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Review

The Application of Biomaterials for the Vaccine, Treatment, and Detection of SARS-CoV-2

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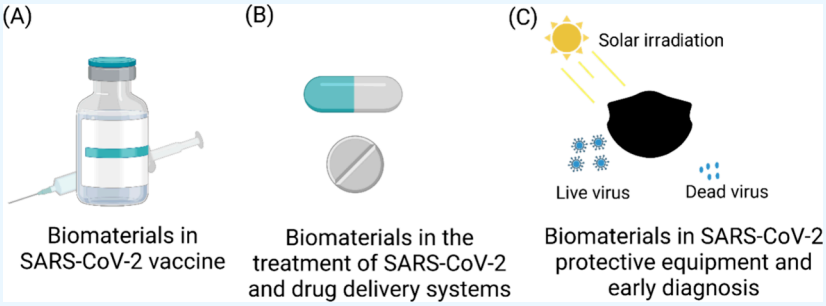

ABSTRACT: The coronavirus disease-19 (COVID-19) pandemic has had a significant impact on human life worldwide since 2019. Specific vaccines and antiviral agents are the most effective means of preventing and treating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Additionally, antiviral protective equipment and early diagnosis also contribute to controlling the spread of COVID-19. The utilization of biomaterials in medicine and pharmaceuticals is crucial to ensure the positive impact of vaccines, antiviral agents, and protective equipment. In this review, we discuss the application of various types of biomaterials, including polymers, lipid nanoparticles, inorganic biomaterials, protein- or peptide-associated biomaterials, self-assembled biomaterials, and other biomaterials, for the vaccine, treatment, and prevention of COVID-19. Finally, we provide a perspective on future opportunities and challenges for developing biomaterials to combat other viral outbreaks and diseases.

1. INTRODUCTION

The coronavirus disease-19 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a global challenge, infecting 750 million people worldwide and causing 6.81 million deaths.[1] Fortunately, biomaterials offer novel strategies to combat COVID-19.[2−4] Before discussing these strategies in detail, it is essential to understand the background of COVID-19.

The SARS-CoV-2 spike (S) protein has a high affinity for the angiotensin-converting enzyme 2 (ACE2) receptor, primarily found on epithelial cells.[5] The innate immune system responds to infection by recruiting immune cells to the site and activating the complement cascade and adaptive immune system.[6] However, this may not provide adequate protection for most individuals, and the infection can rapidly progress to hyperinflammatory cytokine storms and lung damage without therapeutic interventions.[7] Infection with SARS-CoV-2 in humans can lead to pneumonia, acute respiratory distress syndrome (ARDS), acute lung injury, and cytokine storm syndrome.[8,9] Severe COVID-19 can lead to systemic inflammation and multiorgan failure due to increasing cytokine storms.[10] Therefore, developing effective vaccines and drugs to inhibit viral entry and regulate systemic immune responses along with protective equipment and early detection is crucial.

Various antiviral strategies have been proposed to combat the COVID-19 pandemic, in which biomaterials offer a promising approach for treating and preventing infection.[11] There are three main applications for biomaterials in this regard: (I) enhancing the immunogenicity and efficacy of COVID-19 vaccines, (II) preventing infection, and (III) repairing and regenerating damaged tissue. This review will discuss the use of biomaterials as vaccine adjuvants or carriers to deliver anti-SARS-CoV-2 drugs and enhance its efficacy, anti-SARS-CoV-2 drugs, and medical devices or protective equipment to prevent the transmission of COVID-19.

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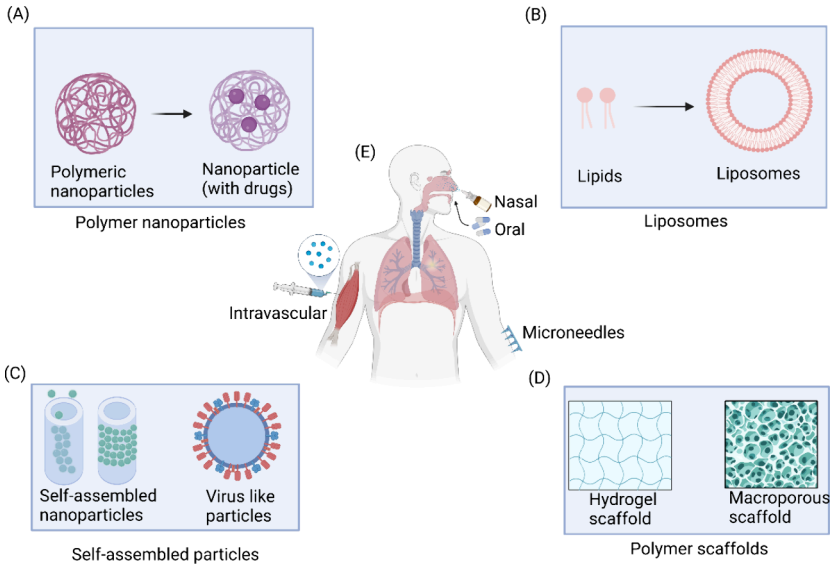

Figure 1. Some key biomaterial platforms in controlled drug delivery and release. These efforts include (A) polymer nanoparticles, (B) liposomes, (C) self-assembled particles, and (D) polymer scaffolds. (E) These biomaterial platforms can be applied in oral, nasal, and intravascular immunizations. Image created with BioRender.com, with permission.

2. BIOMATERIALS HELP TO Anti-SARS-CoV-2 Strategies

The COVID-19 pandemic has prompted scientists worldwide to seek effective strategies to combat the disease. COVID-19 vaccines, anti-SARS-CoV-2 strategies, and early diagnosis are crucial for controlling the spread of the disease. Generally, vaccines without adjuvants have limitations in terms of immunogenicity and stabilization, which can be overcome by using proper adjuvants and delivery systems (Figure 1).[12] For example, recombinant protein vaccines have limited efficacy without adjuvants,[13] and nucleic acid vaccines can be degraded without appropriate delivery systems.[14] Therefore, the application of biomaterials in COVID-19 vaccine adjuvants and delivery systems development has been extensively explored to improve immunogenicity and stability, and minimize side effects (Table 1).[15] In addition to vaccines, anti-SARS-CoV-2 strategies, and antiviral protective equipment and early diagnosis also play a vital role in controlling the spread of COVID-19.[16−19] This review discussed the application of biomaterials as vaccine adjuvants and treatments and for early diagnostics and protective equipment, highlighting their importance in the fight against COVID-19.

2.1. The Application of Biomaterial in SARS-CoV-2 Vaccines. Vaccination is one of the most effective preventive measures against COVID-19.[20] Notably, adjuvants and appropriate drug delivery systems are necessary to enhance the immunogenicity of subunit antigens, facilitate antigen delivery, and control release, respectively.[13,21] Adjuvants can improve the immune response by chemically or physically connecting with antigens, particularly by promoting cellular uptake efficiency to increase antigen-specific immune responses.[22] Similarly, appropriate drug delivery platforms can increase cellular uptake and protect drug payloads from premature action.[23−25] Among nonviral delivery systems for mRNA, lipid nanoparticles (LNPs) are the most clinically advanced.[26] In this section, we discuss the application of adjuvant and delivery biomaterials in anti-SARS-CoV-2 vaccine candidates.

2.1.1. Natural Polymer Biomaterials in SARS-CoV-2 Vaccines. 2.1.1.1. Chitosan. Chitosan, a product derived from the natural polysaccharide chitin through partial deacetylation, can be utilized as an adjuvant for DNA vaccines.[27] These vaccines can be administered orally or nasally due to the mucoadhesive nature of chitosan. Chitosan's positively charged nature is beneficial in serving as a DNA vaccine delivery system by promoting electrostatic interactions with negatively charged DNA vaccines, thereby enabling the DNA plasmids to encode candidate antigens.[28,29] Furthermore, the polymer can protect DNA from degradation by extracellular nucleases when it is bound to the cationic surface or loaded in particles. Chitosan can induce inflammasome and promote cellular and humoral immunity by binding to cell surface receptors such as Toll-like receptor-2 (TLR-2) and stimulating the DNA sensor cGAS-STING pathway to induce dendritic cell (DC) maturation and TH1 immune response in type I interferons. In addition, a mannose-TLR7/8 agonist adjuvant could enhance vaccine-induced humoral and cellular immune responses.[30]

Chitosan is a promising adjuvant for the COVID-19 vaccines. For instance, Tatlow et al. developed an inhaled chitosan-coated DNA vaccine and demonstrated its potential as a preventive COVID-19 vaccine.[31] Another gold-nanostar-chitosan-associated COVID-19 DNA vaccine encoding S protein also contributes to rapid and long-lasting mucosal immunization in the respiratory mucosa and lungs.[32] Cationic chitosan is commonly used to deliver negatively charged DNA, while its quaternary derivatives (trimethylchitosan) can deliver recombinant proteins. Lin et al. developed fucoidan/trimethylchitosan nanoparticles (FUC-TMC NPs) coated with a recombinant S protein vaccine, and when coadministered with cytosine-phosphate-guanosine-oligodeoxynucleotides (CpG-ODNs), robust immunogenicity was observed.[33]

In addition to antibacterial and antiviral activities, chitosan and its derivatives (trimethyl chitosan, carboxylated chitosan, and acylated chitosan) have good biocompatibility and degradability.[34] When used as a drug carrier, chitosan can stabilize the ingredients in the drug, promote drug absorption,

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Table 1. Key Examples of Biomaterials for Anti-SARS-CoV-2 Vaccine and Treatment

approach	biomaterial	applications	activity	refs
Natural polymers	Chitosan	Inhaled chitosan DNA vaccine has obtained sufficient production of secretion protein to compete with the coronavirus.	Inflammasome and TH1 immune response via the STING pathway	31, 227
		Gold-nanostar-chitosan-associated COVID-19 DNA vaccine contributes to rapid and long-lasting mucosal immunization.	Promote TH1 immune response	32
	Alginate	Alginate-based adjuvants showed an enhanced immunogenic response and a TH1/TH2 immune response balance	Balanced TH1/TH2 immune response	38, 43, 45
	Delta inulin	Advax is a nonreactogenic adjuvant based on delta inulin.	Balanced TH1/TH2 immune response	40
		Advax-SM could induce a comparable TH1 immune response induce immunogenicity	TH1 immune response	43, 45
		Advax-CpG55.2 adjuvant could induce a comparable TH1 immune response and anti-SARS-CoV-2 infection effect.	TH1 immune response	43,45
Synthetic polymers	PLGA	Recombinant SA-E-loaded PLGA nanovaccine robust humoral and cellular immunity and comparable levels of IL-2 and TNF-a.	Promote IL-2 and TNF-a cellular responses	51
	Dissolvable hydrogel	Microneedle array (MNA) delivery of the SARS-CoV-2 subunit vaccine could elicit improved antigen-specific antibody responses and long-lasting immune responses compared to traditional needle-based injections.	Promote antigen immunogenicity compared to traditional needles	58
	O2-Cryogels	The oxygen-generating COVID-19 cryogel-based vaccine (Cryogelvax) could recruit DCs at the injection site and then release antigen and adjuvant in a sustained fashion and elicit humoral and cellular immune responses.	Recruit DC; controlled drug release	67
Lipid biomaterials	Cationic lipids	Cationic lipids were used for mRNA-1273 and BNT162b2, which could induce robust humoral and cellular immune response in clinic.	Carry positive charged drugs	78, 79
	Lipid-polymer hybrids	Lipid-polymer hybrids containing fluoxetine hydrochloride could effectively bind with SARS-CoV-2 main protease with comparable biocompatibility.	Enhance antiviral drug activity and bioavailability	179
	Emulsions	The MF59-adjuvanted spike glycoprotein-clamp vaccine showed enough safety and potential efficacy against SARS-CoV-2.	Promote drug dispersion and absorption; help improve drug bioavailability	90
	Liposomes	An RBD vaccine formulated in AS01 could significantly promote vaccine immunogenicity and functional activity.	Significantly enhanced vaccine immunogenicity and functional activity	99
		A hereafter designated RBD nanoparticle formulated in AS03 showed enough immunogenicity.	Promote immunogenicity	106
Inorganic biomaterials	Carbonaceous nanomaterials	Multiwalled carbon nanotubes were more efficient in specific and quick (1 min) detection of SARS-CoV-2 antigen than other 1D/2D carbonaceous nanomaterials	Electrical conductivity, easy functionalization, and high surface area	215
	Gold nanoparticles	Gold nanoparticle (AuNR) could detect RBD-specific antibody levels from fingertip blood samples semiquantitatively and instrument-free.	Help block pseudovirus infection and promote drug delivery	32, 223, 224
	Silica nanoparticles	Silica nanoparticles could also be used to detect and treat SARS-CoV-2.	High potential for drug carriers and detections	182, 183, 206, 218
Protein or peptide associated biomaterials	Short synthetic peptides	A SARS-CoV-2 vaccine based on conjugation of SARS-CoV-2 RBD with IC28 peptide (RBD-IC28-M) evaluated immunogenicity and antigenicity.	Induce robust CD4+ T cell responses and TH1-based immune response	112
Self-assembled biomaterials	Self-assembled nanoparticles	COVID-19 vaccine based on self-assembled nanoparticles showed comparable antiviral activity of the anti-SARS-CoV-2 antibodies.	Induce interferon-γ and interleukin-4 cellular responses	110, 114, 129, 130
	Virus-like particles	VLPs have proven to be a promising approach for anti-SARS-CoV-2 treatment with robust humoral immune responses.	Promote humoral immune response	105, 116, 132, 133, 140, 143
Other potential biomaterials	Saponins	Saikosaponins A could inhibit the interaction between the RBD domain and ACE II receptor.	Inhibit interaction between the RBD domain and ACE2 receptor	187
		Recombinant SARS-CoV-2 S1-Fc protein formulated with AD 11.10 and AD20 Gold+ adjuvant could effectively promote humoral immune responses in mice and nonhuman primates.	Promote humoral immune responses	146
	Bisphosphonates	FH002C coadministrated with spike ectodomain protein (StriFK), significant TH1 and TH2-based immune responses.	Induce TH1 and TH2 immune responses	148

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delay or control the dissolution rate of the drug, help the drug reach the target organ, and prevent the drug from irritating the stomach. In summary, chitosan has the potential to enhance vaccine immunogenicity as an adjuvant or delivery system.

2.1.1.2. Alginate. Alginate, another natural polysaccharide that can be used as a drug delivery carrier, is often complexed with chitosan to deliver a pH-responsive drug. Because the carboxylate acid groups of alginates are negative, they could bind to the positively charged amino groups of chitosan to form alginate/chitosan complex, which is pH-sensitive.[35,36] Studies have demonstrated the efficacy of alginate-based adjuvants in hepatitis A vaccines and the SARS-CoV-2.[37] AbdelAllah et al. showed that the hepatitis A vaccine delivered by alginate-coated chitosan nanoparticles could induce a comparable humoral and cellular immune response in mice.[37] A study on hepatitis B vaccine formulated with chitosan and alginate-based adjuvants showed an enhanced immunogenic response and a TH1/TH2 immune response balance compared to commercial alum-adjuvant vaccines.[38] In addition, alginate is immune-stimulated, tolerable, cheap, and safe, as well as nonirritating and nontoxic.[39] Based on the results, alginate is a considerably efficient delivery biomaterial for vaccines.

2.1.1.3. Advax. Advax, composed of polysaccharide delta inulin microparticles, has been used for developing COVID-19 vaccines due to its nontoxic and nonirritating properties, outstanding immune stimulation properties, and good tolerability.[40] Since these particles cannot be filtered and sterilized, γ radiation is required for sterilization. Delta inulin is less sensitive to sterilizing doses of γ radiation than gamma inulin.[41] Different from alum adjuvant which could induce TH2 bias, Advax marked balanced TH1 and TH2 immune responses.[42] Li and co-workers reported that recombinant SARS-CoV-2 S protein extracellular domain formulated with Advax-SM (Vaxine, Adelaide, Australia) was well-tolerated and could induce a comparable TH1 immune response and anti-SARS-CoV-2 infection effect when administered intramuscularly.[43] When this recombinant protein was coadministered with Advax-CpG55.2 adjuvant (Vaxine Pty Ltd., Adelaide, Australia), they called it the Covax-19/Spikogen vaccine, and robust immune responses and protection were observed in hamster models[44] and clinical trials.[45] Another subunit recombinant S protein vaccine combined with Advax-SM adjuvant was also shown to induce immunogenicity and could be used as a prime-booster vaccine against the ever-mutating SARS-CoV-2.[46] In conclusion, alginate-based adjuvants could increase vaccine efficacy by enhancing both humoral and cellular immune responses.

2.1.2. Synthetic Polymer Biomaterials in SARS-CoV-2 Vaccines. 2.1.2.1. PLGA. Poly(D,L-lactic-*co*-glycolic acid) (PLGA), a synthetic copolymer of poly(lactic acid)/polylactide (PLA) and poly(glycolic acid)/polyglycolide (PGA), is biocompatible and nontoxic and widely used in polymeric drug delivery systems.[47] In commercial settings, different grades of PLGA can be synthesized by their ratio of lactic acid to glycolic acid, inherent viscosity, and molecular weight,[47] while different physical characteristics of PLGA are available depending on the parameters specific to the synthesis method employed.[48] PLGA is approved by the U.S. Food and Drug Administration (FDA).[49] Due to its biocompatibility, biodegradability, low toxicity, and controlled bioavailability, PLGA is used in COVID-19 vaccines as an adjuvant and delivery platform.[50] Huang et al. developed a recombinant SA-E-loaded PLGA nanovaccine that, when administered intramuscularly, demonstrated robust humoral and cellular immunity.[51] In contrast, the S1-E vaccine without an adjuvant or PLGA failed to induce sufficient antibodies to combat SARS-CoV-2. PLGA is also used as a nucleic delivery vehicle, as demonstrated by Li et al.'s development of PLGA-associated particle-in-particle nanoparticles for the delivery of DNA and mRNA in vitro and in vivo. These nanoparticles had sustained release and transfection efficacy and good stability, and promoted TH1 immune response to combat COVID-19.[52] However, PLGA-based plant delivery vehicles may result in reduced efficacy.[53] Overall, PLGA is widely used for the delivery of COVID-19 vaccine adjuvants and delivery.

2.1.2.2. Dissolvable Hydrogels. Dissolvable hydrogels such as carboxymethyl cellulose (CMC) and trehalose are also used in vaccine delivery when developed as microneedle arrays (MNAs). The skin contains many immunologically active accessory cells and antigen-presenting cells, making it an ideal target for vaccination to induce durable adaptive immunity.[54,55] MNAs are a technique that involves fine needles puncturing the skin.[56] Compared to traditional needles, MNAs offer several advantages. First, they induce less pain. Second, MNA delivery generates an accumulation of vaccines in the local skin microenvironment with spatially and temporally controlled release.[57] Third, scientists have indicated that the MNA delivery of the SARS-CoV-2 subunit vaccine can elicit improved antigen-specific antibody responses and long-lasting immune responses compared to traditional needle-based injections.[58] Additionally, Yin and colleagues developed a separable microneedle patch to deliver DNA nanovaccines, which induced durable and potent adaptive immunity.[59] However, only one clinical study has presented the development of MNAs-based delivery of mRNA COVID-19 vaccine (NCT05315362).

2.1.2.3. Crygels. Cryogels, which are scaffold biomaterials with a unique interconnected microporous network, have shown promise in the development of cancer and antivirus vaccines.[60,61] Briefly, during cryogelation, the reactants are controlled in the unfrozen/semifrozen phase to form a cross-linked network during polymerization, and the ice crystals nucleated from the aqueous phase during the freezing process have a porogenic effect.[62] In addition, at temperatures above freezing, these ice crystals melt and form a network of interconnected large pores.[63] Cryogels generally have greater mechanical stability than traditional hydrogels. Cryogel-based vaccines have been reported to enhance the immune response by activating DCs and B cells and recruiting immune cells in situ. Additionally, cryogels have been found to promote the secretion of granulocyte macrophage colony-stimulating factor (GM-CSF), which can enhance immunity.[64−66] Recently, Colombani et al. developed an oxygen-generating COVID-19 cryogel-based vaccine (Cryogelvax) and assessed its immunogenicity. When administered via post-subcutaneous injection, Cryogelvax recruited DCs at the injection site and released antigen and adjuvant in a sustained manner. The released antigens stimulated DC activation, eliciting both TH1 and TH2 immune responses, and generated high levels of binding and neutralizing antibodies to combat SARS-CoV-2 infection.[67]

In summary, synthetic polymer materials, particularly PLGA, play a significant role in the delivery of COVID-19 vaccines. Cryogels have also shown promise as scaffold biomaterials for

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vaccine development, with Cryogelvax exhibiting strong immunogenicity in preclinical studies.

2.1.3. Lipid Biomaterials in SARS-CoV-2 Vaccines. The success of mRNA vaccines developed by BioNTech/Pfizer and Moderna in response to the COVID-19 pandemic has led to increased attention on lipid biomaterials and mRNA technology.[68] Lipid biomaterials, including cationic lipids, lipid-polymer hybrids, emulsions, and liposomes, can be structured by spontaneous formatting of lipid bilayers.[69] Lipid biomaterials have multifunctional properties that enable them to encapsulate both hydrophilic and hydrophobic substances, integrate charged moieties to induce antigen encapsulation, and facilitate targeting ligand uptake by antigen-presenting cells.[70,71]

2.1.3.1. Cationic Lipids. Cationic lipids, which consist of an amine group, a hydrophobic chain, and a linkage group, have been widely used in liposome nanoparticle delivery systems.[72] These lipids, along with ionizable lipids, are composed of lipid nanoparticles (LNPs) that carry a positive charge. The positively charged LNPs allow for the rapid incorporation of nucleic acids that have negative charges and also promote cellular uptake and endosomal escape.[73] However, the use of positively charged LNPs can lead to increased cytotoxicity, low bioactivity, and rapid clearance from the bloodstream.[74−76] Fortunately, the use of ionizable cationic lipids has addressed these biocompatibility issues and improved the efficiency of neutral systems.[77] Recently, the FDA-authorized mRNA-based vaccines, such as BNT162b2 (BioNTech and Pfizer) and mRNA-1273 (Moderna).[78,79], have been formulated using cationic-based LNPs such as ALC-0315 (Acuitas) and SM-102 (Moderna), respectively.[80−82] In addition to cationic lipids, lipid-polymer hybrids have also shown potential efficacy against SARS-CoV-2 infection and have been used in LNPs.[83,84] For example, Khater and colleagues demonstrated that lipid-polymer hybrids containing fluoxetine hydrochloride, a selective serotonin reuptake inhibitor, could effectively bind with the SARS-CoV-2 main protease with comparable biocompatibility.[83]

2.1.3.2. Emulsions. Emulsions are common carriers for lipids and allow controlled hydrolysis and absorption of lipids.[85] An emulsion is a mixture of two completely immiscible liquids, which were named as the dispersed phase and continuous phase. Generally, according to the composition of the dispersed droplets, the emulsion can form oil-in-water (oil is the dispersed phase, and water is in the continuous phase) or water-in-oil (water is the dispersed phase, and oil is in the continuous phase) emulsions.[86] The mechanisms of emulsification were related to many chemical and physical processes and mechanisms such as surface theory, repulsion theory, and viscosity modification.[87] In addition, emulsions promote drug dispersion and absorption and help to improve drug bioavailability. Emulsions of oil-based drugs are precisely dosed and improve skin permeability.[88]

The use of emulsions as adjuvants can stimulate immunity and improve vaccine efficiency. One commonly used oil-in-water nanoemulsion is MF59, which has been licensed as a safe and potent vaccine adjuvant for promoting efficacy against viruses.[89] Many SARS-CoV-2 vaccines, such as the MF59-adjuvanted Sclamp vaccination formulated by Watterson et al., have utilized MF59 as an adjuvant.[90,91] Preclinical trials have shown comparable immunogenicity in both humoral and cellular immune responses.[92] In clinical trials, the MF59-adjuvanted spike glycoprotein-clamp vaccine has demonstrated safety and potential efficacy against SARS-CoV-2.[90] He et al. developed an MF59-like adjuvant with a composition similar to that of MF59, which, when formulated with RBD-HR/trimer protein, elicited robust and sustained immune responses.[91] In addition to MF59, the aluminum-based emulsion adjuvant has also shown a benefit against SARS-CoV-2. For example, the newly developed 3M-052-alum adjuvants promoted a better humoral immune response than alum when coadministered with RBD protein.[93] Overall, emulsions are commonly used as vaccine adjuvants against SARS-CoV-2.

2.1.3.3. Liposomes. Liposomes, which are often composed of phospholipids (phosphatidylcholine), cholesterol, and some other lipids, are small artificial vesicles with spherical shapes. The aqueous solution core is surrounded by a hydrophobic membrane, which hampers the exudation of encapsulated hydrophilic solutes in the core.[94] Encapsulation technologies can be divided into two types: passive encapsulation technologies, which rely on the random capture of molecules during liposome formation, and active encapsulation technologies, which rely on the presence of transmembrane ion gradients or charged lipids.[95] Liposomes could be developed by disrupting biological membranes.[96] Because of their biocompatibility, hydrophobicity and/or hydrophilicity, particle size, and some other properties, liposomes were regarded as vehicles to deliver drugs like therapeutic mRNA and DNA.[97,98]

Kinds of liposomes, AS01 and AS03, have been utilized as vaccine adjuvants against SARS-CoV-2 in commercial settings. AS01 and AS03 adjuvant both could be purchased from InvivoGen. Scaria et al. developed a protein−protein conjugate vaccine based on the RBD antigen using either Alhydrogel or AS01. They found that the vaccine formulated in AS01 significantly enhanced vaccine immunogenicity and functional activity, whereas the vaccine developed in Alhydrogel did not achieve similar results.[99] Another S1 protein-based COVID-19 vaccine formulated with AS01 demonstrated robust humoral responses.[100] However, no relevant clinical studies on AS01 have been reported. In contrast, clinical trials on subunit vaccines with AS03 adjuvant have been conducted.[101−105] Arunachalam et al. developed an RBD nanoparticle (RBD-NP), which when coadministered with adjuvants such as Essai O/W 1849101, AS37 (a TLR7 agonist), CpG1018-alum (a TLR9 agonist), and AS03, only the RBD-NP-AS03 showed significant immunogenicity.[106] Alum adjuvants could improve the poor immunogenicity of CpG1018. No difference was observed in the immunization of S-trimer (a recombinant protein) with CpG1018 plus alum adjuvants or AS03. In summary, emulsions and liposomes have the potential to deliver adjuvants and induce antibodies and cellular immunity. Compared to other biomaterials-based COVID-19 vaccines, many lipids' biomaterials-based COVID-19 vaccines have been approved for use.

2.1.4. Short Synthetic Peptides in SARS-CoV-2 Vaccines. The traditional peptide syntheses need the consideration reaction between the carboxyl group of one amino acid and the amino group of another. Two methods of peptide synthesis are solution synthesis and solid-phase synthesis (SPPS).[107] These synthetic processes include peptide bond formation and/or deprotection, as well as modification of the main- and side-chain. Liquid-phase peptide synthesis is mainly used to synthesize short peptides no more than tetrapeptide. During the solid-phase approach, each peptide is anchored at the side

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chain functional group or C-terminus of an insoluble/soluble polymer. In both approaches, a single N-protected amino acid unit is connected to the free N-terminal amino group of the growing peptide. After deprotection, a new amino group is exposed, which may be attached to another amino acid. After the synthesis is completed, the required peptide is cleaved from the resin under the action of acids of different strengths.[107] However, the two approaches suffer from many complex synthetic steps, high cost, and/or cumbersome purification. Some rapid, mild, inexpensive, and convenient approaches are in development and still need to be improved.[108]

Short synthetic peptides can serve as self-adjuvanting protein biomaterials and can assemble into long nanofibers, which can act as adjuvants. When combined with other antigens, synthetic peptides can be used as self-adjuvanting peptides.[109] Nanofiber-based B and T cell epitopes can regulate adaptive immune responses through local inflammation.[110] Short synthetic peptides such as Pam2Cys and Pam3Cys, which are TLR2 agonists, can induce robust CD4+ T cell responses when fused with ESAT6 protein.[111] IC28 peptide, a TLR5-dependent adjuvant, showed improved immunogenicity and antigenicity when conjugated with recombinant RBD (RBD-IC28-M).[112] Wen's group developed a TLR7 agonist-conjugated SARS-CoV-2-S1 protein vaccine, which activated vital immune cells in vitro and induced robust TH1-based immune responses in vivo.[113] Other studies have also shown promising results with peptide vaccines conjugated with TLR7 agonist (CoVac501)[114] or α-galactosylceramide, an invariant natural killer T cell agonist.[115] These findings suggest that self-adjuvanting proteins could be effective strategies against SARS-CoV-2.

2.1.5. Self-Assembled Nanoparticles in SARS-CoV-2 Vaccines. Nanoparticles (NPs) with self-assembled scaffold structures are capable of carrying the entire S protein or RBD domain in a trimeric configuration.[116] NPs that utilize naturally oligomer-forming molecules can express antigens and scaffold proteins separately or simultaneously. Notably, most NP vaccines against SARS-CoV-2 express antigens and scaffold proteins separately, as NPs are loaded with antigen via a linking system.[117,118] There are two advantages of a separate expression. One is that the NP scaffold can be expressed by *Escherichia coli*, while the production of the antigen portion is eukaryotic-based. *E. coli*-based expression is much cheaper and faster than eukaryotic expression systems.[116] The other is that the linking system allows the antigen to be easily shared by different kinds of NP scaffolds.[119,120]

The icosahedral protein scaffold, I53-50, has shown robust immunogenicity in animal models.[121] Recently, Arunachalam's group developed an I53-50 protein nanoparticle scaffold-based RBD COVID-19 vaccine (RBD-I53-50 NP) and demonstrated its protective effects against SARS-CoV-2 in rhesus macaques.[106] In addition, a phase 1/2 trial indicated that RBD-I53-50 NP could be tolerated and effective when coadministered with AS03 adjuvant.[122] Another I53-50 NP expressing S protein vaccine (S-I53-50 NP) protected macaques from SARS-CoV-2 challenge.[123] Apart from I53-50, self-assembling nanoparticles can also be developed via a ferritin nanoparticle scaffold. Most of these NPs express the RBD domain,[124−126] but seldom express the S protein.[127,128] Many RBD-based mi3 (a self-assembling NP scaffold) vaccines have been generated to fight against SARS-CoV-2.[117,129−131] The RBD-SpyCatcher-mi3 vaccine developed by Halfmann and co-workers showed broadly cross-reactive anti-SARS-CoV-2 antibodies.[129] However, it is uncertain whether ferritin nanoparticle scaffold-based COVID-19 vaccines are more effective than icosahedral protein scaffold-based COVID-19 vaccines. Nevertheless, the use of NPs shows great promise in the COVID-19 vaccine development.

2.1.6. Virus-like Particles in SARS-CoV-2 Vaccines. Similar to NPs, virus-like particles (VLPs) can be produced by self-assembly and are considered a promising platform for vaccine development. VLPs are intrinsically immunogenic substances that carry genetic material and pathogen genes.[132,133] To ensure safety and rendering VLPs replication, the essential gene is removed. Besides their immunogenicity, VLPs can carry foreign antigens or membrane proteins with linking systems and/or scaffold systems.[134] These continuous advances and improvements in VLP technology promote the scope of application in vaccines.

As a safe and effective technique, VLPs are excellent candidates for the COVID-19 vaccine design. For example, research by van Oosten et al. indicated that the AP205 bacteriophage (AP205 VLP) conjugated to the SARS-CoV-2 S1 domain vaccine could induce antibodies that neutralize a broad spectrum of viral variants.[135] Another COVID-19 vaccination based on the SARS-CoV-2 S protein conjugated to adeno-associated virus/phage (AAVP) particles showed comparable humoral immune responses.[136] Other viruses, such as human type 5 adenovirus (Ad5),[137,138], chimpanzee adenovirus (ChAd),[139] and cucumber mosaic virus (CuMV)[140] pseudovirus platforms, are employed in the development of SARS-CoV-2 vaccine candidates. Ad5-based VLPs were found to protect rhesus macaques and mice against SARS-CoV-2 in preclinical trials.[137,138] In addition, clinical trials demonstrated that the Ad5 COVID-19 vaccine is safe, effective, and immunogenic.[141,142] Generally, VLPs can express the S gene. Strategies, such as translating S as a 19 amino acid-deleted S or removing the polybasic cleavage site, were required to improve the immunogenicity of antigen.[139,143] Furthermore, an Ad5-based COVID-19 vaccine has been approved to come into the market in China.[144] In conclusion, VLPs are promising candidates for vaccine development due to their strong immunogenicity, ability to elicit protective neutralizing antibodies, and reliable safety.

2.1.7. Other Potential Biomaterials: Saponins and Bisphosphonates in SARS-CoV-2 Vaccines. Saponins and bisphosphonates (BPs) have been explored as potential COVID-19 vaccine adjuvants. Saponins, which are triterpenoid glycosides or steroids purified from *Quillaja saponaria*, exhibit anti-inflammatory and immunostimulatory properties.[145] Recombinant SARS-CoV-2 S1-Fc protein formulated with saponin-based microemulsion (AD 11.10) and nanoemulsion with synthetic MPL (AD20 Gold+) adjuvant have been found to effectively promote humoral immune responses in mice and nonhuman primates.[146] Saponin-containing adjuvants help promote robust germinal center B and follicular helper T (TFH) cell immune responses.[147] Despite this, the protective effect of the saponins and their molecular mechanisms remain unknown. FH002C is a nitrogen bisphosphonate-modified zinc-aluminum hybrid adjuvant. When coadministrated with spike ectodomain protein (StriFK), significant TH1 and TH2-based immune responses were stimulated, along with reduced lung pathology and symptoms in many animals. Compared to Al001 adjuvant, FH002C adjuvant showed better immunogenicity.[148] Therefore, these biomaterials have potential in anti-SARS-CoV-2 prevention and therapy as drug delivery systems.

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The use of biomaterials as adjuvants and delivery carriers for COVID-19 vaccines has been successful in stimulating both humoral and cellular immune responses to combat COVID-19. While vaccines may not completely inhibit SARS-CoV-2 infection, they can prevent severe COVID-19, hospitalizations, and mortality.[149,150] Furthermore, the neutralization antibodies induced by early proposed SARS-CoV-2 vaccine (based on Wuhan-1) could not induce comparable neutralization antibodies against the newly emerged variants, especially XBB sublineages.[151−156] Therefore, the WHO indicated that developing a vaccine based on XBB.1.5 was suggested.[157] Fortunately, many vaccines with biomaterial adjuvants based on XBB.1.5 showed enough protectivity against Omicron and the newly XBB sublineages, with a high level of neutralizing antibodies against variants of concerns.[158,159] In all, the successful application of biomaterials in COVID-19 vaccines provides hope not only for containing this infectious disease but also for ending other infectious diseases and cancers.

2.2. The Application of Biomaterials in the Treatment of SARS-CoV-2 and Drug Delivery Systems. In addition to their use as adjuvants and delivery vehicles for COVID-19 vaccines, biomaterials themselves have antiviral properties and could be used as carriers for delivering drugs.[160] These antiviral biomaterials could be applied for the treatment of SARS-CoV-2. Furthermore, while many anti-SRAS-CoV-2 agents have been approved by the WHO, their efficacy has been limited by adverse side effects.[161,162] Proper drug delivery platforms could solve these side effects by reducing immune reactions, increasing cellular uptake, and protecting drug payload from premature action.[23−25] There are ongoing discussions about the use of anti-SRAS-CoV-2 and drug delivery biomaterials.

2.2.1. Synthetic Polymers in the Treatment of SARS-CoV-2 and Drug Delivery Systems. Drug delivery using PLGA nanoparticles has recently been explored for anti-SARS-CoV-2 treatments. Many studies on PLGA focus on nanoparticle systems to deliver drugs to targeted tissues and release drugs in a controlled manner. For example, Wu et al. developed PLGA-associated nanoparticles loaded with remdesivir (an ACE inhibitor) and showed its antiviral abilities in vitro.[163] Lopinavir (LPV), an antiviral drug, could be loaded into PLGA nanoparticles coated with macrophage membranes (PLGA-LPV@M) to reduce tissue viral loads in mouse models.[164] Other anti-inflammatory and antiviral drugs, such as celecoxib,[165] quinine,[166] oseltamivir-phosphate,[167] favipiravir,[168] and fingolimod,[169] could be coated on or encapsulated into PLGA polymeric nanoparticles.

2.2.2. Natural Polymers in the Treatment of SARS-CoV-2 and Drug Delivery Systems. Natural polymers, such as chitosan, cellulose, and alginate, have also been studied for their potential in drug delivery for the COVID-19 treatment. Chitosan is a cationic polysaccharide with a high affinity for negatively charged viruses, making it an attractive candidate for antiviral drug delivery.[170] Chitosan nanoparticles loaded with remdesivir have been shown to inhibit SARS-CoV-2 replication in vitro.[171] Similarly, chitosan nanoparticles loaded with interferon-alpha have been shown to improve lung function and reduce viral loads in a mouse model of SARS-CoV-2 infection.[172] Cellulose and alginate have also been explored as drug delivery vehicles for anti-SARS-CoV-2 agents, with promising results in vitro and in animal models.[173,174]

2.2.3. Lipid Biomaterials in the Treatment of SARS-CoV-2 and Drug Delivery Systems. In addition to their use as antigen carriers, lipid biomaterials can serve as nanocarriers for delivering chemotherapeutic agents such as remdesivir, gallium maltolate, and tripterin to achieve potent antiviral effects.[175] Li et al. developed lyophilized remdesivir liposomes (Rdv-lips), which showed higher solubility, faster transition, and better results in treating SARS-CoV-2 compared to the traditional remdesivir cyclodextrin conclusion compound (Rdv-cyc) group with transtracheal injection.[176] Gallium maltolate can disrupt the replication of SARS-CoV-2 but has serious side effects.[177] Torabi et al. demonstrated that nanoparticles carrying gallium maltolate could reduce its side effects and might be a potential treatment for COVID-19.[178] Recently, Que's group suggested that liposomes encapsulating tripterin, a traditional Chinese medicine, could also be a promising treatment for SARS-CoV-2.[179]

2.2.4. Inorganic Materials in the Treatment of SARS-CoV-2 and Drug Delivery Systems. Silica, as an inorganic biomaterial, can be manufactured as silica nanoparticles (SNPs) for COVID-19 treatment and drug delivery. Silica has been continuously used in food and pharmaceutical applications. Mesoporous silica nanoparticles (MSNs), which are produced from silica through colloidal chemistry, are characterized by their high potential for drug carriers and detections.[180] MSNs can be utilized as a vehicle for delivering specific drugs or as a platform for detecting a SARS-CoV-2 infection. Theobald suggested that functionalized SNPs may be useful for delivering DNA/RNA of SARS-CoV-2 without the need for supporting experiments.[181] In contrast, studies of SNPs carrying proteins or antiviral drugs for SARS-CoV-2 have been approved. For instance, Zhang's group prepared MSNs carrying remdesivir for targeted drug delivery in vitro.[182] Mizuta and colleagues developed hybrid SNPs and evaluated their antigen-carrying ability.[183] Importantly, research based on biodegradable mesoporous silica nanoparticles (BMSNs) has demonstrated robust immunogenicity in vivo on high TH1-based humoral and cellular immune responses.[184] In summary, inorganic biomaterial-based drug delivery has been explored in COVID-19 treatment, although few studies have progressed to clinical trials.

2.2.5. Other Potential Biomaterials in the Treatment of SARS-CoV-2 and Drug Delivery Systems. Natural triterpenoids and BPs have potential as a treatment against SARS-CoV-2. In addition to their application in COVID-19 vaccines, as previously discussed, natural triterpenoids could protect the host directly against SARS-CoV-2 invasion.[185] Saikosaponins A, B, and D, derived from *Bupleurum falcatum* L. (Umbelliferae), are major triterpenoid saponins. Saikosaponins D might suppress the cytokine storm of severe COVID-19 patients by inhibiting the expression of several immunomodulatory and anti-inflammatory mediators.[186] Furthermore, a study by Yan et al. demonstrated that Saikosaponins A could inhibit the interaction between the RBD domain and ACE2 receptor.[187] The triterpenoids licorice-saponin A3 could protect host cells from SARS-CoV-2 invasion in vivo.[188] BPs, potent inhibitors of bone resorption, could modulate the function of immune cells.[189] For example, amino-bisphosphonates could stimulate $\gamma\delta$ T cell expansion to reduce acute lung injury.[190] Additionally, it could regulate DCs into active natural killer (NK) cells[191] and inhibit small guanosine triphosphate hydrolases (GTPases) from neutralizing SARS-CoV-2 virions in lysosomes.[192]

In conclusion, while biomaterials can be utilized as antiviral drugs and drug delivery vehicles, which can reduce the side effects of antiviral agents and improve efficacy, few of them are

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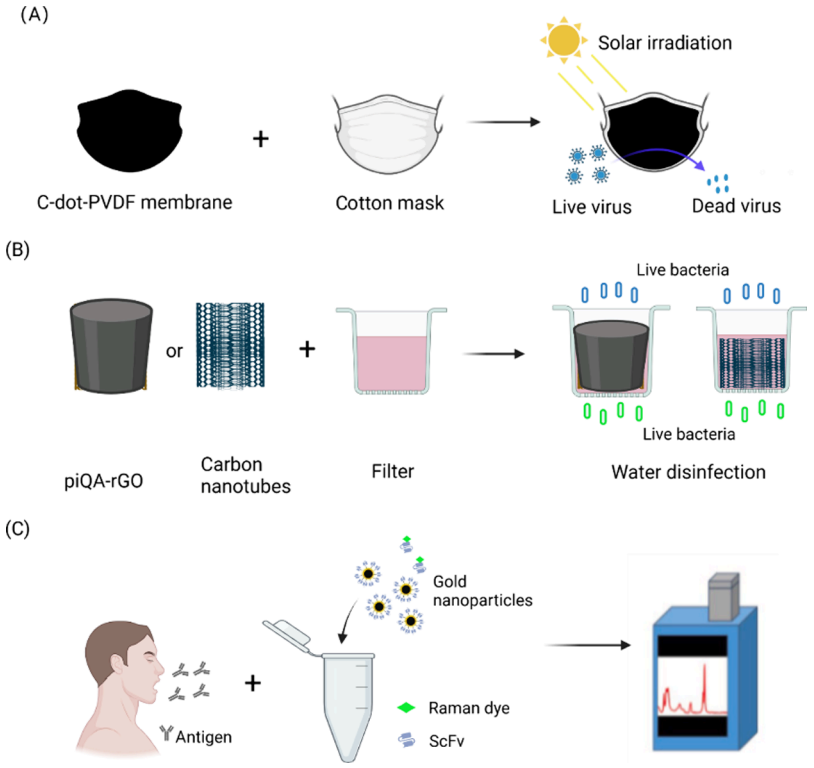

Figure 2. Schematic illustration of the biomaterials-based application of some antiviral protective equipment and early diagnosis. (A) The nanoporous C-dot-PVDF membrane for sunlight-sterilized facemasks. (B) The assembly of the piQA-rGO hydrogel and carbon nanotubes was used as a water filter and disinfection. (C) Application of biomaterials in SARS-CoV-2 diagnosis. Image created with BioRender.com, with permission.

available in the clinic. Developing the applications of biomaterials in other diseases is still of great importance, considering the advantages in reducing side effects and promoting effects.

2.3. The Application of Biomaterials in SARS-CoV-2 Protective Equipment and Early Diagnosis. Apart from serving as adjuvants or delivery platforms for anti-SARS-CoV-2 vaccines and drugs, carefully designed biomaterials themselves can serve as antiviral reagents and be applied in the diagnosis of suspected COVID-19 (Figure 2). For instance, conventional facemasks have been coated with liquid chemicals to create antiviral and antibacterial masks,[193] which are effective in preventing global transmission. In addition, a novel biomaterial-based diagnosis helps to detect SARS-CoV-2 earlier, and faster diagnosis of SARS-CoV-2 infection can help control it early.[194] In this subsection, we present the applications of biomaterials in antiviral prophylaxis and early diagnosis.

2.3.1. Biomaterials in SARS-CoV-2 Protective Equipment. Inorganic biomaterials have been widely utilized in various biomedical fields due to their unique structural properties such as electrical conductivity, easy functionalization, high surface area, and surface-mediated action, especially carbonaceous nanomaterials.[195−197] Laser-induced graphene (LIG) is a type of inorganic biomaterial that can be prepared directly on carbonaceous precursors in an ambient atmosphere.[198] Its excellent surface and electrochemical properties make it a promising material for antibacterial activity.[199−201] In addition, LIG has become a sustainable material because of its environmental safety and low cost. Various factors such as different textures, improved characteristics, conductivity, charge storing capacity, and nucleobase adsorption potential can influence the antiviral capability of LIG.[202−204] Dixit et al. suggested that LIG has a wide range of potential applications in daily COVID-19 prevention technology, such as biosensors, water and air filters, wearable sensors, and so on.[205] Furthermore, single nucleotide polymorphisms (SNPs) could also be utilized to detect SARS-CoV-2. Hildebrandt et al. suggested that SNPs could be used to determine the aerosol transport of SARS-CoV-2.[206] Hill et al. demonstrated that SNPs-based masks and respirators have the potential to become ideal aerosol filtration tools.[207]

2.3.2. Biomaterials in SARS-CoV-2 Diagnosis. Early in the SARS-CoV-2 global pandemic, the genetics-based real-time reverse-transcription polymerase chain reaction (RT-PCR) method was used to detect the patients at first-line. For hospitalized and symptomatic patients, computed tomography (CT) scan of the chest was chosen.[208] Compared with the previous two tests that require specialized equipment and cost a lot, easier approaches, immunoassay by enzyme-linked immunosorbent assays (ELISAs), were developed to detect the levels of IgG and/or IgM in patients' blood.[3] However, high levels of antibodies take several days, and science symptoms appear for the first time. Furthermore, ELISA might cause more errors than RT-PCR and chest CT. So rapid, accurate, low-cost, simple, and portable devices were need. Fortunately, biomaterials have advantages in developing biosensor-based diagnostics.[209]

2.3.2.1. Carbonaceous Biosensors. Graphene oxide (GO) was widely used as nanosensor based on its sensor performance, ease of production, large specific surface area, and high sensitivity.[210] In addition, it can be evenly dispersed in aqueous media and generate highly uniform complexes owing to its

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ACS Omega 2024, 9, 5175−5192

active oxygen-based functional groups and massive hydrophilic polar moieties.[211] In addition, functional linker groups and/or antibodies can bind to the superior hydrophilic active functional groups.[212] However, GO is an insulator nanosheet, and in order to make it suitable for biological applications, improving its conductivity through a reduction process is necessary.[213,214] Hence, Hashemi et al. developed a conjugated reduced-graphene-oxide (rGO)-based immunosensor with Au NSs mounted with monoclonal IgG antibody against spike1 (S1) protein and found that multiwalled carbon nanotubes, especially those with a conjugated reduced-graphene-oxide (rGO)-based immunosensor with Au NSs, were more efficient than other 1D/2D carbonaceous nanomaterials in specific and quick (1 min) detection of SARS-CoV-2 antigen.[215]

2.3.2.2. Gold Nanoparticle Biosensors. Gold nanoparticle (AuNP)-assembled SiO_2 core−satellite nanoparticles (SiO_2@Au CSNPs), probe-gated silica nanoparticles, and silica-encapsulated Au core−satellite (CS@SiO2) nanotags are some examples of inorganic biomaterials that can enhance the detection sensitivity of SARS-CoV-2 nucleocapsid protein and swab samples.[216−218]

Gold nanoparticles can also help block pseudovirus infection and promote the delivery of the COVID-19 DNA vaccine and SARS-CoV-2 detection. For example, Ali et al. prepared a 3D-printed COVID-19 test chip based on gold nanoparticles, indicating its ability to detect COVID-19 antibodies in seconds.[219] Other diagnostic platforms such as AuNP-internalized Au nanodimple substrate (AuNDS)-based surface-enhanced Raman scattering (SERS)-PCR,[220] CRISPR-Cas12a powered visual biosensor coated with gold nanoparticles,[221] and ultrasensitive hyperspectral sensor based on hafnium nanoparticles (HfNPs)[222] can be applied to any virus rapid and sensitive diagnostic test. In a study by Zhu et al., gold nanoparticle (AuNR) was used as an immunosensor, which could detect RBD-specific antibody levels from fingertip blood samples semiquantitatively and instrument-free.[223] CRISPR/CAS-based colorimetric nucleic acid detection could detect SARS-CoV-2 RNA with naked-eye detection.[224] The utilization of biomaterials in preventing the transmission of COVID-19 and early diagnosis is extremely important. However, all of the three methods above (RT-PCR, chest CT and ELISA) can only be used to detect SARS-CoV-2 infection and cannot detect the mutation of the SARS-CoV-2.[225] The amino acid mutations of SARS-CoV-2 should be detected by using genetic sequencing methods.

3. CONCLUSIONS AND PERSPECTIVES

The COVID-19 pandemic is currently spreading rapidly worldwide, posing a significant threat to human life and causing extensive economic and social damage.[226] Scientists worldwide are actively developing approaches to inhibiting COVID-19 infections. Fortunately, biomaterial-based strategies, including natural and synthetic polymers, lipid and inorganic biomaterials, saponins, and BPs, could serve as vaccine adjuvants or antigen delivery carriers, enhancing immunogenicity and improving antigen uptake while controlling antigen targeting. Some of these biomaterials have demonstrated significant abilities to deliver anti-SARS-CoV-2 agents to targeted sites and reduce side effects, although only a few have been used clinically. In addition to vaccines and therapeutics, physical protection and early diagnosis are also critical in preventing SARS-CoV-2 infections. However, the long-term effects of biomaterials on the development and progression of COVID-19 are not well-defined.

The emergence of new SARS-CoV-2 variants has created new challenges for antiviral approaches. The ultimate goal of biomaterials research is to develop a selection criterion based on fundamental understanding, effectively choosing the appropriate biomaterial, and translating it into clinical use. In addition, many drugs and biomaterials would not be tested in clinical trials or marketed due to their toxic side effects, but they had a cost during preclinical trails. In order to reduce costs and improve efficiency of drug development, the organ-on-a-chip systems are of great interest in the future.

In summary, it is hoped that with the deeper exploration of advanced materials, chemistry, biology, computer science, and medicine, composite biomaterials with more advantages can be developed for the detection, treatment, and prevention of infections and cancers.

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ACS Omega 2024, 9, 5175−5192

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[#]Yuan Hu and Lili Liu contributed equally to the manuscript. Yuan Hu and Lili Liu: Conceptualization, Writing - Original draft preparation; Shenghua Zhang: Visualization; Shaoyu Su and XiaoLiang: Writing - Review & Editing, Project administration, Investigation, and Supervision. All authors have approved this manuscript for publication.

Notes

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