiatives enabled quick implementation of prospective experimental medicines and investigational drugs with growing evidence [64].

However, considering the current global health emergency, the absence of verified clinical data on COVID-19 therapeutic agents, as well as the time, expense, and high attrition rate associated with drug development indicate that it is high time to identify a promising medicine. Due to the fact that drug research is costly, time-consuming, and has a high failure rate, time remains critical and of ultimate importance. Significant interest in improvising the existing medications and accelerating the production of vaccines can enable the quick identification of therapeutic candidates. More than 30 categories of substances, coming under conventional pharmaceuticals, environmental and traditional remedies, have been deemed *via* research to date as being potentially effective against COVID-19 where several of these agents have undergone rapid clinical testing and have proven tentative effectiveness against COVID-19 [65]. As of February 2023, there were 8,921 on-going clinical trials, 714 mapped medicines, 3,329 finished studies, and 199 completed vaccination studies [66].

As the introduction of mutant SARS-CoV-2 strains rendered certain vaccinations less-effective and also limited the worldwide availability of COVID-19 vaccines, it supported the rationale for exuberating efforts to discover potential therapeutic approaches; this includes antivirals such as remdesivir, chloroquine (CQ), Kaletra, favipiravir, and hydroxychloroquine (HCQ) along with immunosuppressive drugs such as tocilizumab, and tyrosine kinase inhibitors such as mastinib. These drugs have been used to treat hepatitis C and malaria and were used as monoclonal antibodies for rheumatoid arthritis, HIV treatment, and kinase inhibitors for mast cell tumors in animals [67,68].

### 2.2.1 Antivirals

Remdesivir, a monophosphate prodrug of an adenosine analogue, has been initially used to counter the 2014 Ebola epidemic and was suggested as a possible COVID-19 antiviral drug ($EC_{50}$ = 0.77 M) [69,70]. It possessed a strong selectivity for viral polymerases, reducing the likelihood that it would induce toxicity in humans; a significant obstacle which can induce genetic resistance (obstructing mutation generation) and a substantial half-life. Even though preliminary findings from a short observational trial revealed that 68% of the hospitalized patients experienced clinical improvement, the small number of case studies, and deficit of control group restrict the applicability of remdesivir administration. The US National Institutes of Health on April 29 reported 31% quicker recovery of disease-affected individuals administered with remdesivir than other infected people. Additionally, the governments of the United States, Japan, Australia, Singapore, and Europe have approved it as the novel therapeutic practice for COVID-19 patient's caretaking. In a recent review of the Phase 3 trial as well as a prospective observational analysis of chronic COVID-19-infected individuals, remdesivir indicated a 62% decrease in fatality probability as well as an increase in medical rehabilitation. In Phase-1 investigation study, the medicine was examined as an inhaled, nebulized version on outpatients [71,72].

The anti-HCV medicine sofosbuvir (SFV) is another most popularly employed antiviral drug which has shown to be effective against the novel coronavirus SARS-CoV-2. Approximately 12 clinical trials are currently recruiting and evaluating the efficacy of this medication in combination therapy. Six total investigations, on Phases 2, 3, and 4, have been completed. SFV originally inhibits the HCV NS5B protein, which is homological to NSP12 RNA polymerases of SARS-CoV-2. NSPs 1–14 are structural proteins that aid in RNA binding, replication, protein phosphorylation, and inhibition of the virus' interferon pathway. Hence, antivirals can serve as prospective pharmacological therapeutics for COVID-19 [73]. A Phase 2 multicenter prospective trial for evaluating the effectiveness of coupled SFV/daclatasvir (400 mg/60 mg) in the therapy of COVID-19 subjects with pneumonia is now complete. The primary endpoint shows a reduction of staying admitted in hospital with faster negative PCR [74]. Nevertheless, SFV/ledipasvir, which has passed Phase 4, has been found to be less efficacious in chronic COVID-19 individuals than in those with mild COVID-19 [75].

Similarly, ribavarin, a guanosine analog first used to treat hemorrhagic fever and respiratory syncytial virus, inhibited viral RNA polymerase, and messenger RNA (mRNA) capping. However, due to its lack of *in vitro* activity against SARS, it was discovered to be substantially less effective against SARS-CoV-2 compared to other antivirals. Nevertheless, it has been connected to the beneficial effects in managing of hemolytic anemia, when supplied to co-morbid patients who are reported to suffer from side effects related to heart disease and infertility [76].

### 2.2.2 Protein inhibitors

Lopinavir/ritonavir (LPV/r) was the initially coupled protease inhibitors employed for combating HIV. As lopinavir's oral

bioavailability is poor (it is rapidly metabolized by the Cytochrome P450 enzyme system), ritonavir (a CYP3A4 inhibitor) is administered to increase its plasma half-life. *In vitro*, it was shown to be much less powerful than remdesivir and CQ. In a randomized, open-label trial with 199 COVID-19 patients, LPV/r failed to lower both overall mortality and viral load. This raises the question of whether LPV/r may have a function in the treatment of COVID-19, resulting in the drug's removal from the treatment arm due to its inability to demonstrate a beneficial effect on clinical recovery and mortality reduction [77,78]

Another medication initially used during the onset of epidemic to treat flu-like symptoms in COVID-19 patients was oseltamivir. It is a neuraminidase inhibitor and is commonly administered to treat influenza. However, due to the absence of neuraminidase in coronaviruses, oseltamivir did not show any *in vitro* action against SARS-CoV-2 [79] and was found to be a failure through a retrospective and *in vitro* assessment [29].

Another effective protease inhibitor for the treatment of SARS-CoV-2 infection with a 60% survival rate is camostat mesylate. Inhibiting the host cell serine protease TMPRSS2, which in turn prepares the viral S protein for entrance into human cells, was the main application of this medication for chronic pancreatitis. *In vitro* testing has revealed viral blockage, and eight COVID-19 studies are now being conducted across the globe [79].

### 2.2.3 Anti-parasitic drugs

The drugs HCQ and CQ are another set of drugs, believed to be antimalarial drugs with antiviral activity, as they demonstrated potent *in vitro* activity against SARS-CoV-2 with an $EC_{50}$ of 6.14 and 23.90 M, respectively. However, these drugs were also not devoid of side effects, as they have impaired fatality and adverse effects in the patients who have been administered with these drugs. Furthermore, the viral load was not found to have decreased, prompting the authors to rule out the use of CQ at high doses [65,80,81].

Ivermectin is yet another medicine used to treat SARS-CoV-2. This anti-parasitic medication is suggested for the treatment of intestinal strongyloidiasis, onchocerciasis, lymphatic filariasis, scabies, pediculosis, rosacea, and other neglected tropical illnesses [82]. Despite the fact that several meta-analyses have shown that ivermectin reduces COVID-19 symptoms and the associated death, the trials were not reliable. As the efficacy of therapy remains ambiguous, with both positive and negative findings, the WHO recommended on March 31, 2021, that ivermectin can be used exclusively in clinical studies. The manufacturer (Merck) then made a statement on the resistance of the coronavirus to this anti-infective treatment. In spite of this, ivermectin is still commonly utilized in several South American nations [83].

### 2.2.4 Monoclonal antibodies

In addition to these medications, supplementary pharmacological interventions, including immunomodulatory therapies involving monoclonal antibodies, are being utilized for the successful treatment of SARS-CoV-2. Tocilizumab and sarilumab are common examples among these, which are currently available. Tocilizumab is a recombinant monoclonal antibody that blocks IL-6 receptors and is used to treat immunological response in patients with cytokine-release diseases, which are linked to IL-6 [84]. People with thrombocytopenia and neutropenia are particularly sensitive to the possible side effects of this medicine, including hepatotoxicity and gastrointestinal perforation [85]. At present, there are currently 62 registered studies examining the safety and efficacy of tocilizumab in COVID-19 patients [86].

Despite evidence from recent studies demonstrating tocilizumab's efficacy on the improved survival rate and clinical markers in cytokine release syndrome patients, a retrospective cohort study revealed that tocilizumab did not demonstrate a statistically significant advantage over standard care in terms of clinical progression or mortality [87]. Sarilumab, as an IL-6 receptor-inhibiting monoclonal antibody, which was originally used to treat rheumatoid arthritis [88,89], is presently being evaluated in more than 15 registered clinical studies against SARS-CoV-2. Nevertheless, a recent Phase 3 research revealed that the drug is ineffective for COVID-19 patients requiring ventilation, since it did not reach the study's goals [63]. In addition, FX-1 is a chimeric monoclonal IgG4 antibody that binds to the soluble form of human complement protein-C5a with great affinity. Currently, the intravenous administration of IFX-1 (vilobelimab) to adults with severe COVID-19 is in effect. Its primary functions are the inhibition of anaphylatoxin and C5a. C5a inhibition with IFX-1 appeared to be safe for chronic COVID-19 suspects in a phase two study. Apart from this, the fact that the secondary outcome data favoring IFX-1 are preliminary since the study was not randomized on these endpoints, they encourage the investigation of inhibitory activity of IFx-1 in a 28-day mortality checkpoint on Phase 3 trials [90].

However, hospitalized patients with COVID-19 who were given lopinavir and interferon regimens alongside HCQ in a big multi-center WHO Soliditary study recently saw their death rates remain unchanged. The limited benefits of remdesivir and the need for injectable administration

make it all the more appealing to find new or complementary medication that can bring about comparable or even higher therapeutic advantage and could be provided outdoors of a hospital environment (*i.e.*, orally) [91].

#### 2.2.5 Anticancer drugs

The oral phosphoinositide 3-kinase (PI3 kinase) inhibitor duvelisib (anti- cancer drug) is used for the treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma, and follicular lymphoma [92,93]. In patients experiencing these diseases, duvelisib has been found to dramatically downregulate the expression of inflammatory cytokines and chemokines like G-CSF, GM-CSF, macrophage inflammatory protein-1 α and β, according to Phase II and III trials. According to the researchers, duvelisib was found to reduce COVID-19-associated pneumonia and ARDS by polarizing the macrophages to M1 phenotype, decreasing cytokine signalling/production, and eliminating viral persistence [94]. In this connection, PI3K enzymes were originally found to regulate the cell cycle, apoptosis, DNA repair, angiogenesis, senescence, and cell metabolism [95]. Therefore, it was evident that duvelisib is applicable to COVID-19 patients due to its immune system-associated activity but not of its anticancer efficacy. The effectiveness of duvelisib as monotherapeutic agent in COVID-19 patients has been evaluated, and the trial is now complete (NCT04372602) [96].

Zanubrutinib and opaganib are the other two anticancer drugs used for treating COVID-19 [97,98], where the former is a Bruton tyrosin kinase inhibitor (BTK) used to treat mantle cell lymphoma and the latter is a selective sphingosine kinase-2 (SK2) inhibitor used to treat advanced cholangiocarcinoma and metastatic castration-resistant prostate cancer [99]. Opaganib is a SK2 inhibitor for advanced cholangiocarcinoma and metastatic castration-resistant prostate cancer [96]. Zanubrutinib was initially developed as a BTK inhibitor to treat mantle cell lymphoma [100]. As of March 2022, a Phase II research (NCT04382586) assessing the effectiveness of zanubrutinib in enhancing the survival rate by avoiding respiratory failure in hospitalized patients with COVID-19 and pulmonary distress has concluded (https://clinicaltrials.gov/ct2/show/NCT04382586) [101]. Acalabrutinib (NCT04497948), a second-generation BTK inhibitor, has had its phase II trials discontinued because the patients did not get fulfilled of their key effectiveness goals [102]. However, opaganib has been discovered to suppress viral replication, diminish the hyperimmune inflammatory response, and lessen ARDS-related thrombosis. By suppressing viral replication in human lung tissue, opaganib has demonstrated strong antiviral effectiveness against SARS-CoV-2 in preclinical studies *in vivo* [96]. A Phase 2 clinical research has been completed to evaluate the adverse effects and efficacy of opaganib in COVID-19 patients (NCT04414618) [103].

#### 2.2.6 Corticosteroids

Methylprednisolone and dexamethasone are the two most often used corticosteroids as anti-covid medications [104]. For methylprednisolone, as of November 2023, among the 65 ongoing clinical trials against COVID-19, 35 have been completed and 6 are under recruitment [105]. Methylprednisolone is a corticosteroid with significant anti-inflammatory characteristics that is used for the treatment of arthritis [106] and pneumonia [107]. Post-COVID-19 syndrome patients receiving 20 mg/5 mg of prednisolone are now being enrolled in a Phase III clinical research examining the feasibility of randomized controlled trial in primary care and the efficacy of therapy with prednisolone and/or vitamin B1/6/12. The research also included neurotropic vitamins, including vitamins B1, B6, and B12, to determine the effectiveness of the combination therapy (NCT05638633). This trial is still under recruitment and not yet completed.

#### 2.2.7 Vaccines

Added to conventional drugs, COVID-19 regimens also include vaccines and miscellaneous drugs. Throughout the evolution of vaccinations, the production of COVID-19 vaccines has progressed at an unprecedented rate. Presently, 199 vaccine candidates are in preclinical development and 180 are in clinical development [108].

As of November 2023, a total of 50 vaccines have been approved, and 12 vaccines have been granted emergency use listing (EUL) status by the WHO, which falls under the category of whole virus vaccines and component viral vaccines [109]. The EUL-approved 11 COVID-19 vaccines majorly fall under the sub-divisions of being inactivated, protein subunit, RNA, and non-replicating viral vector-based ones. Yet, the authorized vaccination list also includes DNA-based and virus-like particle-based vaccines [110]. A list of approved vaccines for the three most severely affected countries, including China, the United States, and India, along with their respective dosage schedules, is provided in Table 2.

U.S. Food and Drug Administration agency has approved five COVID-19 vaccines for emergency use. These include Pfizer-BioNTech COVID-19 Vaccines, Moderna COVID-19

**Table 2:** List of vaccines approved by WHO for use in combating COVID-19 in China, USA and India

| Country name | Vaccine | WHO EUL approved | Vaccine type | Number of doses | Route of administration and schedule | Number of countries approved | Number of trials around the world |
|---|---|---|---|---|---|---|---|
| China approved: 8; clinical trial: 35 | Zifivax/receptor-binding domain (RBD) Dimer/ZF2001 | Yes | Protein subunit | 3 | IM/Day 0 + 28 + 6 month | 4 | 21 |
| | V-01 | No | Protein subunit | 2 | IM/Day 0 + 28 | 1 | 3 |
| | Convidecia | Yes | NRV | 2 | IM/Day 0 + 28 | 10 | 14 |
| | Convidecia Air | No | NRV | 1 | Nebulizer/Day 0 | 2 | 5 |
| | KCONVAC | No | Inactivated | 2 | IM/Day 0 + 14/28 | 2 | 7 |
| | Covilo | Yes | Inactivated | 3 | IM/Day 0 + 28 + 28 | 93 | 39 |
| | Inactivated (Vero cells) | No | Inactivated | 2 | IM/Day 0 + 28 | 2 | 9 |
| | CoronaVac | Yes | Inactivated | 2 | IM/Day 0 + 14 | 56 | 10 |
| USA approved: 6; clinical trial: 52 | Nuvaxovid/Novavax | Yes | Protein subunit | 2 | IM/Day 0 + 32 | 40 | 22 |
| | Spikevax | No | RNA | 2 | IM/Day 0 + 28 | 88 | 70 |
| | Spikevax bivalent original/omicron BA.4/BA.5 | No | RNA | 2 | IM/Day 0 + 28 | 33 | 2 |
| | Comirnaty | Yes | RNA | 2 | IM/Day 0 + 21 ± 7 days | 149 | 100 |
| | Comirnaty bivalent original/omicron BA.4/BA.5 | No | RNA | 1 | IM/Day 0 after Primary vaccination | 33 | 4 |
| | Jcovden | Yes | NRV | 1 | IM/Day 0 | 113 | 26 |
| India approved: 12; clinical trial: 16 | COVOVAX (Novavax formulation) | Yes | Protein subunit | 2 | IM/Day 0 + 21 | 6 | 7 |
| | Corbevax | No | Protein subunit | 2 | I0 + 28 M/Day | 2 | 7 |
| | ZyCoV-D | No | DNA | 3 | IM/Day 0 + 28 + 28 | 1 | 6 |
| | GEMCOVAC-19 | No | RNA | 2 | IM/Day 0 + 28 | 1 | 2 |
| | Spikevax | Yes | RNA | 2 | IM/Day 0 + 28 | 88 | 70 |
| | iNCOVACC | No | NRV | 2 | IN/Day 0 + 28 | 1 | 4 |
| | Sputnik Light | No | NRV | 1 | IM/Day 0 | 26 | 7 |
| | Sputnik V | No | NRV | 2 | IM/Day 0 + 21 | 74 | 25 |
| | Jcovden | Yes | NRV | 1 | IM/Day 0 | 113 | 26 |
| | Vaxzevria | Yes | NRV | 2 | IM/Day 0 + 28 | 149 | 73 |
| | Covishield | Yes | NRV | 2 | IM/Day 0 + 84 | 49 | 6 |
| | Covaxin | Yes | Inactivated | 2 | IM/Day 0 + 28 | 14 | 16 |

IM: intra-muscular; IN: intra-nasal; NRV: non-replicating viral vector, RNA: ribonucleic Acid, DNA: deoxy ribonucleic acid. Data retrieved [109].

**Table 3:** Landscape of FDA approved COVID-19 drugs/vaccines

| Drug/vaccine | Type | Status | Year | Clinical trials |
|---|---|---|---|---|
| Pfizer-BioNTech | mRNA vaccine | FDA approved (First authorized COVID-19 vaccine) | 2020 | Multiple trials [115] |
| Moderna | mRNA vaccine | FDA approved | 2020 | Multiple trials [115] |
| Johnson & Johnson | Viral vector vaccine | FDA approved | 2021 | Multiple trials [115] |
| AstraZeneca | Viral vector vaccine | FDA approved | 2020 | Multiple trials [115] |
| Remdesivir | Antiviral | FDA approved | 2020 | Multiple trials, including ACTT trials [116] |
| Dexamethasone | Corticosteroid | FDA approved | 2020 | RECOVERY trial [117] |
| Regeneron's (REGN-COV-2) | Monoclonal antibody | FDA approved | 2020 | Multiple trials [115] |
| Sotrovimab | Monoclonal antibody | Phase III (NCT04545060) | 2020 | COMET-ICE trial and others [118] |
| Molnupiravir | Antiviral | (Phase III) | 2021 | MOVe-OUT [119] |
| Paxlovid (Pfizer) | Antiviral | (Phase III) | 2021 | EPIC-HR [120] |
| Novavax | Protein subunit vaccine | (Phase III) | 2021 | PREVENT-19 [121] |

Vaccines, Janssen COVID-19 Vaccine, the Novavax COVID-19 Vaccine, and Spikevax COVID-19 Vaccine. The first COVID-19 vaccine, licensed by the FDA, is Pfizer-BioNTech COVID-19 Vaccine, which was approved on August 2021 and marketed as comirnaty for individuals aged 16 and older [111]. The vaccine is also still available under EUA, including for individuals aged 12–15 and the administration of a third dose to certain immunocompromised patients. The FDA has recently revised the EUAs for the upgraded (bivalent) Moderna and Pfizer-BioNTech COVID-19 vaccines to permit their use in infants as young as 6 months and also authorized the Novavax COVID-19 vaccine, as adjuvants, as the first booster dose to adults of 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate [112–114]. List of FDA-approved vaccines and key clinical trials undergoing are listed in Table 3.

# 3 Diagnosing with nanotechnology

Nanotechnology is gaining ground against SARS-COV-2 through infection prevention, diagnosis, and therapy [122]. It is a revolutionary drug delivery technique that allows for the identification and neutralization of the pathogen utilizing imperative nanoparticles (NPs), which has several favourable effects such as enhancing the treatment's effectiveness, early diagnosis, and improving safety [123,124]. Diagnosis and neutralization of the COVID-19 virus by nanomedicine is essential, given that SARS-COV-2 is transmitted *via* minute droplets that are expelled during respiration, speaking, sneezing, and coughing. Consequently, these NPs can be engineered to combat causative microorganisms and eliminate viruses prior to their host entry [125]. The preponderance of viral RNA testing techniques are centered on the reverse transcription polymerase chain reaction (RT-PCR) due to its simplicity, high sensitivity, and high accuracy as a result of the exponential increase in RNA produced during the process [126]. Even though RT-PCR methods are widely recognized as conventional techniques for coronavirus detection, there are constraints that must be addressed, such as low extraction efficiency, long drawn out procedures, and contamination-induced false positives [127]. Since vaccine research for SARS shares major similarities with cancer research [128], neither the therapeutic innovations nor the problems associated with SARS-COV-2 infections should be considered separately [129]. Thus, it is crucial to re-evaluate the innovative application of nanotechnology in combating COVID-19.

Metal NPs, magnetic NPs (MNPs), and quantum dots (QDs) have been predominantly used to diagnose coronaviruses. Other NPs, like aptamers, silica NPs (SiNPs), and polymeric NPs, have also been studied for virus detection [130] (Figure 1).

## 3.1 Metal NPs

Unique optical and electrical features (localized surface plasmon resonance [LSPR]) of metals, particularly noble metals such as gold, silver, and copper, have been considered in the development of metal NPs [131] to detect viral cells in biosensing applications including disease marker detection, photocousting imaging, and near-infrared thermal ablation [132]. This is due to the LSPR property for tunable

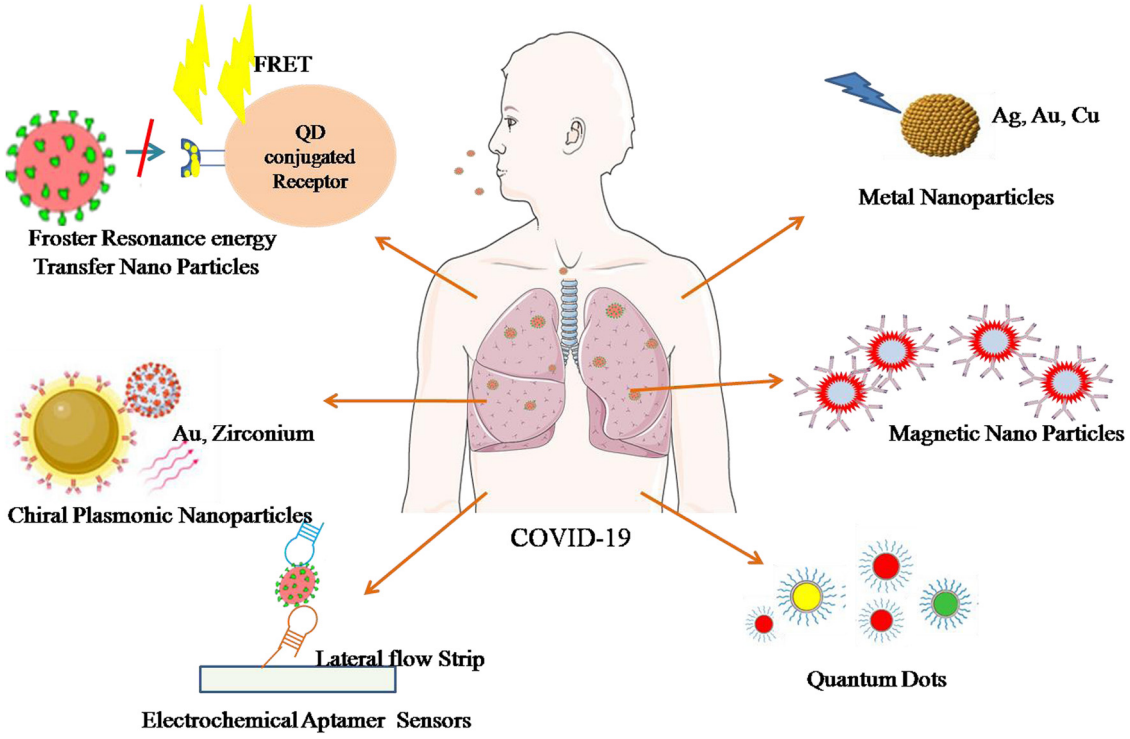


**Figure 1:** Various nanomaterial-based methodologies employed for diagnosis of COVID-19.

electromangnetic light absorption and scattering wavelength in the visible region [133], in which the change in the LSPR extinction maxima of metal NPs is dependent directly on the refractive index of encircling media and the range of NP aggregation, both of which are crucial for NPs to be used in biological applications [134].

Gold NPs (AuNPs) are the most common NPs used in coronavirus diagnosis or detection due to their unique optical properties, stability, and biocompatible properties [135,136]. Kim *et al.* created and utilized a simple colorimetric hybridization technique to detect SARS-CoV, which was based on the synthesis of dsDNA from viral ssRNA by the interaction of viral ssRNA with citrate-coated AuNPs, therefore stabilizing the particle [137]. AuNPs with modified surface properties by functionalizing with biomolecules are used for effective detection of COVID-19 variants without cross reactivity including MERS-CoV, HCoV-HKU1, HCoV-HKU4, SARS-CoV, HCoV-229E, and HCoV-OC43. AuNPs conjugated with streptavidin were used for an RT-LAMP (Reverse Transcriptase Loop-mediated isothermal amplification) assay which in turn was then combined with a vertical flow visualization strip (RT-LAMPVF), for detecting the nucleic acid of COVID-19 variant (MERS-COV). Later, the viral RNA made by RT LAMP was labeled with biotin and fluorescein isothiocyanate (FITC) to make the labeled amplicons, which could bind to streptavidin-functionalized AuNPs to make a complex that changed color when an anti-FITC antibody coated on the detection strip demonstrated it. Within 35 min, the creation of the complex on the strip was obvious to the naked eye. This technique was found to produce a high specificity and effective detection limit of 10 copies of viral RNA/μL. Similarly, a study on using Plasmonic NP study SARS-CoV-2's N gene (nucleocapsid phosphoprotein) was colorimetrically identified by Thiol modified antisense oligonucleotides functionalized AuNPs [138].

## 3.2 MNPs

For the specific identifications of SARS-COV-2, the principle of magnetic efficiency of nanometals is currently being employed to prepare super-paramagnetic NPs (SMNPs) conjugated with amplified viral DNAs and to identify them with silica-coated fluorescent NP-based signalling probes *via* hybridization assay. Recently, scientists have used silica-coated SMNPs in PCR-based assays in order to increase the specific selection of the target cDNA of SARS-COV during the process, thereby allowing the identification of the target cDNA with a limit of detection (LOD) of around $2 \times 10^3$ copies in a time span of 6 h [139].

Nanotechnological approaches, such as protein corona detector panels and magnetic levitation, have also been highlighted by Mahmoudi in his study as having great promise for identifying chronic patients during the early phases of the COVID-19 infection [140]. According to the study, a biomolecular corona is generated in which the introduction of NPs happens in a human environment (*e.g.*, blood plasma) and can lead to instantaneous association with numerous biomolecules, such as proteins, which in turn forms an outer covering of NPs. This can assist in distinguishing the protein corona biomolecule from the others. As a result of the increased affinity of other proteins and the recruitment of additional particles onto the NPs that have previously been included, this method is still susceptible to a number of lacks in correlation. As a consequence, disease-specific protein corona biomolecules were created, the molecules in which the protein corona sensor array technology can define the plasma protein and biomolecule patterns that indicate catastrophic COVID-19 infection at its earliest stages [140]. And also colorimetric nanotechnologies, such as optoelectronic nose [141] and plasmonic NP (AuNPs) technologies [142], can be enhanced or updated for identification of the virus in susceptible individuals at an earliest time point, based on the fingerprint protein corona biomolecular pattern.

A typical MagLev device consists of a pair of permanent magnets with identical poles positioned opposite to one another along the gravity vector. Serving this purpose better, superparamagnetic iron oxide NPs were able to circumvent the instability of proteins in the paramagnetic solution and thereby levitate plasma proteins [140]. A heterogeneity mapping study revealed that the MagLev system cannot only separate corona-coated NPs but also examine the homogeneity/heterogeneity of the protein corona and aid in rapid screening of the homogeneity of corona-coated NPs prior to quantitative analysis of the disease [143].

## 3.3 QDs

Conventional luminous NPs known as QDs are gaining popularity because of their unique photonic and electrical properties. These properties include a substantial quantum yield, anti-photo bleaching action, broad absorbance range, tunable emission wave length, and excellent stability. In addition, it is projected that these QDs will contribute to the advancement of virus detectors and antiviral medications through their enhanced broad-spectrum action, point-of-care (POC) diagnostics, and profitable manufacturing [144–146].

## 3.4 Electrochemical aptamer sensors

A QD-conjugated RNA aptamer particular to the SARS-COV N protein has revealed greater sensitivity for coronavirus detection. In the respective study, authors employed QD-605 with maximum emission at 605 nm to achieve an exceptional detection limit of 0.1 pg/mL SARS-COV N protein mounted on a glass chip. The authors suggest that an optical QDs-based RNA aptamer chip may be able to get around the limitations of other techniques because it is sensitive, specific, easy to use, and can monitor one spot [147]. In another study for detecting N-gene of SARS-COV-2, a surface plasmon resonance aptasensor was constructed where N-gene-targeted aptamer was attached on thiol-altered niobium carbide MXene QD bioplatform. This aptasensor thereby exhibited an LOD of 4.9 pg/mL for N gene through a concentration range of 0.05–100 ng/mL [148]. In addition, photoelectric aptasensors were developed for quantifiable detection of RBD SARS-COV-2. The design included a modified ITO electrode with chitosan/cadmium sulfide (CdS)–graphitic carbon nitride (gC3N4) nanocomposite (gC3N4 and CdS) with immobilized amine-terminal aptamer probes. Results indicated that the aptasensor may be utilized to quantify Sars-Cov-2 RBD concentrations between 0.5 and 32.0 nM, with 0.12 nM LOD [149].

## 3.5 QD-conjugated chiral plasmonic NPs

Another nanohybrid structure with optical resonances that have crucial role in viral detection is chiral plasmonic NPs integrated with QDs. This include far-field coupling and near-field processes, as well as enhanced chiroptical characteristics [150]. In nanostructures, cumulative oscillations of free electrons produce plasmonic phenomena that enable the nanoscale confinement of light, which in turn can enhance the chiroptical interactions [151]. A sensitive chiro-immunosensor, conjugated QDs with chiral gold (Au) nanohybrids, was developed on the view of achieving low values of LOD. Based on self-assembly techniques, an asymmetric plasmonic chiral nanostructure hybrid will broaden the spectrum of circular dichroism reaction to achieve an exclusive plasmonic resonant association with the energized state of QD for LOD. The developed probe was originally utilized for the highly sensitive picomolar level detection of avian influenza A (H5N1) virus. Thus, the applicability of this sensing system was also examined on other viral cultures, including avian influenza A (H4N6), poultry adenovirus, and also coronavirus in respective blood/serum samples [150].

Chiral zirconium NPs assembled with L(+)-ascorbic acid are another example for conjugated plasmonic NPs which is predominantly employed for SARS-COV with LOD of 79.15 EID/50 µL. In this technique, in addition to self-assembly and circular dichroism, these QDs might be conjugated with COV antibodies like bronchitis virus (IBV) to generate an immune link in the vicinity of anti-IBV antibody coupled magneto-plasmonic NPs and a tagged analyte. This in turn produced high sensitivity optical detection for COVs with LOD about 79.15 EID/50 µL [152]. As it has been demonstrated that exciton–plasmon interactions may influence chirality, employing integrated nanostructures as an approach for improving the responsiveness of optical (nano)sensors seems to be a promising idea.

### 3.6 QDs-based Förster resonance energy transfer

A recent study explores a highly sensitive biosensing approach using QD-Förster resonance energy transfer, relying on the resonance energy transfer patterns between distinct partners to pick out the inhibitors of SARS-COV-2. The study focuses on the development of a versatile imaging probe involving the spike receptor binding domain of SARS-COV-2 conjugated to fluorescent QDs. This probe is designed to monitor the binding of the spike protein to the host cell's ACE2 receptor, which is the initial step in SARS-COV-2 infection. The probe can undergo energy transfer quenching while interacting with ACE2-conjugated AuNPs, allowing for the real-time monitoring of this binding event in solution. The study demonstrates that neutralizing antibodies and recombinant human ACE2 effectively block this quenching, indicating a specific binding interaction [153]. For the identification of SARS-COV-2 RNA, a ligand exchange-based CdTe QDs–DNA (Cadmium telluride QDs) nanobiosensor was developed. This nanosensor might be utilized for the quick detection of RNA from SARS-COV-2 in actual samples with results equivalent to RT-PCR with high selectivity and sensitivity of LOD with $2.52 \times 10^{-9}$ mol $L^{-1}$ [154].

### 3.7 QD nanobeads (QBs)

A portable smartphone imaging stage that automates quantitative QD barcode immunoassay and interacts utilizing an internally developed data dashboard was developed for the quantitative assay of SARS-COV-2. Here, a database and dashboard were used to illustrate real-time reporting of test results. The principle of the technique comprises (a) previously coded QD microbeads to identify target antibodies in human blood serum, so as to identify distinct antibody targets; several colors of QD barcoded microbeads were constructed; (b) hand-held instrument to stimulate and photograph the fluorescent microbead; and (c) an application that transmits the data to a controlling facility. The technology was certainly found to be highly sensitive and specific in being reported with an LOD of 1.99 pM for nucleocapsid coated microbeads and 0.11 pM for S1-RBD coated microbeads [155]. Also, lateral flow immuno assay (LFIA) with POC treatment is gaining popularity attributed to its simplicity, ease, speed, plus economic convenience for qualitative analysis [156]. Particularly, detecting SARS-COV-2 infection using colloidal gold NP-based LFIA (AuNP-LFIA) has undergone rapid advancement. In a recent study, a QB-based LFIA (QB-LFIA) for detecting total SARS-COV-2 antibodies in human serum was created. The QB-LFIA makes use of immunoassay construction including two antigens. During the assay process, SARS-COV-2 spike protein conjugated with QB is employed as a detecting probe to bind with specific antibodies in virtue of determining their serum levels. After being prepared, QB-LFIA was approximately an order of magnitude more sensitive than AuNP-LFIA [157].

## 4 Usage of NP regimen for COVID-19

### 4.1 Inhibition of viral attachment and entry into cell

A powerful approach for medication development and therapy is by preventing the process through which the virus attaches to the ACE2 receptor or restrict endocytosis [158]. CQ is one of the medications that are regularly evaluated for this purpose [159]. CQ has been initially found to hinder the NP endocytosis. As structurally SARS-COV-2 is comparable to certain NPs, it has been reported that CQ can prevent the endocytosis of SARS-CoV-2 virus particles [160].

This occurs in the following manner:

(1) CQ-induced inhibition of phosphatidylinositol-binding clathrin assembly protein (PICALM), which in turn prevents endocytosis-mediated absorption of NPs. Generally, in the

endocytosis pathway, PICALM is an accessory protein that, together with clarithrin, facilitates endocytosis.
(2) encasing the molecule inside polymeric NPs like the often used poly lactic acid [161].

The ability of 1.6 nm cationic carbon dots (CDs) produced from curcumin to prevent the invasion of a coronavirus model, porcine epidemic diarrhea virus (PEDV), has been reported in a recent study [162]. At 125 μg/mL, the inhibition efficiency was over 50%, preventing viral entrance at an early stage. The blockage is probably thought to be brought about by electrostatic reactions among the anionic PEDV and the cationic CDs, which negate the effective charge on the virus particles and produced viral aggregation, together with this, the CDs also prevented the formation of reactive oxygen species (ROS), and thereby minimized cell death [162,163]. In cases of respiratory viruses, curcumin-conjugated AgNPs have been reported to possess the ability of viral inhibition and entry [163].

AuNPs have been found to be directly linked with the blockage of cell entry apart from the viral aggregation function. When considering NPs, AuNPs are less toxic than AgNPs. Huang *et al.*, demonstrated the inhibitory activity of AuNPs in his recent study, in which he found a homologous protein that mimics the structural identity with one of the viral protein that is essential for cell fusion and invasion [164]. Pregnancy-induced hypertension (PIH), a peptide that mimics the structure of HR2, was discovered by him. Hence, this peptide can interact with HR1 of virus and prevent the creation of 6HB (six-helix bundle), which is supposed to draw the viral encapsulation within the cell. Through preventing 6HB, the process of cell fusion and subsequent infection are effectively inhibited. Gold nanorods coated with PIH displayed 10 times more suppressive activity at the optimum dose, completely blocking cell fusion [164].

In addition to AuNPs, other biocompatible and less toxic NPs with antiviral action such as SiNPs and selenium NPs (SeNPs) are effectively utilized. Engineered NPs including porous SiNPs break down to form non-toxic silicic acid and are favoured for their antiviral impacts due to their extraordinary biocompatibility and biodegradability properties. These particles, when functionalized separately or conjugated to different moieties (mesoporous SiNPs), act as scavengers of enveloped infection particles and prevent cellular invasion [165,166]. SeNPs remain prominent example for biocompatible NPs against SARS-COV-2 with antiviral efficiency by blocking viral entry when administrated [167]. In a recent study using the anti-inflammatory drug Ebselen, an organic Se species, it was found that the drug can block coronavirus by covalently binding to the virion through cell membranes, when administrated at a concentration of 10 μm. However, when administrated at high concentrations, it was found to be toxic; therefore, nanoselenium or low toxicity selenium for their biocompatibility are considered for their antiviral efficacy in the fight against viral infections [167].

Previous investigations have showed that natural compounds like green tea catechins inhibit encapsulated viruses. Its hydroxyl, galloyl, and pyrogallol groups on B-ring can alter viral antigen expression or genome replication at various phases of viral entry. Green tea polyphenols, like epicatechin gallates, have been identified as powerful viral entry inhibitors efficient of inhibiting the host's glycoprotein CD4 interaction with glycoprotein gp120 of HIV-1, thereby preventing viral infections [168]. Similarly, curcumin, a polyphenol isolated from the plant *Curcuma longa*, has been shown to have antiviral action due to the presence of phenolic hydroxyl groups. Also, ionic gelation was used to encapsulate curcumin in chitosan NPs, which increased its bioavailability after oral administration along with it is *in vitro* antiviral efficacy in feline immunodeficiency virus-infected cats [162]. High-efficiency (homogeneous and stable with polar groups) anti-PEDV coronavirus delivery systems, consisting of glutathione-capped Ag2S nanoclusters and glutathione-modified zinc-sulfide NPs, were produced *via* the curcumin pyrolysis procedure [169,170]. When tested against PEDV, natural compounds like curcumin and glycyrrhizin were found to have multisite inhibition mechanisms, including: (a) blocking the entry of virus by altering the viral surface protein morphology, preventing pathogen's genomic RNA production and replication; (b) reducing ROS production; and (c) stimulating IFN-stimulant genes and downstream of pro-inflammatory cytokines to lower the multiplication of virus. Similarly, the strong interaction of griffithsin (antiviral lectin) with the MERS-COV and SARS-COV-2 glycoprotein regions has also been hypothesized to prevent the cellular entry of viral particles [171,172].

## 4.2 Blocking the viral replication and proliferation

Rectifiers that slow down the rate at which viral particles reproduce or reduce their infectiousness are at consummate significance, as this will prevent the proliferation of these infectious particles and thereby provide time for response of body's first-line immune system to function effectively in combating the virus. This will also prevent the infectious particles from generating mutated versions as their replication is blocked. Several viruses with

positive-sense ssRNA genetic material, phospholipid envelopes, and proteins resemble SARS-CoV-2. Recent coronavirus research has employed several of these viruses as models, and NP efficacy on these viruses may be important for therapeutic development toward SARS-CoV-2 [160].

A recent study has shown that the transmissible gastroenteritis virus (TGEV), one member among the coronavirus family, is much less infectious in the presence of AgNPs and silver nanowires at a concentration below the toxicity limit. In addition to this, AgNPs have been found to limit apoptosis induced by viral inhabitation. This happens when Ag NPs suppress TGEV-induced Pi-p38 protein production to control p38-MAPK-p53 mitochondrial signalling, which in turn regulates TGEV-induced cell death [173]. Furthermore, Du *et al.* have reported that AgNP-modified graphene oxide suppresses porcine reproductive and respiratory syndrome virus (PRRSV), a model virus utilized in coronavirus research, with 59.2% inhibitory efficacy. To add, GO-AgNPs nanocomposite treatment was found to boost IFN-α and ISG production, which directly restricted viral growth [174]. In another investigation, Tong *et al.,* synthesized a glycyrrhizic-acid-based CDs with multisite PRRSV suppression of up to five orders of virus titers. The multiple inhibitory mechanisms include viral invasion and replication inhibition, cell IFN stimulation, and ROS generation inhibition [175]. The work has exemplified the undefined potential of CDs in viral inhibition, which could help in the development of novel strategies of NPs conjugated antiviral therapies.

Haam *et al.* employed porous AuNPs to aim the heme agglutinin (HA) protein on several influenza viruses by exploiting effective goldthiol interconnection (PoGNPs) as it has been one of the most intensively researched viruses due to many worldwide pandemics over the past decades. Because of recurring mutations and growing treatment resistance, influenza A viruses are considered the focus of numerous NP-based medicinal research initiatives. In that particular study, Haam found that PoGNPs suppress the viral infectivity and increased host cell viability to 96.8% from 33.8%. In addition, viruses like H1N1, H3N2, and H9N2 were used to demonstrate the approach's universal effectiveness [176]. In a recent study, Haag *et al.* employed electron microscope imaging to visually demonstrate that AuNPs functionalized with sialic acid-terminated glycerol dendrons effectively and inhibited viral multiplication by targeting the viral HA protein [177]. A benzoxamine-monomer-derived CDs have been found to reduce Zika virus, the causative of a 2015 pandemic in South and North America which in turn shares structural similarity with coronavirus [178]. The CDs have been also found inhibitory to other viruses that are structurally similar to coronavirus, dengue, and Japanese encephalitis virus. Also, they have been found to inhibit adeno-associated virus and porcine parvovirus, non-enveloped viruses, which in turn emphasizes the spectrum of antiviral potential of NPs [178]. Alphaviruses, a similar genus of RNA viruses to coronaviruses, were substantially repressed in Vero (B) cells by cellulose nanocrystals treated with tyrosine sulfate mimetic ligands, whereas human cells were found to be unaffected [179].

## 4.3 Viricidal NPs

Another method of preventing viral infections in addition to blocking the host cell contact, genetic material replication and proliferation of virus is inactivating or destroying the virus directly. In a sophisticated reversible viral investigation, AuNPs coated with 3-mercaptoethylsulfate (MES) produced an inhibitory concentration at $EC_{90}$ (nanomolar range). This in turn is identical to the outcome of heparin, a popular antiviral substance that inhibits pathogen and host contact. However, the authors also discovered that replacement of MES with a 2:1 combination of undecanesulfonic acid (MUS) and 1-octanethiol (OT) could elicit permanent/irreversible viral inactivation of several viruses that specifically target humans, including herpes simplex virus, respiratory synctial virus, dengue virus, as well as human papiloma virus, and lentivirus [180]. As the study reported no cytotoxicity during *ex vivo* and *in vivo* studies on mice and humans, respectively, and as the broad-spectrum model viruses employed in the study shared structural and functional similarities with the coronavirus, this study emphasizes the potential use of MUS:OTAuNPs in SARS-Cov-2 treatment [160].

In a recent study, it was demonstrated that a functionalized mock virus receptor nanodisc, a self-assembled discoidal membrane covered in an amphipathic membrane scaffold protein, can neutralize the infected influenza virus (H1N1) by specific inhibition of viral surface proteins and thereby produce permanent damage to the viral envelope. As a result of various associations with viral target proteins, conjugating sialic acid onto nanodiscs enhanced their antiviral efficacy. It was reported that the functionalized nanodiscs also prompted the virus's fusion machinery to self-disrupt its envelope. This approach is promising for *in vivo* studies due to the biocompatibility of the NPs and the decoy molecules [181]. Gao and colleagues reported the existence of iron oxide NPs with broad-spectrum antiviral activity against flu viruses (H1N1, H5N1, and H7N9). Using the catalytic, enzyme-like, and peroxidase-catalyzing properties of ferromagnetic NP with an

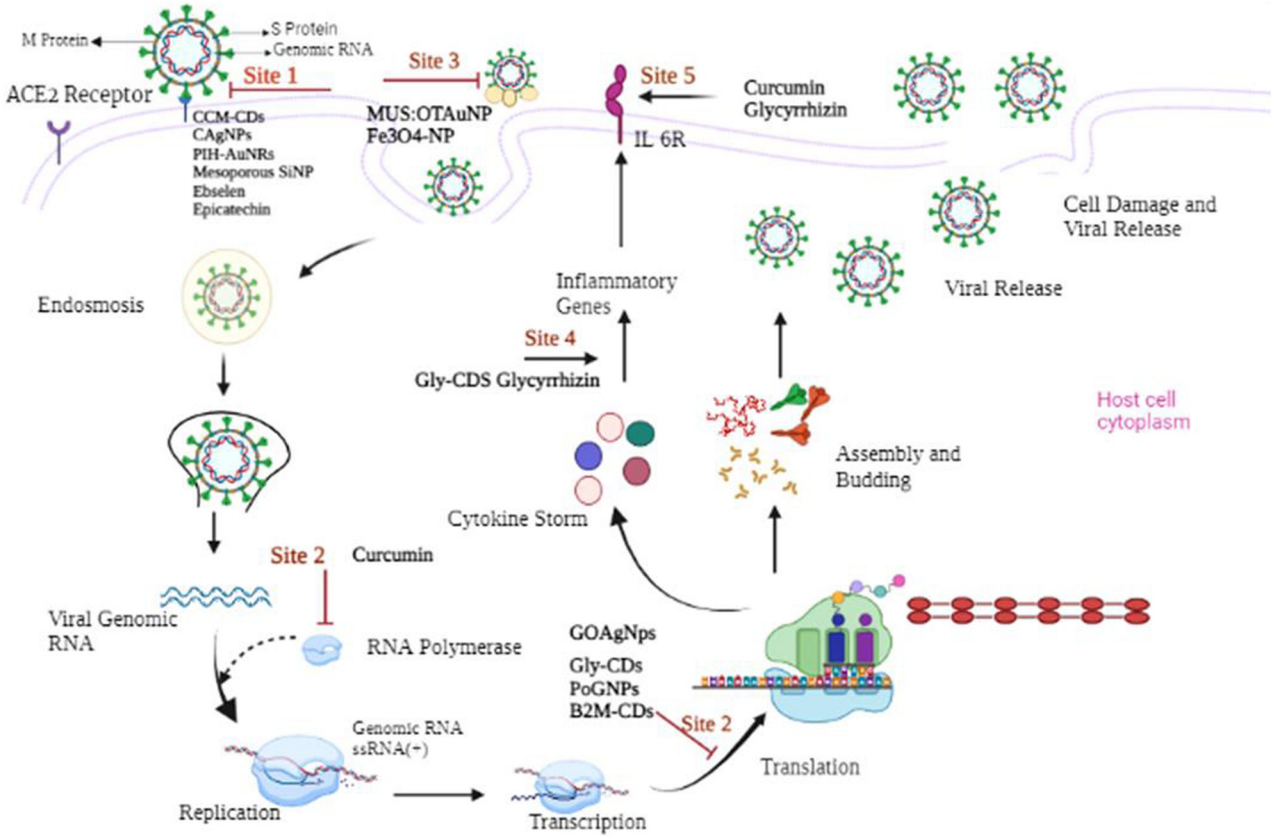


**Figure 2:** Site of activation of nanoformulated drugs at different stages of viral life cycle.

average diameter of 200 nm, it was possible to cause lipid peroxidation of the viral envelope, therefore eliminating the viral surface protein. Interestingly when put on face-masks, these iron oxide nanozymes demonstrated broad spectrum antiviral efficacy [182]. The site of activation of various nanoformulated drugs employed for combating COVID-19 has been illustrated in Figure 2.

Recently, lipid NP (LNP)-based mRNA vaccines are being considered for clinical management for COVID-19. mRNA is a promising therapeutic tool for COVID-19, requiring safe, stable, and targeted delivery systems together with endosomal escape for *in vivo* use. In this way, LNPs, especially in combination with mRNA vaccines, have made clinical strides, notably in combating COVID-19, marking a milestone for mRNA therapeutics. When comparing with cationic lipids and ionizable lipid conjugated vaccines, LNP-mRNAs excel in the safe delivery of mRNA molecules without degradation and effective facilitation of cellular uptake by cell membrane and functional immune response [183]. Two successful vaccines viz: Pfizer-BioNTech (Comirnaty) vaccine (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccine are examples of LNP-mRNA vaccines [184]. In a recent study focused on the development of LNP-mRNA vaccine through *in vivo* studies in mice, researchers were successful in developing an adjuvant lipidoid for LNP-mRNA-based vaccines that could enhance the adjuvanticity of mRNA molecules. This innovation proved effective in improving the safe delivery of mRNA and simultaneous activation of toll-like receptor 7/8-agonistic properties, thereby enhancing the innate immune response [185].

## 5 Limitations of applying nanomedicine in battling SARS-COV-2

Despite the fact that the use of nanomedicine can demonstrate a wide variety of applicability and has received attention from research organizations around the globe, there is nevertheless an obstacle between superior scientific breakthroughs and the sustainable implementation of nanotechnology-based therapeutics. Issues have been raised about their applicability in several physicochemical contexts. Moreover, the surface of nanomaterials can be modified with moieties that might alter their behavior and

characteristics, further complicating the issue of their safety. Until recently, several start-ups were responsible for driving the commercialization of nanotechnology-based medicines. Even now, major drug makers are not showing much enthusiasm for funding the cutting-edge nanotechnology-based therapies. Finding funding to assist the research and development of these novel medications is challenging for small enterprises. Additionally, businesses making nanomedicine-based items are likely to incur significantly higher per-unit expenses [186]. Together with cost, reliability in terms of toxicity and surface functionalization [187] can arise as significant limitations in the use of nanomedicine for the management of COVID-19. Nanotechnology has the potential to revolutionize illness treatment, but like all drugs, nanomaterials must be tested and regulated for safe human usage. This is because, nanomedicine-based reformulation of current medications or usage of inorganic materials that are safe in micron size may have unexpected unfavourable and toxicological consequences due to particles' unique characteristics at the nanoscale. Epidemiological studies that looked at the connection between adverse health outcomes and ambient particulate air pollution were largely responsible for raising public alarm about the usage of NPs in consumer items [187]. Significantly, fine particulate analysis conducted by Samet *et al.* reported that an increase of 10 $g/m^3$ in the concentration of $PM_{10}$ (particulate matter with a diameter of less than 10 μm) was linked to a 0.68 percentage point rise seen in deaths caused by cardiac and respiratory illness in 20 cities across the United States [188].

Ominously, nanowires and nanotubes have promising applications in medication delivery and therapies. However, their structural similarities to asbestos raise safety concerns that they might cause fibrosis and mesothelioma when they are not degraded and cleared from the body after extended contact. In an *in vivo* investigation in which carbon nanotubes were directly applied to the pleural and peritoneal mesothelium, results indicated the formation of fibrosis and granulomas in mice [189]. In a similar study conducted by Sakamoto *et al.*, development of peritoneal mesothelioma in rats following the carbon nanotube intrascrotal injection was observed [190]. Several researches have demonstrated that extended and frequent inhalation of carbon nanotubes results in same toxicological outcomes as mentioned before. Like, 3 months of administration of polydispersed multiwalled CNTs (0.1–10 m) did cause pleural inflammation and granuloma development in rats [191]. Nevertheless, other research have shown that this is the result of clumped and poorly scattered CNT bundles rather than to any intrinsic poisonous characteristic of the bundles assumed to be precisely specified previously [192].

# 6 Outlook beyond COVID-19: diagnostics and pandemic response

The COVID-19 pandemic has yielded valuable insights into pandemic readiness, public health, and healthcare systems, offering guidance for addressing future acute pandemics. Key considerations include the advancement of diagnostic technologies for rapid and accurate testing, the proliferation of accessible POC testing devices, and the integration of digital health tools for real-time monitoring and contact tracing. In vaccine development, the success of mRNA vaccines has set the stage for expedited vaccine creation against various infectious diseases and the exploration of universal vaccine concepts. Collaboration on a global scale and equitable vaccine distribution are crucial for swift access. Antiviral therapies will advance through drug discovery and prophylactic treatments. Being prepared for a pandemic entails improved global surveillance, stockpiling of medical essentials, and strengthened public health infrastructure. Behavioral changes may include enduring hygiene practices, sustained remote work and education options, and adaptable travel and social norms. International cooperation and data sharing will be essential, reflecting a proactive and collaborative approach to future pandemics, with investment in research, healthcare infrastructure, and global unity at its core.

# 7 Conclusions

Each year, infectious diseases cause a staggering number of fatalities. Diversification has resulted in the emergence of numerous new diseases, including bacterial and the majority of them being viral. However, respiratory ailments caused by viruses are one of the key contributors to the rising mortality rate globally. It is essential to remind readers that novel materials are constantly being added on clinical characteristics, analyses, treatment options, and outcomes for COVID-19. Nonetheless, increased steady consideration remains the cornerstone of therapy, and the practical viability of the outcomes is still being evaluated or tested in clinical studies. Nanotechnology has shown to be of great relevance and shown great potential in the realms of antiviral activity and treatment. In modern materials science, nanotechnology is a prominent domain of study. NPs display entirely unique or exceptional properties due to their physical characteristics and morphology. Crystal NPs have been shown to have amazing uses in

areas such as high-sensitivity bio-molecular detection, disease and biochemical diagnostics, and antimicrobial and pharmaceutical chemicals. Thus, nanotechnology has shown both prophylactic and curative efficacy against several different viruses. NP vaccination has the potential to improve healthcare worldwide, and nanotechnology may lead to new approaches in the treatment of clinical patients. NP-based vaccinations can elicit superior protective immune responses than traditional antigen-based immunizations. In addition, studies have shown that nanosized particle based diagnostics can help in the quicker identification of viral infestation in its initial phase, as they offer higher sensitivity and specificity than the currently existing approaches.

**Funding information:** The authors state no funding involved.

**Author contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Conflict of interest:** The authors state no conflict of interest.

## References

[1] Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerg Infect Dis. 2006;12:15–22.
[2] Morens DM, Taubenberger JK, Fauci AS. A centenary tale of two pandemics: The 1918 influenza pandemic and COVID-19, Part I. Am J Public Health. 2021;111:1086–94.
[3] Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020;2:1069–76.
[4] Ruan Y, Wen H, Hou M, Zhai W, Xu S, Lu X. On the epicenter of COVID-19 and the origin of the pandemic strain. Natl Sci Rev. 2023;10:nwac286.
[5] Spiteri G, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. Eurosurveillance. 2020;25:2000178.
[6] Mizumoto K, Kagaya K, Chowell G. Effect of a wet market on coronavirus disease (COVID-19) transmission dynamics in China, 2019–2020. Int J Infect Dis. 2020;97:96–101.
[7] Zibaseresht R. How to respond to the ongoing pandemic outbreak of the coronavirus disease (COVID-19). Eur J Biomed Pharm Sci. 2020;7:1–6.
[8] Lim YX, Ng YL, Tam JP, Liu DX. Human coronaviruses: a review of virus–host interactions. Diseases. 2016;4:26.
[9] Mittal A, Manjunath K, Ranjan RK, Kaushik S, Kumar S, Verma V. COVID-19 pandemic: Insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. PLoS Pathog. 2020;16:e1008762.
[10] Malik YA. Properties of Coronavirus and SARS-CoV-2. Malays J Pathol. 2020;42:3–11.
[11] Hu T, Liu Y, Zhao M, Zhuang Q, Xu L, He Q. A comparison of COVID-19, SARS and MERS. PeerJ. 2020;8:e9725.
[12] Dhama K, Patel SK, Sharun K, Pathak M, Tiwari R, Yatoo MI, et al. SARS-CoV-2 jumping the species barrier: Zoonotic lessons from SARS, MERS and recent advances to combat this pandemic virus. Travel Med Infect Dis. 2020;37:101830.
[13] Olwenyi OA, Dyavar SR, Acharya A, Podany AT, Fletcher CV, Ng CL, et al. Immuno-epidemiology and pathophysiology of coronavirus disease 2019 (COVID-19). J Mol Med. 2020;98:1369–83.
[14] Cheng J, Huang C, Zhang G, Liu D, Li P, Lu C, et al. Epidemiological characteristics of novel coronavirus pneumonia in Henan. Zhonghua jie he he hu xi za zhi. 2020;43:327–31.
[15] da Silva SJR, do Nascimento JCF, Germano Mendes RP, Guarines KM, Targino Alves da Silva C, da Silva PG, et al. Two years into the COVID-19 pandemic: lessons learned. ACS Infect Dis. 2022;8:1758–814.
[16] Fallahi HR, Keyhan SO, Zandian D, Kim S-G, Cheshmi B. Being a front-line dentist during the Covid-19 pandemic: a literature review. Maxillofac Plast Reconstr Surg. 2020;42:1–9.
[17] Greenberg SB. Update on Human Rhinovirus and Coronavirus Infections. Semin Respir Crit Care Med. 2016;37:555–71.
[18] Meini S, Pagotto A, Longo B, Vendramin I, Pecori D, Tascini C. Role of Lopinavir/Ritonavir in the treatment of Covid-19: a review of current evidence, guideline recommendations, and perspectives. J Clin Med. 2020;9:2050.
[19] Laurencin CT, McClinton A. The COVID-19 pandemic: a call to action to identify and address racial and ethnic disparities. J Racial Ethn Health Disparities. 2020;7:398–402.
[20] Romero García C, Iftimi A, Briz-Redón Á, Zanin M, Otero M, Ballester M, et al. Trends in Incidence and Transmission Patterns of COVID-19 in Valencia, Spain. JAMA Netw Open. 2021;4:e2113818.
[21] Nazmunnahar, Ahamed B, Haque MA, Tanbir M, Roknuzzaman ASM, Sarker R, et al. COVID-19 vaccination success in Bangladesh: Key strategies were prompt response, early drives for vaccines, and effective awareness campaigns. Health Sci Rep. 2023;6:e1281.
[22] The World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19whoint/. 2023.
[23] Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Family Med. 2009;7:357–63.
[24] Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14:303–10.
[25] Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA. 2020;323:707–8.
[26] Sahu T. People with chronic bronchitis are at more risk of getting COVID-19. ECS Trans. 2022;107:16359.
[27] Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. Curr Probl Cardiol. 2020;45:100618.
[28] Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020;80:e14–8.
[29] Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55:1–14.
[30] Bhandari S, Singh A, Sharma R, Rankawat G, Banerjee S, Gupta V, et al. Characteristics, treatment outcomes and role of hydroxychloroquine among 522 COVID-19 hospitalized patients in Jaipur

City: An Epidemio-Clinical Study. J Assoc Physicians India. 2020;68:13–9.
[31] Young C, Wood HM, Seshadri RA, Van Nang P, Vaccaro C, Melendez LC, et al. The colorectal cancer-associated faecal microbiome of developing countries resembles that of developed countries. Genome Med. 2021;13:27.
[32] Adab P, Haroon S, O'Hara ME, Jordan RE. Comorbidities and covid-19. BMJ. 2022;377:o1431.
[33] Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. Life Sci. 2020;254:117788.
[34] Group BDW. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
[35] Mayeux R. Biomarkers: potential uses and limitations. NeuroRx J Am Soc Exp NeuroTher. 2004;1:182–8.
[36] Samprathi M, Jayashree M. Biomarkers in COVID-19: An up-to-date review. Front Pediatr. 2020;8:607647.
[37] Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57:389–99.
[38] Vargas-Vargas M, Cortés-Rojo C. Ferritin levels and COVID-19. Rev Panamericana de Salud Publica = Pan Am J Public Health. 2020;44:e72.
[39] Meizlish ML, Pine AB, Bishai JD, Goshua G, Nadelmann ER, Simonov M, et al. A neutrophil activation signature predicts critical illness and mortality in COVID-19. Blood Adv. 2021;5:1164–77.
[40] Ganji A, Farahani I, Khansarinejad B, Ghazavi A, Mosayebi G. Increased expression of CD8 marker on T-cells in COVID-19 patients. Blood Cells Mol Dis. 2020;83:102437.
[41] Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunol Lett. 2020;225:31.
[42] McKenna E, Wubben R, Isaza-Correa JM, Melo AM, Mhaonaigh AU, Conlon N, et al. Neutrophils in COVID-19: Not Innocent Bystanders. Front Immunol. 2022;13:864387.
[43] Dosanjh A. Eosinophil-derived neurotoxin and respiratory tract infection and inflammation: implications for COVID-19 management. J Interferon Cytokine Res. 2020;40:443–5.
[44] Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, et al. D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. BioMed Res Int. 2020;2020:6159720.
[45] Sui J, Noubouossie DF, Gandotra S, Cao L. Elevated plasma fibrinogen is associated with excessive inflammation and disease severity in COVID-19 patients. Front Cell Infect Microbiol. 2021;11:734005.
[46] Kangro K, Wolberg AS, Flick MJ. Fibrinogen, Fibrin, and Fibrin Degradation Products in COVID-19. Curr Drug Targets. 2022;23:1593–602.
[47] Majumdar S, Murphy PM. Chemokine regulation during epidemic coronavirus infection. Front Pharmacol. 2020;11:600369.
[48] Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:25–32.
[49] Baykan EK, Baykan AR, Utlu M, Deve E, Yildiz F, Birdal C, et al. Growth hormone level in COVID-19 patients. North Clin Istanb. 2022;9:470–5.
[50] George S, Pal AC, Gagnon J, Timalsina S, Singh P, Vydyam P, et al. Evidence for SARS-CoV-2 spike protein in the urine of COVID-19 patients. Kidney360. 2021;2:924–36.
[51] Zhang Y, Ong CM, Yun C, Mo W, Whitman JD, Lynch KL, et al. Diagnostic value of nucleocapsid protein in blood for SARS-CoV-2 infection. Clin Chem. 2022;68:240–8.
[52] Thomas L. Antibodies and inflammatory markers may help identify COVID-19 cases and predict severity. News-Medical. https://www.news-medical.net/news/20210126/Antibodies-and-inflammatory-markers-may-help-identify-COVID-19-cases-and-predict-severity.aspx. 2023.
[53] Kostinov M, Svitich O, Chuchalin A, Abramova N, Osiptsov V, Khromova E, et al. Changes in nasal, pharyngeal and salivary secretory IgA levels in patients with COVID-19 and the possibility of correction of their secretion using combined intranasal and oral administration of a pharmaceutical containing antigens of opportunistic microorganisms. Drugs Context. 2023;12:202210–4.
[54] Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24:422.
[55] Hou H, Zhang B, Huang H, Luo Y, Wu S, Tang G, et al. Using IL-2R/lymphocytes for predicting the clinical progression of patients with COVID-19. Clin Exp Immunol. 2020;201:76–84.
[56] Yu J-S, Pan N-N, Chen R-D, Zeng L-C, Yang H-K, Li H. Cardiac biomarker levels and their prognostic values in COVID-19 patients with or without concomitant cardiac disease. Front Cardiovasc Med. 2021;7:599096.
[57] Moon AM, Barritt AS. Elevated liver enzymes in patients with COVID-19: look, but not too hard. Dig Dis Sci. 2021;66:1767–9.
[58] Liu Z, Li J, Long W, Zeng W, Gao R, Zeng G, et al. Bilirubin levels as potential indicators of disease severity in coronavirus disease patients: a retrospective cohort study. Front Med. 2020;7:598870.
[59] Xu Y, Yang H, Wang J, Li X, Xue C, Niu C, et al. Serum albumin levels are a predictor of COVID-19 patient prognosis: Evidence from a single cohort in Chongqing, China. Int J Gen Med. 2021;14:2785–97.
[60] Fan H, Cai J, Tian A, Li Y, Yuan H, Jiang Z, et al. Comparison of liver biomarkers in 288 COVID-19 Patients: A mono-centric study in the early phase of pandemic. Front Med. 2020;7:584888.
[61] Zinellu A, Sotgia S, Fois AG, Mangoni AA. Serum CK-MB, COVID-19 severity and mortality: An updated systematic review and meta-analysis with meta-regression. Adv Med Sci. 2021;66:304–14.
[62] Pourfridoni M, Abbasnia SM, Shafaei F, Razaviyan J, Heidari-Soureshjani R. Fluid and Electrolyte Disturbances in COVID-19 and Their Complications. BioMed Res Int. 2021;2021:6667047.
[63] Chakraborty R, Parvez S. COVID-19: An overview of the current pharmacological interventions, vaccines, and clinical trials. Biochem Pharmacol. 2020;180:114184.
[64] Bergman S, Cennimo DJ, Miller MM, Olsen KM. COVID-19 treatment: investigational drugs and other therapies. Medscape. 2021;1–49.
[65] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14:58–60.
[66] ClinicalTrials.gov. https://clinicaltrials.gov/ct2/covid_view; 2023.
[67] Rodrigues L, Bento Cunha R, Vassilevskaia T, Viveiros M, Cunha C. Drug repurposing for COVID-19: A review and a novel strategy to identify new targets and potential drug candidates. Molecules. 2022;27:2723.
[68] De Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci. 2020;117:6771–6.
[69] Lin HXJ, Cho S, Meyyur Aravamudan V, Sanda HY, Palraj R, Molton JS, et al. Remdesivir in Coronavirus Disease 2019 (COVID-19) treatment: a review of evidence. Infection. 2021;49:401–10.

[70] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269–71.
[71] Lamb YN. Remdesivir: first approval. Drugs. 2020;80:1355–63.
[72] Pimentel J, Laurie C, Cockcroft A, Andersson N. Clinical studies assessing the efficacy, effectiveness and safety of remdesivir in management of COVID-19: A scoping review. Br J Clin Pharmacol. 2021;87:2663–84.
[73] Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15:327–47.
[74] El-Bendary M, Abd-Elsalam S, Elbaz T, El-Akel W, Cordie A, Elhadidy T, et al. Efficacy of combined Sofosbuvir and Daclatasvir in the treatment of COVID-19 patients with pneumonia: a multicenter Egyptian study. Expert Rev Anti-Infect Ther. 2022;20:291–5.
[75] Elgohary MA, Hasan EM, Ibrahim AA, Abdelsalam MFA, Abdel-Rahman RZ, Zaki AI, et al. Efficacy of Sofosbuvir plus Ledipasvir in Egyptian patients with COVID-19 compared to standard treatment: a randomized controlled trial. J Med life. 2022;15:350–8.
[76] Tan EL, Ooi EE, Lin C-Y, Tan HC, Ling AE, Lim B, et al. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. Emerg Infect Dis. 2004;10:581.
[77] De Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, Van Nieuwkoop S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother. 2014;58:4875–84.
[78] Chakraborty R, Parvez S. COVID-19: An overview of the current pharmacological interventions, vaccines, and clinical trials. Biochem Pharmacol. 2020;180:114184.
[79] Sonawane K, Barale SS, Dhanavade MJ, Waghmare SR, Nadaf NH, Kamble SA, et al. Homology modeling and docking studies of TMPRSS2 with experimentally known inhibitors camostat mesylate, nafamostat and bromhexine hydrochloride to control SARS-Coronavirus-2. Preprint: ChemRxiv. Cambridge: Cambridge Open Engage; 2020.
[80] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71:732–9.
[81] Gautret P, Lagier J-C, Parola P, Meddeb L, Mailhe M, Doudier B, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56:105949.
[82] Temple C, Hoang R, Hendrickson RG. Toxic effects from ivermectin use associated with prevention and treatment of Covid-19. N Engl J Med. 2021;385:2197–8.
[83] Alvarez-Moreno C, Cassell JA, Donkor CM, Head MG, Middleton J, Pomat W, et al. Long-term consequences of the misuse of ivermectin data. Lancet Infect Dis. 2021;21:1624–6.
[84] Sun H, Zhao X, Zhou Y, Wang J, Ma R, Ren X, et al. Characterization of oral microbiome and exploration of potential biomarkers in patients with pancreatic cancer. BioMed Res Int. 2020;2020:1–11.
[85] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395:1054–62.
[86] Price CC, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G, et al. Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019: Survival and clinical outcomes. Chest. 2020;158:1397–408.
[87] Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43–9.
[88] Yip RML, Yim CW. Role of interleukin 6 inhibitors in the management of rheumatoid arthritis. J Clin Rheumatol Pract Rep Rheumatic Musculoskelet Dis. 2021;27:e516–24.
[89] Atal S, Fatima Z. IL-6 inhibitors in the treatment of serious COVID-19: a promising therapy. Pharm Med. 2020;34:223–31.
[90] Vlaar APJ, de Bruin S, Busch M, Timmermans S, van Zeggeren IE, Koning R, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. Lancet Rheumatol. 2020;2:e764–73.
[91] Pan H, Peto R, Karim QA, Alejandria MM, Henao-Restrepo AM, Hernández-García C, et al. WHO solidarity trial consortium, remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. Lancet (London, Engl). 2022;399:1941–53.
[92] Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer. 2019;18:26.
[93] Vangapandu HV, Jain N, Gandhi V. Duvelisib: a phosphoinositide-3 kinase δ/γ inhibitor for chronic lymphocytic leukemia. Expert Opin Investig Drugs. 2017;26:625–32.
[94] Goldsmith SR, Covut F, Fiala M, Xiang Z, Iqbal Z, Moore N, et al. Duvelisib for critically Ill patients with coronavirus disease 2019: An investigator-initiated, randomized, placebo-controlled, double-blind pilot trial. Open Forum Infect Dis. 2023;10:ofad518.
[95] Anastasia A, Rossi G. Novel drugs in follicular Lymphoma. Mediterr J Hematol Infect Dis. 2016;8:e2016061.
[96] Dowarah J, Marak BN, Yadav UCS, Singh VP. Potential drug development and therapeutic approaches for clinical intervention in COVID-19. Bioorg Chem. 2021;114:105016.
[97] Smith CD, Maines LW, Keller SN, Katz Ben-Yair V, Fathi R, Plasse TF, et al. Recent Progress in the Development of Opaganib for the Treatment of Covid-19. Drug Des Dev Ther. 2022;16:2199–211.
[98] Costa B, Vale N. A review of repurposed cancer drugs in clinical trials for potential treatment of COVID-19. Pharmaceutics. 2021;13:815.
[99] Kifle ZD. Bruton tyrosine kinase inhibitors as potential therapeutic agents for COVID-19: A review. Metab Open. 2021;11:100116.
[100] Song Y, Zhou K, Zou D, Zhou J, Hu J, Yang H, et al. Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Blood. 2022;139:3148–58.
[101] BeiGene. Covid-19 Infection and Pulmonary Distress Treatment With Zanubrutinib in Hospitalized Participants. https://clinicaltrialsgov/study/NCT04382586. 2022.
[102] Acerta Pharma BV Acalabrutinib Study With Best Supportive Care in Participants Hospitalized With COVID-19. https://clinicaltrialsgov/study/NCT04497948. 2021.
[103] Winthrop KL, Skolnick AW, Rafiq AM, Beegle SH, Suszanski J, Koehne G, et al. Opaganib in coronavirus disease 2019 Pneumonia: Results of a randomized, placebo-controlled phase 2a trial. Open Forum Infect Dis. 2022;9:ofac232.
[104] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006;3:e343.

[105] ClinicalTrials.gov. https://clinicaltrials.gov/search? cond = Covid19&intr = Methylprednisolone. 2023.
[106] Hansen TM, Kryger P, Elling H, Haar D, Kreutzfeldt M, Ingeman-Nielsen MW, et al. Double blind placebo controlled trial of pulse treatment with methylprednisolone combined with disease modifying drugs in rheumatoid arthritis. BMJ (Clin Res Ed). 1990;301:268–70.
[107] Meduri GU, Shih MC, Bridges L, Martin TJ, El-Solh A, Seam N, et al. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med. 2022;48:1009–23.
[108] Yadav T, Kumar S, Mishra G, Saxena SK. Tracking the COVID-19 vaccines: The global landscape. Hum Vaccines Immunother. 2023;19:2191577.
[109] COVID-19 Vaccine Tracker. https://covid19trackvaccinesorg/. 2022.
[110] Ndwandwe D, Wiysonge CS. COVID-19 vaccines. Curr Opin Immunol. 2021;71:111–6.
[111] The United States Food and Drug Administration. COVID-19 Vaccines for 2023-2024. https://wwwfdagov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines-2023-2024. 2023.
[112] Wodi AP, Ault K, Hunter P, McNally V, Szilagyi PG, Bernstein H. Advisory committee on immunization practices recommended immunization schedule for children and adolescents aged 18 years or younger - United States, 2021. MMWR Morb Mortal Wkly Rep. 2021;70:189–92.
[113] Hause AM, Marquez P, Zhang B, Myers TR, Gee J, Su JR, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among persons aged ≥ 12 Years - United States, August 31-October 23, 2022. MMWR Morb Mortal Wkly Rep. 2022;71:1401–6.
[114] The United States Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Changes to Simplify Use of Bivalent mRNA COVID-19 Vaccines. https://wwwfdagov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-changes-simplify-use-bivalent-mrna-covid-19-vaccines. 2023.
[115] ClinicalTrials.gov. Views of COVID-19 Studies Listed on ClinicalTrials.gov (Beta). https://classicclinicaltrialsgov/ct2/covid_view. 2023.
[116] Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci. 2020;6:672–83.
[117] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.
[118] Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early Treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med. 2021;385:1941–50.
[119] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 2022;386:509–20.
[120] Niraj N, Mahajan SS, Prakash A, Sarma P, Medhi B. Paxlovid: A promising drug for the challenging treatment of SARS-COV-2 in the pandemic era. Indian J Pharmacol. 2022;54:452–8.
[121] Áñez G, Dunkle LM, Gay CL, Kotloff KL, Adelglass JM, Essink B, et al. Safety, immunogenicity, and efficacy of the NVX-COV-2373 COVID-19 vaccine in adolescents: A randomized clinical trial. JAMA Netw Open. 2023;6:e239135.
[122] Rasmi Y, Saloua KS, Nemati M, Choi JR. Recent progress in nanotechnology for COVID-19 prevention, diagnostics and treatment. Nanomaterials. 2021;11:1788.
[123] Chowdhury NK, Choudhury R, Sonawane GA, Mavinamar S, Lyu X, Pandey RP, et al. Nanoparticles as an effective drug delivery system in COVID-19. Biomed Pharmacother. 2021;143:112162.
[124] Dheyab MA, Khaniabadi PM, Aziz AA, Jameel MS, Mehrdel B, Oglat AA, et al. Focused role of nanoparticles against COVID-19: Diagnosis and treatment. Photodiagnosis Photodyn Ther. 2021;34:102287.
[125] Dheyab MA, Aziz AA, Jameel MS, Noqta OA, Khaniabadi PM, Mehrdel B. Excellent relaxivity and X-ray attenuation combo properties of Fe3O4@Au CSNPs produced via Rapid sonochemical synthesis for MRI and CT imaging. Mater Today Commun. 2020;25:101368.
[126] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020;25:2000045.
[127] Emery SL, Erdman DD, Bowen MD, Newton BR, Winchell JM, Meyer RF, et al. Real-time reverse transcription-polymerase chain reaction assay for SARS-associated coronavirus. Emerg Infect Dis. 2004;10;311–6.
[128] Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). J Microbiol Biotechnol. 2020;30:313–24.
[129] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. The. N Engl J Med. 2020;382:1969–73.
[130] Mokhtarzadeh A, Eivazzadeh-Keihan R, Pashazadeh P, Hejazi M, Gharaatifar N, Hasanzadeh M, et al. Nanomaterial-based biosensors for detection of pathogenic virus. Trends Anal Chem TRAC. 2017;97:445–57.
[131] Unser S, Bruzas I, He J, Sagle L. Localized Surface Plasmon Resonance Biosensing: Current Challenges and Approaches. Sensors (Basel, Switz). 2015;15:15684–716.
[132] Ai K, Huang J, Xiao Z, Yang Y, Bai Y, Peng J. Localized surface plasmon resonance properties and biomedical applications of copper selenide nanomaterials. Mater Today Chem. 2021;20:100402.
[133] Sui M, Kunwar S, Pandey P, Lee J. Strongly confined localized surface plasmon resonance (LSPR) bands of Pt, AgPt, AgAuPt nanoparticles. Sci Rep. 2019;9:16582.
[134] Loiseau A, Asila V, Boitel-Aullen G, Lam M, Salmain M, Boujday S. Silver-based plasmonic nanoparticles for and their use in biosensing. Biosensors. 2019;9:78.
[135] Li W, Cao Z, Liu R, Liu L, Li H, Li X, et al. AuNPs as an important inorganic nanoparticle applied in drug carrier systems. Artif Cells Nanomed Biotechnol. 2019;47:4222–33.
[136] Wang J, Drelich AJ, Hopkins CM, Mecozzi S, Li L, Kwon G, et al. Gold nanoparticles in virus detection: Recent advances and potential considerations for SARS-COV-2 testing development. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2022;14:e1754.
[137] Kim H, Park M, Hwang J, Kim JH, Chung D-R, Lee K-S, et al. Development of label-free colorimetric assay for MERS-CoV using gold nanoparticles. ACS Sens. 2019;4:1306–12.
[138] Moitra P, Alafeef M, Dighe K, Frieman MB, Pan D. Selective naked-eye detection of SARS-CoV-2 mediated by N gene targeted

antisense oligonucleotide capped plasmonic nanoparticles. ACS Nano. 2020;14:7617–27.
[139] Gong P, He X, Wang K, Tan W, Xie W, Wu P, et al. Combination of functionalized nanoparticles and polymerase chain reaction-based method for SARS-CoV gene detection. J Nanosci Nanotechnol. 2008;8:293–300.
[140] Mahmoudi M. Emerging Biomolecular Testing to Assess the Risk of Mortality from COVID-19 Infection. Mol Pharmaceutics. 2021;18:476–82.
[141] Li Z, Askim JR, Suslick KS. The optoelectronic nose: Colorimetric and fluorometric sensor arrays. Chem Rev. 2019;119:231–92.
[142] Saha K, Agasti SS, Kim C, Li X, Rotello VM. Gold nanoparticles in chemical and biological sensing. Chem Rev. 2012;112:2739–79.
[143] Ashkarran AA, Dararatana N, Crespy D, Caracciolo G, Mahmoudi M. Mapping the heterogeneity of protein corona by ex vivo magnetic levitation. Nanoscale. 2020;12:2374–83.
[144] Maddali H, Miles CE, Kohn J, O'Carroll DM. Optical biosensors for virus detection: prospects for SARS-COV-2/COVID-19. ChemBioChem. 2021;22:1176–89.
[145] Shi JC. Application of nanomaterials-based optical sensors for virus detections. J Phys: Conf Ser. 2021;1906:012028.
[146] Liang Y, Mao G, Dai J, Ma Y. Biofunctionalized semiconductor quantum dots for virus detection. J Semicond. 2023;44:023101.
[147] Roh C, Jo SK. Quantitative and sensitive detection of SARS coronavirus nucleocapsid protein using quantum dots-conjugated RNA aptamer on chip. J Chem Technol Biotechnol. 2011;86:1475–9.
[148] Chen R, Kan L, Duan F, He L, Wang M, Cui J, et al. Surface plasmon resonance aptasensor based on niobium carbide MXene quantum dots for nucleocapsid of SARS-CoV-2 detection. Microchim Acta. 2021;188:316.
[149] Tabrizi MA, Nazari L, Acedo P. A photo-electrochemical aptasensor for the determination of severe acute respiratory syndrome coronavirus 2 receptor-binding domain by using graphitic carbon nitride-cadmium sulfide quantum dots nanocomposite. Sens Actuators B: Chem. 2021;345:130377.
[150] Ahmed SR, Nagy É, Neethirajan S. Self-assembled star-shaped chiroplasmonic gold nanoparticles for an ultrasensitive chiro-immunosensor for viruses. RSC Adv. 2017;7:40849–57.
[151] Shetty MG, Melanthota SK, Daimari NK, Biswas R, Mazumder N, Babitha KS. Synthesis, conjugation, and applications of chiral nanoparticles as plasmonic probes. Recent Advances in Plasmonic Probes: Theory and Practice. Vol. 33. Cham: Springer International Publishing; 2022. p. 365–87.
[152] Ahmed SR, Kang SW, Oh S, Lee J, Neethirajan S. Chiral zirconium quantum dots: A new class of nanocrystals for optical detection of coronavirus. Heliyon. 2018;4:e00766.
[153] Gorshkov K, Susumu K, Chen J, Xu M, Pradhan M, Zhu W, et al. Quantum dot-conjugated SARS-CoV-2 Spike Pseudo-virions enable tracking of angiotensin converting enzyme 2 binding and endocytosis. ACS Nano. 2020;14:12234–47.
[154] Bardajee GR, Zamani M, Sharifi M. Efficient and versatile application of fluorescence DNA-conjugated CdTe quantum dots nanoprobe for detection of a specific target DNA of SARS Cov-2 virus. Langmuir. 2021;37:10223–32.
[155] Zhang Y, Malekjahani A, Udugama BN, Kadhiresan P, Chen H, Osborne M, et al. Surveilling and tracking COVID-19 patients using a portable quantum dot smartphone device. Nano Lett. 2021;21:5209–16.
[156] Chen X, Leng Y, Hao L, Duan H, Yuan J, Zhang W, et al. Self-assembled colloidal gold superparticles to enhance the sensitivity of lateral flow immunoassays with sandwich format. Theranostics. 2020;10:3737–48.
[157] Zhou Y, Chen Y, Liu W, Fang H, Li X, Hou L, et al. Development of a rapid and sensitive quantum dot nanobead-based double-antigen sandwich lateral flow immunoassay and its clinical performance for the detection of SARS-CoV-2 total antibodies. Sens Actuators B: Chem. 2021;343:130139.
[158] Chitsike L, Duerksen-Hughes P. Keep out! SARS-CoV-2 entry inhibitors: their role and utility as COVID-19 therapeutics. Virol J. 2021;18:1–17.
[159] Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:1–10.
[160] Medhi R, Srinoi P, Ngo N, Tran H-V, Lee TR. Nanoparticle-Based Strategies to Combat COVID-19. ACS Appl Nano Mater. 2020;3:8557–80.
[161] Lima TL, Feitosa RD, Santos-Silva D, Santos-Silva D, Maria A, Siqueira EM, et al. Improving encapsulation of hydrophilic chloroquine diphosphate into biodegradable nanoparticles: a promising approach against herpes virus simplex-1 infection. Pharmaceutics. 2018;10:255.
[162] Ting D, Dong N, Fang L, Lu J, Bi J, Xiao S, et al. Multisite inhibitors for enteric coronavirus: antiviral cationic carbon dots based on curcumin. ACS Appl Nano Mater. 2018;1:5451–9.
[163] Yang XX, Li CM, Huang CZ. Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection. Nanoscale. 2016;8:3040–8.
[164] Huang X, Li M, Xu Y, Zhang J, Meng X, An X, et al. Novel gold nanorod-based HR1 peptide inhibitor for middle east respiratory syndrome coronavirus. ACS Appl Mater Interfaces. 2019;11:19799–807.
[165] de Souza e Silva, Hanchuk JM, Santos TDM, Kobarg Jr MI, Bajgelman MC, Cardoso MB. Viral inhibition mechanism mediated by surface-modified silica nanoparticles. ACS Appl Mater Interfaces. 2016;8:16564–72.
[166] Osminkina L, Timoshenko VY, Shilovsky I, Kornilaeva G, Shevchenko S, Gongalsky M, et al. Porous silicon nanoparticles as scavengers of hazardous viruses. J Nanopart Res. 2014;16:1–10.
[167] He L, Zhao J, Wang L, Liu Q, Fan Y, Li B, et al. Using nano-selenium to combat coronavirus disease 2019 (COVID-19)? Nano Today. 2021;36:101037.
[168] Hamza A, Zhan CG. How can (-)-epigallocatechin gallate from green tea prevent HIV-1 infection? Mechanistic insights from computational modeling and the implication for rational design of anti-HIV-1 entry inhibitors. J Phys Chem B. 2006;110:2910–7.
[169] Tong T, Hu H, Zhou J, Deng S, Zhang X, Tang W, et al. Glycyrrhizic-acid-based carbon dots with high antiviral activity by multisite inhibition mechanisms. Small. 2020;16:1906206.
[170] van der Meel R, Sulheim E, Shi Y, Kiessling F, Mulder WJM, Lammers T. Smart cancer nanomedicine. Nat Nanotechnol. 2019;14:1007–17.
[171] O'Keefe BR, Giomarelli B, Barnard DL, Shenoy SR, Chan PK, McMahon JB, et al. Broad-spectrum in vitro activity and in vivo efficacy of the antiviral protein griffithsin against emerging viruses of the family Coronaviridae. J Virol. 2010;84:2511–21.
[172] Millet JK, Séron K, Labitt RN, Danneels A, Palmer KE, Whittaker GR, et al. Middle East respiratory syndrome coronavirus infection is inhibited by griffithsin. Antivir Res. 2016;133:1–8.
[173] Lv X, Wang P, Bai R, Cong Y, Suo S, Ren X, et al. Inhibitory effect of silver nanomaterials on transmissible virus-induced host cell infections. Biomaterials. 2014;35:4195–203.
[174] Du T, Lu J, Liu L, Dong N, Fang L, Xiao S, et al. Antiviral activity of graphene oxide–silver nanocomposites by preventing viral entry

and activation of the antiviral innate immune response. ACS Appl Bio Mater. 2018;1:1286–93.
[175] Du T, Liang J, Dong N, Liu L, Fang L, Xiao S, et al. Carbon dots as inhibitors of virus by activation of type I interferon response. Carbon. 2016;110:278–85.
[176] Kim J, Yeom M, Lee T, Kim H-O, Na W, Kang A, et al. Porous gold nanoparticles for attenuating infectivity of influenza A virus. J Nanobiotechnol. 2020;18:54.
[177] Papp I, Sieben C, Ludwig K, Roskamp M, Böttcher C, Schlecht S, et al. Inhibition of influenza virus infection by multivalent sialic-acid-functionalized gold nanoparticles. Small. 2010;6:2900–6.
[178] Huang S, Gu J, Ye J, Fang B, Wan S, Wang C, et al. Benzoxazine monomer derived carbon dots as a broad-spectrum agent to block viral infectivity. J Colloid Interface Sci. 2019;542:198–206.
[179] Zoppe JO, Ruottinen V, Ruotsalainen J, Rönkkö S, Johansson LS, Hinkkanen A, et al. Synthesis of cellulose nanocrystals carrying tyrosine sulfate mimetic ligands and inhibition of alphavirus infection. Biomacromolecules. 2014;15:1534–42.
[180] Cagno V, Andreozzi P, D'Alicarnasso M, Jacob Silva P, Mueller M, Galloux M, et al. Broad-spectrum non-toxic antiviral nanoparticles with a virucidal inhibition mechanism. Nat Mater. 2018;17:195–203.
[181] Kong B, Moon S, Kim Y, Heo P, Jung Y, Yu S-H, et al. Virucidal nanoperforator of viral membrane trapping viral RNAs in the endosome. Nat Commun. 2019;10:185.
[182] Qin T, Ma R, Yin Y, Miao X, Chen S, Fan K, et al. Catalytic inactivation of influenza virus by iron oxide nanozyme. Theranostics. 2019;9:6920–35.
[183] Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6:1078–94.
[184] Wilson B, Geetha KM. Lipid nanoparticles in the development of mRNA vaccines for COVID-19. J Drug Deliv Sci Technol. 2022;74:103553.
[185] Han X, Alameh M-G, Butowska K, Knox JJ, Lundgreen K, Ghattas M, et al. Adjuvant lipidoid-substituted lipid nanoparticles augment the immunogenicity of SARS-CoV-2 mRNA vaccines. Nat Nanotechnol. 2023;18:1105–14.
[186] Bosetti R. Cost-effectiveness of nanomedicine: the path to a future successful and dominant market? Nanomed (London, Engl). 2015;10:1851–3.
[187] Thorley AJ, Tetley TD. New perspectives in nanomedicine. Pharmacol Ther. 2013;140:176–85.
[188] Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 US cities, 1987–1994. N Engl J Med. 2000;343:1742–9.
[189] Poland C, Duffin R, Kinloch I, Maynard A, Wallace W, Seaton A, et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos like pathogenicity in a pilot study. Nat Nanotechnol. 2008;3:423–8.
[190] Sakamoto Y, Nakae D, Fukumori N, Tayama K, Maekawa A, Imai K, et al. Induction of mesothelioma by a single intrascrotal administration of multi-wall carbon nanotube in intact male Fischer 344 rats. J Toxicol Sci. 2009;34:65–76.
[191] Ma-Hock L, Treumann S, Strauss V, Brill S, Luizi F, Mertler M, et al. Inhalation toxicity of multiwall carbon nanotubes in rats exposed for 3 months. Toxicol Sci. 2009;112:468–81.
[192] Pauluhn J. Subchronic 13-week inhalation exposure of rats to multiwalled carbon nanotubes: toxic effects are determined by density of agglomerate structures, not fibrillar structures. Toxicol Sci. 2010;113:226–42.