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Review Article

Recent advances in health biotechnology during pandemic

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ABSTRACT

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in 2019, cut the epoch that will make profound fluctuates in the history of the world in social, economic, and scientific fields. Urgent needs in public health have brought with them innovative approaches, including diagnosis, prevention, and treatment. To exceed the coronavirus disease 2019 (COVID-19) pandemic, various scientific authorities in the world have procreated advances in real time polymerase chain reaction (RT-PCR) based diagnostic tests, rapid diagnostic kits, the development of vaccines for immunization, and the purposing pharmaceuticals for treatment. Diagnosis, treatment, and immunization approaches put forward by scientific communities are cross-fed from the accrued knowledge of multidisciplinary sciences in health biotechnology. So much so that the pandemic, urgently prioritized in the world, is not only viral infections but also has been the pulsion in the development of novel approaches in many fields such as diagnosis, treatment, translational medicine, virology, microbiology, immunology, functional nano- and bio-materials, bioinformatics, molecular biology, genetics, tissue engineering, biomedical devices, and artificial intelligence technologies. In this review, the effects of the COVID-19 pandemic on the development of various scientific areas of health biotechnology are discussed.

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INTRODUCTION

SARS-CoV-2 infection, which first appeared in Wuhan, China in December 2019 spread all over the world in a short time and became the most critical public health issue. Protection, immunization, and treatment against SARS-CoV-2, which has identified five variants circulating so far, have changed the social and economic statements all over the world. Of the 630 million cases caused by these circulating variants, which have varying characteristics in terms of contagion, disease severity, risk of re-infection, diagnosis, and vaccine performance, more than 6 million died [1].

SARS-CoV-2 is typically characterized by symptoms such as fever, cough, sore throat, muscle pain, anosmia,

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and headache [2,3]. The entry of the viral pathogen into human cells begins with the interaction of the receptor binding region in the S1 subunit of the Spike (S) protein and the human angiotensin-converting enzyme 2 (ACE2) protein and occurs when the S2 region mediates the membrane fusion [4,5]. Although ACE2-mediated SARS-CoV cell entry has been described much earlier, the exploring of rapid transmission of SARS-CoV-2 and the causes of its aggressive systemic effects were the first approaches of the pandemic [6,7]. When the genome similarities with other viral pathogens were examined in the first studies to elucidate the characteristic features of the infection at the molecular level, it was found that it shows 79% sequence similarity with SARS-CoV [8].

The entry of the SARS-CoV-2 into the cell, the escape from the immune system mechanisms, and the regulation of the human immune system have been explained, by analyzing the structural and non-structural proteins of the virus [9–11]. The pathogenic characterization of the virus has strengthened the basic knowledge for diagnosis, immunization, and treatment processes. The first need to prevent the spread of viral infection was methods to ensure its rapid identification and diagnostics. Many protocols that allow diagnosis by RT-PCR have been defined and the pathogenic virus profile has been evaluated during infection periods [12,13]. However, although it has low sensitivity compared to RT-PCR methods, easy-to-use, inexpensive, and rapid antigen tests have also been developed to prevent the spread of COVID-19 [14].

Parallel to these, vaccine and therapeutic development studies have started to combat the pandemic. Initial approaches have been made to propose vaccines and anti-viral agents, thanks to the identification of SARS-CoV-2 and human ACE2 receptor interactions [15]. Initial reports focused on the development of new therapeutics, or the re-proposing of existing therapeutics that inhibit the binding or fusion of the viral pathogen in other CoVs, by interacting with specific sites in the proteins [16,17]. Various types of vaccines have been developed by scientific committees for immunization against SARS-CoV-2 [18,19]. All these efforts provide synergy in the combat against SARS-CoV-2 and played a major role during the pandemic.

During COVID-19, many other disciplines have also contributed to therapeutic, diagnostic, or immunization approaches in addition to molecular, genetic, and immunity of SARS-CoV-2 (Figure 1). For instance, it has been contributed greatly to the acceleration of the approaches of predicting treatment output or developing therapeutic agents when the data obtained from basic sciences are integrated with artificial intelligence technologies [20,21]. Additionally, as well as the use of materials science in SARS-CoV-2 biosensor applications and diagnostic tests, increasing vaccine efficacy with functional biomaterials for vaccine release, and reducing virus transmission of special nanomaterials have been suggested [22,23]. Even, tissue engineering approaches have been proposed for use in analyzing the pathogenic properties of the viral agent [24]. At the same time, the contribution of material sciences cannot be ignored in the production of easy-to-use/produce, safe and low-cost equipment that can be used in diagnosis and treatment [25]. During COVID-19, many scientists from different disciplines of health biotechnology contributed to overcoming this challenging pandemic.

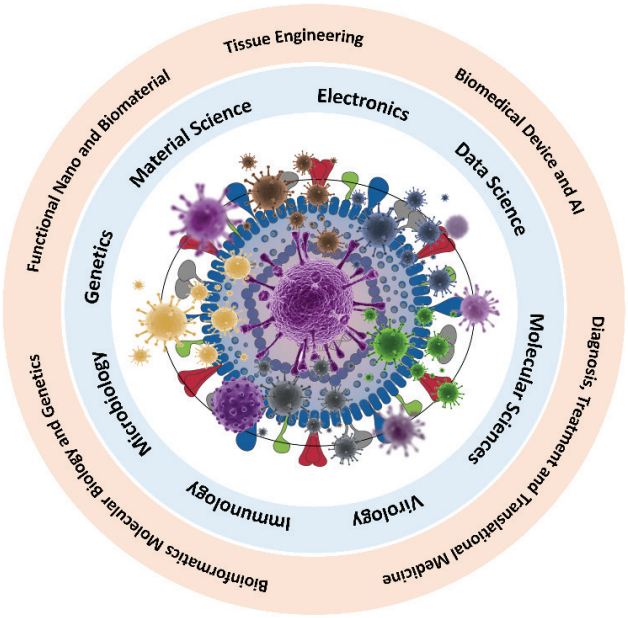

Figure 1. COVID-19 and disciplines in health biotechnology.

CHARACTERISTICS AND PATHOLOGY OF SARS-COV-2

Coronaviruses contain four structural proteins including Membrane (M), Envelope (E), Nucleocapsid (N), and Spike (S). S glycoprotein, which consists of transmembrane trimethric glycoproteins, is the protein that determines virus diversity and host tropism. A series of protease cleavage processes are initiated in the viral S protein that binds to the host protein ACE2 via Receptor Binding Domain (RBD) in the S1 subunit [4,5]. Following cleavage at the S1/S2 cleavage site, the S1 and S2 subunits are bounded via non-covalent bonds, with the S1 subunit stabilizing S2 in its pre-membrane fusion state. With the cleavage of the S2 subunit, membrane fusion is initiated through conformational changes and entry of virus into is completed [26]. In the first studies, RaTG13 (96.2% sequence identity) found in *Rhinolophus* bat was associated with coronavirus origin. However, genomic similarity maps on the RBD in the S1 subunit of the S protein, the key player of the infection, pointed to other possibilities such as PCoV-GD origin [4,27]. In the initial phase of the pandemic, genetic analyses of the ACE2 receptor in different populations showed that

the population had different suspectibility profiles depending on the genetics of the population [28]. In addition, in studies on the molecular mechanisms of the severity of symptoms, especially ACE2 expression profile and systemic effects of infection have been associated [29].

Cytokine release begins with the contribution of macrophages and monocytes and immune responses in the host are eventuated, following the infection. SARS-CoV-2 has been reported to exhibit a cytokine storm-related severity profile mediated by inflammatory mediators such as IL-1β, IFN-γ, IP10, IL-2R and IL-6 [30]. Cytokine storm leads to fibroblast proliferation followed by ECM and fibrin deposition resulting in disruption of lung alveolar structure. These changes in lung tissue lead to severe clinical outcomes including acute respiratory distress syndrome (ARDS), acute lung injury, fibrosis, pulmonary embolism, deep vein thrombosis, and even death [31]. In order to prevent these devastating clinical outcomes, the first efforts have been carried out for rapid and reliable diagnosis of the virus.

DIAGNOSTICS: FIRST STEP OF COMBAT AGAINST SARS-COV-2

Early and rapid detection of the disease is crucial for controlling the virus transmission. The golden standard method in SARS-CoV-2 detection is suggested as viral RNA extraction and RT-PCR technique on nasopharyngeal swab samples [32–34]. The limitations such as being an invasive method, requirement for special training, inducing patient discomfort and cough or sneeze, and increasing the risk of cross-transmission due to the close contact of the health professionals and crowded hospitals makes this sampling technique not so desirable for massive screening [33,34].

The S and N proteins of SARS-CoV-2 are the main targets of host antibody reactions following viral infection [35]. The S glycoprotein is frequently the focus of rapid antigen tests and vaccines because it possesses RBD that enables viruses to adhere to the ACE2 receptor on human cells, which are highly expressed on the epithelial cells of the oral mucosa [36]. Since ACE2 is expressed in human oral tissue, particularly in oral tongue, buccal mucosa, and gingival tissues, the oral cavity may be thought of as a significant point of virus entry. The RBD protein is also the focus of antibody detection assays that are helpful in seroepidemiological investigations, risk assessment of the individual, and figuring out how long the anti-RBD antibody response will last [37].

Human saliva and the salivary glands are potential sources of SARS-CoV-2 transmission, on the other hand, saliva can be a potential tool in detecting the disease [38,39] and microbial species such as Epstein–Barr virus, herpes simplex virus, hepatitis A, B, and C viruses, Rabies virus, cytomegalovirus, human papillomavirus, human immunodeficiency virus, Norovirus, and many more [33,38]. Moreover, dental biofilms of symptomatic COVID-19 patients harbor SARS-CoV-2 RNA and may serve as a potential reservoir with an essential role in SARS-CoV-2 transmission [40]. SARS-CoV-2 RNA can be detected in supragingival and subgingival biofilms, irrespective of the periodontal condition, and systemic viral load [41]. Oral fluids both saliva as well as gingival crevicular fluid (GCF) reduce the need for specialized health workers and can be self-collected outside hospitals. Being economical, easier to ship and transport than serum samples, not clotting like blood, being handled efficiently, having reduced nosocomial transmission risk are the other benefits of oral fluids [33,34]. Compared to saliva, GCF comprises highly concentrated biological components. Saliva is thought to have about 500 times fewer antibodies than blood, while GCF is thought to have at least more than 500 times more than saliva. It has been demonstrated that highly concentrated GCF is noticeably more sensitive to Ig concentrations and may represent circulating Ig concentrations after immunization [36] but still, further research is necessary to determine whether saliva and GCF indicate similar levels of immunoglobulin response to a blood sample.

Silva et al. conducted a systematic review investigating the saliva samples for SARS-CoV-2 diagnosis in 2020. In total, 39 studies were included and the authors reported that saliva samples have similar performance when compared with the nasopharyngeal swabs, suitable for epidemiological purposes, and valuable for detecting asymptomatic and pre-symptomatic infections, and suggested saliva as a promising resource in the SARS-CoV-2 detection [33]. Fakheran et al. conducted another review, and reported that the method of sampling provides proper accuracy and reliability regarding viral load monitoring based on RT-PCR technique [42]. Azzi et al. classified diagnostic methods for detecting SARS-CoV-2 on saliva samples as molecular tests (rRT-PCR), point-of-care tests (reverse transcription loop-mediated isothermal amplification (RT-LAMP), Specific Highsensitivity Enzymatic Reporter UnLOCKing (SHERLOCK), which is a combination of viral RNA amplification, LAMP and Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) technologies), antibody testing (lateral flow assay, LFA) and enzyme-linked immunosorbent assay (ELISA) in a review article [43]. Recent articles investigating the potential of implementing microfluidistics approach in SARS-CoV-2 detection [44].

The current literature supports that human saliva can be a preferable sample collection method for the COVID-19 diagnosis, however, there is insufficient evidence to suggest its use for mass screening [45,46]. Taken together, supra and subgingival dental biofilm, saliva, and GCF are each regarded as reservoirs for SARS-COV-2, similarly, clinical samples taken from nasopharynges and oropharynges, secretions from the lower respiratory tract, bronchoalveolar lavage fluid, rectal swabs, blood, and feces. Just as GCF is a potential reservoir for SARS-COV-2, it also has the potential to reflect serum antibody levels, and collecting GCF or saliva is a more favorable noninvasive sampling method than blood collection.

BIOACTIVE SUBSTANCES FROM NATURAL SOURCES AGAINST SARS-COV-2

During the pandemic, bioactive substances that can be used to develop resistance in the body to viruses (SARS-CoV-2) or to evaluate it for use in the production of antiviral drugs has gained a lot of significance. For this reason, scientific authorities have focused on approaches to reduce the risk of transmission by limiting viral load capacity or to re-purpose other active agents that may show anti-SARS-CoV-2 activity.

ORAL AND NASAL CARE PRODUCTS TO DECREASE VIRUS TRANSMISSION

The oral cavity is an important side of entry for the SARS-CoV-2 virus [47]. Human-to-human transmission routes can be droplets and aerosol particles. The mobility of a single droplet is limited by its size. When talking, eating, coughing, sneezing, or even breathing; products of saliva droplets with microorganisms and viruses are released and distributed. Each cough (approximately equivalent to a 5-min chat) or sneeze can produce about 3,000 or 40,000 saliva droplets, respectively [32,38]. The salivary glands are the primary replication site of SARS-CoV-2 [48]. SARS-CoV-2 is transmitted through the nose and mouth, and it is reported that oral transmission is 3-5 times more common than nasal transmission. For example, it has been reported that the viral load in the saliva of individuals infected with the delta variant is 1,260 times higher than in individuals infected with previous strains [49]. As the salivary glands are the primary site of SARS infection, reducing the viral load in saliva reduces the risk of transmission from infection-carrier and can help reduce the severity of SARS-CoV-2 [49,50].

Antiseptic agents such as cetylpyridinium chloride (CPC), povidone-iodine (PVP-I), and delmopinol hydrochloride to oral care products has been frequently used during the pandemic period to reduce the viral load in the mouth [51]. The efficacy of nasal spray and gargle solutions prepared with different PVP-I concentrations (0.4%, 0.5%, 0.6% and 1%) against SARS-CoV-2 has been demonstrated [52,53]. A hypertonic alkaline nasal irrigation (HANI) solution, which is based on Lake Van, Türkiye, has recently been introduced. It contains potassium, sulfate, bicarbonate, sodium, chloride and has a pH of 9.3 (12 g/L sodium chloride (NaCl), 2 g/L sodium sulfate, 0.8 g/L potassium chloride, 0.1 g/L calcium chloride dihydrate, 1.1 g/L magnesium sulfate heptahydrate, and 4 g/L sodium bicarbonate). The hypertonic component of HANI creates a hyperosmolar extracellular space and the SARS-CoV-2 undergoes conformational changes in this alkaline and hypertonic environment, inhibiting its cell fusion function [7,54,55] . However, in the use of mouthwashes containing antimicrobials to reduce the viral load, the contact time of the mouthwash with the oral mucosa is short [56] Investigation of longer-term receptor binding/blocking proteins to reduce viral load in the saliva still attracts researchers [56,57]. Plant cell bioencapsulation is being developed as a new strategy to deliver drugs against pathogens colonizing the oral cavity by reducing SARS-CoV-2 in saliva to reduce re-infection and transmission [58]. The use of viral trap proteins (CTB-ACE2, FRIL) expressed from plant cells and transmitted through the gum to reduce the amount of viral load in saliva is one of the most important approaches recently. In recent studies, it has been aimed to reduce the viral load in the oral mucosa of proteins produced from plants placed in the gum and viral trap proteins transmitted through the gum to reduce the transmission of SARS-CoV-2 or influenza viruses [56,58].

Nasal and oral irrigation methods provide mechanical cleaning, symptomatic relief, and can help prevent virus transmission by reducing viral load. They should be considered an important method in infection control and the prevention of its spread. Based on the information available in the literature, it appears that nasal or oral irrigation with certain solutions can reduce the nasopharyngeal viral load of SARS-CoV-2. This is likely due to the changes in the conformation of the viral S protein caused by the substances in the nasal lavage solutions, as well as the mechanical cleaning provided by the irrigation. However, it is important to note that irrigation methods are not a substitute for other preventive measures such as vaccination, wearing masks, and practicing good hand hygiene.

FOOD SUPPLEMENTS

Functional foods and superfoods contain a variety of nutrients (i.e vitamins, minerals, flavonoids , etc.,) that seem to be beneficial for us to fight diseases. During the pandemic period, an increase has been observed in studies to improve the immune system with food products or nutritional supplements. Several dietary components and active compounds have been explored as health-promoting agents. Flavonoids are one of the most promising active compounds against SARS-CoV-2 due to their excellent anti-inflammatory, antiviral, antioxidant properties and immunomodulatory activity [59,60]. Some common flavonoids such as Quercetin, Rosmrinic acid, Hesperitinapigenin and Luteolin have better in vitro inhibitory activity. Numerous studies have demonstrated that these compounds were able to inhibit the major targets of SARS-CoV-2 [61,62] (Table 1).

Worldwide consumption of dietary supplements has increased during the COVID-19 pandemic. Although these compounds appear promising in the treatment of COVID-19, there is currently insufficient evidence that any ingredient in food or any diet to follow definitively prevents or treats COVID-19. Further experimental and clinical studies are certainly needed to confirm this suggestion to provide a comprehensive evaluation of the substance's potential use as a food additive or health supplement.

Table 1. Flavonoid-rich compounds against SARS-CoV-2

Natural Sources (mg/100g fresh weight)	Flavonoid	Uses & Health Benefits	SARS-CoV-2 target	Ref.
*Dill (79) *Fennel leaves (46.8) *Onions (45) *Chili pepper (32.6)	Quercetin	Numerous health advantages, including those related to the cardiovascular system, the prevention of cancer, the reduction of inflammation, and the alleviation of asthma symptoms.	M^{pro}, TMPRSS2	[63,64]
*Ginkgo biloba (68.47) *Spinach (55) *Kale (47) *Dill (40)	Kaempferol	Therapeutic effects include those antioxidant, anti-inflammatory, antimicrobial, anticancer, cardiovascular, nervous system, diabetes, osteoporosis, estrogenic/antiestrogenic, anxiolytic, analgesic, and antiallergic agents.	ACE-2, S	[62–64]
*Grape, black (45) *Grape, white (45) *Grape juice (62) *Wine, red (79)	Myricetin	Fights cancer, type 2 diabetes, liver damage, heart disease, obesity, and osteoporosis	M^{pro}, TMPRSS2	[64–66]
*Raw Chinese Celery (34.87) *Oregano (1028.75) *Juniper berries (69.05) *Radicchio (37.96) *Dried Parsley (19.75) *Peppermint fresh (11.33) *Thyme fresh (51)	Luteolin	Many health benefits, including: protection from sun and free radicals; enhancement of cardiovascular and nervous system health; reduction of the risk of cancer; and many more uses.	M^{pro}, ACE-2, S	[64,67]
*Grapefruits (115-384 mg/L) *Sour orange (>100mg/L) *Tomatoes (0.68)	Naringenin	The effects of this compound include those of an anti-diabetic, anti-atherogenic, depressive, immunomodulatory, anti-tumor, anti-inflammatory, DNA-protective, hypolipidemic, antioxidant, peroxisome proliferator-activated receptor (PPAR) agonist, and a memory-improving PPARs activator.	M^{pro}, ACE-2	[64,68–70]
*Orange (citrus sinensis) (970) *Peppermint dried (480.85) *Tangor or Clementine (39.9) *Sweet orange (28.6)	Hesperidin	Cardiovascular health, type 2 diabetes, inflammation reduction, cutaneous functions, wound healing, protection from ultraviolet radiation, anti-cancer effects, reduced risk of infection, and lighter skin are just a few of the benefits.	M^{pro}, ACE-2, RBD-S	[64,69,71]
*Green tea (10-80) *Dark chocolate (46-61) *Beans (35-55) *Apple (10-43) *Red raspberry (2-48)	Catechin	Effects against cancer, obesity, diabetes, cardiovascular disease, infection, the liver, and the nervous system	M^{pro}	[64,72]
*Red raspberry raw (0.53) *Strawberry raw (0.50) *Beans (1.63)	Cyanidin	Strengthening the body's natural defenses against free radicals, inflammation, cancer, diabetes, toxicity, cardiovascular disease, and neurological disorders.	M^{pro}, RdRp	[64,73]
*Olive oil extra virgin (1.17) *Olive oil virgin (0.10) *Olive oil refined (0.03) *Marjoram dried (4.40) *Italian oregano (3.50) *Rosemary (0.55)	Apigenin	Many diseases, including diabetes, Alzheimer's, forgetfulness, depression, insomnia, cancer, etc.	M^{pro}	[64,74]

ALGAL PRODUCTS

The production of bioactive substances that can be used to create resistance in the body against viruses such as SARS-CoV-2 or to evaluate it in the production of antiviral drugs has gained much more importance during the pandemic period [75]. In this context, microalgae are a very powerful weapon in the fight against the pandemic, as it is one of the leading sources of biomass rich in bioactive substances [76]. Due to their distinctive and rich composition, they have the potential to be useful in the prevention and treatment of several contagious and fatal viruses, including SARS-CoV-2 [77] and also they can be used as a vaccine carrier [78].

Numerous investigations have revealed that the bioactive components such as sulfated polysaccharides, astaxanthin, c-phycocyanin, and lectins from algal biomass have therapeutic benefits, including antibacterial, antiviral, antifungal, anti-tumor, and neuroprotective actions [79,80]. Kwon et al. reported that sulfated polysaccharides are tightly bound to the S proteins of SARS-CoV-2, and accordingly, these polysaccharides can be used in the diagnosis and treatment of viral diseases [81]. Sami et al. investigated the antiviral activity of polysaccharides such as carrageenan, fucoidan, ulvan, agar, and alginate obtained from algae against various viruses and stated that algal polysaccharides can be used in antiviral treatments against viruses [82]. Tzachor et al. stated that Arthrospira platensis extracts, which are rich in C-phycocyanin content with a pigment-binding feature, can be used to prevent virus-induced cytokine storms such as COVID-19 and influenza. They have also emphasized that these extracts can be used as nutritional supplements in high-risk groups such as the elderly and chronic patients [83]. Berndt et al. also produced the recombinant SARS-CoV-2 spike receptor binding domain (RBD) protein, which is used as an antigen in vaccines developed against SARS-CoV-2, using C. reinhardtii microalgae [84]. Gülsoy, and Ünlü evaluated the antiviral activity of Antarctic microalgae C. pyrenoidosa OZCIMEN.001 and C. variabilis YTU.ANTARCTIC.001 against SARS-CoV-2, respectively. It was found that, C. pyrenoidosa OZCIMEN.001 and C. variabilis YTU.ANTARCTIC.001 showed 100% antiviral activity when diluted 1/2 times in environments where the virus was present [85,86]. The antiviral action mechanism of some components obtained from algae is summarized in Table 2. Although algal-derived compounds are effective against SARS-CoV-2 or similar viruses and related symptoms, more research is needed in this area [87].

FUNCTIONAL NANO AND BIOMATERIALS AGAINST SARS-COV-2

Evaluating the efficacy and safety of a drug or vaccine and using it for therapeutic purposes is a time-consuming and complex process that requires the collaboration of experts from various disciplines such as drug metabolism, pharmacology, medicinal chemistry, and clinical research [96]. During COVID-19, the rapid increase in the number of patients worldwide prompted immediate actions to identify and control virus cases. Nanoformulations have been identified as promising potentials in this context due to their exceptional benefits. This section will discuss nanoformulations developed for COVID-19 diagnosis and treatment.

Table 2. Antiviral effect mechanism of algal components

Algae	Compound	Virus	Mechanism	Ref.
Sargassum henslowianum	Fucoidan	HSV-1	Blocking adsorption to the host cell	[88]
Red Algae	Neoagarohexaos	Norovirus	Strengthening the immune system through activation of TLR4 signaling	[89]
U. pertusa	Ulvan	VSV	Inhibition of virus replication	[90]
Sargassum fusiforme	Polysaccharide	ALV-J	Blocking adsorption to the host cell	[91]
Monostroma nitidum	Polysaccharide	EV71	Blocking early steps of the viral life cycle by downregulating the host PI3K/Akt	[92]
Ascophyllum nodosum	Polysaccharide	HIV-1, HBV, HCV	Inhibition in the early stage of viral infection	[93]
Nizamuddinia zanardinii	Fucoidan	HSV-2	Blocking virus adsorption	[94]
Monostroma latissimum	Polysaccharide	EV71	Inhibition of viral replication by targeting the viral capsid protein VP1	[95]

SURFACE DESIGN STRATEGIES FOR PROTECTION

Virus-contaminated materials lead to the spread of disease, so antiviral materials became even more important during the COVID-19 pandemic. Studies to prepare antiviral materials for use in protective equipment (face masks, gloves), personal products (cell phones, brushes), food packaging, and textiles (wet wipes, protective clothing) have intensified during the pandemic [97]. Antiviral mechanism collapses the integrity of subcellular structures, disrupt the cell membrane, or inhibit protein synthesis [98]. Strategies based on contact-killing and surface repelling commonly have been used for these antiviral mechanisms. In contact killing strategies, the surface composition of the materials have been modified using biocidal agents (e.g., polycations, graphene, metal oxides, or nanoparticles) [99]. For example, positively charged polycations can disrupt the membrane by binding to the active site of the viral capsule [100]. Tuñón-Molina et al. prepared an antiviral facial protective equipment made up of polyethylene terephthalate and the surfaces coated with benzalkonium chloride that inhibits the envelope of RNA viruses. The proposed face shield inactivated the viruses after 1 min [101]. Graphene is a useful biocidal agent in the design of antiviral materials due to its sharp edges to disrupt the membrane and its ability to form reactive oxygen species (ROS) [102]. Fukada et al. reported a SARS-CoV-2 inactivation route by using graphene oxide (GO) nanosheets. S and N proteins decomposed due to the adsorption of negatively charged GO and inactivated the virus. Therefore, it can be used as a coating in the design of clothes, filters, and masks to prevent virus transmission [103].

Metallic nanoparticles such as silver [104], copper [105], zinc [106], and titanium dioxide [107] also used widely due to their antimicrobial mechanisms like lipid peroxidation, ROS generation, and damage to genetic material [108]. It is known that silver (Ag) ions and nanoparticles have antibacterial, anti-cancer, anti-inflammatory, antiplatelet, anti-angiogenesis, and antifungal properties. Silver nanoparticles (AgNPs) have antiviral properties in addition to these superior properties [109]. Since materials such as personal protective equipment and air conditioning systems do not have an intrinsic antimicrobial/virucidal effect, they have become the primary focus for combating COVID-19. The anti-infective coating made of silver has been shown to inactivate the virus which adheres to surfaces for about 12 hours [110]. Balagna et al. have designed Ag nanocluster/silica composite sputter coating directly Filtering FacePiece 3 (FFP3) face mask and examined the virucidal effect of Ag against SARS-CoV-2. With this coating, the composite have showed that Ag was able to completely reduce SARS-CoV-2 to zero on the mask [111]. It has been stated that this coating can apply to various surfaces such as metallic, glass, and ceramics, so it can have great importance for security in a crowded area (i.e. such as supermarkets, hospitals, and schools) to inhibit the spread of SARS-CoV-2.

Hosseini et. al. fabricated a transparent antimicrobial coating including Ag-oxide particles in a silicate matrix to cover the touchscreen and the virus was inactivated by 95.4% after 1 h. [112]. In surface repelling strategies, the antiviral effect is obtained by nanopatterns that prevent the attachment of organisms onto the material surfaces. Lithographic techniques, wet-etching techniques, direct writing techniques, and instability-induced polymeric patterning are the main techniques for surface nano patterning [113,114]. Hasan et. al formed randomly aligned nano ridges on the aluminum (Al) alloy by using wet-etching techniques and obtained high antiviral activity against SARS-CoV-2 within 6 h [115]. In another study, a porous surface composed of parallel rectangular grooves and rectangular pillars was prepared on Al surfaces using a lithographic technique and less virus survival rate was shown on these surfaces [116].

Zhou et al. prepared a polymer film using AgNPs and nanoscale conical pillars by spray coating and nanoimprinting lithography. The enhanced antiviral effect shown on these surfaces compared to only AgNPs ones. They are ideal candidates to use in plastic products and food packaging [114]. Moreover, many recent studies combined photosensitive compounds with antiviral strategies [117,118]. When photosensitizer is excited with light and reacts with oxygen, ROS or singlet oxygen that induces oxidative damage to biological species is produced [113]. For instance, Zhang et al. prepared a cellulose wipe combined with cationic conjugated oligomer electrolytes (c-OPE) via the simple dip-coating process. The c-OPE-coated wipes showed a 2.46 log inactivation value against SARS-CoV-2 when compared to uncoated ones after 10 min light-activation [118].

NANO-DIAGNOSTIC SYSTEMS

During the pandemic, molecular assays such as PCR or nucleic acid hybridization to detect SARS-CoV-2, serological and immunological assays based on the detection of patients' antibodies or antigenic proteins in infected individuals have been commonly used tests in the diagnosis of COVID-19 [119]. The mono- and poly-clonal antibodies are widely used in diagnosis to detect antigens and antibodies for SARS-CoV-2 [120–123].

Nano-diagnostic systems have advantages such as increasing the efficiency of conventional diagnostic tools, reducing macro-scale production or diagnostic costs, increasing sensitivity, and shortening the turnaround time [124]. Thanks to these features, nano-diagnostic systems are beneficial for diagnosing newly emerging infections such as COVID-19 [125]. The large number of samples to test during the pandemic is a significant challenge for hospital laboratories. This situation has brought nano-diagnostic systems to the forefront with advantages such as high accuracy, fast detection, and low cost, which can meet

the need for simple and fast procedures to identify positive cases [126,127]. In addition, nanomaterials are suitable candidates for the development of biosensors for the detection of various viruses, including SARS-CoV-2, due to their unique physicochemical properties that differ from bulk materials and their ability to be easily functionalized with biorecognition molecules such as antibodies, peptides, and aptamers [128].

The design strategies of nano-diagnostic systems based on developing tools detect SARS-CoV-2 RNA or disease-related antigens and antibodies. For instance, lateral flow test kits have been developed using cellulose nanoballs, colloid gold, and fluorescent nanoparticles. These tests, which approved for emergency use by the FDA during the pandemic, facilitated the early detection of the disease, continuous monitoring, and patient surveillance in cases of COVID-19 [129]. On the other hand, nanotechnology-based colorimetric bioassays have attracted much attention for the design of biosensors with simple and visual outputs without the need for complex instruments. Moitra et al. developed plasmonic nanoparticles by coating gold nanoparticles (AuNPs) with thiol-modified antisense oligonucleotides specific to the N phosphoprotein gene of SARS-CoV-2 [130]. They showed that with this analysis method, which works with the principle of surface plasmon resonance exchanges and allows detection with the naked eye, they could diagnose positive cases within 10 min from isolated RNA samples. Lee et al. developed a colorimetric lateral flow immunoassay using AuNP-antibody conjugates. They showed that this test provides sensitive detection in 15 min with a limit of detection (LOD) value of 5×10^4 copies/ml [131]. Furthermore, they showed that this lateral flow kit could accurately detect all positive and negative samples from 19 clinical validated by RT-PCR. The use of biosensors developed for the detection of SARS-CoV-2 RNA or marker proteins such as S and N as nano-diagnostic systems investigated by many researchers. Zhao et al. developed an electrochemical sensor capable of detecting the RNA of SARS-CoV-2 using GO with calixarene functionality [132]. They showed that this sensor could practically detect the RNA of SARS-CoV-2 using a smartphone without nucleic acid amplification and reverse transcription. They also stated that the LOD value determined in clinical samples for this sensor is 200 copies/ml, the lowest value ever published for RNA measurements. Fabani et al. aimed to improve the performance and increase the sensitivity of the electrochemical sensor they designed by using screen-printed electrodes modified with carbon black nanomaterial to detect S or N protein of SARS-CoV-2 in saliva [133]. They have shown that the biosensor can perform rapid analysis as quickly as 30 min with a low LOD. They also stated that this miniaturized and portable device has a high potential for market entry thanks to its easy use and non-invasive sampling features. Song et al. developed a smartphone-based upconversion luminescence diagnostic platform using oligo-modified nanoprobes and gold nanoprobes for rapid point-of-care detection of the SARS-CoV-2 N gene [134]. They reported that the luminescence platform achieved a LOD of 11.46×10^{-15} M without amplification. The assay produced consistent and reliable diagnostic results in nine clinical samples confirmed by RT-qPCR within 20 min.

The use of nano-diagnostic systems to detect immunoglobulins associated with COVID-19 has been beneficial for accurately detecting suspected cases or obtaining information about the prognosis of the disease. Chen et al. developed a rapid and sensitive lateral flow immunoassay using lanthanide-doped polystyrene nanoparticles to detect anti-SARS-CoV-2 IgG in human serum [126]. They stated that the test could detect IgG antibodies in 10 min using a 100 µl aliquot of serum sample (1:1000 dilution), and it can allow rapid and sensitive detection of anti-SARS-CoV-2 IgG in human serum, allowing identification in suspected cases. On the other hand, it is known that IgA is an alternative biomarker for the early stages of COVID-19 infection. Roda et al. developed a colorimetric and chemiluminescence format lateral flow immunoassay immunosensor that can measure the color signal provided by nanogold-labeled anti-human IgA for the detection of IgA in serum and saliva [135]. They showed that the lateral flow test was sensitive enough to detect IgA from serum and saliva samples. Hryniewicz et al. developed an impedimetric biosensor to monitor SARS-CoV-2 seroconversion by using polypyrrole synthesized in both spherical and nanotubular morphology and AuNPs, 3-mercaptopropionic acid and covalently bound SARS-CoV-2 N protein [136]. They showed that polypyrroles in nanotubular morphology could measure 0.4 ng/ml of monoclonal antibody and detect specific antibodies in human serum in less than one hour and with precision.

NANOVACCINES

Vaccination is the most effective medical intervention for controlling and preventing infectious diseases such as SARS-CoV-2. Until recently, more than 130 vaccine candidates for SARS-CoV-2 were under development, including more than 20 in Phase 2 or 3 studies [137]. Recent advances in nanotechnology have accelerated the development of nanovaccines, in which nanoparticles used to deliver vaccines and improve their efficacy. Nanovaccines are nanosized particles with dimensions ranging from 1-1000 nm that carry virus-associated antigens (Figure 2). They can protect the antigens from enzymatic breakdown, allow for controlled or prolonged release of antigens and promote the uptake of antigens by targeting specific immune cells. Therefore, nanovaccines have intrinsic adjuvant effects since they can improve the ability of antigens to activate immune cells [138].

The most intensively researched nanovaccine formulations include polymeric nanoparticles, lipid nanoparticles, liposomes, virosomes, protein nanoparticles, and

virus-like particles (VLPs). Polymeric nanostructures can be promising strategies for vaccine development against SARS-CoV-2. They have excellent features such as good bioavailability, drug loading, prolonged release, and stability and can transport virus-associated antigens on their surface or within their core. Natural and synthetic polymers such as gelatin, hyaluronic acid, alginate, polylactic acid (PLA), PGA (polyglycolic acid), poly lactic-co-glycolic acid (PLGA), polyethyleneimines (PEI), and polyamidoamine (PAMAM) can be widely used as vaccine carriers [139]. Polymeric nanostructures categorized as particles, micelles, nanogels, and polymersomes, as well as core-shell structures in which polymeric particles are covered with lipids, cell membranes, or proteins [140] In a study, intranasal administration of SARS-CoV-2 S glycoprotein RBD-loaded chitosan nanoparticles into mice induced mucosal immunity by increasing IgG and IgA responses and increased antibody responses including serum IgG, IgG1, IgG2a, IgA and neutralizing antibodies. These findings demonstrated that RBD-loaded chitosan nanoparticles could mimic the natural route of SARS-CoV-2 infection and thereby stimulate both local mucosal and systemic immune systems [141]. Shahjin et al. developed a multiple polymer-based microsphere system for the encapsulation of whole chemically inactivated SARS-CoV-2 to provide sustained antigen release. Polymers with different biodegradation rates, such as polycaprolactone (PCL), PLGA, and PLLA were mixed to achieve early and late release of SARS-CoV-2 antigens from the degrading components, thereby minimizing the need for repetitive dosing and improving antiviral immunity [142].

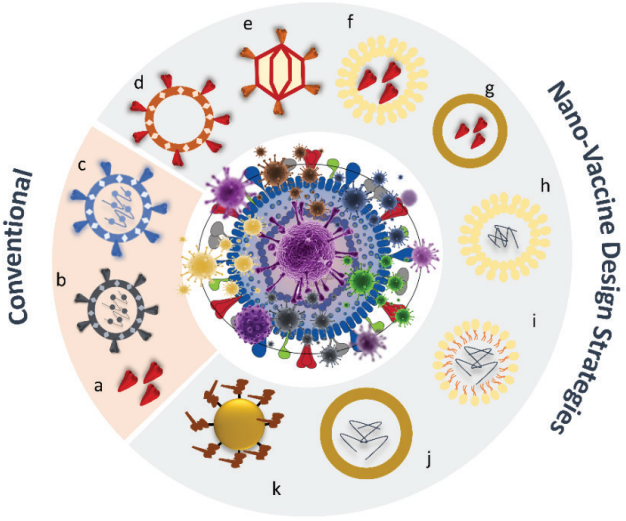

Figure 2. Nano-vaccine design strategies a) subunit; b) inactivated; c) live-attenuated; d) virosome; e) virus-like; f) liposomal, and g) polymeric carrier for subunit; h) liposomal, i) micellar, and j) polymeric carrier for mRNA; k) antigen conjugated metallic nanoparticle.

Solid lipid nanoparticles (SLNs) are complex lipid spheres with solid hydrophobic cores measuring 50 to 1000 nm in size. They are biocompatible and have a high antigen-loading capacity. Because ionizable lipids in SLNs are quickly protonated into cationic forms in the acidic environment of endosomes, which then interact with the anionic phospholipids in the endosomal membrane, disrupting the membrane bilayer and allowing antigens to release into the cytosol, SNLs can naturally facilitate antigen entry into endocytic vesicles. mRNA-loaded SNLs vaccines, in particular, cause the release of mRNA into the cytosol, where it is transcribed into an antigenic protein, resulting in improved immune responses to the infection [143]. Consequently, two SLNs formulated mRNA vaccines, mRNA1237 (ModernaTX, Inc.) and BNT162b2 (Pfizer-BioNTech) have been clinically approved for human administration against SARS-CoV-2. They reported to provide 94.1% and 95% protection against SARS-CoV-2 infection, respectively, without any significant side effects [144].

VLPs are biomimetic nanostructures with diameters ranging from 20 to 100 nm containing small fragments of virus-derived structural proteins. Their structures are similar to natural viruses with the exception that they lack viral genomes. VLPs can elicit robust cellular and humoral immune responses, as well as high titers of neutralizing antibodies. However, few studies conducted to determine the protective effects of VLP-based vaccinations against SARS-CoV-2 [145]. A research team developed a SARS-CoV-2 VLP as vaccine candidate, Novavax, containing the coronavirus recombinant S protein. The assessment of immunogenicity and safety of co-formulation of Novavax with saponin-based adjuvant, Matrix-M (NVX-CoV2373) are ongoing in Phase 2 studies [146].

NANOTHERAPEUTICS

ANTIBODY BASED PROPHYLACTIC/ THERAPEUTIC FORMULATIONS

Passive immunization with protective antibodies that might give susceptible individuals instantaneous immunity is one of the most efficient methods for controlling the pandemic [147]. Various studies have proven the prophylactic and therapeutic efficacy of antibody therapies against viral infections that cause pandemics. It is shown that both mono- and poly-clonal antibodies can be used for antibody therapies [148–150]. However, it is substantially more expensive to produce monoclonal antibodies than polyclonal antibodies. It is known that their production also takes much time and demands a lot of expertise and training [151]. In this context, polyclonal IgY antibodies obtained from chickens have become an internationally accepted practice since 1996 [152]. Due to IgY's superior capabilities to IgG, its use as a prophylactic and therapeutic agent has grown throughout time [153–155]. IgY's ability to

be obtained from egg yolk without harming the animal and without suffering is a significant advantage. In addition, the production process is straightforward, and a large amount of production (100-150 mg of IgY per egg) is possible [156]. The large production volumes of IgY make them excellent candidates for prophylactic and therapeutic use during the pandemic [157].

These antibodies have tremendous promise for prophylactic and therapeutic usage in the ongoing COVID-19 pandemic [158]. IgY antibodies allow it to recognize certain mammalian conserved protein epitopes due to the significant evolutionary distance between mammals and birds [159]. Neutralizing IgY antibodies may offer a potential passive immunization against infections caused by emerging pathogens, including SARS-CoV-2. It can also provide safe use as a nasal, mouth spray, and mouthwash [158]. IgY also does not interact with or activate the mammalian complement system or Fc receptors. Therefore, it does not trigger the disease's antibody-dependent development and may even stop complement-mediated harmful inflammatory reactions [155]. Therefore, administering neutralizing IgY intravenously may be helpful to treat SARS-CoV-2 infection [160]. Before COVID-19, IgY has been thoroughly investigated for treating several respiratory viruses [161,162]. The treatment of pathogenic coronaviruses with these antibodies has also proved effective [163]. In viral pathogenesis and infection, the S protein plays an important role. Therefore, it recognized as a crucial target for raising long-lasting neutralizing antibodies [164]. The S1 subunit is where most neutralizing epitopes are found [165]. As a result, the SARS CoV-2 S protein discovered epitope is a strong candidate for developing antibody-based therapy as an immunotherapeutic agent [166]. Bao et al. produced IgY targeting the S1 subunit of SARS-CoV-2 and reported that it might be a good candidate for COVID-19 pre-and post-exposure prophylactic or therapeutic [167]. Similarly, Lu et al. have reported that IgY targeting the S1 subunit is effective against SARS-CoV-2 [160].

Since mucosal immunity is limited in controlling viral infections [167], IgY-based mucoadhesive formulations such as nasal or oral sprays can help strengthen the barrier function of the nasal, oral, and gastrointestinal mucosa [166]. To determine if anti-SARS-CoV-2 IgY antibodies can be employed in nasal or oral spray formulation, Shen et al. generated anti-SARS-CoV-2 IgY. They assessed the persistence time in the mouse nasal and oral cavities [168]. The study showed that IgY was retained in the nasal and oral cavities at detectable concentrations for several hours after administration for SARS-CoV-2 infection. According to these findings, anti-SARS-CoV-2 IgY can be administered orally or nasally and remain in the upper respiratory tract for several hours, depending on the application method. To capture the virus in the nasal mucosa, Frumkin et al. designed nasal drops for RBD-specific IgY antibodies [155]. The result indicated that new emerging variants including *alpha*, *beta*, *delta*, and *omicron* neutralized by anti-SARS-CoV-2 RBD IgY antibodies. According to another study, intranasal injection of RBD-specific IgY (IgY anti-RBD S) efficiently blocked the viral S glycoproteins' crucial initial attachment to human ACE2. In addition, it was stated that when administered as an intranasal agent, IgY had an excellent safety profile [169]. The development of nasal spray treatments for SARS-CoV-2 is ongoing, and early clinical studies have confirmed that this approach is safe and can be used to prevent the respiratory spread of SARS-CoV-2 [170]. Finally, since SARS-CoV-2 is not transmitted only by nasal inhalation (eye, nose, or mouth contact), active IgY antibodies can be easily formulated by incorporating them into sterile ophthalmic solutions [171].

ANTIMICROBIAL POLYMERS

In the treatment site, using a new drug molecule for the treatment of COVID-19 and related bacterial infections was nearly impossible because it must be developed and FDA-approved, which typically takes a decadelong study [172]. Therefore, the development of antimicrobial drug systems was urgently needed to combat this pandemic infection [173–175]. Hence, combination or actively targeted formulations of existing drugs and antibiotics can play a key role in the treatment [176]. Moreover, due to a large number of hospitalized COVID-19 patients receiving antibiotics, antibiotic resistance is expected to be further increased [177–179]. The purpose of including antibiotics in the clinical care of COVID-19 was either to manage any co-existing bacterial infections or to make use of its probable antiviral properties [180]. Pathogenic bacterial multidrug resistance to antibiotics is one of the biggest global health crises [181,182]. Bacterial infection mortality has increased dramatically in recent years, threatening public health.

To overcome these problems, it is now more necessary than ever to continue developing efficient treatments for bacterial infections that use different action mechanisms from antibiotics [179]. Here, polymers offer great potential in the development of novel antimicrobial materials due to their easier production and modification, mechanical properties, biocompatibility, and biodegradability (if necessary). The COVID-19 pandemic has given great impetus to the development of new antimicrobial polymers, which can be effective against most viruses, bacteria, and also fungi. Consequently, we would like to give a brief overview of the materials in which we mainly focus on antiviral and antibacterial polymers developed during and after the COVID-19 pandemic.

Antimicrobial polymers show outstanding antiviral activity either inherently or by integrating with antimicrobial agents. While inherent antimicrobial polymers show their activity by contacting the pathogen, antimicrobial agent integrated polymers act as a carrier and exhibit their activity by providing controlled release of the agent (Figure 3) [183–185]. Chitosan and PEI are two important examples of polycations (polyelectrolytes with positive charges)

that exhibit inherent antimicrobial activity. Carrageenans and PLGA are some examples of carrier-type antimicrobial polymers in the literature. These inherently antimicrobial materials, ranging from nano-scaled polymers [186] and nanoparticles [187] to macro-scaled thin films [188] and hydrogels [189], have gathered a lot of attention in this research area. These antimicrobial polymers play a leading role in the development of various approaches for the use of polymeric materials against the SARS-CoV-2 virus and related bacterial pathogens [190]. In this regard, antimicrobial polymers draw interest in food packaging [191], textile, surface coating [185], and drug delivery systems [192].

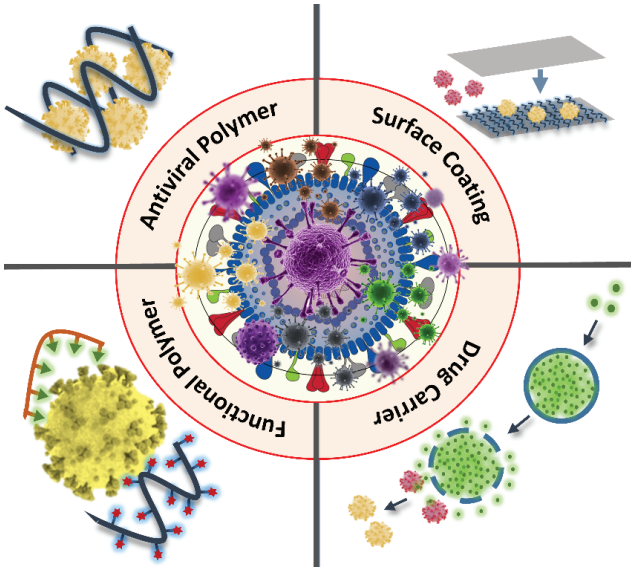

Figure 3. Antiviral applications of polymers.

In the study of Pyrć et al., the antiviral activity of chitosan against SARS-CoV-2 was investigated in vitro and in vivo, and it was shown that it has the potential to be used as a nasal spray against SARS-CoV-2 viral infection [193]. Emam et al. developed ACE-2 loaded modified polyacrylonitrile nanofibers to prevent the risk of SARS-CoV-2 viral infection caused by airborne particles. The study demonstrated a remarkable approach to the development of stable antiviral protective masks [194]. Sulphated polysaccharides were shown to be antiviral polymers with effective antiviral and low cytotoxic properties for the treatment of SARS-CoV-2 infection [195]. In the study of Sharif et al., an edible gelatin and Persian gum-based film with antiviral activity was developed for preventing the transmission of foodborne viruses [196].

Remdesivir used in COVID-19 treatment has a high potential of preventing virus replication by inhibiting RNA-dependent RNA polymerase. However, remdesivir's therapeutic effect is restricted because of its extremely poor solubility and toxicity at high doses, as well as its low tissue distribution, especially in the lungs; thus, it is needed to be preserved by a carrier system. For instance, Halevas et al., obtained 2, 2-bis(hydroxymethyl)propionic acid (bis-MPA) based dendritic systems employed as nano-carriers of remdesivir [174]. According to the results, encapsulated remdesivir kept its activity while increasing its aqueous solubility compared to free remdesivir. Additionally, Vartak et al. formulated a stable aerosolized nano-liposomal carrier for remdesivir against COVID-19 [197]. The results showed that the drug released totally within 50 hours in vitro, had a high encapsulation efficiency and nano-size.

To prevent foodborne viruses and bacteria, Amankwaah et al. have designed edible films that can be used as antibacterial agents for food packaging [198]. Green tea extract was added to the chitosan solution, and the resulting dried edible films demonstrated efficiency in lowering murine norovirus infection potential. Additionally, the films demonstrated antibacterial activity against Listeria innocua and *E. coli*, which were used a stand-in for foodborne pathogenic microorganisms.

The majority of COVID-19 masks are biocide-free. As a result, developing antibacterial nanonet and filtering materials as reusable protection materials capable of intercepting and destroying pathogens is critical for reducing cross- and post-infection caused by current masks. Tian et al. produced polystyrene grafted by 5, 5-dimethylhydantoin, and trimethylamine nanofiber membranes (PSDT/PU-(PNNMs)) by electrospinning [199]. The efficient and stable antibacterial characteristics were provided by the covalently integrated membranes with intrinsic N-halamine and quaternary ammonium salt groups. This nanonet system improved the high air filtration of fine particles and the low-pressure drop and showed superior antibacterial and antiviral activity against *E. coli*, *S. aureus*, and *E. coliphage*. Besides bacterial air filtration, the designed material has the potential to be used in water treatment and food packaging.

POLYMER-BASED NANOPARTICLES

During the COVID-19 pandemic, in the search for new and effective treatments, one of the promising areas of research has been the use of polymer-based nanoparticles for drug delivery (Figure 4). Polymeric nanoparticles are colloidal particles consisting of natural or synthetic polymers, with sizes ranging from 10 to 900 nm. While these nanoparticles increase the drug loading capacity thanks to their high surface area they can overcome biological barriers in the body and deliver the drug to tissues that are difficult to access, such as the central nervous system [200,201]. In this process, they help maintain the stability of the drug and increase its bioavailability while increasing its circulation time in the blood. Considering the features such as carrying multiple drugs, adjustable release kinetics, and targeting, these systems have now become the target of many

scientific areas [202–204]. One of these areas is the fight against COVID-19.

Anti-inflammatory drugs and broad-spectrum antivirals (i.e., Remdesivir, Favipiravir, Lopinavir/Ritonavir, Chloroquine, Daclatasvir, and Dexamethasone) continue to be treatment options in the treatment of COVID-19 patients [205–207]. On the other hand, the effective concentrations of these drugs have serious side effects. To reduce the side effects of these drugs and to use the advantages mentioned above, many studies have been carried out involving the use of polymeric nanoparticles. Wu et al. developed Remdesivir-loaded Lisinopril-labeled PLGA-NPs that target the ACE1 receptor for highly efficient co-delivery of both hydrophilic and hydrophobic agents [208]. In this context, Uçar et al., synthesized Oseltamivir-phosphate-loaded PLGA-NPs modified with SARS-CoV-2 S-binding peptide 1 (SBP1) targeting the ACE2 receptor [209]. The researchers reported that the sustained release of nanoparticles continued for two months according to the Higuchi kinetic model. Gattani and Dawre developed Favipiravir-loaded PLGA-NPs and encapsulated these NPs in a heat-sensitive gel to increase nasal permeability [210]. The results showed that the gel containing nanoparticles had a longer release time of 30 hours and showed good mucoadhesive properties supporting nasal permeability. In 2020, Bioavanta-Bosti announced the potential to integrate Novochizol™ chitosan aerosol nanoparticle technology, which has been shown to strongly adhere to lung epithelial tissues, into anti-COVID-19 drugs [211]. For this purpose, they invited drug developers and clinical researchers to work together. Studies have revealed that polymeric nanoparticles are preferred due to their long-term sustained release, targeting, and modification to the desired properties. However, further research and clinical trials are needed to fully understand the potential of polymer-based nanoparticles for the treatment of COVID-19.

INORGANIC-BASED NANOPARTICLES

Quantum dots (QDs), graphene, and metal nanoparticles such as magnetic, Au, Ag, titanium, zirconia platinum, silica, and their hybrid or composite nanostructures are some examples of engineered inorganic-based nanoparticles [212,213]. Inorganic-based nanoparticles produce via occurring alkoxide polycondensation reactions including hydrolysis reactions or chemical reducing reactions of metal oxide ions in some applications [214,215]. With the advances in technologies realized on various inorganic

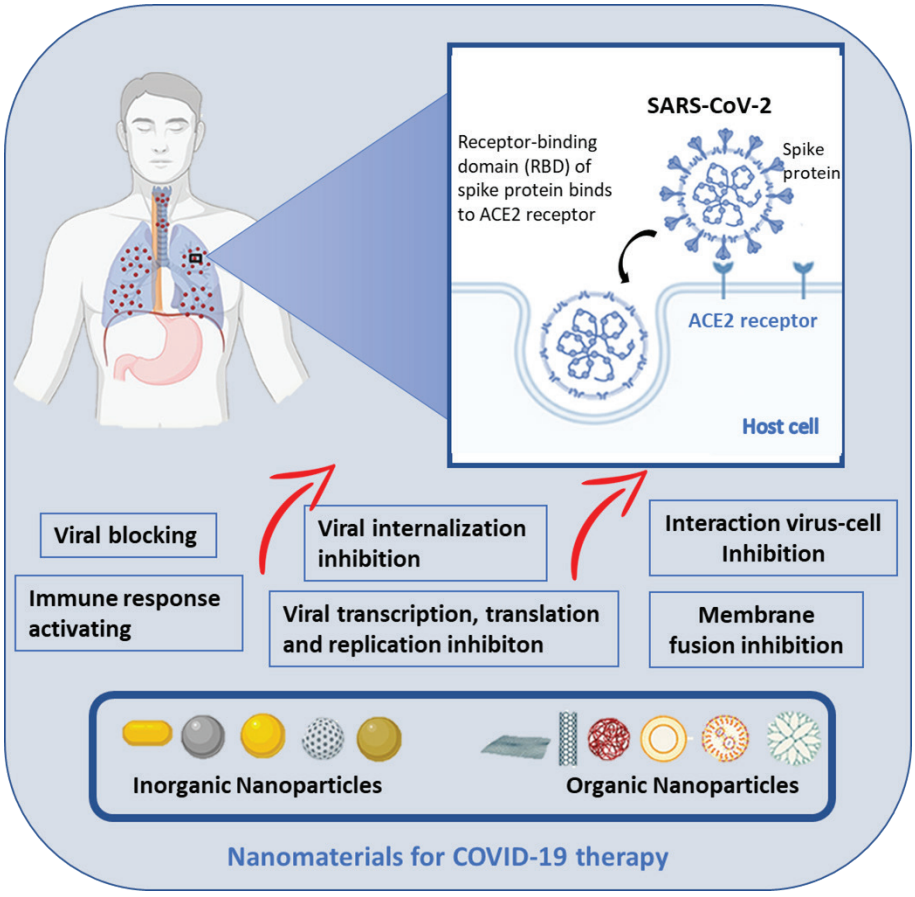

Figure 4. Nanomaterials that are used for COVID-19 treatment strategies.

nanoparticles mentioned above, they have been widely used to control COVID-19 due to their unique properties for drug delivery systems, imaging systems, antiviral facemasks and sensors [216,217]. Some of the key characteristics that will lead to biological applications of the inorganic NPs are regulated stability, increased permeability, high functionalization potential, biocompatibility, non-toxicity, site-specific targeting, and controlled release activation [216,218].

Silica NPs are known as very useful materials in drug delivery systems because of their high specific surface area, high porosity, low bulk density, biocompatibility, non-toxic nature, high adsorption capacities, controllable and functional surface, and porosity properties [219,220]. Like other inorganic nanoparticles, silica NPs have the capacity to encapsulate and carry anti-SARS-CoV-2 therapeutic molecules [221]. To bind to the RBD of the viral S proteins via electrostatic interactions and block the S protein from further binding with the host receptor, Neufurth et al. designed silica NPs encapsulated polyphosphate (polyP) [222]. Encapsulation of silica NPs with PolyP (silica/polyP nanoparticles) stabilized degradable polyP against alkaline phosphatase and this drug delivery system showed a slow release of polyP in vitro over 24 h.

Graphene quantum dots (GQDs) with their unique physicochemical properties are the next generation of effective antiviral nanomaterials [223,224]. GQDs have attracted great interest in the healthcare field due to their excellent biocompatibility, relative non-toxicity, easy modification, inertness, high surface/volume ratio, multivalent properties, and high solubility in aqueous solutions, and therefore GQDs can inhibit viral entry into cell [225,226] Hsieh et al. demonstrated that N-functionalized GQDs are vital in the interaction of the COVID-19 S protein with its RBD. Moreover, the addition of polyethylene glycol to the structure was observed to be valuable for the dispersion and adsorption of GQDs on the pathogen surface, resulting in enhanced virus inhibition [226]. QDs can be used in the treatment of SARS-CoV-2 not only by themselves but also as a drug delivery system. Molecular dynamics (MD) study showed that the use of graphene oxide quantum dots (GOQD) as a drug delivery system for Carmofur (an effective drug for the treatment of COVID-19) created an effective system against COVID, and the π-π stacking of the structure together with hydrogen bonding contributed significantly to the stability of the Carmofur-GOQD complex [226].

Inorganic NPs are of particular interest not only because they deliver the therapeutic agent that is loaded or adsorbed on its surface, but also because they allow the stimulus-sensitive properties and intrinsic abilities of some species (such as radiation and magnetic properties) to be monitored following in vivo administration to the body of humans or various animals using medical imaging (i.e., Theranostics) [226].

Arkaban et al. developed Fe–SiO2@PDA NPs nanosystem as a biodegradable Remdesivir delivery system, and magnetic resonance imaging (MRI) contrast agent [227]. In the study, Fe(III) doped and Rd-loaded mesoporous SiO2-NPs were synthesized and theranostic Fe–SiO2@PDA-NPs were formed by coating with Polydopamine (PDA) as a "gatekeeper" for controlled release. Doping of Fe(III) into SiO2 NPs induced a biodegradability and drug release rate, and also support contrast efficacy in Fe–SiO2 for MRI.

TISSUE ENGINEERING Approaches

Thanks to tissue engineering, which is a multidisciplinary science, engineering applied to biological systems has led to the emergence of new technologies and created solutions to the most important problems of the 21st century [228,229]. Most biomedical research aims to identify the mechanisms of human disease or to develop effective methods of diagnosis, prevention, or therapeutic intervention via learning more about the disease. The inability to use human subjects in the early stages of basic scientific research and the inability of animal models to examine the pathophysiology of many human diseases have led scientists to develop alternative disease model strategies [230,231]. With the recent advances in tissue engineering and microfabrication, significant progress made in addressing this shortcoming in disease modeling [232] (Figure 5).

ORGANOID AND MICROFLUIDICS-BASED DISEASE MODELLING AND DRUG SCREENING PLATFORMS

In the context of COVID-19, the development of in vitro models of infectious diseases is very important in two respects. First, by determining the host-pathogen interactions of a known disease or a never encountered disease, the infection mechanisms can be better explained at the molecular and cellular levels. Rapid identification of host-pathogen interactions can change the course of epidemics by providing a prompt understanding of the pathophysiology of infection. Another importance of in vitro disease models is that they are an excellent tool for high-throughput and rapid screening of diagnostic strategies and potential therapeutics during pandemics or epidemics [233]. In this way, hypothetically developed therapeutics can be screened using physiologically relevant in vitro models, meeting the critical need for diagnosis and treatment of disease.

In efforts to model in vitro disease, different cell types are gaining attention, including primary cells, enhanced cell lines, and more recently induced pluripotent stem cell (iPSCs) derivatives [234]. African green monkey renal epithelial cells (Vero E6), especially used as a gold standard in viral infection models, have been applied to screen for many potential therapeutics in the COVID-19 due to interferon deficiency [235–237]. Besides, various cell lines such as Calu3, Huh7, Caco2, 293T, and U251 were found to support the replication of SARS-CoV-2 and were investigated for in vitro model development and therapeutic screening

[238,239]. In addition, human airway epithelial (HAE) cells used for modeling lung infections, including tracheobronchial and alveolar cells, which are one of the first targets of human respiratory viruses, are other potential 2D cellular systems that can be used to create a disease model of SARS-CoV-2 [240].

For many years, traditional 2D monolayer static cultures have been an important first step towards gaining an understanding of host cell-virus interactions, replication, and adaptation mechanisms of infectious disease. It has also been used to screen for many antiviral drugs. However, 2D monolayer static models often fail to mimic tissue and organ-level structures and functions in living organisms that are central to disease etiology [232]. Due to the lack of extracellular matrix, 2D models cannot mimic the in vivo conditions encountered by viruses, such as cell-cell interfaces and shear forces, apical-basal polarity, and endogenous factors, and this affects the accuracy of the results [241]. The 3D cell culture approach that is based on in vitro generation of the natural and complex microenvironment found in living organisms is a promising area where the physiological environment in which disease occurs can be better represented. For this reason, tissue engineering tools that aim to construct complex tissue architectures and organs using cell, scaffold, and biosignal molecule components have attracted a lot of attention for the creation of effective 3D cell culture systems with high reliability [230,231]. In the specific case of SARS-CoV-2, various tissue engineering-based systems such as synthetic tissue development on scaffolds, organoids, organ-on-chip, and 3D bioprinting can be useful as 3D in vitro disease models.

Organoids are 3D organ models that display similar organization of the cell types that the native organ has and similar tissue-specific functions. Organoids for SARS-CoV-2 infection enable researchers to illuminate the pathogenesis of viral infection on organs, test candidate drugs and validate therapeutic strategies [242]. Considering that COVID-19 is a respiratory system disease, human lung organoids generated from pluripotent stem cells have recently been used for high throughput screening of imatinib, mycophenolic acid, and quinacrine dihydrochloride as inhibitors of SARS-CoV-2 entry and found to be effective [243]. Lapatinib treatment also exhibited suppressed viral replication on human lung organoids generated from adult stem cells obtained from lung biopsies. A study using native ECM hydrogels to create 3D models demonstrated that 3D models successfully produced by embedding human bronchial epithelial cells in Matrigel can be infected with SARS-CoV-2 [244]. A similar study showed that human lung 3D cultures produced from embryonic stem cells cultured on Matrigel could be used to evaluate the antiviral effects of candidate compounds in SARS-CoV-2 infection [243]. In addition, to study the SARS-CoV-2 infection in other ACE2-expressing tissues and organs, colon, kidney, liver,

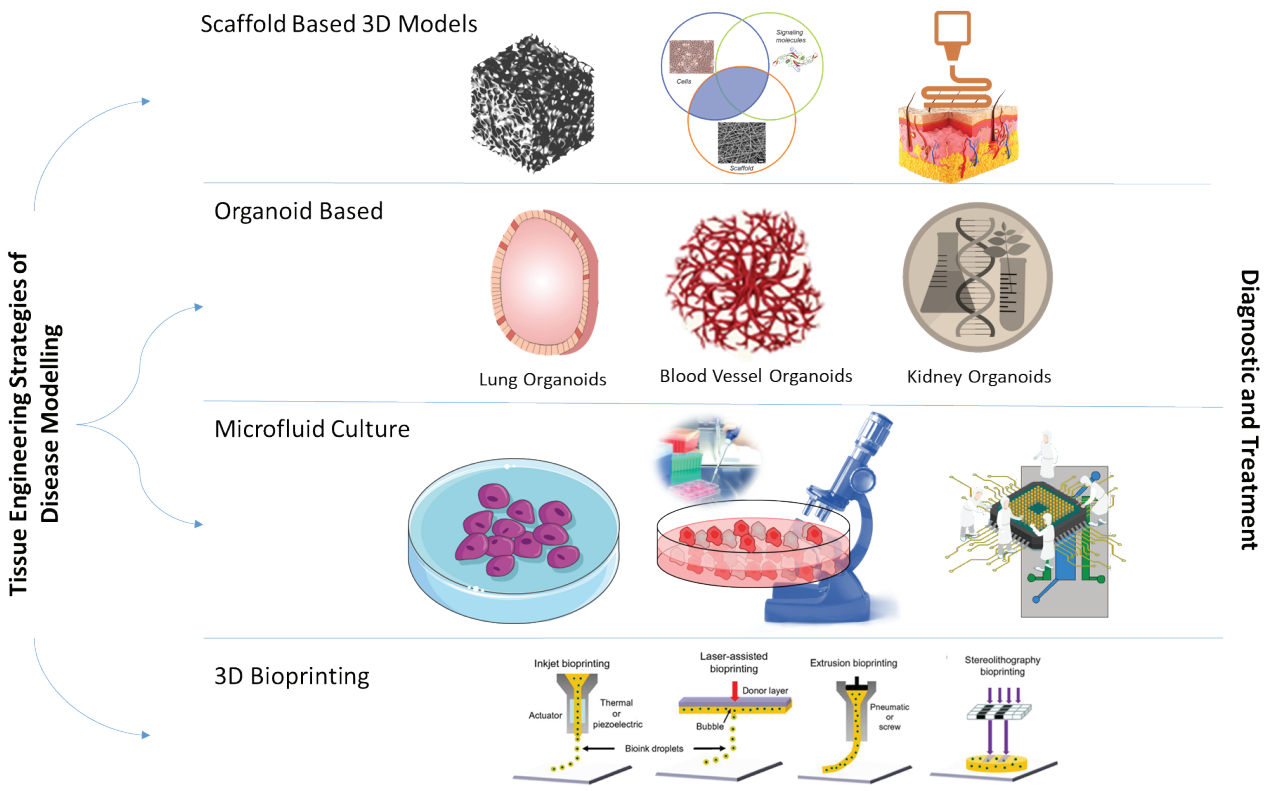

Figure 5. Tissue engineering strategies in SARS-CoV-2 diagnosis and treatment.

brain, tonsil, nose, retinal and cardiac organoids are developed [245,246]. Organ-on-chip technology, on the other hand, exploits the advantages of organoids and microfluidic systems for better simulation of the in vivo microenvironment and for high-throughput drug testing.

Si et al. constructed a microfluidic bronchial-airway-on-a-chip lined by human bronchial-airway epithelium and pulmonary endothelium which model human-lung responses to infection by potential pandemic respiratory viruses including SARS-CoV-2 [247]. Based on their broad spectrum anti-viral activity by dynamic fluid flow in Airway chips, they tested FDA-approved (for other medical indications) drugs such as chloroquine, hydroxychloroquine, amodiaquine, toremifene, clomiphene, arbidol, verapamil, and amiodarone. Only three of these drugs, amodiaquine, toremiphene, and clomiphene, effectively prevented viral infection without causing cytotoxicity. Hydroxychloroquine, chloroquine, and arbidol, which reduced infection in Huh-7 cells, did not affect SARS-CoV-2 entry in human Airway Chips and failed to demonstrate clinical benefits in human clinical trials, demonstrating the clinical relevance of organ-on-chip technology in terms of drug testing compared to 2D cell culture. Multiple organoids located in different compartments that are interconnected via microchannels and mimic systemic blood circulation, organ proximity, and connectivity can also be found on organ-on-chip platforms. [242,248,249]. The combination of different tissues plays a key role to observe the multi-organ response to drugs, which is particularly important for SARS-CoV-2 infection, since multiorgan involvement is apparent in disease prognosis [250].

Zhang et al. proposed a human alveolar chip mimicking the alveolar-capillary barrier by coculture of the human alveolar epithelium, microvascular endothelium, and circulating immune cells under fluidic flow. They noticed the immune cell recruitment, endothelium detachment, and increased inflammatory cytokines release upon SARS-CoV-2 infection, suggesting the crucial role of immune cells involved in alveolar barrier injury and inflammation. They also tested Remdesivir as a potential drug candidate for COVID-19 and showed a decrease in viral infection. They also applied the drug with immune cells (peripheral blood mononuclear cells) via vascular channels in the chip. They showed that remdesivir treatment could restore the damage to epithelial layers and endothelial layer to some extent indicating the potential role of Remdesivir in suppressing SARS-CoV-2 replication and decreasing the virus-induced injury of the alveolar-capillary barrier [251].

In addition, recent remarkable developments are 3D bioprinting (3DB) technologies. 3DB which is aiming to solve the problems encountered in traditional three-dimentional cell culture and optimize natural tissue formation is a rapidly developing field in tissue engineering that aims to mimic the complex microarchitecture of tissues. Due to the versatility of bioprinting that allows the creation of complex tissue architectures, it can serve as an effective tool for the development of 3D in vitro models to study the mechanisms of SARS-CoV-2 infection in the lung during the pandemic as well [230,252]. It has been reported that a 3DB alveolar barrier produced with a micro-extrusion bioprinter is organized into a thin layer and can form multilayered clusters between epithelial and endothelial cells incorporated into Matrigel™ [253].

Considering terms of the COVID-19 pandemic and possible future pandemics, it is clear that all new technologies in tissue engineering hold promise for understanding disease pathophysiology and screening for effective therapeutics during pandemics and outbreaks. The effective use of tissue engineering tools in pandemics has the potential to change the course of epidemics by enabling fast and effective steps to be taken.

BIOMEDICAL DEVICES AND ARTIFICIAL INTELLIGENCE

TELEMEDICINE DURING PANDEMIC

Due to the lack of a specific treatment for SARS-CoV-2, preventing the spread of the virus has been the main purpose of the fight against COVID-19. This exceptional situation has challenged the health system in the whole world and revealed the need for modification in health care delivery [254]. The concept of telemedicine, the use of which began in the 1970s, consists of the provision of remote health care [255]. Telemedicine has become increasingly popular during the pandemic as a way to provide medical care remotely. This technology allows patients to consult with healthcare providers via videoconference, phone, or other forms of electronic communication. One of the main advantages of telemedicine is that it allows patients to receive medical care without having to leave their homes, which can be especially beneficial for those at high risk such as the elderly or immunocompromised. Telemedicine can also be used to provide mental health support to people who may be struggling with anxiety or depression as a result of the pandemic. Providing virtual counseling sessions can help to ensure that people have access to the support they need during this difficult time. Besides, it can also help to reduce healthcare costs. Traditional in-person medical appointments can be expensive and time-consuming, but telemedicine can be a more convenient and cost-effective alternative.

Although 1% of healthcare recipients could benefit from telemedicine services in the pre-pandemic period, a prompt and significant increase took place during the pandemic to protect individuals as well as physicians [256,257]. Telemedicine has been used as a triage method for COVID-19 and a way of managing all other diseases. Some disciplines such as internal medicine, oncology, pulmonology, cardiology, psychiatry, neurology, surgery, and dermatology used telemedicine for non-COVID-19 cases`

chronic complications [258]. On the other side, there are also some limitations to telemedicine. There may be certain conditions in which diagnosis and treatment without an in-person examination would be difficult or even impossible. Additionally, some people may not have access to the technology or internet connection needed to use telemedicine services. Despite these limitations, telemedicine has proven to be an effective way to provide medical care during the COVID-19 pandemic. As the world continues to grapple with the virus, telemedicine is likely to become an increasingly important tool for healthcare providers and patients alike.

BIOMEDICAL EQUIPMENTS

There had been several R&D developments for electromechanical devices and medical consumables during the COVID-19 pandemic. In Turkey, the Ministry of Health in cooperation with the Ministry of Industry and Technology including with the private sector has initiated domestic respiratory equipment production. This domestic respirator was first used in city hospitals and successful results were obtained. At the end of May 2020, more than 1000 domestic respirators were exported all around the globe [259].

In India, Mahindra & Mahindra, an automobile company, teamed up with Skanray Technologies (Skan-Ray) a medical equipment retail manufacturer, started to design and manufacture a new ventilator that is easy to use and easy to produce. Design, development, assembly, prototype testing, transportation, and logistics were carried out by these companies. The price of the new ventilator is 7500 INR which makes it 99.25% cheaper than the cost of an imported ventilator [260].

In the USA, General Motors came together with Ventec Life System, an American medical device company that started to produce ventilators. The Ventec-designed ventilators are fabricated at General Motors factories. 30000 ventilators were purchased by the US government [260].

In Spain, Seat, an automotive manufacturer company, took action to manufacture emergency ventilators at its Martorell facilities. These devices were utilized by the Spanish Medicines and Medical Devices Agency for clinical trials [261].

In Canada, The Milan Mechanical Ventilator has played an important role during the COVID-19 pandemic. It has low cost, no moving mechanical parts, requires compressed oxygen, and a medical air supply to operate. It performed well in stability tests when thoroughly tested against ISO standards. Emergency use permission granted from the FDA for use in hospitals. In addition, temporary authorization granted by Canada Medical Device Authorization. Then, with these, supporting documents, mass production provided and a serious amount of export made to other countries [262].

The CDC guideline highlight the precautions to be taken regarding bioaerosols contaminated from oral microflora. The risk of viral contamination may be lower if the oral viral load is decreased. Personal protection barriers, preprocedural mouth rinses, rubber dams, saliva ejectors, high volume evacuation systems, HEPA filters, UV light, and ozonization are the key infection control methods that could be preferred by health professionals [263]. For instance, an aerosol protection box could be used to protect dental staff from contaminated aerosols generated during dental procedures [264].

BIOMEDICAL DEVICES AND TEST KITS FOR DIAGNOSIS

During the COVID-19 pandemic, the development of point-of-care (POC) devices has increased to early detect and control the spread of the disease. Although the conventional methods including RT-PCR and loop mediated isothermal amplification (LAMP) are reliable and sensitive for COVID-19 diagnosis, they either require specialized personnel and bulky laboratory instruments and lack portability [265].

In China, the birthplace of COVID-19, there had been several studies for fast and reliable test kits. A test kit named "SARS-CoV-2 Antibody test" produced by Biologix Corporation was evaluated on 596 clinical cases. As a result, 361 tests were confirmed as COVID-19 cases and 235 were excluded. The sensitivity of this test kit was found as 86.43%. The specificity was 99.57%, and the total consistency appeared as 91.61% [266]. The test kit named "Diagnostic Kit for IgM/IgG Antibody to Coronavirus (SARS-CoV-2)" developed by Zhuhai Livzon Diagnostic Inc. was evaluated with 644 samples. As a result, 286 COVID-19 cases were clinically diagnosed, and 358 cases were clinically excluded. The sensitivity of the test kit has appeared as 90.6%. The specificity was 99.2% and the overall agreement appeared to be 95.3% [266].

In the evaluation report of the test kit named "WONDFO® One Step COVID-19 (SARS-CoV-2 Antibody) Test" produced by Guangzhou Wondfo Biotech, 38 PCR-positive, and 10 PCR-negative results were reported. As a result of the evaluation, the positive rate of this diagnostic kit in the performance report was determined as 100%, the negative rate as 90%, and the total compliance rate appeared as 97.92% [266]. 208 subjects were evaluated for "Eugene® SARS-CoV2 (COVID-19) IgG/IgM Rapid Test" produced by Shanghai Eugene Biotech. Of these subjects, 55 resulted as PCR-positive, and 153 resulted as PCR-negative. Finally, the sensitivity was determined as 96.4%, the specificity as 98.7%, and the accuracy was determined as 98.1% [266]. On the other hand, in the evaluation report of the test kit called "Standard™ Q COVID-19 IgM/IgG Duo Test" produced by the SD Biosensor, 40 samples were evaluated. Of these, 24 of them were PCR-positive and 16 were PCR-negative. As a result here, the specificity appeared to be

100%. Results 7 days after the first PCR, cutoff values were obtained as 91.7% for IgM and 79.2% for IgG. The cutoff for IgM was 100% just nine days after the first PCR. The initial PCR value for IgG after 12 days was 100% [266]. Finally, "VivaDiag™ COVID-19 IgM/IgG Rapid test" produced by the manufacturer of VivaChek Laboratories have analyzed over three separate analyzes via 80 positive cases, 70 positive cases, and 50 negative cases. The total positive coincidence rate of 80 positive cases was 81.25%. The total positive coincidence rate of 70 positive cases was 97.1%. The total negative coincidence rate of 50 negative cases was 100% [266].

In a recent report, Lomae et al. developed a smartphone-assisted paper-based electrochemical (ePAD) biosensor to detect SARS-CoV-2 [267]. The ePAD was fabricated via the screen-printing method and modified with pyrrolidinyl peptide nucleic acid (acpcPNA) via the formation of an aldehyde group based on the periodate oxidation of OH- of cellulose. Then, the acpcPNA probe was immobilized on the electrode surface due to the generation of covalent attachment. Finally, the hybridization occurred between the target complementary DNA (cDNA) and acpcPNA probe as the biorecognition element in the presence of [Fe (CN)6]3−/4− as the redox active indicator. Under optimal conditions, the developed biosensor exhibited a linear range from 0.1 to 200 nM and a limit of detection (LOD) of 1.0 pM using the amperometric method. In addition, the biosensor was validated for the detection of SARS-CoV-2 in ten nasopharyngeal swab samples including seven of SARS-CoV-2 positive and three of SARS-CoV-2 negative with a 100% agreement result with RT-PCR. The biosensor has advantages that it offers rapid, sensitive, disposable, and POC detection of SARS-CoV-2 nucleocapsid N gene.

Klark et al. developed an electrochemical capillary driven immunoassay (eCaDI) for POC detection of SARS-CoV-2 N protein [268]. At first, the device was fabricated using the screen-printing method on polyethylene terephthalate (PET). The sequential delivery and precise flow control of reagents and washing steps were achieved using adhesive tapes, allowing an automated operation by the end-user. The working electrode was modified with a sandwich strategy via incubation of aged casein blocker, IgG antibodies against SARS-CoV-2 N proteins, and conjugated secondary antibody. Finally, 3,3',5,5'-tetramethylbenzidine (TMB) was introduced to the electrode surface, followed by two min chronoamperometry measurement to detect SARS-CoV-2. The eCaDI showed a LOD of 68 equiv PFU/ml. The biosensor demonstrated stability over seven weeks. The applicability of the eCaDI was successfully shown in the presence of influenza A and Sindbis virus. The developed biosensor has advantages that it is low-cost, sensitive, short turnover time compared to ELISA, prevents the steps to be employed by trained personnel, and can detect nine different SARS-CoV-2 variants including *omicron* at the POC.

THE USE OF ARTIFICIAL INTELLIGENCE IN MEDICAL DEVICES

Artificial intelligence (AI) is the concept of machines performing tasks that require human intelligence. Machine learning (ML) is a technique to develop AI systems, in which, the algorithms are trained on a provided data set to calculate the desired output [269]. Systems can be developed for tasks such as classification, regression, or clustering with various machine learning techniques like Deep Learning (DL), Support Vector Machines (SVMs), Convolutional Neural Networks (CNNs), or Generative Adversarial Networks (GANs) (Figure 6) [269–271]. With the onset of the COVID-19 pandemic, much data have been obtained on the SARS-CoV-2 virus, the symptoms and pathophysiology of the infection, and the systemic long-term effects on individuals after infection. Processing these data and using it for various purposes in integration with artificial intelligence technologies has emerged as the state-of-art approach. AI systems have supported healthcare professionals in various forms in the fight against COVID-19 [272]. These applications can be evaluated under five sections:

Diagnosis and screening: Several radiological, molecular, and serological technologies are used in the diagnosis of COVID-19. AI tools can provide help to evaluate patient data from such devices quickly and effectively. Wang et al. developed a system for screening the disease using computed tomography (CT) devices. The authors adopted the GoogleNet Inception v3 CNN as a predefined model and the system reached a total accuracy of 89.5% on internal validation and 79.3% on external testing dataset [273]. Ahsan et al. compared the performance of six different DL approaches (VGG16, InceptionResNetV2, ResNet50, MobileNetV2, ResNet101, and VGG19) to detect SARS-CoV-2 infection from chest X-ray (CXR) images. For the binary models (COVID-19 and normal), VGG16 and MobileNetV2 achieved accuracy of up to 100%, on both small balanced and larger imbalanced dataset. Further, multi-class VGG16 models (COVID-19, Pneumonia, and normal) reached an accuracy of 91% [274]. Low et al. emphasized the importance of the data produced with standard operating procedures to ensure adequate training of the models for identification of COVID-19 on CT and CXR images. In their review article, the data from the open-source websites were reported to be insufficient [269]. Zhao and Bell reported that the DL applications in lung ultrasound (LUS) imaging of COVID-19 patients are promising, but limited by the operator factor, lack of a large balanced data set and explainability of the system results [275]. Combining multi-modality data such as CT, CXR, and LUS is another approach for developing such systems [276]. Deulofeu et al. developed two ML classifier systems for the diagnostic analysis of human nasopharyngeal (NP) samples by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) using

Extreme Gradient Boosting Trees (XBOOST), and SVMs techniques. The authors applied 10-fold cross-validation method on both models and the binary classifier models achieved over 90% accuracy [270]. Rohaim et al. proposed DL-CNNs to enhance the results of the reverse-transcribed loop-mediated isothermal amplification (LAMP) assay. The accuracy of diagnosis is improved with DL model (98%) when compared to the sum of the absolute difference threshold value method (81.25%) [277]. Schuller et al. reviewed the potential of computational speech and sound analysis in the crisis of pandemic, and potential use-cases are listed as risk assessment, diagnosis, monitoring the spread, monitoring of social distancing and effects, monitoring of treatment and recovery, and generation of speech and sound utilizing GANs. The authors also reported that the time, collecting patient data, model sharing, real-world audio processing, green processing, trustability of results and ethics are the main challenges [271].

Drug discovery and vaccine design: Lv et al. reviewed the AI/ML-based methods in the field of drug and vaccine development. The authors classified the model's architecture as network-based, expression-based, and integrated docking simulation algorithms, and data quality and algorithm design were reported as challenges in the field [278]. Russo et al. criticized the role of emerging technologies in vaccine discovery. The authors reported that Silico Trials (IST), a new class of computational methods can be employed for faster vaccine development and evaluation. Combination of several technologies was suggested as another solution, however, this strategy is not yet be effectively adopted, as stated in the expert opinion section [279]. Novel drug and vaccine design can be performed using GANs [280]. Target identification and validation, drug design and optimization, lead optimization, and preclinical and clinical development are all about the use of artificial intelligence by Wang et al [281] The findings demonstrated that AI might significantly improve medication development by decreasing development times and enhancing quality control. Data quality, algorithmic design, and regulatory approval were also mentioned as problems and limitations of AI in drug discovery and development.

Contact tracing: Digital contact tracing applications have been reported to be used in 36 countries by Lalmuanawma et al., demonstrating their significance as a public health tool for halting the spread of COVID-19. These programs use Bluetooth, GPS, or GSM to gather the information that may be evaluated with AI and ML. Analyzing these data can be done in a centralized fashion, a decentralized fashion, or a hybrid fashion [282]. However, privacy concerns have been brought to light by the extensive usage of digital contact tracing. Bengio et al. [283] addressed these concerns by reporting on the significance of maintaining data privacy in digital contact tracking. The authors recommend using pseudonymization, de-identification, or data aggregation to address privacy issues. This would protect individuals' privacy while also facilitating disease surveillance and management. Evidence for the efficacy of digital contact tracking in preventing the transmission of SARS-CoV-2 is provided by Ferretti et al. The authors utilized mathematical modeling to speculate on how stopping the spread of disease by digital contact tracing and other public health measures would affect the overall rate of transmission [284] Importantly, the authors show that digital contact tracing is useful for preventing the transmission of SARS-CoV-2, making this an essential outcome of the study. The authors use mathematical modeling to quantify the influence of digital contact tracing and other public health initiatives on disease transmission, indicating that digital contact tracing can play an important role in containing the pandemic. In essence, digital contact tracing applications are a vital tool for stopping the spread of COVID-19. However, precautions must be taken

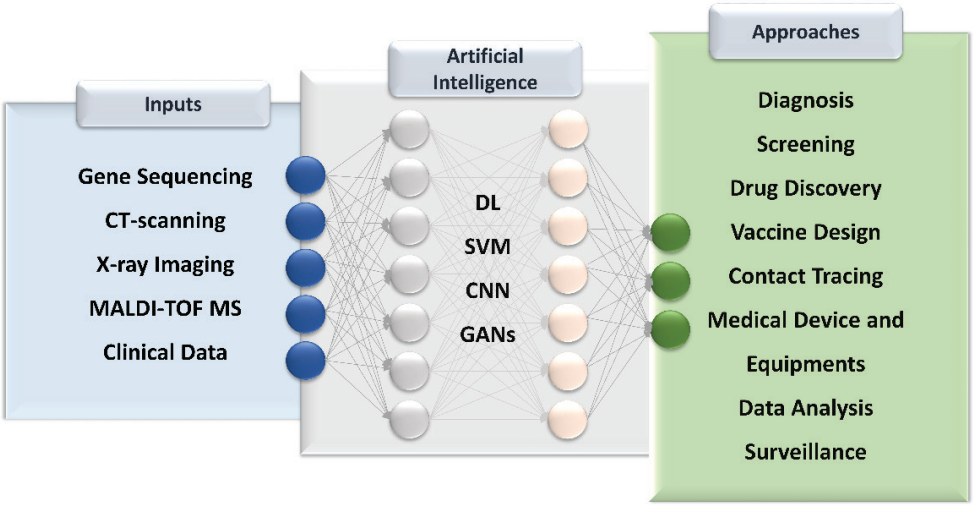

Figure 6. Use of AI methods in Combat to COVID-19.

to guarantee that sensitive personal information is safeguarded and privacy is maintained when these applications are used [283,285].

Medical devices and equipment: Tracking COVID-19 patients' vital indicators with the help of wireless wearable sensors and ML analysis is becoming increasingly critical. Sensors and cutting-edge data analysis methods are brought together in this cutting-edge technology to keep tabs on patients' health and spot any changes [285]. As an example, Wintjens et al. did a study where they employed ML-classifier systems to determine who was COVID-19 positive and who was not. To do this, scientists used a device called an electronic nose to analyze the air for volatile organic chemicals. A negative prediction value of 0.92 was shown by the ML model, which was built on artificial neural network architecture [286]. Using DL-CNNs designs like VGG16, VGG19, ResNet101, NASNet, DenseNet121, MobileNet, Xception, EfficientNet, and InceptionV3, Kogilavani et al. created a non-contact sensing system to detect COVID-19 patients. The system used ultrasound and RFID-based sensor technologies to keep an eye on breathing issues, and the VGG16 model had an accuracy of 99.76 percent [285]. Research in this paper centers on a novel approach to remote monitoring of patients with COVID-19: the combination of wearable sensors and machine learning. Patients' vital signs can be monitored with the help of the COVID-19 decompensation index (CDI) model shown here, which makes use of gradient boosted decision trees. This research demonstrates the promise of combining wearable sensors with machine learning for remote monitoring of COVID-19 patients, and it also identifies the obstacles that must be overcome to make this technology truly useful. The authors draw the conclusion that remote monitoring based on machine learning and utilizing wearable sensors can be an instrumental tool in the early detection of COVID-19 symptoms and in halting the spread of the disease. The results of the study lend credence to the hypothesis that integrating wearable sensors with machine learning algorithms can improve the quality of health monitoring for patients with COVID-19 [287].These research efforts show the promise of combining ML analysis with wireless wearable sensors to monitor critical metrics in COVID-19 patients and provide better, more immediate data on their health. Potentially, this technique could be crucial in the fight against COVID-19 and in enhancing patient outcomes.

Data analysis and surveillance: Kolozsvári et al. proposed an ensemble-based system to predict the daily number of newly diagnosed infections in six countries and forecast the first and second pandemic waves. Two Recurrent Neural Networks (RNNs) models were trained on publicly available data and extra features were added with transfer learning. The root mean squared logarithmic errors were reported to be in the range of 0.057 and 0.513 for the first, and 0.064 and 0.528 for the second model [288]. Patel et al. developed a system for predicting the disease severity based on socio-demographic, clinical, and blood panel profile data. Performance of several ML classifiers are compared (random forest, multilayer perceptron, SVMs, gradient boosting, extra tree classifier, adaboost) and the random forest algorithm reached AUC value of 0.80 for predicting intensive care need and 0.82 for predicting the need for mechanical ventilation. Models developed on quantitative data are reported to be less prone to errors and subjectivity [289].

Fatima et al. utilized Natural Language Processing (NLP) and DL methods to detect the rumors in the news and the tweets. In total, 9200 comments from Google and 34779 tweets were analyzed in terms of veracity, stance, and sentiment, and the accuracy of the proposed models were in the range of 84.97% and 99.97% [290]. Flores and Young released an article on ethical considerations for applying machine learning methods to social media data. The authors reported that the researchers should adhere to ethical principles of respect for persons, beneficence, and justice, to ensure scientific progress with public safety and confidence [291].

CONCLUSION

To combat the coronavirus disease 2019 (COVID-19) pandemic, numerous scientific groups from all over the world have advanced diagnostic tests, rapid diagnostic kits, vaccinations for immunization, and the repurposing of pharmaceuticals for therapy. Scientific communities' suggestions for methods of diagnosis, therapy, and immunization rely on the knowledge gathered by multidisciplinary sciences in health biotechnology. So much so that the development of novel approaches in numerous fields, including diagnosis, treatment, translational medicine, virology, microbiology, immunology, functional nano- and bio-materials, bioinformatics, molecular biology, genetics, tissue engineering, biomedical devices, and artificial intelligence technologies, has been driven by the pandemic, which is urgently prioritized around the world. The enthusiastic developments in all these disciplines show what kind of challenges the world will face in case of the pandemic that may occur in the future and how strong the scientific world's hand is in tackling these urgent health issues. On the other hand, with its devastating results, this pandemic has also revealed the fact that the multidisciplinary approaches of the scientific world should be continued comprehensively.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

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