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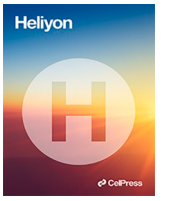

Review article

Biomedical equipments, vaccine and drug in the prevention, diagnosis and treatment of COVID-19

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ABSTRACT

SARS-CoV-2 virus caused an infectious disease, named COVID-19. Biomedical equipments, vaccine and drug have played a crucial role in the prevention, diagnosis and treatment. Nevertheless, up to now, there still has been no literature summarizing the diagnosis, prevention and treatment of this infectious disease from the perspective of biomedical equipments. Thus, this review wants to give an overview on the biomedical equipments, vaccine and drug in the prevention, diagnosis and treatment of this disease, and avoids the overlap with previous research, more emphasis on biomedical equipments, and less emphasis on biomaterials. The existing problems in the current research and application were summarized, and the future research direction was proposed, so as to provide reference to deal with similar viral infections in the future.

1. Introduction

SARS-CoV-2 virus caused an infectious disease, named COVID-19. And it is easy to mutate and spreads quickly [1]. As at June 1, 2023, 689,713,442 infected cases have been reported globally, among them, 6,885,239 people died. It greatly endangered human health and life in the past three years, and mainly transmitted through human and air, especially close contact within 1 m [2]. Zhong et al. analyzed 1099 confirmed cases, and found that the clinical symptoms included cough (67.8%), fever (88.7%), shortness of breath (18.6%) and headache (13.6%) [3]. During the evolution and development of COVID-19, biomedical equipments, vaccine and drug have played an extremely crucial role in diagnose, prevention and treatment. Summarize and analyze the applications of biomedical equipments, vaccine and drug in the diagnose, prevention and treatment of this disease, so as to provide reference to deal with similar viral infections in the future.

Biomedical equipments mainly include personal protective equipments (masks and protective clothing), diagnosis equipments and treatment equipments (Extracorporeal Membrane Oxygenation). Ordinary medical masks and protective clothing can isolate the virus, but can not actively kill the virus. However, metal and its oxide, graphene oxide, quaternary ammonium salt and other anti-virus components modified protective articles can effectively kill the virus and improve the prevention effect. In addition, fast and precise detection of the virus is also very important. COVID-19 detection technologies of diagnosis equipments include polymerase chain reaction (PCR), CRISPR, IgM/IgG antibody detection method, and nano detection technology. PCR is mainly used for daily detection. Each detection method has its own advantages and disadvantages, so they can be worked together to ameliorate detection efficiency, sensitivity and accuracy.

There is no specific drug to treat the infected cases up to now. Vaccination can not only reduce the infection rate, but also reduce the death rate of severe cases, which is also an effective mean of prevention [4]. Patients with mild condition mainly take rest and

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strengthen supportive treatment, while patients with severe condition mainly combined the treatment of extracorporeal membrane oxygenation and anti-inflammatory.

Previously, Ertas et al. [5] summarized the biomaterials for diagnosis, prevention and treatment, mainly included: 1) tissue engineering for infection studies, like stem cells embedded in alginate, hyaluronic acid, matrigel, collagen, gelatin, polydopamine, and hydrogels, have been used for the viral infection treatment; 2) biomaterials used for diagnosis, like genetics-based infection detectors, nanobiomaterial-based biosensors and label-free biomaterial-based biosensors; 3) biomaterials uesd for prophylaxis and treatment, like antiviral drugs, and anti-inflammatory drugs for therapeutics, and nanotechnology to inhibit viral surface receptors for vaccines; 4) biomaterials used for treatment of viral infection consequences, such as antithrombotic materials; 5) biomaterials used for drug delivery, such as cationic polymer chitosan, PLGA nanoparticles coating with polydopamine and poly (ethylene glycol), and coiled-coil hydrogels, etc. Nevertheless, up to now, there still has been no literature summarizing the prevention, diagnosis and treatment of this disease from the perspective of biomedical equipments. Thus, this review wants to give an overview on the biomedical equipments, vaccine and drug in the prevention, diagnosis and treatment of this disease, and avoids the overlap with previous research.

2. Materials and methods

Web of Science is the most important citation database from publishers. This database comprehensively collecting over 1.7 billion cited literature and 159 million records, and can track interdisciplinary research ideas. The content of the core collection has been carefully selected with unique selectivity, establishing an independent and comprehensive editing process to ensure excellent quality of the journal. Each article and all cited articles in each journal have been indexed, creating the most comprehensive and complete citation network. Millions of researchers trust this database to make excellent research, gain insight, and make correct decision for the future development.

To make a comprehensive review, articles were searched on Web of Science. For this review, mainly includes two parts, one is biomedical equipments, the other is vaccine and drug, and more emphasis on biomedical equipments, less emphasis on biomaterials, so as to avoid the overlap with previous research.

Biomedical equipments mainly include personal protective equipments (masks and protective clothing), diagnosis equipments and treatment equipments (Extracorporeal Membrane Oxygenation):

1) Personal protective equipments. First, set keywords as: virus killing performance (topic) + protective (topic) + COVID-19 (topic), searched on Web of Science. Then, only the references directly related to protective equipments (masks and protective clothing),

Table 1
Enhancing the virus killing performance of personal protective equipments.

Functional coatings	Methods	Main properties	Reference (s)
Ag_2O	Stöber sol-gel method	Thickness 2.4 mg/mm^2, the virus can reduce 99.3% after contacting for 1 h	[6]
CuO	High-temperature oxidation and sintering	Thickness 30 μm, the infectivity decreased by 99.9% after contacting for 1 h	[7]
CuO	1)Dposit polydopamine, and then grow a thin copper layer on the polydopamine through chemical deposition; 2) CuO suspended and dispersed in the polydopamine solution, and then sprayed	The inactivation efficiency of the two methods in 1 h was 99.98% and 99.88% respectively	[8]
ZnO	Zinc oxide/Nylon 66 composite fabric	Reduce the virus titer by about 100 times, and after 50 times of standardized washing, the virus inactivation ability remains stable	[11]
Cu–Zn	Core-shell nanowire containing copper and zinc (Cu@ZIF-8), and then dip it onto polypropylene medical mask	1 μg Cu@ZIF-8 inhibit 55% virus replication after 48 h	[12]
ZnO–Ag	PMMA/ZnO–Ag nanofibers	Diameter of the nanofibers 450 nm	[13]
TiO_2	Nano-titanium dioxide suspension used for coating	After 1 min irradiation of ultraviolet, the human coronavirus genome has not been detected by RT-qPCR	[14]
Graphene	CO_2 laser irradiation on polyimide film in air and nitrogen respectively to produce laser-induced graphene (LIG) and hydrophobic laser-induced graphene (HLIG)	Virus killing achieved by applying 2–3 AAA batteries or exposing LIG to sunlight; the efficacy of HLIG in killing HCoV-OC43 and HCoV-229E were 97.5% and 95% respectively	[18]
Graphene	Covalently grafted quaternary pyridine cationon the surface of LIG	Surface potential +35 mV; after 20 min irradiation, 99% of HCoV-OC43 and 100% of HCoV-229E were inactivated	[19]
Graphene	Graphene deposited on the commercially available non-woven surgical mask by dual-mode laser induction method	Superhydrophobic, static contact angle of 141°; Under sunlight, surface temperature rapidly rise to more than 80 °C, can kill viruses	[20]
Graphene	Electron cyclotron resonance sputtering system; ultrasonic extrusion system, graphene nano-sheets embeded into the smooth fiber fabric to prepare the graphene modified mask	Superhydrophobic, static contact angle of 157.9°; under sunlight, rapidly rise to 110 °C	[21]
Quaternary ammonium salt	Mask filter layer dipped into 0.1% benzalkonium chloride solution for 1 min, then dried at 60 °C	After contact for 1 min, the virus inhibition rate was >99%	[25]

and really had SARS-CoV-2 virus killing performance results are reserved. At last, these references were mainly categorized according to metals and metal oxides, graphene and graphene oxide, and quaternary ammonium salt.

2) Technologies for diagnosis equipments. First, set keywords as: Technologies (topic) + diagnosis (topic) + COVID-19 (topic), searched on Web of Science. Then, these references were classified to polymerase chain reaction (PCR) technology, CRISPR technology, IgM/IgG antibody detection technology, and nanotechnology for detection.
3) Treatment equipments (Extracorporeal Membrane Oxygenation). Set keywords as: Extracorporeal Membrane Oxygenation (topic) + COVID-19 (topic), searched on Web of Science, mainly included VV ECMO and VA ECMO.

For vaccine and drug: 1) Set keywords as: vaccine (topic) + COVID-19 (topic), searched on Web of Science; 2) Set keywords as: drug treatment (topic) + COVID-19 (topic), searched on Web of Science, then these references were divided into two parts: anti-inflammatory treatment and new drug development for treatment.

Due to no literature summarizing the prevention, diagnosis and treatment of this disease from the perspective of biomedical equipments, this article started from this point to give a review. The existing problems in the current research and application were summarized, and the future research direction was proposed, so as to provide reference to dispose of other viral infections in the future.

3. Enhancing the virus killing performance of biomedical equipments in the prevention of COVID-19

Virus spreads through aerosols or respiratory droplets, personal protective equipments are necessary to prevent COVID-19, but masks can only capture aerosols and cannot actively kill the virus. The virus remains infectious in masks, and the used masks may become pollutants, leading to secondary transmission or cross infection, Therefore, integrating anti-virus ingredients into the filter layer of the mask can effectively kill the virus, improve the prevention effect. The commonly used anti-virus ingredients mainly include metals and their oxides, graphene oxide and quaternary ammonium salts (Table 1).

3.1. Metals and metal oxides

Metals and metal oxides have excellent antiviral functions, like zinc (Zn), copper (Cu), silver (Ag), titanium (Ti), etc. On the one hand, they can produce ROS and rapidly oxidize the organic biomacromolecules, thus inactivating the virus. On the other hand, they can cause the denaturation and inactivation of specific proteins of the virus by releasing low concentrations of metal ions, thus causing the apoptosis of the virus.

Silver has been used as a container to keep from food spoilage. It is one of the most famous antibacterial and anti-viral materials, and has broad applications. Hosseini et al. [6] prepared silver oxide anti-virus coating by using the improved Stöber sol-gel method. First, the glass sheet was treated by oxygen plasma, and the Ag_2O-TEOS ethanol solution is dispersed on the glass sheet. Then, evaporation, self-assembly and heat treatment, a silver oxide coating is obtained, and then SARS-CoV-2 virus solution is dripped on the silver oxide coating. When the thickness of silver oxide coating is 2.4 mg/mm^2, the virus can reduce 99.3% after contacting with the silver oxide coating for 1 h.

However, copper-based antiviral materials are relatively cheap and easy to manufacture, and are the most promising antiviral materials. CuO can produce ROS and release copper ions, causing the denaturation or degradation of virus biomacromolecules, thus

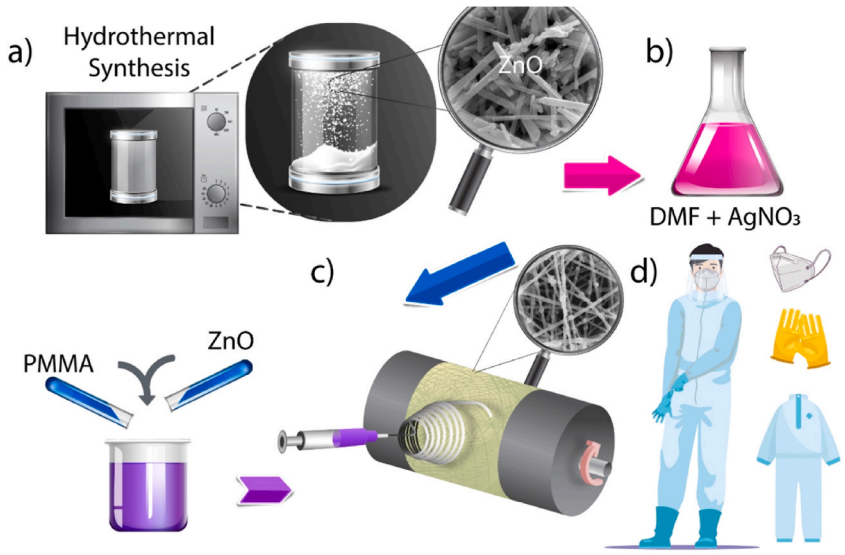

Fig. 1. The preparation process of PMMA/ZnO–Ag nanofiber, which has excellent anti-virus performance, can be used in the field of respirators, protective clothing, gloves and other protective articles. Reprinted with permission from Ref. [13]. Copyright 2021 American Chemical Society.

leading to virus inactivation. Hosseini et al. [7] studied the inactivation effect of CuO coating on SARS-CoV-2 virus. First, the CuO was suspended and dispersed in ethanol solution, and the uniformly dispersed suspension was obtained after ultrasonic treatment, and then dropped onto the slide. Then, after high-temperature oxidation and sintering, the sample was slowly cooled overnight, and the thickness of CuO coating about 30 μm. The virus suspension was dropped on CuO coating, and the infectivity of virus decreased by 99.9% after 60 min. However, the extract of CuO coating had no effection on the infectivity of virus, indicating that the virus was inactivated by solid contact. The contact inactivation of CuO benefits from electrostatic interactions. At pH 7.4, the net charge of spike protein is about +3.5 mV, while the Zeta potential of CuO in the culture medium is −17 mV, so virus will be electrostatic adsorbed to the surface of CuO coating, thus inactivating the virus. Behzadinasab et al. [8] prepared two kinds of anti-virus sprayed coatings. The first is to deposit polydopamine, and then grow a thin copper layer on the polydopamine through chemical deposition. In the second method, CuO was suspended and dispersed in the polydopamine solution, and then sprayed on the surface of the object at one time. The virus inactivation efficiency of the two coatings in 1 h was 99.98% and 99.88% respectively.

Compared with silver and copper, zinc has higher biological safety and lower price than silver. ZnO can release zinc ions and absorb ultraviolet light to produce superoxide, hydrogen peroxide, and hydroxyl radicals, thus damaging carbohydrates, lipids, DNA and RNA [9]. Zinc can also inhibit RNA transcription, hinder the replication of virus, and can up regulate the IFN α of JAK/STAT1 signaling pathway in leukocytes to improve the antiviral property [10]. Gopal et al. [11] prepared zinc oxide/nylon 66 composite fabric, which can reduce the titer of virus by about 100 times, and after 50 times of standardized washing, the virus inactivation ability remained stable.

Single metal element has its own advantage and disadvantage when applied to anti-virus, while the combination of different metal elements can effectively improve anti-virus performance, reduce biological toxicity and costs. Kumar et al. [12] prepared a core-shell nanowire containing copper and zinc (Cu@ZIF-8), and then dip it onto polypropylene medical mask, 1 μg Cu@ZIF-8 could inhibit 55% SARS-CoV-2 virus replication after 48 h. Karagoz et al. [13] prepared multifunctional polymethylmethacrylate (PMMA) electrospun nanofibers containing ZnO nanorods and Ag nanoparticles (Fig. 1). Firstly, ZnO nanorods were dispersed in N, N-dimethylformamide (DMF) solvent, then the surfactant Triton X-100 was added, and the ultrasonic treatment was performed for 20 min. Then PMMA was added, and stirred for 3 h to dissolve in DMF. Finally, $AgNO_3$ solution was added, and stirred until the color turns dark brown. The obtained solution was transferred to syringe, and electrospinned on a rotating collector (600 rpm). The nanofibers diameter was 450 nm. PMMA/ZnO–Ag nanofibers have excellent antiviral properties against coronaviruses and influenza viruses. The PMMA/ZnO–Ag electrospun nanofiber has antiviral and self-cleaning functions, and has good application prospects in the field of protective articles such as masks, protective clothing and gloves.

In addition, titanium as the metal element has to be mentioned. Titanium-based coatings are one of the most powerful anti-virus materials. They have strong photooxidation effect to organic substances and relatively low toxicity. Khaiboullina et al. [14] studied the effect of nano-titanium dioxide in killing human coronavirus. First, prepared nano-titanium dioxide suspension, then coated on a clean cover glass, dried to form a translucent coating, and then put the human coronavirus on the top layer of the cover glass. After 1 min irradiation of ultraviolet, the human coronavirus genome has not been detected by RT-qPCR, confirming that the human coronavirus genome has been completely decomposed. Nano-titanium dioxide has photocatalysis characteristic. After being irradiated by ultraviolet, the electron-hole pairs are generated at the same time. The free electrons are conducive to the production of ROS free radicals, which can decompose organic substances, thus producing a strong anti-virus effect.

3.2. Graphene and graphene oxide

Graphene is 2D lamellar material formed by hexagonal arrangement of carbon atoms, and graphene oxide is its oxide. Graphene oxide binds with virus mainly through electrostatic interaction, hydrogen bonding and redox reaction [15]. The thin graphene oxide sheet is easy to bend and can wrap microorganisms, thus inhibiting the proliferation and spread of microorganisms. Raval et al. [16] studied the graphene and virus interaction through theoretical calculation. With the increase of graphene nanosheet layers, its surface reaction ability increases, and the virus binding efficiency also increases. It has a layer dependent inhibition on the virus spike receptor, and has a good application prospect in personal protection.

More importantly, the graphene oxide can absorb light [17], and will produce high temperature under sunlight, which has the photothermal effect. High temperature can inactivate various viruses. Surgical masks are crucial to prevent virus transmission. However, masks cannot kill the virus and are basically disposable, which increases the economic and environmental costs. Graphene oxide modified masks and protective clothing endow superhydrophobic and photothermal properties, enhance anti-virus ability and reusability.

Huang et al. [18] produced laser-induced graphene (LIG) and hydrophobic laser-induced graphene (HLIG) by using CO_2 laser irradiation on polyimide film in air and nitrogen respectively. LIG and HLIG can also be produced by CO_2 laser irradiation on wood, paper, cloth and other polymers, without high temperature, high pressure and a large amount of chemicals. It is a green, safe and efficient production method. When sunlight illuminated, LIG rises to 62 °C. 10 × 10 cm^2 LIG could be heated to 50 °C by 7.5 V DC voltage. 46 °C is enough to kill the virus, which can be achieved by applying 2–3 AAA batteries or exposing LIG to sunlight. Under sunlight, the inactivation effect of LIG on coronavirus kept stable, and decreased slightly after repeated use. The efficacy of hydrophobic HLIG in killing HCoV-OC43 and HCoV-229E were 97.5% and 95% respectively. The photothermal and hydrophobical effects significantly improved the virus inactivation ability. Mild, low-cost and reusable HLIG can be used to enhance the viruses-killing ability in surgical masks.

Gu et al. [19] covalently grafted quaternary pyridine cation (LIG+) on the surface of LIG, and achieved the goal of highly effective antibacterial and antiviral. Microorganisms are inactivated after solar irradiation on LIG + for 10 min. LIG + also showed a strong

killing effect on coronavirus. After 20 min irradiation, 99% of HCoV-OC43 and 100% of HCoV-229E were inactivated.

Zhong et al. [20] deposited graphene on the commercially available non-woven surgical mask by dual-mode laser induction method (Fig. 2a and b). The surface of the treated mask was superhydrophobic, with a static contact angle of 141° (Fig. 2c), and the droplets containing virus would be rebounded (Fig. 2d). Under sunlight, its surface temperature can rapidly rise to more than 80 °C, which can kill bacteria and viruses, thus achieving the purpose of reuse.

Lin et al. [21] deposited graphene film on the silicon substrate to prepare graphene nano-sheets with high edge density, and then removed the graphene nano-sheets from the silicon substrate through high-frequency electric engraving device, and embeded the graphene nano-sheets into the smooth fiber fabric to prepare the graphene modified mask by ultrasonic extrusion system. The mask has excellent hydrophobic performance and excellent filtration performance, with bacterial filtration efficiency of 100%. The mask can rapidly rise to 110 °C under sunlight. The hydrophobicity and photothermal properties of the graphene modified mask are superior to the aforementioned laser-induced graphene coated mask.

De Maio et al. [22] studied the virus captured by graphene in solution, and found that graphene almost completely inhibited the virus infectivity. Moreover, graphene functionalized cotton, non-woven fabrics and polyurethane have almost completely eradicated the infectivity of COVID-19, and can be used to prepare anti-virus masks. The superhydrophobicity of graphene increases the ability of protective articles to resist the invasion of virus aerosols. Its excellent photothermal and electrothermal behaviors can generate local high temperatures to inactivate microorganisms, include SARS-CoV-2 virus.

3.3. Quaternary ammonium salt

Quaternary ammonium salt has positive charge and can capture micro-aerosol droplets, virus particles and various microorganisms with a size greater than 100 nm. It can deprotect the lipid protective layer by encapsulating the virus, thus killing the virus. Ogilvie et al. [23] used benzalkonium chloride solution (0.2%) prepared in the laboratory and three commercially disinfectants, carried out SARS-CoV-2 virus inactivation experiment. Mostly, the disinfectants can completely inactivate virus within 15 s. The virus inactivation effect will not be changed even in soil or in diluted hard water.

Cassera et al. [24] used the commercially available quaternary ammonium salt antimicrobial agent: octadecane silane coupled quaternary ammonium salt (SiQAC-C18) coating, and solidified on the stainless steel sheet. After more than 40 days, they evaluated two different virus isolates, and the virus genome exposed to SiQAC-C18 was significantly degraded. The surface treated by SiQAC-18 can destroy the virus membrane, degrade the viral RNA, and can be used as a durable anti-virus surface treatment agent.

Marti et al. [25] dipped the mask filter layer into 0.1% benzalkonium chloride solution at 25 °C for 1 min, and then dried to constant weight. The dry weight of benzalkonium chloride in the mask filter layer reached 0.46 ± 0.13%. After contact with virus for 1

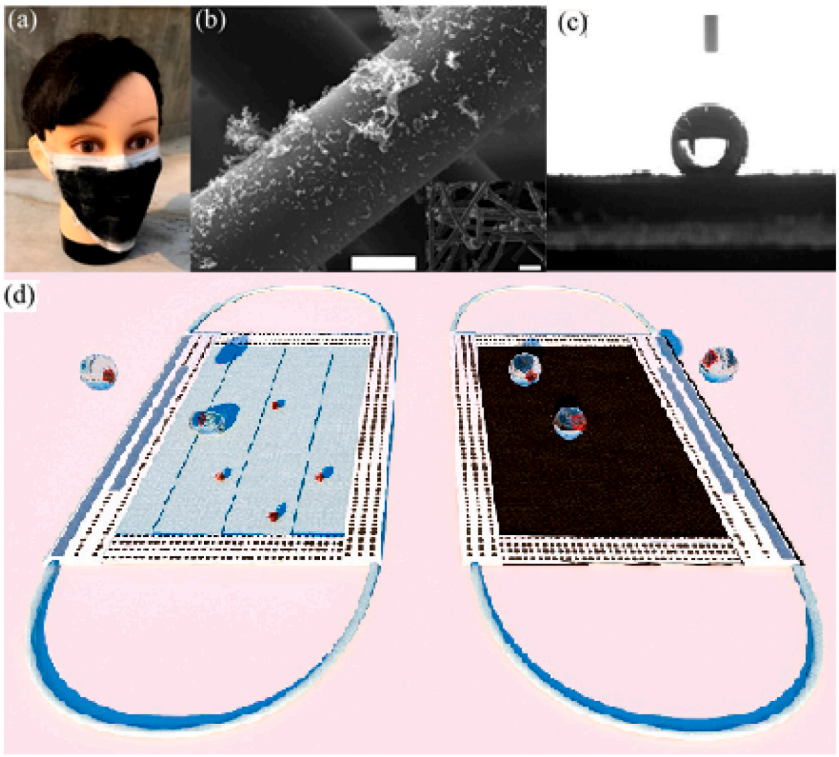

Fig. 2. Microstructure of superhydrophobic graphene modified mask, and the diagram for its self-cleaning anti-virus. Reprinted with permission from Ref. [20]. Copyright 2020 American Chemical Society.

min, the virus inhibition rate was >99%. Quaternary ammonium compounds inactivate bacteria and viruses by destroying the phospholipid bilayer membrane, glycoprotein envelope, and echinocandin interacting with ACE2 receptor. They are widely used as additives for wet wipes, sprays, and hand sanitizers, as well as for manufacturing antibacterial clothes, gloves, etc.

At present, commercial quaternary ammonium salts are only constructed in stable chemical bonds, which are difficult for degradation, and play a negative impact on the ecological environment, causing drug resistance and biological toxicity. Zhang et al. [26] used 2-(trimethylamino)-ethyl methacrylate and aliphatic mercaptans with different carbon atoms (carbon atoms 2, 10, 12 and 14) as starting materials to produce quaternary ammonium salts containing ester bonds and thioether bonds under mild conditions by Michael addition reaction. These two chemical bonds can be hydrolyzed and have broad-spectrum inactivation ability to a variety of microorganisms, and can be used as an environmentally friendly substitute for currently used disinfection products.

Although quaternary ammonium salt has good virus inactivation effect, it also has some biological safety problems. Zheng et al. [27] studied the bioaccumulation in human body and the content in blood before and during the pandemic. They selected 18 kinds of quaternary ammonium compounds with different alkyl chain length, and studied the bioaccumulation of quaternary ammonium compounds. Among them, C12 quaternary ammonium compounds have the slowest clearance rate in the body, indicating that this quaternary ammonium compound preferentially accumulates in blood. As the use of compounds increased, the concentration of quaternary ammonium compounds in the samples during the pandemic was significantly higher than that in the samples collected before the pandemic, which provided important information for the toxicology assessment of quaternary ammonium compound disinfectants.

4. Technologies for biomedical equipments in the diagnosis of COVID-19

4.1. PCR technology

PCR is an amplification technology of nucleic acid, which can amplify nucleic acid targets by tens of thousands to billions of times. It has been widely used in life science and medicine. Real-time fluorescence quantitative PCR can detect nucleic acid quantitatively. A fluorescent dye added to the sample to be detected. After each round of amplification, the fluorescent dye will combine with the newly generated nucleic acid. Determine whether there is a target nucleic acid molecule according to the Ct value required to reach the predetermined threshold. Zhang et al. [28] summarized the application of PCR technology in virus nucleic acid detection. The virus genetic matter is single stranded RNA. First, through reverse transcriptase, RNA is reverse transcribed into cDNA, and then PCR amplification is carried out. PCR is the detection method recommended by official organization. Large-scale detection results showed that real-time fluorescence quantitative PCR will have a "false negative" problem, mainly because the virus quantity of the sample to be tested is lower than the detection limit of the instrument, so it is essential to improve the real-time fluorescence quantitative PCR sensitivity (Table 2).

Digital PCR has higher accuracy and sensitivity. The "positive recovery" of COVID-19 patients is because of the low viral load during recovery period, which cannot be detected by routine real-time fluorescent quantitative PCR. Yu et al. [29] used digital PCR to detect 76 cases, and confirmed that the viral load of nasopharyngeal swabs was significantly lower than sputum, and for samples in the recovery period, digital PCR can still accurately detect. Dong et al. [30] also used digital PCR to detect. The sensitivity of real-time fluorescent quantitative PCR for detecting throat swab samples ranged from 30% to 60%, while the diagnostic accuracy, sensitivity and specificity of reverse transcription digital PCR for detecting COVID-19 reached 93%, 91% and 100% respectively. Reverse transcription digital PCR is a highly accurate and sensitive detection method, which is suitable for detecting throat swab samples of suspected patients and isolated personnel who may not have clinical symptoms. However, digital PCR has high requirements for instruments, which limits its clinical application. The research and development of fast, accurate and low-cost detection instruments is

Table 2
Technologies for diagnosis of COVID-19.

Technologies	Read-out time	Sensitivity/specificity	Reference (s)
Digital PCR	Long detection time	91%/100%	[30]
CRISPR-Cas12	Fast (<40 min)	95% positive prediction consistency; 100% negative prediction consistency	[33]
Multiple cross displacement amplification and CRISPR	–	100%	[35]
IgM/IgG	Fast (<15 min)	91.89%/97.92%	[45]
MXenes	–	Detection limit 5×10^{-9} M	[48]
Electrochemical immunosensor by combining magnetic beads with carbon black based screen printed electrodes	Fast (30 min)	Detection limits of N protein and S protein in saliva were 8 ng/mL and 19 ng/mL	[54]
Nano enzyme chemiluminescence	Fast (<16 min)	Linear range is 0.2–100 ng/mL, detection limit 0.1 ng/mL	[55]
SWCNs based field effect transistor	Fast (<5 min)	Detection limits for nucleocapsid protein antigen and spike protein antigen are 0.016 fg/mL and 0.55 fg/mL	[57]
Electrochemical diagnosis, electrode coated with graphene oxide and gold nanoparticles	Fast (<1 min)	Sensitivity 0.0048 μAμg.mL^{-1}. cm^{-2} respectively, detection limit 1.68×10^{-22} μg mL^{-1}	[58]

still the focus of both academia and industry.

In addition, virus genome is degraded easily. The highly degraded fragmented nucleic acid is not conducive to the detection of mutation points. Zhang et al. [31] jointly used ligase detection technology and fluorescent quantitative PCR technology to establish a method to detect the fragmented virus S gene D614G, which has good discrimination for 5 pmol/L viral RNA, and can detect the mutation point of viral RNA with a minimum length of 40 nt.

4.2. CRISPR technology

CRISPR and its related Cas protein opens up a new way for molecular diagnosis. CRISPR system includes Cas protein and gRNA. gRNA can guide Cas protein to recognize and cut RNA or DNA molecules with specific sequences. When Cas13a protein specifically cleaves target RNA, that will lead to fluorescence emission. The detection time of this technology is shorter than RT-PCR, but there is still possible to miss the target, and the accuracy and reliability need to be further verified [32]. Broughton et al. [33] developed lateral flow method combined with Cas12 to detect respiratory swab extracts. The test included 36 COVID-19 cases and 42 other respiratory virus infected cases, with 95% positive prediction consistency and 100% negative prediction consistency, providing a fast (<40 min), accurate and easy to implement detection method. Wang et al. [34] detected virus and variants through transcriptional amplification of CRISPR-Cas13. The connection process and Cas13a/crRNA recognition both ensure sequence specificity, can detect 82 copies of virus, and can strictly distinguish the key mutation point D614G of virus variants, with high sensitivity and accuracy.

At the same time, many researchers also combined CRISPR technology with other biotechnology to further enhance sensitivity, accuracy and detection speed. Zhu et al. [35] combined multiple cross displacement amplification technology and CRISPR technology to visually detect COVID-19 on the lateral flow biosensor. The detection is very sensitive, and can detect 7 copies of target genes. The detection results of 37 infected samples were all positive, while the detection results of 77 non-infected samples were all negative, so detection results were accurate and reliable. Xiong et al. [36] developed three line lateral flow detection technology based on CRISPR/Cas9 to detect virus. The detection sensitivity and reliability were improved by simultaneously detecting E and Orf1ab genes through colloidal gold test strips. Double gene analysis was performed on 64 clinical nasopharyngeal swab samples, and the method has 100% negative prediction consistency and 97.14% positive prediction consistency. Yang et al. [37] combined the side effect of Cas13a with the hybrid chain reaction (HCR) and designed a hairpin reporter gene. When the target is recognized, it will be cut, thus releasing the starting sequence, triggering the hybrid chain reaction. The reaction product will be adsorbed on the desulfurized biotin modified fiber, and then detect the fluorescence emission. This method can quickly detect virus with the Amor sensitivity.

CRISPR needs to extract nucleic acid in advance, a large number of reagents and multiple steps. It will delay the detection process and hinder the use of this detection technology in resource poor environments. Ramachandran et al. [38] combined microfluidics and CRISPR through electric field for rapid diagnosis of COVID-19. Combining microfluidics, chip controlled electric field and CRISPR technology, they used isokinetic electrophoresis to automatically purify target RNA from nasopharyngeal swab samples, and put Cas12 gRNA, reporter gene and target into microfluidic chips. Gradient electric fields can control and accelerate CRISPR analysis. It takes about 35 min from sampling to obtaining detection results, the aim of rapid detection was realized. Zhang et al. [39] used a colorimetric method combining reverse transcriptase polymerase amplification technology and CRISPR-Cas12a technology to detect COVID-19, used gold nanoparticles to target N and ORF1ab regions. After the viral genome is amplified by reverse transcriptase recombinase polymerase, the dsDNA produced by the method activates Cas12a. After *trans*-cracking, the DNA substrate is gradually hydrolyzed from the gold nanoparticles, and the surface plasmon resonance will change. The naked eye can observe the phenomenon. This method has the sensitivity of one copy of the viral genome sequence, which can effectively avoid other false positive event of β coronavirus, and significantly improved the specificity of detection.

4.3. IgM/IgG antibody detection technology

SARS-CoV-2 virus invades human lung tissue through spike glycoprotein S and ACE2 of respiratory epithelial cells, leading to pneumonia. The virus nucleocapsid protein N has strong immunogenicity and specificity, but the antibody to N protein is produced in large quantities 10 days after the virus infection, which is not conducive to early diagnosis. Most of the commercial virus antibody detection kits choose S protein as the detection target, and most of them are S protein IgG antibody detection kits. After 3–5 days infection with virus, most of the specific IgM antibodies were positive, and then the specific IgG antibodies began to turn positive. IgM antibody concentration level increases with the development of the disease. After treatment, IgM antibody gradually disappears; while the IgG antibody gradually increased, and the titer increased significantly in the recovery period.

Zhong et al. developed a rapid IgM antibody detection kit, which uses colloidal gold immunochromatography to detect COVID-19 IgM antibody, only 10 μL blood is needed, which can obtain the results within 15 min. It is one simple, efficient, sensitive and specific method, and can be used for on-site rapid diagnosis [40]. For some infected persons with false-negative RT-PCR nucleic acid detection, the IgM antibody kit was positive, indicating that IgM antibody detection can complement nucleic acid detection.

Detection mechanism of COVID-19 IgG antibody: Recombinant virus antigen S protein is sprayed on the test line of test paper. As the sample contains IgG antibody, it will combine with the antigen at the test line to produce bands visible to the naked eye, and the diagnosis is positive for COVID-19, but negative if there is no band at the test line. Sun et al. [41] selected six domestic IgG antibody detection kits (colloidal gold method), and compared the detection effects of various kits on COVID-19. They tested 15 clinically confirmed cases and 20 negative samples of healthy people. Among them, the positive detection rate of three kits was 90.0%–100.0%, that of one kit was 80.0%–90.0%, and that of two kits was 70.0%–80.0%; The negative rate of the six kits was 100.0%. Nie et al. [42] used fluorescence immunochromatography to detect COVID-19 IgG antibodies. They prepared virus recombinant N protein, and the

rabbits were immunized with recombinant N protein to obtain polyclonal antibodies, sprayed polyclonal antibodies on nitrocellulose test strips, and used recombinant N protein labeled fluorescent particles as antigen to establish fluorescence immunochromatography. This method has good sensitivity and specificity, which can be used for rapid screening of antibodies.

In addition, many researchers detect COVID-19 IgM and IgG simultaneously to improve specificity and sensitivity. Zeng et al. [43] used colloidal gold method and fluorescence immunochromatography to detect COVID-19 specific IgM and IgG, including 87 blood samples from patients and 42 blood samples from the control group. The sensitivity of colloidal gold method for detecting IgM and IgG were 54.02% and 93.10% respectively, and the specificity of that were 100.00% and 97.00% respectively. The sensitivity of fluorescence immunochromatography for detecting IgM/IgG were 93.10%/96.55%, and the specificity of that were all 97.62%. The sensitivity of fluorescence immunochromatography to detect IgM is significantly higher than that of colloidal gold method. There is no difference in the specificity of the two methods to detect IgM and IgG. Ding et al. built a rapid detection method for IgM-IgG antibodies. They introduced aggregation induced emission materials as signal units, which greatly improved the sensitivity for the antibody detection. The test paper also has the advantages of fast, simple, and so on. Thirty antibody positive cases (75%) were detected in 40 COVID-19 patients, of which 16 cases were IgM positive (40%), 28 cases were IgG positive (70%). And there was no IgM and IgG detected in the healthy control group and the non COVID-19 disease group [44]. Cui et al. [45] used quantum dots immunofluorescence method to detect IgG and IgM antibodies. 74 confirmed patients (26 in non convalescent period, 48 in convalescent period) were selected, and 48 healthy blood samples were used as negative controls. They confirmed that the combined detection method has high sensitivity and specificity. Lin et al. [46] developed a portable system integrates diagnostic microchip, microfluidic immunoassay technology and portable fluorescence detector. It can simultaneously detect the IgG/IgM/antigen of COVID-19 on site, and has the merits of fast (<15 min), simple, high specificity and sensitivity.

4.4. Nanomaterials for detection

Nanomaterials have been widely used for biological detection, including Mxenes, noble metal nanoparticles, nano-magnetic microspheres, nano-enzymes, graphene, carbon nanotubes, etc., so biosensors and detectors based on nanomaterials are promising in early detection of COVID-19 [47]. Among them, Mxenes is a kind of two-dimensional inorganic compound, which has conductivity, hydrophilicity, high transmittance, biocompatibility, high carrier mobility, etc. Its specific surface area is large, so it is easy to absorb organic molecules, and has excellent SERS. SERS detection technology has high sensitivity, can rapid detect in situ, which is widely used in the field of analysis and detection. Peng et al. [48] made Ta_2C and Nb_2C nanosheets, which exhibit excellent SERS performance. Under the excitation with 532 nm, SERS sensitivity of Nb_2C and Ta_2C MXenes were 3.0×10^6 and 1.4×10^6, can accurately identify the virus spike protein.

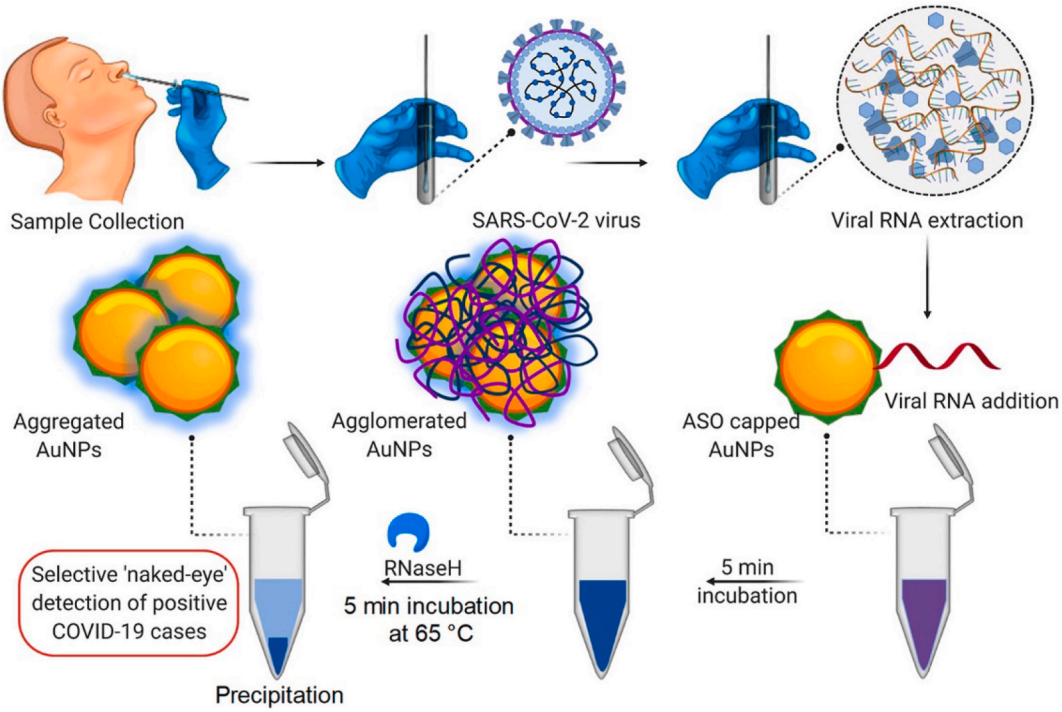

Fig. 3. A gold nanoparticles colorimetric method, detect Covid-19 with naked eyes. Reprinted with permission from Ref. [51]. Copyright 2020 American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Noble metal nanoparticles have surface plasmon resonance properties. When the light falls on the noble metal nanoparticles, free electrons separated from the metal nucleus. The electrons oscillated, and stimulated surface plasmon resonance and causing strong light absorption. Das et al. [49] proposed a sandwich plasma model, using gold nanorod assisted enhanced plasma to detect virus spike protein, and the sensitivity of BK7 glass prism mirror plasma resonance sensor increased by 111.11 deg RIU $^{-1}$. Funari et al. [50] detected the antibody to virus spike protein through the gold nanopin in the optical microfluidic chip. Antigen-antibody binding caused the displacement of the gold nanopin surface plasmon resonance wavelength. It took up to 30 min to complete the detection. Moitra et al. [51] developed a gold nanoparticles colorimetric method based on for naked eye test of COVID-19 (Fig. 3). Gold nanoparticles were modified with antisense oligodeoxynucleotides to specifically recognize virus nucleocapsid phosphoprotein and complete the detection within 10 min. When exposed to the specific RNA sequence, the gold nanoparticles will selectively aggregate, resulting in changes in surface plasmon resonance. In addition, sediment can be observed through the aggregation of gold nanoparticles, which can be observed by eyes without complicated instruments.

Chen et al. [52] reported a side stream immunoassay based on lanthanide doped polyethylene terephthalate nanoparticles, which can quickly and sensitively detect COVID-19 IgG antibodies. Nitrocellulose membrane coated with recombinant nucleocapsid phosphoprotein, and IgG antibody could be specifically captured. This method was used to detect 7 PCR positive samples and 12 negative samples (but clinical suspicion of COVID-19 cases). One negative sample was identified as COVID-19 IgG positive, while the others were consistent with the PCR results. The detection process took 10 min. This method can quickly and sensitively detect COVID-19 IgG antibody, and can positively identify suspicious cases.

Immunomagnetic beads can specifically capture target molecules by immobilizing antibodies/antigens on the magnetic nanoparticles surface, and achieve the purpose of enriching and separating low concentration target molecules by magnetic field, which can improve the detection sensitivity. Zhang et al. [53] used immunomagnetic beads to enrich SARS-CoV-2 virus, and studied its detection sensitivity. 2 mL, 600 μL and 200 μL samples were enriched with magnetic beads, equivalent to 20, 6 and 2 times enrichment. The Ct value of enriched samples is significantly lower than that of ordinary samples. 20 times enrichment of samples will cause Ct value decrease by 3. This method significantly improves the sensitivity of nucleic acid detection and could be used for the detection of weakly positive samples. Fabiani et al. [54] built a rapid detection method by using magnetic beads based electrochemical immunosensor, which can detect spike protein and nucleocapsid protein. Magnetic beads can support of the immune chain, and alkaline phosphatase was also used for the immune label. The detection limits of N protein and S protein in saliva were 8 ng/mL and 19 ng/mL. Compared with PCR, the detection results have high reliability, rapid analysis, and portability.

Liu et al. [55] used nano enzyme chemiluminescence test paper to detect COVID-19 antigen quickly and sensitively. First, carboxyl-modified Co–Fe nanoparticles were synthesized by hydrothermal method, added to NaAc aqueous solution, and then hemin was added to the reaction system drop by drop, stirring at room temperature for 2 h, magnetic separation and purification, washing, drying, and then Co–Fe@heme peroxidase nanoenzyme was obtained. Then, nanoenzyme and enzyme-catalyzed chemiluminescence immunoassay are integrated on the side flow test strip. The detection limit of nanoenzyme chemiluminescence test paper for the virus recombinant spike antigen is 0.1 ng/mL, the linear range is 0.2–100 ng/mL, and the detection sensitivity for the fake virus is 360 $TCID_{50}$/mL, and fast detected within 16 min.

Pinals et al. [56] used near-infrared carbon nanotube sensor to rapidly detect the spike protein. ACE2 is a host protein with high binding power to virus spike protein. SWCNs were modified by ACE2 through non covalent bonds. When the nanosensor is contacted with spike protein for 90 min, the fluorescence intensity can be increased twice. After contacting 35 mg/L virus like particles, 73% of the fluorescence response was displayed. Shao et al. [57] used the EDC/NHS coupling method to prepare virus antibody functionalized SWCNs based field effect transistor for detection. The detection limits are 0.016 fg/mL and 0.55 fg/mL for nucleocapsid protein antigen and spike protein antigen, respectively, the detection time is less than 5 min.

Hashemi et al. [58] designed an electrochemical rapid diagnosis kit consisting of a fixed/screen printed electrode. The electrode is coated with graphene oxide coating of coupling sensitive compounds and gold nanoparticles. Through the interaction with glycoprotein, the virus could be detected within 1 min, and the sensitivity and detection limit for virus can reach 0.0048 μAμg.mL^{-1}. cm^{-2} and 1.68 × 10^{-22} μg mL^{-1} respectively, it also can be quickly and specifically identified even in the incubation period.

5. Biomedical equipments (extracorporeal membrane oxygenation) in the treatment of COVID-19

Infected patients may have acute respiratory distress syndrome and acute lung injury. These complications will also cause multiple organ failure and increase patient mortality. When virus arrives at the alveoli, its spike protein binds to ACE2, and then enters AECII cells through transmembrane protease serine 2 (TMPRSS2). Macrophages and pulmonary dendritic cells perceive the virus antigen, initiate the immune response, release pro-inflammatory cytokines, cause cytokine storms, and then damage and destroy the alveolar and capillary membranes, causing plasma to leak into the alveolar and pulmonary interstitial space, forming diffuse edema, causing dyspnea and hypoxemia. Therefore, extracorporeal membrane oxygenation (ECMO) as a protective ventilation measure has been used clinically to save the lives of severe patients.

Li et al. [59] analyzed the effects of ECMO for infected patients at the early stage of infection. Eight patients were supported by ECMO, seven of whom received VV ECMO support, and one patient received VA ECMO. Four of them died, 3 of them were out of danger after ECMO support, but still continued to use mechanical ventilation, and another patient has been using VV ECMO. Before ECMO, the ratio of oxygen partial pressure to inhaled oxygen fraction was between 54 and 76, both of which were far below 100. Therefore, ensuring timely, effective and safe ECMO support is the key to improve clinical results of severe cases, and extracorporeal membrane oxygenation is an indispensable medical measure in the intensive care process of patients.

Ramanathan et al. [60] searched and analyzed the literature on ECMO therapy for COVID-19 patients published from December 1,

2019 to January 10, 2021. A total of 1896 patients were reported, 98.6% of whom were treated with VV ECMO, which was the main mode for use. The combined inpatient mortality was 37.1%, of which the combined mortality of VV ECMO group was 35.7%, and age growth was the risk factor for death. The ECMO support duration was 15.1 days in 1844 patients. 1583 ECMO complications were reported, and the most common was renal complication.

6. Vaccine and drug in the prevention and treatment of COVID-19

6.1. Vaccination in the prevention of COVID-19

No specific drugs for COVID-19, vaccination has become effective preventive measure. Vaccination in large areas can reduce the transmission rate of virus and reduce severe mortality. Lei et al. [61] developed a cationic nanocarrier for recombinant protein vaccine, which can target the receptor binding region of spike protein, induce effective antibody response, and thus generate immune protection. Three kinds of cationic nano-carriers were selected: PEI, DOTAP and chitosan. Anionic L and Neutral L were set as control groups. Anionic liposomes consist of phosphatidylcholine and cholesterol, cholesterol hemisuccinate, while neutral liposomes consist only of phosphatidylcholine and cholesterol. When the vaccine is loaded on the cationic nano-carrier and administered to the nasal mucosa, the specific IgG and IgM titers are higher than those in the anionic liposome and neutral liposome control groups, which significantly improves the vaccine induced IgG antibody response. The intramuscular vaccination of the vaccine has also achieved similar results, which is a safe and low-cost SARS-CoV-2 vaccine carrier. Abhyankar et al. [62] developed a vaccine preparation with liposome adjuvant loaded with virus spike subunit. It can produce strong neutralizing antibodies, and can protect mice from fatal infection. Two immunizations can prevent lung injury and remove the virus from the lung. Wu et al. [63] used replication deficient human adenovirus type 5 to load virus spike protein, and one vaccination could completely protect mice from infection. In addition, one vaccination can also protect ferrets from upper respiratory tract infection. In addition to normal intramuscular vaccination, intranasal mucosal vaccination can also provide ideal protection.

Except the scientific research of vaccine in the laboratory, major pharmaceutical companies around the world have made great contribution in the research, development and production of vaccine. The vaccine (AZD1222) jointly developed by Oxford University and AstraZeneca; and Ad26.COV2.S of Johnson & Johnson are composed of non-replicating adenovirus vectors, which can replicate the virus S protein; the mRNA-1273 (NCT04405076) of Moderna, BNT162b2 jointly developed by BioNTech and Pfizer, and BANCOVID of Globe Biotech belong to mRNA vaccines. These mRNA vaccines target S protein (or specific region of S protein). INO-4800 of Inovio Pharmaceuticals Ltd., GX-19 of Genexine Ltd. and ZyCoV-D of Zydus Cadila Ltd. are DNA vaccines targeting S protein. COVAX-19 of Vaxine PTY Ltd. and NVX-CoV2373 of Novavax Ltd. belong to protein vaccine. China National Pharmaceutical Ltd., Kexing Ltd. and Kangxinuo Ltd. produced three inactivated vaccines and one adenovirus vector vaccine. As of October 21, 2022, Our World in Data of Oxford University reported that there were 12 858 868 434 doses of vaccine inoculated in the world, with a coverage rate of 68.39%. Moreover, three doses vaccination can reduce death by more than 90%. Among patients over 60 years old, the death risk of those who have not vaccinated is 21 times that of those who have vaccinated ($\geq$2 doses of vaccine). The fatality rates of non-vaccinated population, two doses vaccination, and three doses vaccination are 2.87%, 0.14% and 0.03% respectively. Thus, vaccination can block the transmission of COVID-19, and can also greatly reduce the severe mortality, playing a good preventive effect.

6.2. Anti-inflammatory treatment of COVID-19

COVID-19 can destroy the host immune system and cause cytokine storms of infected people. Many manifestations of infected patients are directly attributable to inflammatory factors. Cytokine storm treatment is the key factor to save the severe patients. Glucocorticoids can be used in patients with overactivated inflammatory response in a short time. Adjusting the dose of glucocorticoids can effectively inhibit IL-6 and other cytokines, and can effectively reduce mortality. The drugs blocked the IL-6 signal transduction pathway, could be used to treat the severe COVID-19 patients. During the cytokine storm, their efficacy is particularly significant [64]. The suddenly activated macrophages are the key factor leading to the cytokine storm. Reactive microglia will release excessive proinflammatory factors, which will lead to neuropathological problems in the brain of COVID-19 patients. Therefore, the life-threatening cytokine storm can be eliminated by consuming activated macrophages and microglia. Chlorophosphonate is an effective consumer of macrophages and microglia, while liposome-encapsulated chlorophosphonate can effectively induce the death of macrophages. The activated macrophages and microglia are consumed by the liposome-encapsulated chlorophosphonate, which can be used to treat cytokine storms and alleviate multiple organ failure [65].

Satta et al. [66] modified nano-liposomes with hACE2 to form liposome-hACE2 complex. A Lenti-Spike expressing D614G was prepared by imitating virus. Both Lenti-Spike and SARS-CoV-2 virus induce mouse and human key cytokines and chemokines to stimulate macrophages and produce strong inflammatory reaction. Lipo-hACE2, as a competitive inhibitor, can inhibit macrophage inflammation. After intravenous injection of Lenti-Spike, the inflammation of macrophages and tissues in mice increased, while Lipo-hACE2 treatment eliminated the inflammatory reaction.

Curcumin has antioxidant, anti-tumor, antibacterial, antiviral, anti-diabetes and anti-inflammatory properties. Asadirad et al. [67] studied the nanocurcumin on inflammatory cytokines for infected patients. 60 patients were divided into nanocurcumin and control group. The nanocurcumin group took 240 mg nanocurcumin every day for 7 days, while the control group gave placebo treatment. In addition, all the people gave standard treatment (lopinavir/ritonavir (Kaletra®) 400mg/100 mg tablets twice daily; subcutaneous injection 44 μg IFN- β-1a once every other day. Nanocurcumin can be used as a supplementary drug, play an anti-inflammatory role and inhibit inflammatory complications, and significantly improve most clinical manifestations. The mortality of nanocurcumin and

control groups were 18.5% and 25%, so the nanocurcumin reduced the mortality.

What is more interesting is that both COVID-19 and tumors have abnormal inflammatory. Aldea et al. [68] discussed the researches of using anticancer drugs to treat COVID-19: anti cytokine therapy to treat inflammatory storm, and immunocheckpoint inhibitors to improve antiviral defense are all conducive to the treatment of infected patients, anti-cancer drugs are regarded as effective antiviral therapy. For mild and moderate cases, anti PD-1 can improve the virus clearance rate, and anti androgen drugs can block the TMPRSS2 receptor entering the cells. For severe cases, JAK/STAT and BTK inhibitors can reduce inflammatory signals and control cytokine storms. Anti-cytokine (anti-IL-6 receptor) directly reduces cytokine storm. Corticosteroids are used to treat malignant tumors of the blood system and COVID-19 severe patients who need respiratory support, which enhances the survival rate of severe cases and has been included in the standardized treatment scheme for critical application.

6.3. New drug development for treatment of COVID-19

Although no specific drug, research and development has been ongoing (Table 3). Nanoparticle delivery system can send drugs to specific tissues, and decrease the toxicity of drug [69]. Balitinib (BTB) can interrupt the signal transduction of various cytokines related to COVID-19, target the host factor of the virus entering the cell, inhibit the up regulation of ACE2, and has good anti-virus effect. Anwer et al. [70] prepared glycolide-lactide copolymer (PLGA), lecithin and stearic acid composite nanoparticles by one-step precipitation method, which improved the release performance and bioavailability of BTB. PLGA is used as hydrophobic core to encapsulate insoluble drug BTB. Lecithin and stearic acid are assembled into lipid shell around PLGA. Pharmacokinetics in vivo showed that compared with pure BTB suspension, lipid-coated polymer nanoparticles prolonged the circulation time in vivo, and increased the bioavailability of BTB by three times. Lipid-coated polymer nanoparticles opened up a more potential route for drug delivery.

Nanoparticles with photothermal function can also be used to kill virus in vivo. Cai et al. [71] modified photothermal nanoparticles with virus antibody to inactivate virus (Fig. 4). First, the semiconductor polymer dithiophene-benzothiadiazole copolymer (PCPDTBT) and the biocompatible stearylglycerol-phosphate-ethanolamine-polyglycol-NHS ester (DSPE-PEG2000-NHS) are dissolved in THF, and then the dioctadecyl-tetramethylindole tricarbocyanine iodide (DiR) is added, and then injected into PBS, ultrasonic treatment, and the organic solvent is removed by rotary evaporation, the resulted nanoparticles with semiconductor polymer as core and biocompatible polyethylene glycol as shell. The virus neutralizing antibody was added into nanoparticle solution, stirred at 4 °C overnight, so as to connect the neutralizing antibody to the nanoparticle. The neutralizing antibody modified nanoparticles can effectively capture virus-like particles. In addition, the nanoparticles also have photothermal function, which can generate heat after irradiation and inactivate the virus.

Li et al. [72] also reported a multifunctional alveolar macrophage (AM)-like nanoparticles, and used for treatment through photothermal inactivation ability. The prepared nanoparticles coated with AM membrane on the polymer core, which could block coronavirus into host cells and absorb pro-inflammatory cytokines. In order to improve the antiviral effect, an aggregation induced emission photothermal matter was incorporated into the nanoparticles to inactivate virus under near-infrared irradiation. In the animal infection experiment, the treatment of infected mice with near-infrared light irradiation of AM-like nanoparticles can reduce the viral load and cytokine level, reduce lung injury and inflammation, and significantly increase the survival rate. Crucially, this treatment strategy can treat COVID-19 in early clinical stage, reduce infection and transmission risk by atomizing inhalation of nanoparticles, and then irradiating the respiratory tract with near-infrared light.

Sun et al. [73] developed a spherical gold nanoparticles with cocktail neutralizing aptamer (SNAP), inhibited virus infection and mutation escape (Fig. 5). By virtue of the steric hindrance effect and the polyvalent aptamer assembly of the gold nanoparticles, SNAP had a semi maximum inhibitory concentration of 142.80 fM for virus. More importantly, the cooperative blocking strategy makes the extensive neutralization activity of nanoparticles, and provides a new path for the antiviral drugs development.

Donskyi et al. [74] studied the inhibition effect of graphene materials with bisulfate/alkyl functional groups on SARS-CoV-2 virus. The graphene surface is functionalized by polyglycerol sulfate (PGS) and different length of fatty chain. The graphene derivative can destroy the envelope of coronavirus, thus irreversibly inhibiting virus infection. The modified graphene with short alkyl chain showed

Table 3
New drug development for treatment of COVID-19.

Drugs	Delivery systems	Properties	Reference (s)
Balitinib (BTB)	Glycolide-lactide copolymer (PLGA), lecithin and stearic acid composite nanoparticles by one-step precipitation method	Increased the bioavailability of BTB by three times	[70]
Neutralizing antibody	Semiconductor polymer as core and biocompatible polyethylene glycol as shell	Completely block the virus infection, photothermal inactivate the virus	[71]
Multifunctional alveolar macrophage (AM)	AM as shell, polymer as core	Block the entry of coronavirus into host cells, absorb various pro-inflammatory cytokines, photothermal property	[72]
Cocktail neutralizing aptamer	Gold nanoparticles	Semi maximum inhibitory concentration of 142.80 fM for SARS-CoV-2 virus	[73]
Graphene with bisulfate/alkyl functional groups	–	Graphene with long fatty chain (>C9) has stronger inhibition and destruction effect on coronavirus	[74]

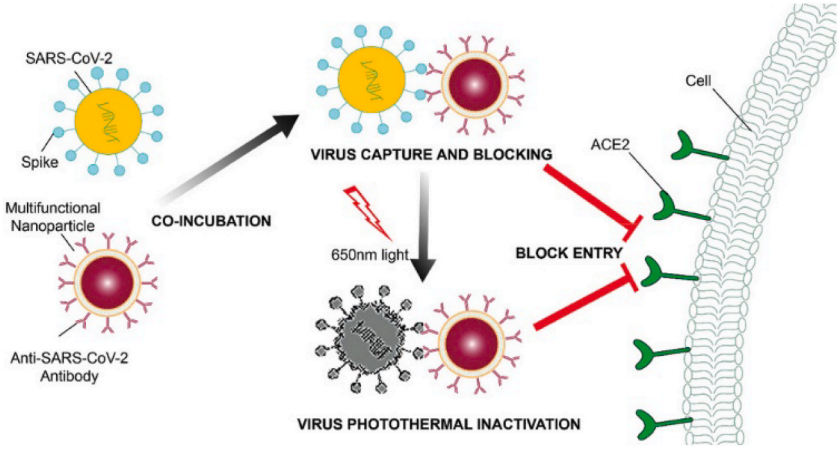

Fig. 4. The neutralizing antibody binds to photothermal nanoparticles to inactivate virus. Reprinted with permission from Ref. [71]. Copyright 2022 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

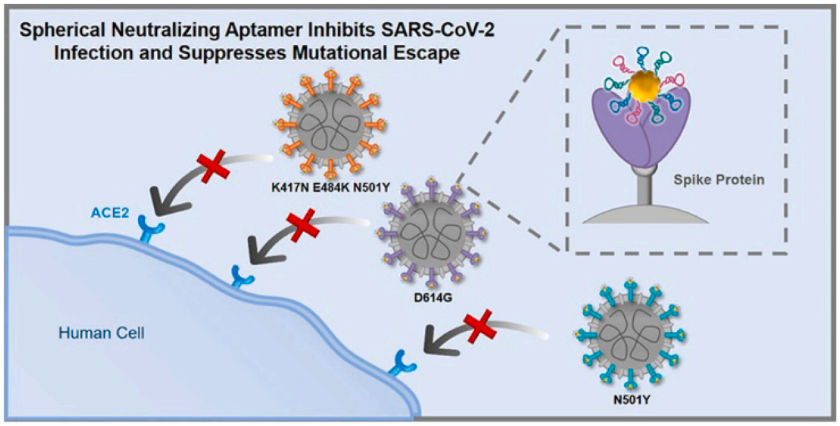

Fig. 5. Spherical neutralizing aptamer inhibits Covid-19 infection and mutation escape. Reprinted with permission from Ref. [73]. Copyright 2022 American Chemical Society.

moderate virus inhibition effect and had no significant toxicity to cells; the modified graphene with long fatty chain (>C9) has stronger inhibition and destruction effect on coronavirus. PGS first interacts with virus through electrostatic interactions, and then the long enough fat chain can break the viral envelope. This study found that within a large concentration window (10–100 times), the modified graphene material has excellent antiviral activity, but has no significant toxicity to human cells.

7. Outlook and future perspectives

Ordinary masks cannot actively kill SARS-CoV-2 virus, and the used masks may become pollutants, leading to secondary transmission or cross infection. The use of metal and its oxide, graphene and graphene oxide, quaternary ammonium salt and other antivirus ingredients to modify protective articles can effectively kill the virus and improve the prevention effect, but the biological safety of nanoparticles is still the focus of attention, and the leaching and diffusion of nanoparticles should be minimized. At the same time, the safety evaluation of nanomaterials should be strengthened. Graphene material can cross the biological barrier, whether it will be inhaled by the human body when combined in the mask, whether it will cause biological toxicity. After sunlight or applied voltage (<3 V), the graphene material could rise to more than 100 °C rapidly. The virus is indeed inactivated, but it will also burn the human body. How to control the temperature and improve the safety is also one important subject. In addition, the water permeability, air permeability, temperature control and other properties of protective articles also need to be further studied to improve wearing comfort. However, specific drugs for viruses still need to be further studied, perhaps traditional Chinese medicine can open a new door for the treatment of viruses. At the same time, developing a simple, convenient, efficient, accurate and low-cost virus detection technology is still research goal in the future.

8. Summary and conclusions

Biomedical equipments, vaccine and drug have played a crucial role in the prevention, diagnosis and treatment of COVID-19. Metal and its oxides, graphene and graphene oxides, and quaternary ammonium salt were used to modify respirators and protective clothing to enhance the virus killing performance. Technologies for diagnosis equipments, such as polymerase chain reaction (PCR) technology, CRISPR technology, IgM/IgG antibody detection technology, and nanomaterials for detection, were described. And developing a simple, convenient, efficient, accurate and low-cost detection technology is also a research direction in the future. ECMO as a protective ventilation measure has been used clinically to save the lives of severe patients, and anti-inflammatory drugs were also used for the treatment. Moreover, vaccination can reduce the transmission rate of virus and the mortality rate of severe cases. Most important, the research and development of specific drugs for virus also need to pay more attention in the future.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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