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CRITICAL REVIEW

Understanding and combating COVID-19 using the biology and chemistry of SARS-CoV-2

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Abstract

The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms of COVID-19 can range from asymptomatic to severe, which could lead to fatality. Like other pathogenic viruses, the infection of SARS-CoV-2 relies on binding its spike glycoprotein to the host receptor angiotensin-converting enzyme 2 (ACE 2). Molecular studies suggested that there is a high affinity between the spike glycoprotein and ACE 2 that might arise due to their hydrophobic interaction. This property is mainly responsible for making this virus highly infectious. Apart from this, the transmissibility of the virus, prolonged viability in certain circumstances, and rapid mutations also contributed to the current pandemic situation. Nanotechnology provides potential alternative solutions to combat COVID-19 with the development of *i.* nanomaterial-based COVID-19 detection technology, *ii.* nanomaterial-based disinfectants, *iii.* nanoparticle-based vaccines, and *iv.* nanoparticle-based drug delivery. Hence, this review provides diverse insight into understanding COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Angiotensin-converting enzyme 2 (ACE2) · Omicron · Molnupiravir · Nanotechnology · PAXLOVID™ · Quercetin · Remdesivir · Vaccine

Abbreviations

+ ssRNA	Positive-sensed single-stranded ribonucleic acid
$3CL^{pro}$	3-Chymotrypsin-like protease
ACE 2	Angiotensin-converting enzyme 2
AgNPs	Silver nanoparticles
ATP	Adenosine triphosphate
AuNPs	Gold nanoparticles
BFE	Bacterial filtration efficiency
CDC	Centers for Disease Control and Prevention
cDNA	Complementary deoxyribonucleic acid
COVID-19	Coronavirus disease 2019
CoVs	Coronaviruses
DNA	Deoxyribonucleic acid
FDA	United States Food and Drug Administration
FFR	Filtering facepiece respirators
GI	Gastrointestinal
HCoV	Human coronavirus
ICTV	International Committee on Taxonomy of Viruses
IPC	Infection prevention and control
IV	Intravenous
LNPs	Lipid nanoparticles
MC	Monte Carlo
MD	Molecular dynamics
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
mRNA	Messenger RNA
NAAT	Nucleic acid amplification test
nCoV	Novel coronavirus
NIOSH	National Institute for Occupational Safety and Health
NPs	Nanoparticles
NsPs	Non-structural proteins
PFE	Particulate filtration efficiency

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pI	Isoelectric point
PL^{pro}	Papain-like protease
PP	Polypropylene
PPE	Personal protective equipment
RATs	Rapid antigen tests
RBD	Receptor-binding domain
RdRp	RNA-dependent RNA polymerase
RDV	Remdesivir
RNA	Ribonucleic acid
RT-PCR	Real-time reverse transcription-polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS2	Transmembrane serine protease 2
UAE	United Arab Emirates
USA	United States of America
VOC	Variants of concern
VOC-LUM	VOC lineages under monitoring
VOI	Variant of interest
VUM	Variants under monitoring
WHO	World Health Organization

Introduction

Coronaviruses (CoVs) belong to the family Coronaviridae in the order of Nidovirales, which are positive-sensed single-stranded RNA viruses (+ssRNA) surrounded by an envelope [1–4]. The name "Corona" stands for 'crown' in Latin, given due to the distinctive crown-like appearance of their spike proteins, which allow the virus to interact with the host cell receptors, a key step necessary to penetrate the host cell surface. This group of viruses is sub-divided based on the difference in the protein sequence into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus (Fig. 1) [3–6].

Alpha- and Betacoronaviruses are known to infect humans that include seven types of coronaviruses: *i.* HCoV-229E, *ii.* HCoV-NL63, *iii.* HCoV-OC43, *iv.* HCoV-HKU1, *v.* SARS-CoV, *vi.* MERS-CoV, and *vii.* SARS-CoV-2 [3, 4, 7]. HCoV stands for human coronavirus where HCoV-229E and HCoV-NL63 are alpha-CoVs while HCoV-OC43 and HCoV-HKU1 are beta-CoVs. These human coronaviruses usually cause mild symptoms such as the common cold (or acute rhinitis) or gastrointestinal infection, which causes diarrhea [3]. In contrast, SARS-CoV, MERS-CoV, and SARS-CoV-2, which are beta-CoVs, are highly transmittable and pathogenic, causing a higher chance for patients to develop severe acute respiratory infections like pneumonia [3]. According to

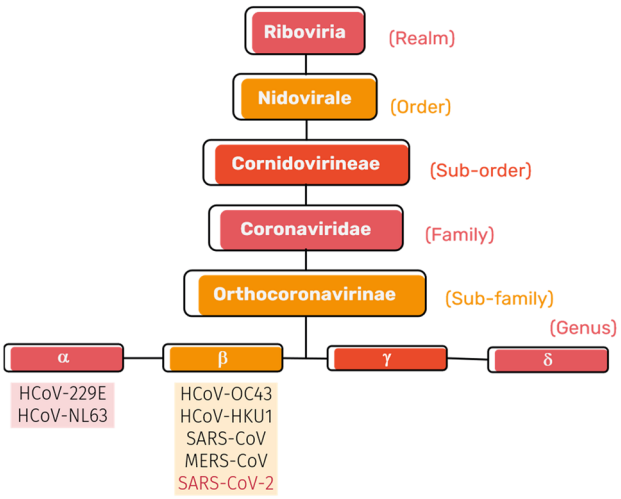

Fig. 1 Classification of human coronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2

epidemiological data, SARS-CoV and MERS-CoV are zoonotic pathogens that can be transmitted between animals and humans during close interaction [3, 6]. In 2002, the severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV in Guangdong Province of China was identified to be transmitted from bats to humans via civet cats as the intermediate host [8]. A decade later in 2012, the Middle East respiratory syndrome (MERS) outbreak caused by MERS-CoV from Saudi Arabia was investigated to be from camels to humans [3, 6].

In December 2019, Wuhan, the capital of Hubei Province of China, experienced an outbreak of unidentified pneumonia disease associated with a novel coronavirus (nCoV) [4]. The term nCoV is a provisional name given to the new strain of coronavirus, which has not previously been identified in humans. This new strain of the virus was initially referred to as 2019-nCoV before it was named severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) [1, 6]. This name was chosen because the virus is genetically related to SAR-CoV which caused the SARS outbreak back in 2002. On the 11th of February 2020, the name of the disease caused by SAR-CoV-2 was announced as *coronavirus disease 2019* (COVID-19) by the World Health Organization (WHO). The World Health Organization (WHO) then declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic on the 11th March 2020. Coming from the beta-CoV genus, SAR-CoV-2, the seventh strain of human coronavirus, is the third zoonotic CoV after SARS-CoV and MERS-CoV [1, 8]. The source of COVID-19, however, is still actively being investigated, although initial studies have shown that the CoVs found in bats and pangolins are highly related to SAR-CoV-2 [8]. This is because neither of the

CoVs found in these mammals is sufficiently genetically similar to serve as its direct reservoir [8].

According to WHO, as of 1st July 2022, there have been more than 545 million confirmed COVID-19 cases, including more than 6 million deaths. Previously, there were four SARS-CoV-2 variants of concern (VOC) which are *i.* Alpha (B.1.1.7), *ii.* Beta (B.1.351), *iii.* Gamma (P.1), and *iv.* Delta (B.1.617.2) (Table 1). However, on 26th November 2021, WHO classified a new variant of concern which was first reported by scientists in South Africa, known as the Omicron variant (B.1.1.529). Subsequently, Omicron is currently the dominant variant circulating globally. These are caused by mutations, especially in the spike protein receptor-binding domain (RBD) that enhances viral replication in the upper respiratory tract and in vivo transmission [9]. It was reported that Omicron possesses the most mutation sites and the mutations in its spike protein were approximately three to four times greater than the four previously circulating VOCs [10, 11]. Weng et al. reported that the Omicron variant had 50 consensus mutations, while Alpha, Beta, Gamma, and Delta had 22, 18, 23, and 29 mutations, respectively [11, 12]. These mutations have also shown increased infectivity and antibody resistance [13]. In addition, variants that were previously classified as variants of interest (VOI) include *i.* Epsilon (B.1.427 and B.1.429), *ii.* Zeta (P.2), *iii.* Eta (B.1.525), *iv.* Theta (P.3), *v.* Iota (B.1.526), *vi.* Kappa (B.1.617.1), *vii.* Lambda (C.37), and *viii.* Mu (B.1.621) (Table 1).

Table 1 Classification of SARS-CoV-2 variants as of 7th June 2022 by the World Health Organization [14]

	WHO label	Pango lineage	Country and date of the earliest documented samples	Designation date
Previous circulating VOCs	Alpha	B.1.1.7	UK, September 2020	**VOC:** 18th December 2020 **Previous VOC:** 9th March 2022
	Beta	B.1.351	South Africa, September 2020	**VOC:** 18th December 2020 **Previous VOC:** 9th March 2022
	Gamma	P.1	Brazil, November 2020	**VOC:** 11th January 2021 **Previous VOC:** 9th March 2022
	Delta	B.1.617.2	India, October 2020	**VOI:** 4th April 2021 **VOC:** 11th May 2021 **Previous VOC:** 7th June 2022
Current circulating VOC	Omicron	B.1.1.529	South Africa, November 2021	**VUM:** 24th November 2021 **VOC:** 26th November 2021
VOC-LUMs	Omicron	BA.4	South Africa, January 2022	–
		BA.5	South Africa, January 2022	–
		BA.2.12.1	USA, December 2021	–
		BA.2.9.1	Multiple countries, February 2022	–
		BA.2.11	Multiple countries, March 2022	–
		BA.2.13	Multiple countries, February 2022	–
Previously circulating VOIs	Epsilon	B.1.427 B.1.429	USA, March 2022	**VOI:** 5th March 2021 **Previous VOI:** 6th July 2021
	Zeta	P.2	Brazil, April 2020	**VOI:** 17th March 2021 **Previous VOI:** 6th July 2021
	Eta	B.1.525	Multiple countries, December 2020	**VOI:** 17th March 2021 **Previous VOI:** 20th September 2021
	Theta	P.3	Philippines, January 2021	**VOI:** 24th March 2021 **Previous VOI:** 6th July 2021
	Iota	B.1.526	USA, November 2020	**VOI:** 24th March 2021 **Previous VOI:** 20th September 2021
	Kappa	B.1.617.1	India, October 2020	**VOI:** 4th April 2021 **Previous VOI:** 20th September 2021
	Lambda	C.37	Peru, December 2020	**VOI:** 14th June 2021 **Previous VOI:** 9th March 2022
	Mu	B.1.621	Colombia, January 2021	**VOI:** 30th August 2021 **Previous VOI:** 9th March 2022

The current estimated incubation period for SARS-CoV-2 is 5–6 days [15] or even shorter for the Omicron variant [16]. However, it can also take up to 14 days for an infected individual to develop symptoms [15]. Symptoms of COVID-19 can range from asymptomatic to severe (acute respiratory infections and intestinal infections), which could lead to fatality. However, the most common symptoms reported are *i.* fever, *ii.* fatigue, *iii.* dry cough, *iv.* loss of smell or taste, and *v.* sore throat [17]. Researchers have found that pre-existing health conditions such as high blood pressure, obesity, and diabetes in patients can enhance the severity of the disease and susceptibility to infection. Furthermore, post-COVID-19 symptoms or long COVID was also reported by a significant number of patients who have recovered from COVID-19 infection [17, 18]. These are symptoms such as *i.* fatigue, *ii.* shortness of breath, and *iii.* cognitive dysfunction (e.g., lack of mental focus and clarity, confusion, and forgetfulness) which persist for more than 12 weeks from initial symptoms [17, 18].

Different areas of chemistry and biology play a key role in understanding everything from the structure and pathogenesis of SARS-CoV-2 to preventive measures and treatment for COVID-19. Biochemistry, for instance, helps us understand the structure of SARS-CoV-2, its viral proteins, viral genome, and pathogenic mechanisms [19]. On the other hand, organic and pharmaceutical chemistry plays a crucial role in identifying potential antiviral drugs, synthesizing antiviral compounds, and developing effective antiviral drugs against COVID-19 [19]. Furthermore, biomaterial chemistry and nanotechnology aid in the research and development of better diagnosis, preventive measures, and drug delivery system using nanomaterials for the prevention and treatment of COVID-19 [19, 20]. The efficiency of drug delivery, for instance, can be improved with the different types of nanostructures which include *i.* metallic nanoparticles, *ii.* liposomes, *iii.* fullerenes, *iv.* graphene, *v.* carbon nanoparticles, and *vi.* polymeric nanoparticles [20].

Structure of SARS-CoV-2

Biochemistry plays a crucial role in understanding the structure of SARS-CoV-2. The structure of SARS-CoV-2 consists of *i.* a positive-sensed single-stranded RNA genome (+ssRNA), *ii.* a lipid-bilayer viral membrane, *iii.* nucleocapsid (N) proteins, *iv.* membrane (M) proteins, *v.* spike (S) glycoproteins, and *vi.* envelope (E) proteins (Fig. 2) [19, 21]. The single-stranded RNA genome is composed of 30,000 nucleotides which encode for four structural proteins (N protein, M protein, E protein, and S glycoprotein) and non-structural proteins (NsPs) such as 3-chymotrypsin-like protease ($3CL^{pro}$), papain-like protease (PL^{pro}), helicase (H), and RNA-dependent RNA polymerase (RdRp) [2, 5, 19]. N protein functions to encapsulate and protect the single-stranded RNA genome. M protein supports the viral assembly and is responsible for the shape of the viral membrane. In contrast, E protein has a crucial role in virus assembly, envelope formation, host cell membrane permeability and virulence [5, 19]. The S glycoprotein comprises an S1 and S2 subunit in each spike monomer which is responsible for binding to the host cell receptor and fusion of the viral and cellular membranes, respectively [22–24]. Therefore, the S1 subunit which recognizes the protein receptor is called the receptor-binding domain (RBD) [19]. Furthermore, S protein is the main antigen component in all structural proteins that interact with the host cell receptors angiotensin-converting enzyme 2 (ACE 2) [22–24]. ACE 2 is a zinc-dependent metalloenzyme present in the lungs (type II alveoli cells),

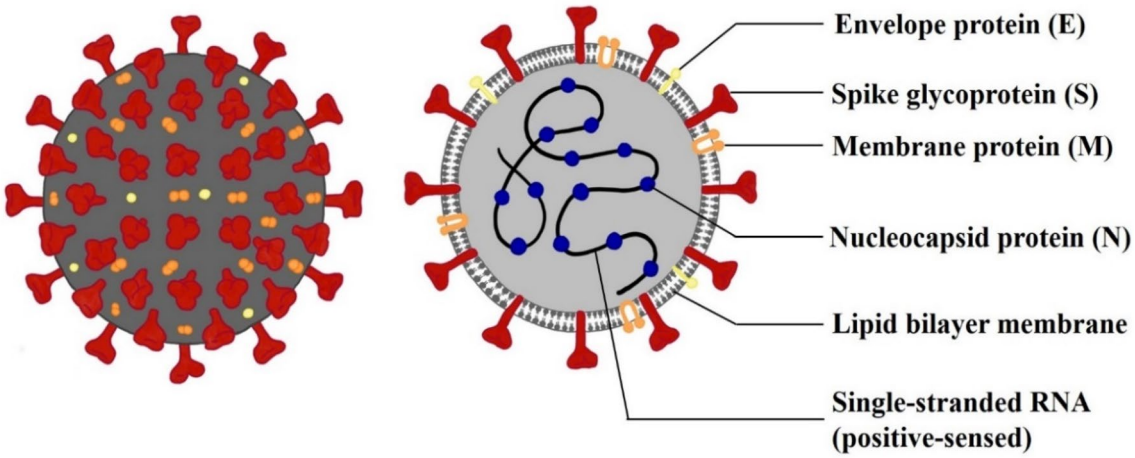

Fig. 2 Schematic drawing of the SARS-CoV-2 structure showing the single-stranded RNA genome (ssRNA), nucleocapsid (N) protein, membrane (M) protein, envelope (E) protein, spike (S) protein, and lipid-bilayer viral membrane

gastrointestinal (GI) tract, kidneys, and blood vessels [25]. This may suggest that enhanced binding between S protein of SARS-CoV-2 and ACE 2 may be responsible for increased disease severity (respiratory infection or GI infection) and high transmission rate of COVID-19.

Mechanism of SARS-CoV-2 pathogenesis

As illustrated in Fig. 3, the S1 subunit of the spike (S) protein of SARS-CoV-2 mediates binding to the receptors' angiotensin-converting enzyme 2 (ACE 2) to enter the host cell [22–24]. The transmembrane serine protease TMPRSS2 then releases the S2 subunit of the S protein to fuse SARS-CoV-2 with the host cellular membrane [21, 26]. After the entry into the host cell (endocytosis), the viral positive-sense single-stranded RNA (+ssRNA) is released into the cytosol, where ribosomes translate it into two large polypeptides known as pp1a and pp1ab [2, 19, 27]. These two large polypeptides are then transformed into mature non-structural proteins (NsPs) such as RNA-dependent RNA polymerase (RdRp) and structural viral proteins (S, M, N, and E proteins) by two viral proteases: *i.* 3-chymotrypsin-like cysteine protease ($3CL^{pro}$) which is the main protease and *ii.* papain-like protease (PL^{pro}) [19, 21]. RdRp mediates RNA replication, which causes multiple copies of the genome to be produced. Hence, more SARS-CoV-2 is generated as NsPs and the replicated viral genome self-assembles. Lastly, these synthesized virions are then secreted out (by exocytosis) from the infected cell, infecting other host cells.

Molecular interaction between SARS-CoV-2 and ACE2 receptor

Physical forces like *i.* hydrophobic effect, *ii.* electrostatic forces, *iii.* van der Waals forces, *iv.* hydrogen bonding, *v.* ionic bonding, and *vi.* entropy plays a crucial role in understanding protein–protein interactions. The binding interactions between the S protein of SARS-CoV-2 and ACE 2 receptor can be studied by using molecular dynamics (MD) simulations, which is a computer simulation method to analyze the physical movements of atoms and molecules, and the Monte Carlo (MC) sampling approach. Research by Li et al. has found that hydrogen bond pairing does not dominate the interaction between SARS-CoV-2 and ACE 2, as only several hydrogen bonds were identified [28]. However, simulation results of the hydration layer by using the MD method showed the existence of a large area of hydrophobic surfaces on SARS-CoV-2 RBD and ACE 2 [28]. This result suggests that the high affinity between SARS-CoV-2 and ACE 2 may be due to the hydrophobic effect among the hydrophobic surface areas of these two proteins at the binding site. Furthermore, a study by a group of computational chemists led by Amin showed that ACE 2 exhibited a negative electrostatic potential at the RBD, while SARS-CoV-2 showed positive electrostatic potential. This study has also found that mutations in the S protein of SAR-CoV-2 cause enhanced affinity toward ACE 2 due to the increase in electrostatic interactions [19, 22, 29].

Transmission routes of SARS-CoV-2

The transmission of SARS-CoV-2 can be spread through three major routes: *i.* droplet transmission, *ii.* aerosol transmission, and *iii.* contact transmission [5, 30]. Droplet transmission is the spread caused by respiratory water droplets carrying the virus via coughing and sneezing. Similarly, aerosol transmission spreads fine, infectious respiratory water droplet nuclei that sustain in the air and can be inhaled directly into the lower respiratory tract. On the other hand, contact transmission can be either direct (direct contact with an infected person) or indirect (contact with virus-contaminated surfaces). Door knobs, handrails, and lift buttons, for instance, are common virus-contaminated surfaces that may cause indirect contact transmission. Adsorption of SARS-CoV-2 to these surfaces can be further facilitated by van der Waals and electrostatic attractions [31].

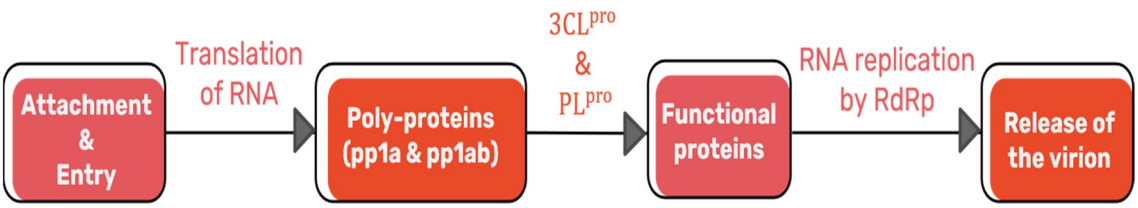

Fig. 3 Mechanism of SARS-CoV-2 pathogenesis

Persistence and viability of SARS-CoV-2 on different surfaces

Enveloped viruses such as SARS-CoV-2 can survive on inanimate surfaces. The quantity of adsorbed viruses is influenced by surface charge, size, stability, and steric conformation of the virus's outer surface proteins. Moreover, the persistence and viability of SARS-CoV-2 differ with the characteristics of the inanimate surfaces, surface proteins, and environmental conditions such as relative humidity, pH, and temperature [5, 31]. Studies have shown that SARS-CoV-2 has longer viability on plastics, glass, metals (stainless steel and zinc), latex, paper, and cardboard pieces [5, 31, 32]. Regarding this, Chin et al. reported that at 22 °C and 65% relative humidity, SARS-CoV-2 retained its infectivity for 4 days on plastics and stainless steel [33]. However, under the same temperature and relative humidity, SARS-CoV-2 retained its infectivity on paper for only 30 min (Table 2) [33]. On the other hand, SARS-CoV-2 could also have different survivability on a single surface at different temperatures and relative humidity. Research by Biryukov et al. observed that SARS-CoV-2 decayed more rapidly when temperature and relative humidity increased, and the type of inanimate surface did not impact the decay rate [32].

Diagnostic testing for SARS-CoV-2

Detection of SARS-CoV-2 is part of a necessary process to reduce community spread, especially by identifying asymptomatic infected individuals to be isolated. The types of specimens to be collected for SARS-CoV-2 diagnostic testing are *i.* upper respiratory specimen (e.g., nasopharyngeal or oropharyngeal), *ii.* lower respiratory specimen (e.g., sputum or lavage), *iii.* rectal swabs, or *iv.* blood (including serum and plasma). According to WHO and the Centers for Disease Control and Prevention (CDC) guidelines, a nasopharyngeal swab (upper respiratory specimen) is the preferred specimen required for detecting SARS-CoV-2 [34]. However, saliva is also an alternative specimen that has been considered for SARS-CoV-2 detection [34]. Nasopharyngeal specimen is the mucous secretion collected by cotton swab from the nasopharynx. Upon collection, the swab is placed immediately into a sterile tube containing a viral transport medium. Currently, there are several types of diagnostic testing methods, which include *i.* nucleic acid amplification test (NAAT) such as real-time reverse transcription-polymerase chain reaction (RT-PCR), *ii.* rapid antigen tests (RATs), and *iii.* SARS-CoV-2 antibody tests [21, 34].

Table 2 Persistence and time for complete inactivation of SARS-CoV-2 on different surfaces at 22 °C and 65% relative humidity [33]

Surface	Persistence	Complete inactivation
Plastic	4 d	7 d
Stainless steel	4 d	7 d
Glass	2 d	4 d
Cloth	1 d	2 d
Paper	30 min	3 h
Wood	1 d	2 d

Reverse transcription-polymerase chain reaction

Reverse transcription-polymerase chain reaction (RT-PCR) is a type of nucleic acid amplification test (NAAT) that amplifies viral nucleic acids until they are at detectable levels. Hence, it is the most reliable and standard diagnostic method for SARS-CoV-2 due to its high sensitivity, specificity, and accuracy. However, RT-PCR testing is time-consuming and requires expensive laboratory instruments, reagents, and skilled laboratory personnel [34]. In addition, this technique detects the presence of SARS-CoV-2 nucleic acids based on specific genes such as S, E, N, and RdRP genes in specimens of the infected individual [35, 36]. RT-PCR involves five steps which include *i.* specimen collection, *ii.* sample storage at 2–8 °C, *iii.* RNA extraction and purification using silica or magnetic particle-based methods, *iv.* reverse transcription of the viral RNA to a single-stranded complementary DNA (cDNA) using reverse transcriptase enzyme, and *v.* real-time detection of the fluorescent signals during the amplification of the specific genes of gene fragments [34, 35].

Rapid antigen test

Rapid antigen test (RATs), detects the presence of viral proteins (antigens) expressed by SARS-CoV-2 in nasopharyngeal or oropharyngeal specimens of the infected individual [35]. The technology for RATs is similar to that of a pregnancy test, as the presence of these antigens will be shown by a fluorescent or colored band on the test strip (Fig. 4) [34]. Since it is a cheap and rapid technique, this diagnostic method is currently available as at-home test kits. However, this method produces a higher rate of false negative results, as it can only detect antigens (viral protein) if the virus is actively replicating [35].

Antibody test

On the other hand, an antibody test which is a serology test is a method to test for past infections. It is an indirect test in detecting SARS-CoV-2, as this technique detects the

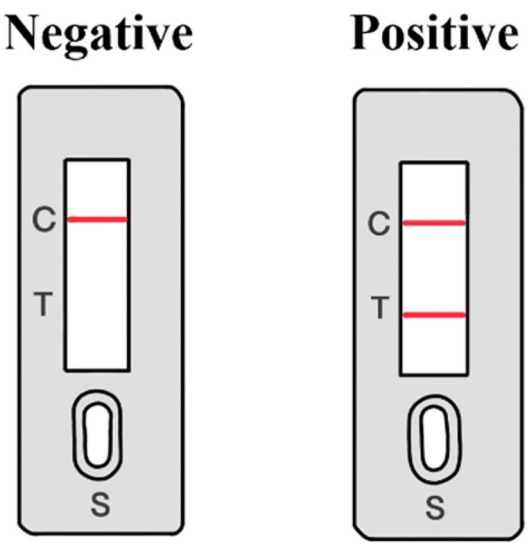

Fig. 4 Rapid antigen test kit showing negative and positive signs

antibodies produced specifically in response to fight with SARS-CoV-2. This is a quick method to detect the presence of SARS-CoV-2 antibodies, but this cannot confirm the active infection status of an individual.

Preventive measures

Prevention of infection is a major strategy to slow down the spread of COVID-19. Interventions such as social distancing, personal protective equipment (PPE), and chemical sanitizations are examples of COVID-19 preventive measures. PPE is a garment or equipment that protects the user against any health or safety risk. The most commonly used PPE for respiratory and body protection during the pandemic includes masks or respirators, gloves, gown/aprons, goggles, and face shields [37]. However, the choice of PPE and level of protection for the general public and health-care workers during this COVID-19 pandemic is based on the risk of exposure. On the other hand, usage of soap water, hand sanitizers, and disinfecting inanimate surfaces with chemicals (e.g., bleach and hydrogen peroxide) are examples of chemical inactivation and preventive measures.

Face masks

Face masks cover the users' nose and mouth, which act as physical barriers that prevent respiratory droplets transmission. It protects a healthy person from getting infected and also prevents onward transmission by an infected person. Therefore, the usage of face masks has become a worldwide health-care necessity during this COVID-19 pandemic. Masks are divided into three categories which include *i.* fabric face masks, *ii.* medical or surgical masks, and *iii.* respirators. Polymers such as polypropylene (PP), polyethylene, polyesters, polyamides, polycarbonates, and polyphenylene oxide are usually used for fibers in medical masks and medical respirators due to their hydrophobic and nonabsorbent properties [38]. Furthermore, WHO has developed specific guidelines and strategies on infection prevention and control (IPC). According to WHO, medical masks are recommended for health-care workers in clinical settings, people with mild symptoms (e.g., fatigue, slight cough, and sore throat), people with chronic health conditions (e.g., obesity, diabetes, cancer, chronic respiratory disease, and cardiovascular disease), patients with suspected or confirmed COVID-19, and home caregivers for suspected or confirmed COVID-19 patients. On the other hand, non-medical or fabric masks can be used by the general public under the age of 60 years with no health conditions. In general, face masks should possess five characteristics: *i.* particulate filtration efficiency (PFE), *ii.* bacterial filtration efficiency (BFE), *iii.* fluid resistance, *iv.* differential pressure, and *v.* flammability [30]. In addition, the four main characteristics which determine the mask performance are *i.* filtration, *ii.* breathability, *iii.* fit, and *iv.* performance under different environmental conditions [39].

A medical/surgical mask is most widely and commonly used by health-care workers and the general public. Medical/surgical masks are fluid-resistant disposable masks that can filter particles of size 0.04–1.3 μm [40]. It covers the nose and mouth of the user, but is not designed to seal tightly against the user's face [30, 37, 41]. As a result, they are not able to completely protect the user against airborne infectious agents such as coronavirus. Surgical masks usually consist of either three layers (3-ply) or four layers (4-ply). A three-ply surgical mask consists of three layers: *i.* an exterior hydrophobic layer, *ii.* a central filter layer, and *iii.* internal tender moisture-absorbing layer [41]. The function of the first layer is to repel water droplets; the second layer filters out germs and aerosols, while the third layer absorbs moisture from the user. A four-ply surgical mask is similar to a three-ply surgical mask, but with an additional central filtering layer or activated carbon filter [41]. In addition, the most commonly used material to make these medical masks is non-woven polypropylene (PP) as it is hydrophobic, nontoxic, breathable, inexpensive, provides filtration, and does not absorb humidity [30, 38]. Furthermore, its filtering mechanism is based on Brownian diffusion, entrapment, inertial collision, gravity sedimentation, and electrostatic adsorption [42].

Respirators, which are also known as filtering facepiece respirators (FFR), seal tightly against the user's face and are capable of protecting the user from infectious agents [41]. Surgical N95 respirators, for instance, is the most widely used surgical respirators, especially by health-care workers. It is a CDC/National Institute for Occupational

Safety and Health (NIOSH)-certified disposable half-mask filtering facepiece respirator that has 95% or above filtering efficiency for particle size of about 0.3 µm [38, 40]. Furthermore, it is effective in filtering non-oily particles such as coronaviruses as "N" means that the respirator is not resistant to oil [41]. It compises four layers which include *i.* a hydrophobic non-woven polypropylene (PP) outer later, *ii.* two layers of melt-blown non-woven PP, *iii.* a modacrylic support layer, and *iv.* a hydrophobic non-woven PP (Fig. 5) [30, 38]. The filter layers operate on four principles, which are *i.* inertial impaction, *ii.* interception, *iii.* diffusion, and *iv.* electrostatic attraction [30].

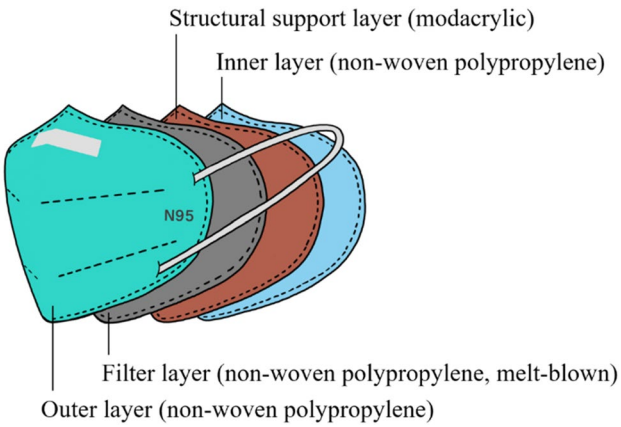

Fig. 5 Four layers of an N95 mask

Chemicals used for prevention of SARS-CoV-2

Soap

Usage of soap which is a surfactant is an effective way of killing SARS-CoV-2. Surfactant (surface-active agents) molecules are sodium salt with a long chain of fatty acids known as amphiphile [19]. Amphiphile consists of two parts: *i.* fat-like long-chain tail, which is hydrophobic, and *ii.* a $COO^{-}Na^{+}$ head, which is hydrophilic or lyophobic. Due to hydrophobic interactions, when soap is dissolved in water, the molecules would arrange in such a way as to form micelles (Fig. 6a) [19]. As the lipophilic tails are oriented inward, any dirt on our skin will be trapped to be rinsed away along with water. As shown in Fig. 6b, the lipid-bilayer membrane of SARS-CoV-2 is structurally similar to amphiphiles found on surfactant molecules. The connection of lipids in the viral membrane is the weakest connection due to the structure of the virus being self-assembled [19]. Hence, some surfactant molecules will compete with the lipids and attach to the viral membrane. This is done by bonding its hydrophilic head with water, while its lipophilic tail bonds to the lipid resulting in push–pull interactions that eventually break the viral membrane [19]. As SARS-CoV-2 structurally falls apart, the fragments of the virus get trapped in the micelle and get washed away with water. Furthermore, WHO guidelines recommend frequent hand washing with soap and water for at least 20 s to effectively prevent the disease [43].

Alcohol-based hand sanitizers

In addition to soap and water, the usage of rubbing alcohol or alcohol-based hand sanitizer is also an effective alternative way to kill SARS-CoV-2 when soap water is inaccessible.

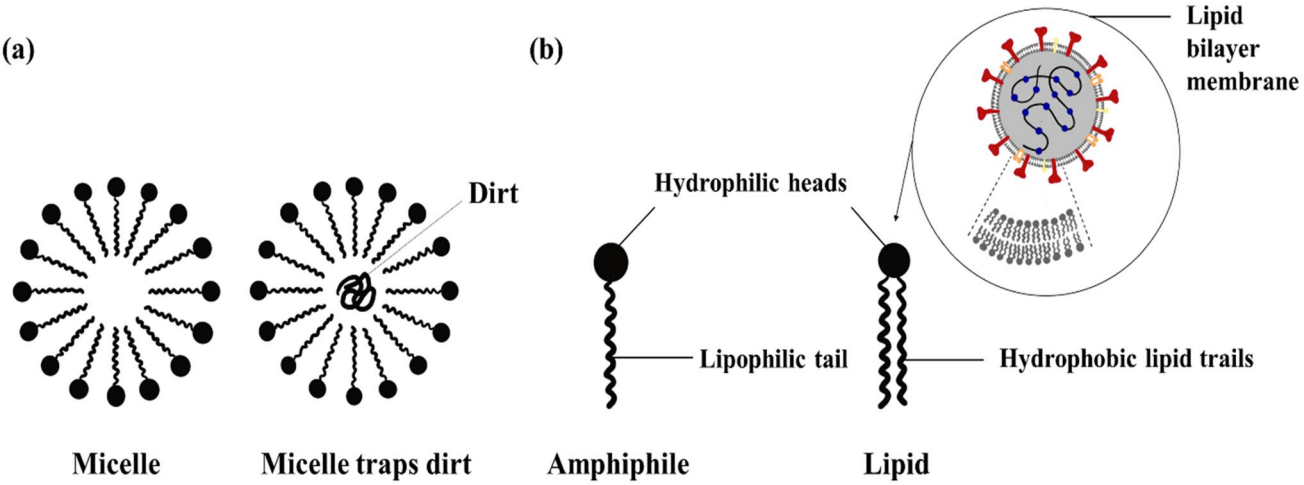

Fig. 6 **a** Hydrophobic tails of amphiphile faces inward to form micelle which traps dirt and **b** structure of amphiphile and lipid on the lipid-bilayer membrane of SARS-CoV-2

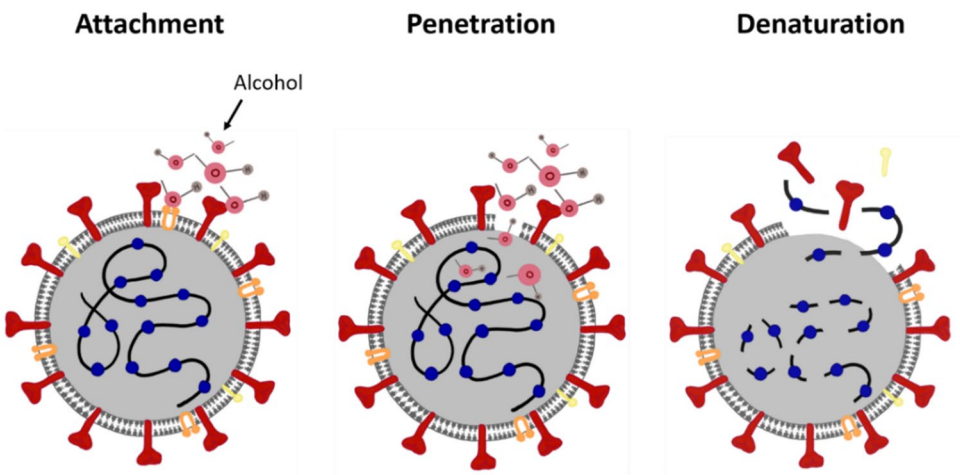

Fig. 7 Antiviral action and mechanism of alcohol against enveloped viruses like SARS-CoV-2 [43]

The components of alcohol-based hand sanitizers are *i.* alcohol (ethyl alcohol or isopropanol), *ii.* water, *iii.* glycerol, and *iv.* hydrogen peroxide. Among the four components, alcohol plays a crucial role in destroying SARS-CoV-2. In a recent study, two standardized World Health Organization formulae are known as WHO formulation 1, which consists of 85% ethanol, and WHO formulation 2, which consists of 75% isopropanol, were proven to be efficient in inactivating SARS-CoV-2 [44–46]. This is because enveloped viruses like SARS-CoV-2 are highly sensitive toward these alcohols, as they can dissolve the lipid molecules of the viral membrane which inactivates the virus as its structure collapses (Fig. 7) [19, 43, 44, 47]. Alcohols are also amphiphilic compounds similar to lipid molecules. Therefore, they possess both hydrophilic and hydrophobic (or lipophilic) properties, allowing them to enter through the lipid-bilayer viral envelope, which leads to alteration in its fluidity. This is because the presence of polar oxygen atoms from alcohols increases the internal affinity of the membrane for water [43]. Thus, its protein structures are also destabilized and denatured, causing the virus to lose its biological activities and hence inactivated [19, 43].

Vaccines against COVID-19

Seven different classes of vaccines developed against SARS-CoV-2, which are *i.* messenger RNA (mRNA), *ii.* DNA, *iii.* inactivated viruses, *iv.* viral vector (non-replicating and replicating), *v.* protein subunit, *vi.* viral-like particles, and, *vii.* live attenuated [48, 49]. Currently, there are different types of authorized vaccines used against SARS-CoV-2, which include *i.* BNT162b2 vaccine by Pfizer and BioNTech, *ii.* mRNA-1273 vaccine by Moderna, *iii.* AZD1222 by AstraZeneca and University of Oxford, *iv.* CoronaVac by Sinovac, *v.* BBIBP-CorV by Sinopharm, and, *vi.* JNJ-78436735 by Janssen Pharmaceuticals Companies of Johnson and Johnson (Table 3) [49, 50]. These vaccines remove the ability of SARS-CoV-2 to cause severe symptoms of COVID-19, hospitalization, intensive care unit admission, and death. However, these vaccines may cause short-lived side effects such as *i.* pain at the injection site, *ii.* headache, *iii.* mild fever, *iv.* fatigue, and *v.* chills. These side effects could be more pronounced after the second dose, but usually resolve within 24–72 h. In addition, these vaccines should also be given to individuals who had a history of asymptomatic or symptomatic SARS-CoV-2 infection after 90 days [48].

Messenger RNA

Messenger RNA (mRNA) vaccines are a new type of vaccine technology that has been scientifically relevant since early in the twenty-first century. These vaccines can be developed rapidly and are cost efficient. Both BNT162b2 by Pfizer and BioNTech and mRNA-1273 by Moderna are examples of

Table 3 Authorized COVID-19 vaccines [48–50]

Name	Developer	Vaccine type	No. of doses	Timing of doses
BNT162b2	Pfizer, BioNTech	mRNA	2	3 weeks
mRNA-1273	Moderna	mRNA	2	4 weeks
BBIBP-CorV	Sinopharm	Inactivated	2	3 weeks
CoronaVac	SinoVac	Inactivated	2	2 weeks
AZD1222	Oxford University, AstraZeneca	Viral vector	2	4–12 weeks
JNJ-78436735	Johnson and Johnson	Viral vector	1	–

authorized mRNA vaccines against SARS-CoV-2 [48, 51]. These vaccines are cationic lipid nanoparticles-encapsulated (LNP) mRNA of the SARS-CoV-2 expressing spike (S) proteins, which are unable to cause disease [48, 49, 52]. The lipid nanoparticle barrier functions to protect the mRNA, which is easily broken down. Next, these modified mRNA provide genetic instructions for human cells to produce the spike (S) proteins that cause an immune response, eliciting the production of antibodies, $CD4^+$ and $CD8^+$ T cells [51]. Hence, the body will be able to develop a certain degree of immunity against SARS-CoV-2. BNT162b2 vaccine, for instance, requires two doses given 3 weeks apart and has an efficacy rate of 95%, 7 days after a double dose [48, 49, 52, 53]. However, dealing with BNT162b2 is challenging in rural areas, since the storage temperature of this vaccine is − 70 °C and the undiluted vials can only be stored at room temperature for not more than 2 h [48, 54]. In addition, the BNT162b2 vaccine is approved for the age group of 16 years and older [48]. mRNA-1273, on the other hand, also requires two doses given 4 weeks apart. It has an efficacy rate of 94.1%, 14 days after the second dose [48, 52]. mRNA-1273 is recommended for the age group of 18 years and above [54]. Furthermore, mRNA-1273 can be stored for 30 days between 2 and 8 °C [54].

There are differences in the number of doses required for different COVID-19 vaccines to reach their maximum level of protection against the virus. Two doses of these mRNA vaccines have been shown to significantly reduce the risk of SARS-CoV-2 infections and severe COVID-19 symptoms. However, COVID-19 vaccine boosters or additional doses are also required to further enhance and restore protection, which has been decreased over time after previous primary vaccinations, especially when Omicron is currently causing surges around the world. A study conducted by Edara et al. using serum from mRNA-vaccinated individuals showed that at 2–4 weeks after the primary series of vaccinations, a 30-fold reduction in neutralizing activity against Omicron (B.1.1.529) was observed [55]. In addition, their findings also showed that the majority of the naive vaccinated individuals have lost detectable neutralizing antibodies against Omicron (B1.1.529) after 6 months [55]. Hence, CDC recommends a booster of either BNT162b2 by Pfizer and BioNTech or mRNA-1273 by Moderna for the age group of 5 years and older after completing their primary series of vaccinations. A second booster, on the other hand, is recommended for adults of age 50 years and older and individuals of age 12 years and older with moderately or severely impaired immune systems. However, a study by Korves et al. reported that booster vaccine effectiveness for mRNA vaccines has shown lower vaccine effectiveness against infection with Omicron than Delta with 54% and 70% reduction in infection during Omicron and Delta predominance, respectively [56].

Inactivated virus

Inactivated virus vaccines against COVID-19 are a type of vaccine which contains inactivated SARS-CoV-2 through physical, chemical, or radiation processes, and hence are unable to replicate and cause disease [52, 57]. BBIBP-CorV manufactured by Sinopharm Group in association with Beijing Institute of Biological Products and CoronaVac vaccine by Sinovac Biotech are both approved inactivated vaccines used by many countries against SARS-CoV-2 [48, 49, 57]. BBIBP-CorV, for instance, requires two doses to be given 3 weeks apart. It has an efficacy rate of 79.34% and 86% in China and the UAE, respectively [48]. The CoronaVac vaccine is a formalin-inactivated and alum adjuvanted vaccine [49]. It also requires two doses to be given 2 weeks apart and has been reported to have 50.38% efficacy. In addition, both vaccines should be stored and transported in the refrigerator at 2–8 °C.

Viral vector

The AZD1222 vaccine manufactured by AstraZeneca in collaboration with Oxford University is one of the authorized vector vaccines against COVID-19. It utilizes the non-replicating chimpanzee adenoviral vector ChAdOx1 with the double-stranded DNA segment of the RNA, which codes for the S protein antigen of SARS-CoV-2 [48, 49, 52, 58]. AZD1222 should be given to individuals of age 18 years and older in two doses with an interval of 4–12 weeks [48]. JNJ-78436735 manufactured by Janssen Pharmaceuticals Companies of Johnson and Johnson, on the other hand, utilizes adenovirus type 26 (Ad26) vector carrying the S gene of SARS-CoV-2, which was also used for the development of Ebola vaccine [48, 52]. It is a one-dose vaccine for individuals aged > 18 years old with 66% efficacy globally [48]. Furthermore, this vaccine is safe to be administered for pregnant women who may develop more severe COVID-19 symptoms [50].

Therapeutic approaches

Although vaccines are developed and authorized for protection against hospitalizations and deaths, there have still been major vaccine breakthroughs due to the constant viral mutations. Therefore, there is an urgent need to develop more effective treatments and drugs to mitigate the current pandemic. Currently, some repurposed drugs are being used to reduce the complications of COVID-19 based on their symptoms. Research has suggested that antiviral medicines such as remdesivir (RDV) are most effective in the early stages of COVID-19 when the patient's immune system is challenged to prevent the replication of SARS-CoV-2 [50].

In contrast, immunosuppressive or anti-inflammatory drugs are more effective in the acute stages of COVID-19 when the patient is experiencing tissue damages due to severe immune or inflammatory reactions [50]. Hence, certain promising antiviral drugs have been authorized for the treatment of COVID-19, which include *i.* remdesivir, *ii.* molnupiravir, and *iii.* PAXLOVID™.

Remdesivir

Remdesivir (RDV), which was developed to treat Ebola, is an antiviral drug act as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) enzyme of SARS-CoV-2 [21, 59]. It is the first antiviral drug approved by the United States Food and Drug Administration (FDA) to treat COVID-19 patients [59]. Remdesivir is given to patients by intravenous (IV) administration. The recommended dosage for remdesivir is 200 mg IV once, followed by 100 mg IV once daily for 4 days [60]. However, treatment may be extended to 10 days if there is no improvement in recovery by day 5 [60]. Furthermore, its structure is composed of three fragments which include *i.* nucleobase (adenine) derivative, *ii.* pentose sugar, and *iii.* phosphoramidate unit (Fig. 8) [19].

In the host cell, remdesivir (prodrug) is converted into the nucleoside derivate GS-441524 (Fig. 9). GS441524 is an active compound of remdesivir, which targets RdRp and competes with endogenous nucleotides (ATP) at the RdRp for incorporation into viral RNA [61]. Incorporation of the triphosphate form of remdesivir instead of ATP interrupts viral RNA replication and, thus, inhibits SARS-CoV-2 viral replication [61].

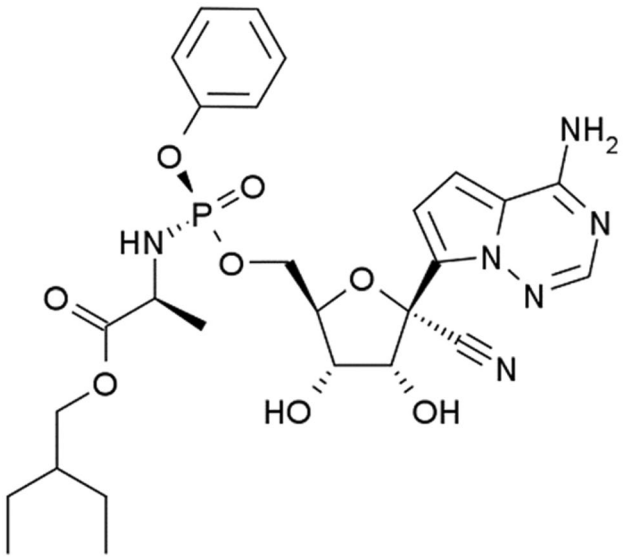

Fig. 8 Structure of remdesivir (molecular formula: $C_{27}H_{35}N_6O_8P$)

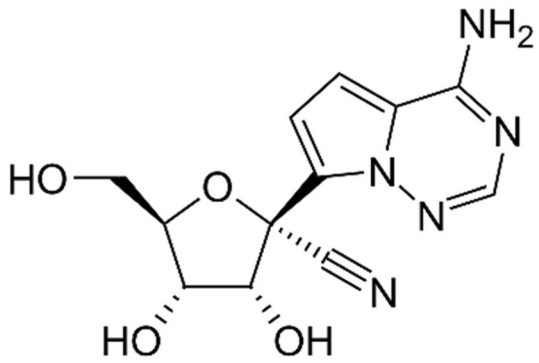

Fig. 9 Structure of GS-441524 (molecular formula: $C_{12}H_{13}N_5O_4$)

Molnupiravir

Molnupiravir is an orally administered and directly acting antiviral interventional drug developed by Emory University (USA), Ridgeback Biotherapeutics, and Merck [62]. It was originally developed for the treatment of influenza [62]. However, molnupiravir, which is a pyrimidine ribonucleoside analog, also acts by inhibiting RdRp of SARS-CoV-2 to induce RNA mutagenesis. First, molnupiravir ($C_{13}H_{19}N_3O_7$) (Fig. 10a) is converted to EIDD-1931 ($C_9H_{13}N_3O_6$) (Fig. 10 b) in the body and then to EIDD-1931-triphosphate ($C_9H_{16}N_3O_{15}P_3$) (Fig. 10c) through phosphorylation by the host kinases [62]. Next, EIDD-1931-triphosphate acts as an alternate substrate and competes with the endogenous nucleotides at the RdRp enzyme of SARS-CoV-2 [62]. This causes inhibition of the normal functions of RdRp, causing it to generate mutated RNA copies of SARS-CoV-2 [62]. Hence, this prevents SARS-CoV-2 to reproduce and spread. Moreover, the reducing property (better electron donor than electron acceptor) of molnupiravir also contributes to its antiviral activity, as it affects the conditions required for viral infection [62].

PAXLOVID™

PAXLOVID™ is an orally administered antiviral drug developed by Pfizer Inc. It contains nirmatrelvir (PF-07321332) (Fig. 11 a) and ritonavir (Fig. 11 b) [63]. Both PF-07321332 and ritonavir are protease inhibitors. PF-073321332 works by interacting with $3CL^{pro}$, the main protease of SARS-CoV-2. It blocks its ability to transform pp1a and pp1ab into non-structural and structural proteins, which eventually stops the replication process of SARS-CoV-2 [64]. Furthermore, ritonavir functions as a booster as it slows down the metabolism of PF-073321332 and, hence, allows a higher concentration to remain active in the body for a longer period [64].

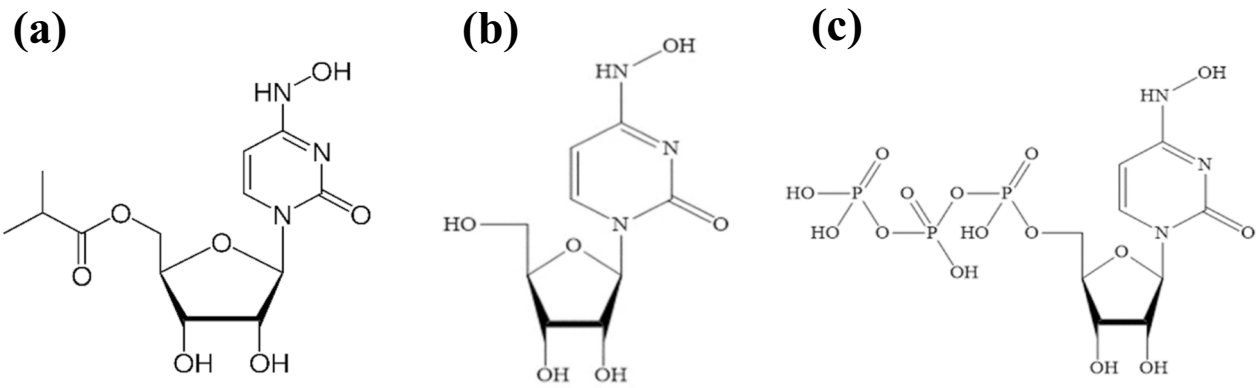

Fig. 10 **a** Structure of molnupiravir (molecular formula: $C_{13}H_{19}N_3O_7$), **b** structure of EIDD-1931 (molecular formula: $C_9H_{13}N_3O_6$), and **c** structure of EIDD-1931-triphosphate (molecular formula: $C_9H_{16}N_3O_{15}P_3$)

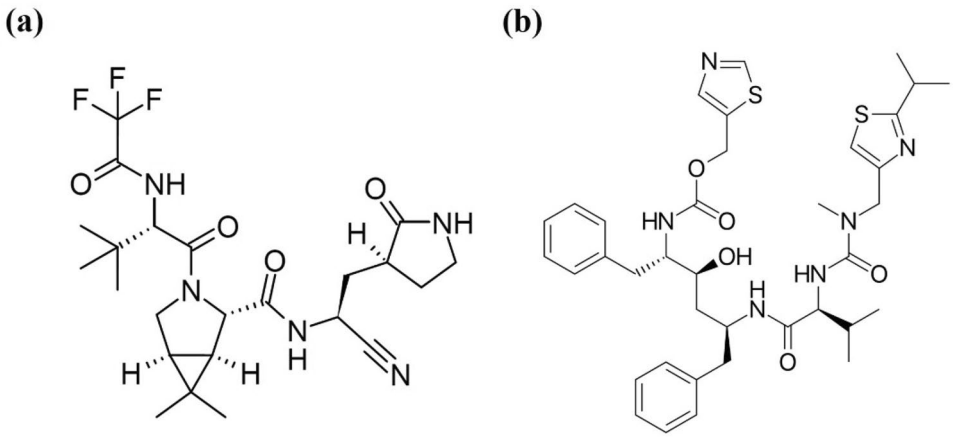

Fig. 11 **a** Structure of nirmatrelvir (PF-07321332) (molecular formula: $C_{23}H_{32}F_3N_5O_4$), and **b** structure of ritonavir (molecular formula: $C_{37}H_{48}N_6O_5S_2$)

Nature-based agents as possible COVID-19 inhibitors

Apart from well-established antiviral drugs in the treatment and inhibition of COVID-19, the possible naturally sourced agents should also be given some attention. Natural products are known to contain a multitude of metabolites with a wide range of therapeutic actions. These natural compounds are known to possess medicinal properties including antiviral activities. The bioactive components reportedly found in plants have been shown to exhibit robust antiviral activity. The isolation, purification, and identification of several phytochemicals from crude extracts have demonstrated antiviral activities such as against POLIO, HIV-1, adenoviruses, hepatitis, and influenza [65]. Natural products have been tested for coronaviruses and have been shown to show potential in coronavirus treatment [66].

More recently the BA.5 and BA.4 variants from the Omicron lineage have continued to increase, with the proportion of BA.5 variants increasing globally [67]. The highly contagious new subvariants BA.4 and BA.5 are driving the next waves of Omicron infections in several countries. There should be a multifaceted strategy to combat this global health pandemic including sourcing drugs from natural products, as they can work through multitargets and elicit their actions via different biochemical mechanisms [68].

Compounds such as quercetin have been reported to reduce the viral replication of rhinoviruses in infected mice [69]. More recently, preliminary randomized clinical studies involving quercetin have reported that following treatment of COVID-19 patients with quercetin, a proportion of the patients tested negative for the SARS-CoV-2 virus following a week of treatments with a protein of these patients having their symptoms diminished indicating the [70]. An *in silico* study involving about 8000 small molecule candidates has shown that quercetin was among the top candidates for binding with the ACE 2 interface on the S protein. Such binding will eventually reduce the ability of the virus to interact with host cells and thereby reduce the infectability of the virus.

Quercetin is known to possess anti-inflammatory activities that might also help to prevent the consequences of the COVID-19 infection. COVID-19 infection triggers a cascade of inflammatory reactions as evident from reports on the elevated levels of cytokines and inflammatory indices such as IL-1β, IL-6, IL-10, and D-dimer in severely ill COVID-19 patients compared to those with moderate symptoms [71].

In addition, quercetin is a flavonoid that is widely found in several foods, and as some preliminary studies have shown has the potential to be further explored as a potentially useful compound to add to the COVID-19 treatment regime.

Nanotechnology-based approaches for the diagnosis, prevention, and treatment of COVID-19

Nanotechnology is a study that encompasses the understanding of diverse disciplines including chemistry, biology, and technology of nanomaterials, which are at dimensions between approximately 1–100 nm [20]. According to dimensions in the nanoscale, nanostructures are classified into four categories: *i.* zero-dimensional nanostructures (e.g., fullerene), *ii.* one-dimensional nanostructures (e.g., nanofibers), *iii.* two-dimensional nanostructures (e.g., nanofilms, nanolayers, and nanocoatings), and *iv.* three-dimensional nanostructures (e.g., nanoparticles) [20, 72]. The dimensions of these nanostructures determine their functions and applications in nanotechnology [72]. Nanotechnology has a range of applications such as *i.* biomolecular detection and diagnostics, *ii.* therapeutics, *iii.* DNA sequencing, *iv.* pharmaceuticals, and *v.* sensors [20]. Therefore, it is established that the different fields in nanotechnology can contribute to providing alternative solutions to combat COVID-19. This includes the development of *i.* nanomaterial-based COVID-19 detection technology, *ii.* nanomaterial-based disinfectants, *iii.* new nanoparticle-based vaccines, and *iv.* nanoparticle-based drug delivery [20, 73].

Gold nanoparticles (AuNPs) for instance, are nanomaterials that have been investigated for COVID-19 detection. AuNP-based nano-devices use an AuNP-based electrochemical immunosensor for COVID-19 detection [73]. The biosensor comprises a competitive immunoassay, performed on an array of nanostructured electrodes that are capable of immobilization of different antigens for multiplexed detection [73]. In addition, an increase in the number of nanostructured electrodes per array chip can also facilitate high-throughput screening of hundreds of samples in a single step which reduces the time and cost associated with the overall assay [73].

Furthermore, it has been established that SARS-CoV-2 can survive on objects and surfaces ranging from a few hours to a few days. However, currently, the available chemical disinfectants provide only a temporary solution and are harmful and toxic substances to humans. Therefore, the unique physicochemical properties of silver nanoparticles (AgNPs) have been widely investigated for their antiviral activity against SARS-CoV-2. AgNPs work by releasing Ag^+ ions, which are nontoxic to humans and have good long-term stability that curbs the growth of viruses such as SARS-CoV-2 and prevents proliferation by prohibiting the activity of respiratory system enzymes [73]. Therefore, Ag^+ can be sprayed on surfaces such as doorknobs, handrails, and wound dressing for disinfection.

The application of nanoparticles (NPs) in vaccine formulations has a crucial role in the structuring and delivery of vaccines, as they can act as assistants and carriers to deliver antigens to their intended targets [73]. In addition, NPs also speed up the development of COVID-19 vaccines. Nanoparticle-based delivery approaches have been used in the current mRNA-based COVID-19 vaccines such as BNT162b2 and mRNA-1273, as the mRNAs are embedded in lipid nanoparticles (LNPs) [48, 49, 52]. However, these developed vaccines are normally treated through intramuscular injections that can only be operated by health-care professionals and must be stored at low temperature which causes storage and distribution difficulties. Therefore, self-administered nanoparticle-based vaccines (nanovaccines) such as micro-needle patches offer a new approach for protection against SARS-CoV-2 [73]. Micro-needle patches for COVID-19 are polymer-encapsulated S and N protein-encoding DNA vaccines to stimulate an immune response for SARS-CoV-2 [74].

There are different types of nanostructured materials that can be used for drug delivery vesicles such as *i.* metallic nanoparticles, *ii.* liposomes, *iii.* fullerenes, *iv.* graphene, *v.* carbon nanoparticles, and *vi.* polymeric nanoparticles [20]. Liposomes and polymeric nanoparticles, for instance, prolong the drug half-life, improve the solubility of hydrophobic drugs, and reduce potential immunogenicity [20].

Future outlook

The COVID-19 pandemic has led to an unprecedented loss of human lives worldwide. Despite the continuous global research to understand COVID-19, it has yet to be eradicated. Furthermore, it is well known that the COVID-19 pandemic will not be the last, as there is still a possibility that another zoonotic coronavirus may emerge in the future. Therefore, it is crucial to strengthen global research and development in science and technology with interdisciplinary collaborations. The following are the main future outlooks to understand SARS-CoV-2 better, advance in detecting and preventing SARS-CoV-2 infections, and develop effective treatments for COVID-19.

- SARS-CoV-2 is the third zoonotic coronavirus after SARS-CoV and MERS-CoV. Therefore, for future early detection, prevention, and treatment of novel coronaviruses, more research is required to identify and describe the mechanism of these viral mutations to infect humans and their ability to persist in the human population. Especially, information on the mutational trend in the spike protein is important to develop future effective vaccines.
- The knowledge of the origin and reservoir of SARS-CoV-2 remains scarce. Therefore, it is crucial to comprehensively investigate the zoonotic origin and reservoir through multidisciplinary collaboration and carefully coordinated studies to help prepare for future destructive outbreaks caused by novel viruses.
- The ability of asymptomatic patients to spread SARS-CoV-2 has been proven. Therefore, further study on these asymptomatic patients is crucial to discover effective, reliable, and rapid screening methods and improve the accuracy of early diagnosis. Current COVID screening methods imply identifying more reliable early detection markers for such viruses.
- Single-use PPE, which is mostly made of highly hydrophobic and non-degradable materials like polypropylene, causes environmental pollution and ecosystem damage. Hence, to address the impacts of single-use PPE on the environment, more research on sustainable materials should be carried out to develop PPE that can be disinfected and reused without losing its protective properties.
- Traditional disinfecting method (e.g., soap water and alcohol-based sanitizers) is a temporary solution to prevent indirect contact transmission from virus-contaminated surfaces. Hence, more research on nanocoating materials plays a leading role in developing a novel surface disinfection approach. The use of environmentally friendly natural products is an alternative to the existing disinfectants.
- Majority of the vaccines available or under development target the healthy population of age group 18 years and older. Multidisciplinary collaboration between material science, chemistry, and biomedical science plays an essential role in developing vaccines for different populations such as infants, children below the age of 5 years, and individuals with underlying medical conditions.
- The main target for current vaccines against COVID-19 is mostly based on the spike (S) glycoprotein of SARS-CoV-2, which constantly develops mutations. Therefore, vaccine research and development should focus on different approaches to maintain its effectiveness.
- Mammals including dogs, cats, tigers, and lions were reported to be infected with SARS-CoV-2 after close contact with a human that is infected with COVID-19. Although there is no evidence that these infected mammals can spread SARS-CoV-2 and infect people, more studies in this area are required.
- Amphiphilic molecules such as soap were shown to be effective in breaking the lipid-bilayer membrane of SARS-CoV-2, causing its structure to fall apart. Therefore, identifying antiviral compounds that target the lipid-bilayer membrane of SARS-CoV-2 may be a viable therapeutic strategy.
- Since the long-term side effect of the existing vaccines is a major concern, it is necessary to develop an appropriate animal model to address this issue.

Conclusion

This review has provided an overview of all aspects of COVID-19, such as *i.* the structure of SARS-CoV-2, *ii.* molecular interaction between SARS-CoV-2 and ACE 2 receptor, *iii.* mechanism of SARS-CoV-2 pathogenesis, *iv.* transmission routes of SARS-CoV-2, *v.* persistence and viability of SARS-CoV-2 on different surfaces, *vi.* the materials and methods currently used for diagnosis, prevention, vaccines, and treatment for COVID-19, and *vii.* different approaches for the diagnosis, prevention, and treatment of COVID-19 using nanotechnology. The chemistry perspective has helped to understand different aspects of COVID-19. A study using molecular dynamics simulations suggested that the high affinity between the S glycoprotein and ACE 2 may be due to the hydrophobic effect among the hydrophobic surface areas of S glycoprotein and ACE 2 at the binding site. In addition, another study also found that the enhanced affinity of SARS-CoV-2 toward ACE 2 is due to the increase in electrostatic interactions caused by mutations in the S glycoprotein. Furthermore, the study of the persistence and viability of SARS-CoV-2 on different surfaces showed that it has longer persistence and viability on materials such as plastics, glass, and stainless steel compared to copper, paper, and cardboard. Another research has also shown that the increase in temperature and relative humidity increases the decay rate of SARS-CoV-2. The mechanism of cleansing action of soaps involves two steps: *i.* destruction of the lipid-bilayer viral membrane by surfactant molecules, and *ii.* micelle formation. On the other hand, alcohols found in alcohol-based hand sanitizers, which are also amphiphilic compounds, inactivate SARS-CoV-2 by destabilizing and denaturing its protein structures. Lastly, using nanomaterials such as gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) has been found to be a potential alternative detection and preventive method, respectively. Hence, in conclusion, research collaborations between biology and chemistry with other disciplines such as material science, biomedical science, and nanotechnology play an important role in understanding all aspects of COVID-19 to develop

an effective diagnosis, prevention, and treatments for this infectious disease caused by SARS-CoV-2.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

References

1. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW, Penzar D, Perlman S, Poon LLM, Samborskiy DV, Sidorov IA, Sola I, Ziebuhr J (2020) The Species severe acute respiratory syndrome-related coronavirus: Classifying 2019-NCoV and Naming It SARS-CoV-2. Nat Microbiol 5(4):536–544. https://doi.org/10.1038/s41564-020-0695-z
2. Jha N, Jeyaraman M, Rachamalla M, Ojha S, Dua K, Chellappan D, Muthu S, Sharma A, Jha S, Jain R, Jeyaraman N, Prajwal GS, Satyam R, Khan F, Pandey P, Verma N, Singh S, Roychoudhury S, Dholpuria S, Ruokolainen J, Kesari K (2021) Current Understanding of Novel Coronavirus: Molecular Pathogenesis, Diagnosis, and Treatment Approaches. Immuno 1(1):30–66. https://doi.org/10.3390/immuno1010004
3. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY (2020) Zoonotic Origins of Human Coronaviruses. Int J Biol Sci 16(10):1686–1697. https://doi.org/10.7150/ijbs.45472
4. Amin SA, Jha T (2020) Fight against novel coronavirus: a perspective of medicinal chemists. Eur J Med Chem 201:112559. https://doi.org/10.1016/j.ejmech.2020.112559
5. Aydogdu MO, Altun E, Chung E, Ren G, Homer-Vanniasinkam S, Chen B, Edirisinghe M (2021) Surface Interactions and Viability of Coronaviruses: Surface Interactions and Viability of Coronaviruses. J R Soc Interface 18(174):20200798. https://doi.org/10.1098/rsif.2020.0798
6. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R (2020) COVID-19 infection: origin, transmission, and characteristics of human Coronaviruses. J Adv Res 24:91–98. https://doi.org/10.1016/j.jare.2020.03.005
7. Zhou Z, Qiu Y, Ge X (2021) The taxonomy, host range and pathogenicity of coronaviruses and other viruses in the nidovirales order. Anim Dis 1(5):1–28. https://doi.org/10.1186/s44149-021-00005-9
8. World Health Organization. WHO-Convened Global Study of Origins of SARS-CoV-2 : China Part (14 January-10 February 2021). *Jt. WHO-China Study Team Rep.* 2021.
9. Escalera A, Gonzalez-Reiche AS, Aslam S, Mena I, Laporte M, Pearl RL, Fossati A, Rathnasinghe R, Alshammary H, van de Guchte A, Farrugia K, Qin Y, Bouhaddou M, Kehrer T, Zuliani-Alvarez L, Meekins DA, Balaraman V, McDowell C, Richt JA, Bajic G, Sordillo EM, Dejosez M, Zwaka TP, Krogan N, Simon V, Albrecht RA, van Bakel H, Garcia-Sastre A, Aydillo T (2022) Mutations in SARS-CoV-2 Variants of Concern Link to Increased Spike Cleavage and Virus Transmission. Cell Host Microbe. https://doi.org/10.1016/j.chom.2022.01.006
10. Shao W, Zhang W, Fang X, Yu D, Wang X (2022) Challenges of SARS-CoV-2 Omicron variant and appropriate countermeasures. J Microbiol Immunol Infect 55(3):387–394. https://doi.org/10.1016/j.jmii.2022.03.007
11. Weng S, Shang J, Cheng Y, Zhou H, Ji C, Yang R, Wu A (2022) Genetic Differentiation and Diversity of SARS-CoV-2 Omicron Variant in Its Early Outbreak. Biosaf Heal 4(3):171–178. https://doi.org/10.1016/j.bsheal.2022.04.004
12. Goutam Mukherjee A, Ramesh Wanjari U, Murali R, Chaudhary U, Renu K, Madhyastha H, Iyer M, Vellingiri B, Valsala Gopalakrishnan A (2022) Omicron Variant Infection and the Associated Immunological Scenario. Immunobiology 227(3):152222. https://doi.org/10.1016/j.imbio.2022.152222
13. Chen J, Wang R, Gilby NB, Wei G-W (2022) Omicron variant (B.1.1.529): infectivity, vaccine breakthrough, and antibody resistance. J Chem Inf Model 62(2):412–422. https://doi.org/10.1021/acs.jcim.1c01451
14. Parra-Lucares A, Segura P, Rojas V, Pumarino C, Saint-Pierre G, Toro L (2022) Emergence of SARS-CoV-2 Variants in the World: How Could This Happen? Life 12(2):194. https://doi.org/10.3390/life12020194
15. WHO. Diagnostic Testing for SARS-CoV-2. 2020.
16. Tanaka H, Ogata T, Shibata T, Nagai H, Takahashi Y, Kinoshita M, Matsubayashi K, Hattori S, Taniguchi C (2022) Shorter Incubation Period among COVID-19 Cases with the BA.1 Omicron Variant. Int J Environ Res Public Health 19(10):6330. https://doi.org/10.3390/ijerph19106330
17. van Kessel SAM, Olde Hartman TC, Lucassen PLBJ, van Jaarsveld CHM (2022) Post-Acute and Long-COVID-19 symptoms in patients with mild diseases: a systematic review. Fam Pract 39(1):159–167. https://doi.org/10.1093/fampra/cmab076
18. Alkodaymi MS, Omrani OA, Fawzy NA, Shaar BA, Almamlouk R, Riaz M, Obeidat M, Obeidat Y, Gerberi D, Taha RM, Kashour Z, Kashour T, Berbari EF, Alkattan K, Tleyjeh IM (2022) Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. Clin Microbiol Infect 28(5):657–666. https://doi.org/10.1016/j.cmi.2022.01.014
19. Adhikari B, Sahu N (2021) COVID-19 into chemical science perspective: chemical preventive measures and drug development. ChemistrySelect 6(9):2010–2028. https://doi.org/10.1002/slct.202100127
20. Khan AU, Khan M, Cho MH, Khan MM (2020) Selected nanotechnologies and nanostructures for drug delivery nanomedicine and cure. Bioprocess Biosyst Eng 43(8):1339–1357. https://doi.org/10.1007/s00449-020-02330-8
21. Amawi H, Abu Deiab GI, Aljabali A, Alaa AA, Dua K, Tambuwala MM (2020) COVID-19 Pandemic: an overview of epidemiology, pathogenesis, diagnostics and potential vaccines and therapeutics. Ther Deliv 11(4):245–268. https://doi.org/10.4155/tde-2020-0035
22. Hatmal MM, Alshaer W, Al-Hatamleh MAI, Hatmal M, Smadi O, Taha MO, Oweida AJ, Boer JC, Mohamud R, Plebanski M (2020) Comprehensive structural and molecular comparison of spike proteins of SARS-CoV-2, SARS-CoV and MERS-CoV, and Their Interactions with ACE2. Cells 9(12):2638. https://doi.org/10.3390/cells9122638
23. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X (2020) Structure of the SARS-CoV-2 Spike Receptor-Binding Domain Bound to the ACE2 Receptor. Nature 581(7807):215–220. https://doi.org/10.1038/s41586-020-2180-5
24. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D (2020) Structure, Function, and Antigenicity of the

SARS-CoV-2 Spike Glycoprotein. Cell 181(2):281–292. https://doi.org/10.1016/j.cell.2020.02.058
25. Karges J, Cohen SM (2021) Metal complexes as antiviral agents for SARS-CoV-2. ChemBioChem 22(16):2600–2607. https://doi.org/10.1002/cbic.202100186
26. Xie Y, Karki CB, Du D, Li H, Wang J, Sobitan A, Teng S, Tang Q, Li L (2020) Spike Proteins of SARS-CoV and SARS-CoV-2 Utilize Different Mechanisms to Bind With Human ACE2. Front Mol Biosci 7:591873. https://doi.org/10.3389/fmolb.2020.591873
27. Harrison AG, Lin T, Wang P (2020) Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends Immunol 41(12):1100–1115. https://doi.org/10.1016/j.it.2020.10.004
28. Li J, Ma X, Guo S, Hou C, Shi L, Zhang H, Zheng B, Liao C, Yang L, Ye L, He X (2020) A Hydrophobic-Interaction-Based Mechanism Triggers Docking between the SARS-CoV-2 Spike and Angiotensin-Converting Enzyme 2. Glob Challenges 4(12):2000067. https://doi.org/10.1002/gch2.202000067
29. Amin M, Amin M, Amin M, Sorour MK, Kasry A (2020) Comparing the binding interactions in the receptor binding domains of SARS-CoV-2 and SARS-CoV. J Phys Chem Lett 11(12):4897–4900. https://doi.org/10.1021/acs.jpclett.0c01064
30. Karmacharya M, Kumar S, Gulenko O, Cho YK (2021) Advances in facemasks during the COVID-19 Pandemic Era. ACS Appl Bio Mater 4(5):3891–3908. https://doi.org/10.1021/acsabm.0c01329
31. Joonaki E, Hassanpouryouzband A, Heldt CL, Areo O (2020) Surface chemistry can unlock drivers of surface stability of SARS-CoV-2 in a variety of environmental conditions. Chem 6(9):2135–2146. https://doi.org/10.1016/j.chempr.2020.08.001
32. Marquès M, Domingo JL (2021) Contamination of inert surfaces by SARS-CoV-2: persistence, stability and infectivity. A Review. Environ Res. 193:110559. https://doi.org/10.1016/j.envres.2020.110559
33. Aboubakr HA, Sharafeldin TA, Goyal SM (2021) Stability of SARS-CoV-2 and other coronaviruses in the environment and on common touch surfaces and the influence of climatic conditions: a review. Transbound Emerg Dis 68(2):296–312. https://doi.org/10.1111/tbed.13707
34. Gitman MR, Shaban MV, Paniz-mondolfi AE, Sordillo EM (2021) Laboratory diagnosis of SARS-CoV-2 Pneumonia. Diagnostics 11(7):1270
35. Kevadiya BD, Machhi J, Herskovitz J, Oleynikov MD, Blomberg WR, Bajwa N, Soni D, Das S, Hasan M, Patel M, Senan AM, Gorantla S, McMillan JE, Edagwa B, Eisenberg R, Gurumurthy CB, Reid SPM, Punyadeera C, Chang L, Gendelman HE (2021) Diagnostics for SARS-CoV-2 infections. Nat Mater 31(5):593–605. https://doi.org/10.1038/s41563-020-00906-z
36. Ahmadi S, Rabiee N, Fatahi Y, Hooshmand SE, Bagherzadeh M, Rabiee M, Jajarmi V, Dinarvand R, Habibzadeh S, Saeb MR, Varma RS, Shokouhimehr M, Hamblin MR (2021) Green chemistry and coronavirus. Sustain Chem Pharm 21:100415. https://doi.org/10.1016/j.scp.2021.100415
37. Rossettie S, Perry C, Pourghaed M, Zumwalt M (2020) Effectiveness of Manufactured Surgical Masks, Respirators, and Home-Made Masks in Prevention of Respiratory Infection Due to Airborne Microorganisms. Southwest Respir. Crit. Care Chronicles 8(34):11–26. https://doi.org/10.12746/swrccc.v8i34.675
38. Tcharkhtchi A, Abbasnezhad N, Zarbini Seydani M, Zirak N, Farzaneh S, Shirinbayan M (2021) An Overview of filtration efficiency through the masks: mechanisms of the aerosols penetration. Bioact Mater 6(1):106–122. https://doi.org/10.1016/j.bioactmat.2020.08.002
39. Schilling K, Gentner DR, Wilen L, Medina A, Buehler C, Perez-Lorenzo LJ, Pollitt KJG, Bergemann R, Bernardo N, Peccia J, Wilczynski V, Lattanza L (2021) An Accessible Method for Screening Aerosol Filtration Identifies Poor-Performing Commercial Masks and Respirators. J Expo Sci Environ Epidemiol 31:943–952. https://doi.org/10.1038/s41370-020-0258-7
40. Chaudhary G, Chaudhry A, Malik G, Chaudhry N, Kochhar AS, Marya A, Venugopal A, Alam MK (2021) Analyzing the Effectiveness and Efficacy of Different Types of Masks and Respirators: A Review. Int Med J 28(4):455–461
41. Das S, Sarkar S, Das A, Das S, Chakraborty P, Sarkar J (2021) A Comprehensive review of various categories of face masks resistant to Covid-19. Clin Epidemiol Glob Heal 12:100835. https://doi.org/10.1016/j.cegh.2021.100835
42. Dharmaraj S, Ashokkumar V, Hariharan S, Manibharathi A, Show PL, Chong CT, Ngamcharussrivichai C (2021) The COVID-19 Pandemic Face Mask Waste: A Blooming Threat to the Marine Environment. Chemosphere 272:129601. https://doi.org/10.1016/j.chemosphere.2021.129601
43. Singh D, Joshi K, Samuel A, Patra J, Mahindroo N. (2020) Alcohol-Based Hand Sanitizers as First Line of Defense against SARS CoV-2: A Review of Biology, Chemistry and Formulations. Epidemiol. Infect. 2020, 148. Doi:https://doi.org/10.1017/S0950268820002319.
44. Opatz T, Senn-Bilfinger J, Richert C (2020) Thoughts on what chemists can contribute to fighting SARS-CoV-2 – A short note on hand sanitizers, drug candidates and outreach. Angew Chemie - Int Ed 59(24):9236–9240. https://doi.org/10.1002/anie.202004721
45. Leslie RA, Zhou SS, Macinga DR (2021) Inactivation of SARS-CoV-2 by commercially available alcohol-based hand sanitizers. Am J Infect Control 49(3):401–402. https://doi.org/10.1016/j.ajic.2020.08.020
46. Kratzel A, Kratzel A, Todt D, V'kovski P, Steiner S, Steiner S, Gultom M, Gultom M, Thao TTN, Thao TTN, Ebert N, Ebert N, Holwerda M, Holwerda M, Steinmann J, Steinmann J, Niemeyer D, Dijkman R, Dijkman R, Kampf G, Drosten C, Steinmann E, Thiel V, Thiel V, Pfaender S (2020) Inactivation of Severe Acute Respiratory Syndrome Coronavirus 2 by WHO-Recommended Hand Rub Formulations and Alcohols. Emerg Infect Dis 26(7):1592–1595. https://doi.org/10.3201/eid2607.200915
47. Ingólfsson HI, Andersen OS (2011) Alcohol's Effects on Lipid Bilayer Properties. Biophys J 101(4):847–855. https://doi.org/10.1016/j.bpj.2011.07.013
48. Abdulla ZA, Al-Bashir SM, Al-Salih NS, Aldamen AA, Abdulazeez MZ (2021) A Summary of the Sars-Cov-2 vaccines and technologies available or under development. Pathogens 10(7):788. https://doi.org/10.3390/pathogens10070788
49. Kashte S, Gulbake A, El-Amin SF, Gupta A (2021) COVID-19 Vaccines: rapid development, implications challenges and future prospects. Hum Cell 34(3):711–733. https://doi.org/10.1007/s13577-021-00512-4
50. Salahshoori I, Mobaraki-Asl N, Seyfaee A, Mirzaei Nasirabad N, Dehghan Z, Faraji M, Ganjkhani M, Babapoor A, Shadmehr SZ, Hamrang A (2021) Overview of COVID-19 disease: virology, epidemiology, prevention diagnosis, treatment, and vaccines. Biologics 1(1):2–40. https://doi.org/10.3390/biologics1010002
51. Anand P, Stahel VP (2021) Review the safety of Covid-19 MRNA vaccines: a review. Patient Saf Surg 15(20):1–9. https://doi.org/10.1186/s13037-021-00291-9
52. Aydemir S, Selvi HR, Dumlu MR, Arıca S, Şimşek F (2021) COVID-19 Vaccines. Eur Arch Med Res 37(3):134–140. https://doi.org/10.4274/eamr.galenos.2021.93695
53. Lamb YN (2021) BNT162b2 MRNA COVID-19 vaccine: first approval. Drugs 81(4):495–501. https://doi.org/10.1007/s40265-021-01480-7
54. Tavilani A, Abbasi E, Kian Ara F, Darini A, Asefy Z (2021) COVID-19 Vaccines: current evidence and considerations. Metab Open 12:100124. https://doi.org/10.1016/j.metop.2021.100124
55. Edara VV, Manning KE, Ellis M, Lai L, Moore KM, Foster SL, Floyd K, Davis-Gardner ME, Mantus G, Nyhoff LE, Bechnak S,

Alaaeddine G, Naji A, Samaha H, Lee M, Bristow L, Gagne M, Roberts-Torres J, Henry AR, Godbole S, Grakoui A, Saxton M, Piantadosi A, Waggoner JJ, Douek DC, Rouphael N, Wrammert J, Suthar MS (2022) MRNA-1273 and BNT162b2 MRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 Omicron Variant. Cell Reports Med 3(2):100529. https://doi.org/10.1016/j.xcrm.2022.100529

56. Korves C, Izurieta HS, Smith J, Zwain GM, Powell EI, Balajee A, Ryder K, Young-Xu Y (2022) Relative Effectiveness of Booster vs. 2-Dose MRNA Covid-19 Vaccination in the Veterans Health Administration: Self-Controlled Risk Interval Analysis. Vaccine. https://doi.org/10.1016/j.vaccine.2022.06.047
57. Dong Y, Dai T, Wei Y, Zhang L, Zheng M, Zhou F (2020) A systematic review of SARS-CoV-2 vaccine candidates. Signal Transduct Target Ther 5(1):237. https://doi.org/10.1038/s41392-020-00352-y
58. Lundstrom K (2020) Application of viral vectors for vaccine development with a special emphasis on COVID-19. Viruses 12(11):279. https://doi.org/10.3390/v12111324
59. Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Höbartner C, Cramer P (2021) Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nat Commun 12(1):279. https://doi.org/10.1038/s41467-020-20542-0
60. Niknam Z, Jafari A, Golchin A, Danesh Pouya F, Nemati M, Rezaei-Tavirani M, Rasmi Y (2022) Potential therapeutic options for COVID-19: an update on current evidence. Eur J Med Res 27(1):1–15. https://doi.org/10.1186/s40001-021-00626-3
61. Blaess M, Kaiser L, Sauer M, Csuk R, Deigner HP (2020) COVID-19/SARS-CoV-2 infection: lysosomes and lysosomotropism implicate new treatment strategies and personal risks. Int J Mol Sci 21(14):4953. https://doi.org/10.3390/ijms21144953
62. Imran M, Arora MK, Mohammed S, Asdaq B, Khan SA, Ali AM, Al-shammeri AM, Alhazmi BD, Harshan AA (2022) Discovery, development, and patent trends on molnupiravir. Molecules 26(19):5795
63. Zhang C (2022) Fluorine in Medicinal Chemistry: In Perspective to COVID-19. ACS Omega 7(22), 18206–18212. https://doi.org/10.1021/acsomega.2c01121.
64. Ahmad B, Batool M, Ain QU, Kim MS, Choi S (2021) Exploring the Binding Mechanism of PF-07321332 SARS-CoV-2 Protease Inhibitor through Molecular Dynamics and Binding Free Energy Simulations. Int J Mol Sci 22(17):9124. https://doi.org/10.3390/ijms22179124
65. Ben-Shabat S, Yarmolinsky L, Porat D, Dahan A (2020) Antiviral Effect of Phytochemicals from Medicinal Plants: Applications and Drug Delivery Strategies. Drug Deliv Transl Res 10(2):354–367. https://doi.org/10.1007/s13346-019-00691-6
66. Adem, S., Eyupoglu, V., Sarfraz, I., Rasul, A., Ali, M. (2020) Identification of potent COVID-19 Main Protease (Mpro) inhibitors from natural polyphenols: an in silico strategy unveils a hope against CORONA. https://doi.org/10.20944/preprints202003.0333.v1.
67. World Health Organization (2022) COVID-19 weekly epidemiological update. World Heal. Organ. 1–11.
68. Isidoro C, Chiung-Fang Chang A, Sheen LY (2022) Natural products as a source of novel drugs for treating SARS-CoV2 Infection. J Tradit Complement Med 12(1):1–5. https://doi.org/10.1016/j.jtcme.2022.02.001
69. Ganesan S, Faris AN, Comstock AT, Wang Q, Nanua S, Hershenson MB, Sajjan US (2012) Quercetin inhibits rhinovirus replication in vitro and in vivo. Antiviral Res 94(3):258–271. https://doi.org/10.1016/j.antiviral.2012.03.005
70. Pierro Di F, IqtadarBertuccioliDerosaMaffioliTogniRivaAllegrini SAGPSAP (2021) Potential clinical benefits of quercetin in the early stage of COVID-19: results of a second, pilot, randomized, controlled and open-label clinical trial. Int J Gen Med 14:2807–2816
71. Huang Q, Wu X, Zheng X, Luo S, Xu S, Weng J (2020) Targeting Inflammation and Cytokine Storm in COVID-19. Pharmacol Res 159:105051. https://doi.org/10.1016/j.phrs.2020.105051
72. Kheirollahpour M, Mehrabi M, Dounighi NM, Mohammadi M, Masoudi A (2020) Nanoparticles and Vaccine Development. Pharm Nanotechnol 8(1):6–21. https://doi.org/10.2174/2211738507666191024162042
73. Al-Douri Y, Khan MM, Robert Jennings J, Abd El-Rehim AF (2021) Nanomaterial-Based Biosensors for COVID-19 Detection. Crit Rev Solid State Mater Sci. https://doi.org/10.1080/10408436.2021.1989665
74. Yin Y, Su W, Zhang J, Huang W, Li X, Ma H, Tan M, Song H, Cao G, Yu S, Yu D, Jeong JH, Zhao X, Li H, Nie G, Wang H (2021) Separable Microneedle Patch to Protect and Deliver DNA Nanovaccines against COVID-19. ACS Nano 15(9):14347–14359. https://doi.org/10.1021/acsnano.1c03252