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REVIEW

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Recent progress on drugs discovery study for treatment of COVID-19: repurposing existing drugs and current natural bioactive molecules

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Abstract

COVID-19 has been a major global health concern for the past three years, and currently we are still experiencing coronavirus patients in the following years. The virus, known as SARS-CoV-2, shares a similar genomic identity with previous viruses such as SARS-CoV and MERS-CoV. To combat the pandemic, modern drugs discovery techniques such as in silico experiments for docking and virtual screening have been employed to design new drugs against COVID-19. However, the release of new drugs for human use requires two safety assessment steps consisting of preclinical and clinical trials. To bypass these steps, scientists are exploring the potential of repurposing existing drugs for COVID-19 treatment. This approach involves evaluating antiviral activity of drugs previously used for treating respiratory diseases against other enveloped viruses such as HPV, HSV, and HIV. The aim of this study is to review repurposing of existing drugs, traditional medicines, and active secondary metabolites from plant-based natural products that target specific protein enzymes related to SARS-CoV-2. The review also analyzes the chemical structure and activity relationship between selected active molecules, particularly flavonol groups, as ligands and proteins or active sites of SARS-CoV-2.

Keywords COVID-19, SARS-CoV-2, Coronavirus, Repurposing drugs, Natural products, Antiviral agents

Introduction

COVID-19, also known as coronavirus disease 2019, is a highly infectious illness that is caused by the novel coronavirus, which has been officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was first discovered on December 31, 2019, in Wuhan, China, as a cluster of pneumonia cases. Later, on March 27, 2020, World Health Organization (WHO) declared the outbreak a global pandemic, as it had spread to numerous countries around the world [1, 3, 5].

An outbreak of SARS was first reported in Guangdong, China, in November 2002 [7]. This disease was later identified in Hong Kong in late February 2003, and it subsequently spread globally to North America, Europe, and other parts of Asia [9, 11]. However, phylogenetic analysis showed that SARS coronavirus (SARS-CoV) differed from previously known coronavirus [13]. In June 2012, another coronavirus-related respiratory illness, the Middle East respiratory syndrome (MERS), caused by MERS coronavirus (MERS-CoV), emerged in the Middle East, particularly in Saudi Arabia, and was spread to humans by dromedary camels [14, 16, 17].

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MERS-CoV is phylogenetically related to bat coronavirus (SARS-CoV-2), the virus that causes COVID-19.

The genomic characteristics of SARS-CoV-2 indicate that it is closely related (88% identity) to two bat-derived SARS-like coronavirus, bat-SL-CoVZC45 and bat-SL-CoVZXC21, were detected in *Rhinolophus pusillus* bats from Zhoushan, eastern China, in 2018 [19, 21]. Additionally, Zhou et al. reported that a coronavirus strain, SARSr-Ra-BatCoV-RaTG13, isolated from *Rhinolophus affinis* bats in Pu'er, China, in 2013, has an overall genome identity of 96.2% to SARS-CoV-2n. This close phylogenetic relationship to RaTG13 suggests that SARS-CoV-2 originated in bats [22].

According to Lam et al. [18], receptor-binding domain (RBD) of SARS-CoV-2 spike (S) protein exhibits extremely high sequence similarity to Guangdong pangolin (97.4% amino acid similarity). The amino acids of this pangolin coronavirus, GX/P2V, are identical to the five critical residues of RBD, while RaTG13 has only one identical amino acid to SARS-CoV-2. It is worth noting that SARS-CoV-2 rapidly spread among human populations. The lack of insertion of the polybasic cleavage sites in the spike protein of pangolin coronavirus contributed to this phenomenon.

Lau et al. [23], stated that the genome backbone of SARS-CoV-2 evolved from bat coronavirus, its RBD region was likely acquired from pangolin coronavirus, causing SARS-CoV-2 to become a recombinant virus. Additionally, SARS-CoV-2 RBD has distinct evolutionary characteristics compared to other *Sarbecovirus* species, particularly in terms of subunit cleavage sites. While the genomic characteristics of SARS-CoV and MERS-CoV are more distant from SARS-CoV-2, with similarities of 79% and 50%, respectively, RBD of SARS-CoV-2 within lineage B was found to be closer to that of SARS-CoV [21].

However, viruses are known to enhance their infectivity by acquiring mutations that allow viruses to evade human immune responses, including those triggered by vaccines and drugs. The original strain of SARS-CoV-2 underwent mutations primarily in its spike protein (S) that resulted in the emergence of several variants, such as α, β, γ, δ, and Omicron variants (Table 1). The number and location of mutations within the spike protein influences the characteristics and potential risks of each variant in evading infection by circumventing human antibodies and immune responses [24]. Recent surge in COVID-19 cases, known as the third wave, has been attributed to the Omicron variant, specifically the B.1.1.529 strain. The high reinfection rate and greater transmissibility of this variant are believed to be due to the large number of mutations in the spike protein. Therefore, addressing the nature of the virus and developing effective treatment to overcome current and future waves of infections should be a top priority.

Structure of coronavirus

The size of the virus ranges from 20 to 300 nm and it is capable of infecting and replicating cells. It contains genes and proteins enclosed within a lipid layer envelope or a non-enveloped one. Specifically, SARS-CoV-2 has a diameter ranging from 60 to 140 nm with a spike protein size of approximately 9 to 12 nm. Its virion is spherical, sometimes pleomorphic, with a diameter of 78 nm and resembles a solar corona. Goldsmith et al. and Tshibangu et al. stated that the virus contains a helical nucleocapsid within an envelope [29, 30].

According to Wang and Liang [31], viruses associated with acute respiratory infections include influenza,

Table 1 General information on some major identified SARS-CoV-2 variants/strains

Variant/strain name	Country origin	First identified	Mutation sites	Refs.
SARS-CoV-2 (Hu-1)	China	December 2019	Wild type	[18, 22, 23]
Alpha (α) B.1.1.7 20I/501Y.V1	United Kingdom	September 2020	N501Y; P681H; 69/70 deletion	[2, 24]
Beta (β) B.1.351 20H/501Y.V2	South Africa	October 2020	K417N; E484K; N501Y	[24]
Gamma (γ) P.1 20 J/501Y.V3	Brazil	November 2020	K417T; E484K; N501Y	[24, 25]
Delta (δ) B.1.617.2	India	December 2020	T19R; L452R; T478K; D614G; P681R; D960N; 157/158 deletion	[26, 27]
Omicron (O) B.1.1.529	Bostwana and South Africa	November 2021	N440K; G446S; G339D; E484A; A76V; Q493R; Q498R; G496S; T547K; Y505H; N679K; H655Y; N764K; N856K; D796Y; Q954H; S375F; L981F; N969K; S371L; L212I; S373P	[28]

parainfluenza, picornaviruses, coronavirus (CoV), adenoviruses, and respiratory syncytial viruses. The human coronavirus (HCoV) has a complex structure, with an RNA genome inside the nucleocapsid protein, coated by spike glycoproteins and an envelope on the outer side (Fig. 1). The viral envelope is composed of structural membrane containing spike (S), envelope protein (E), and membrane lipoprotein (M). The viral lipid bilayer envelope, which is sensitive to desiccation, heat, and amphiphiles such as soap and detergents, is more susceptible to sterilization outside the human cell environment than the non-enveloped virus. However, the glycoproteins in the viral envelope helps the virus bind to the receptor sites on the host membrane to avoid the human immune system. Therefore, coronavirus binds to its primary receptor, the cellular angiotensin-converting enzyme 2 (ACE2), through its spike glycoproteins. Once the spike binds to the receptor, the cell and viral membrane fuses directly, causing the virion RNA genome inside the capsid to enter the host cell or endocytosis [1, 3, 32, 33].

Viruses can spread through the stages of their life cycle, which include cellular entry, translation, replication of the viral genome, and egress from the host cell to infect new cells [34]. While interferon (IFN) plays a crucial role in the host defence against viruses, [32, 35], efforts have also been focused on disrupting specific stages of the virus life cycle to inhibit and prevent viral infection. In particular, disrupting the viral envelope has been identified as a promising approach to impede viral egress [36, 37]. The lipid bilayer composition can be disrupted through lysis, exocytosis, or direct budding from the plasma membrane.

Modes of action of antiviral agents related to virus life cycle

In accordance with previous studies, various targets have been identified for developing antiviral drugs based on the virus life cycle, namely (1) inhibitors of fusion or entry, which targets the interaction between the virus and the host cell membrane, (2) uncoating inhibitors, a technique used to acidify the viral interior to weaken electrostatic interaction, (3) nucleic acid synthesis terminators, used to block viral enzymes, (4) integrase inhibitors, utilized to target the attachment of host cell DNA to the viral genome through the replication step, (5) protease inhibitors, often combined with reverse transcriptase inhibitors, and (6) release inhibitors, used to hinder or block the receptor from viral protein attachment [38–41].

Drugs targets for inhibiting viral infections are started by blocking the initial step of viral attachment to the receptor. This was achieved through receptor blockade by using a monoclonal antibody against the major cellular receptor or by employing specific inhibitor compounds [42]. For soluble receptors, blocking can be accomplished by disrupting the interaction between the glycosylated extracellular domains of the receptor and the hydrophobic transmembrane region on the virus. It usually blocks viral replication in cell culture form and prevents the attachment of the mutant virus to the receptor. This blockade effectively inhibits viral replication in

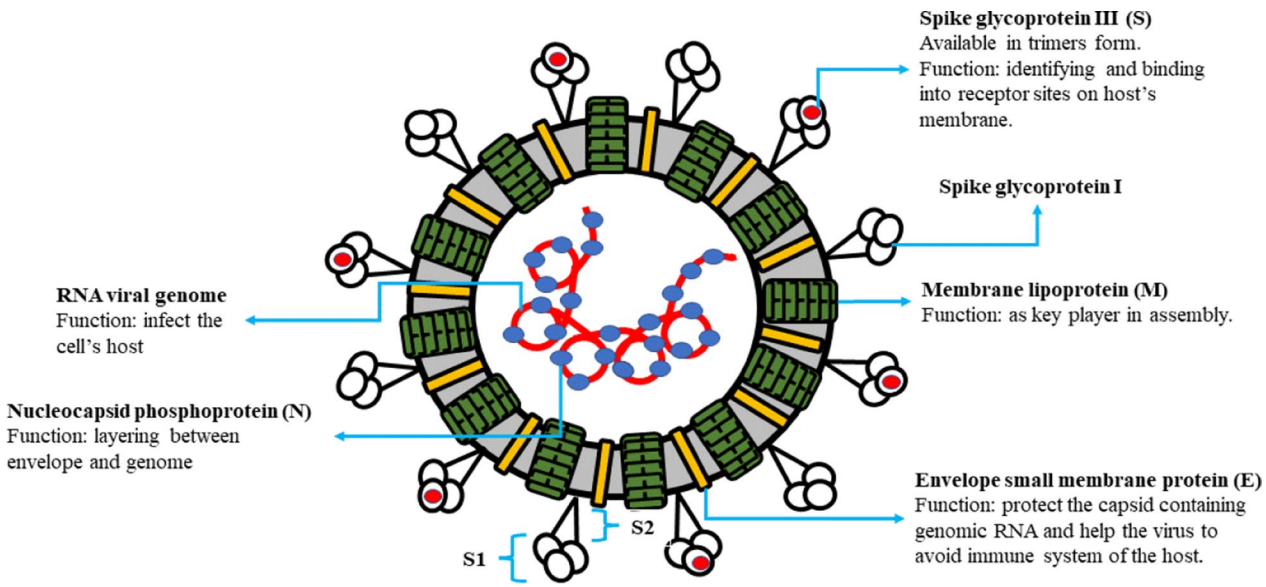

Fig. 1 Schematic of human coronavirus. ***S*** spike glycoprotein consisting of S1 and S2 parts, ***M*** membrane, ***E*** envelope protein, ***N*** nucleocapsids protecting the viral genome

cell cultures and decrease the affinity of the virus to bind to the receptor, making it less virulent and nonviable [42].

McKinlay et al. [42], suggested a mechanism for blocking viral entry into host cells by inhibiting the attachment of the virus to the host cell receptor. The first step in viral infection involves the attachment of the virus to the cellular receptor on the surface of the host cell, with the ACE2 receptor contributing to the attachment of coronavirus to the host cell, as shown in Fig. 2. The binding pocket of the virion capsid protein, containing hydrophobic amino acid side chains, interacts with the hydrophobic domains of the soluble receptor through van der Waals physical interactions. This interaction dissolves the virion capsid proteins or viral envelope in the outer space of the host cell, releasing the virion RNA genome, which becomes damaged by its surrounding conditions. The virion genome cannot replicate or maintain its genomic structure unless inside the host cell. Another mechanism for blocking the virus from releasing its viral genome during the uncoating process of the virion capsid or viral envelope is by providing inhibitor compounds that act as chelating agents within a hydrophobic pocket of the

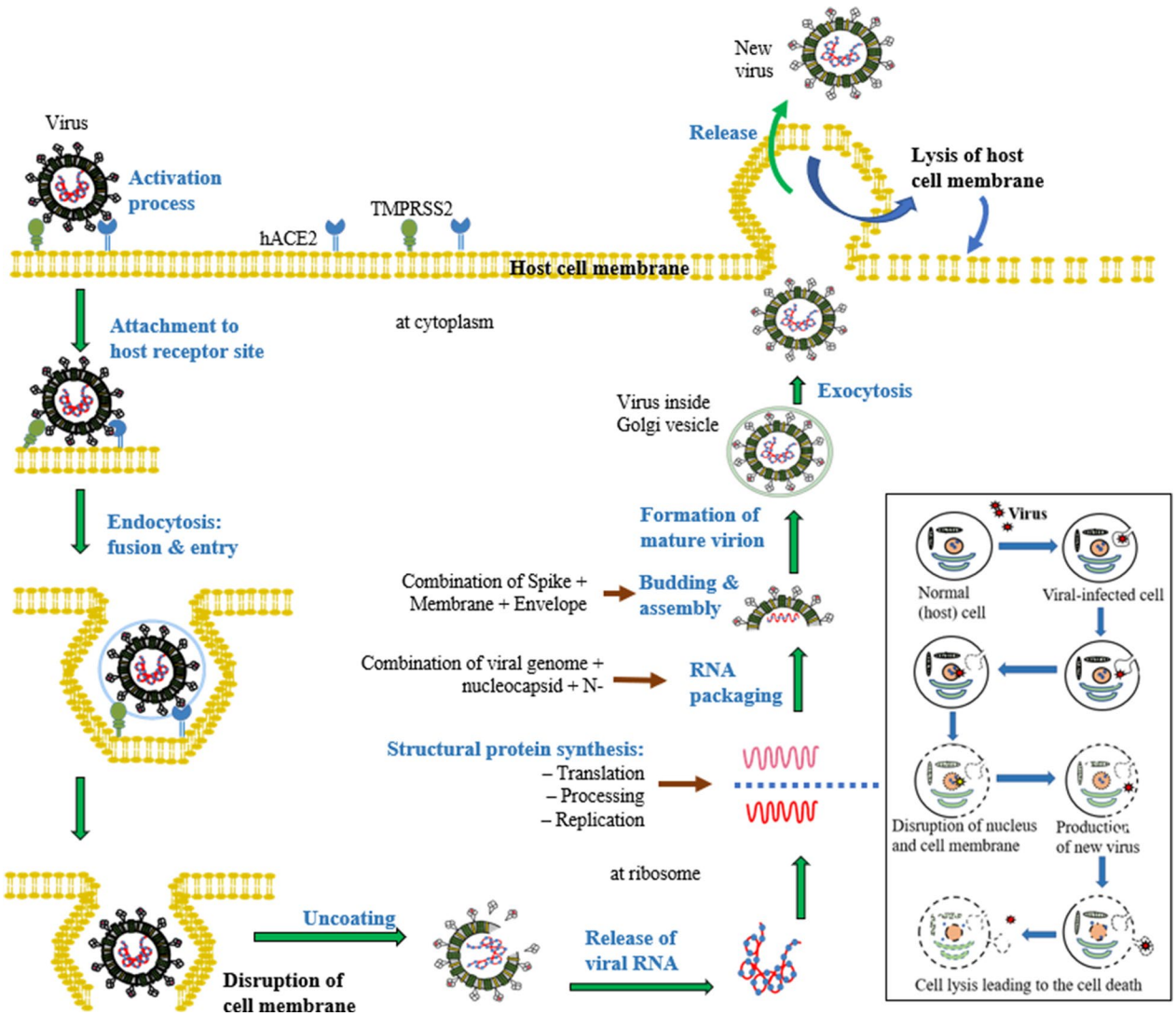

Fig. 2 Coronavirus life cycle starts from entering a host cell (infection) until the production and release of a new virus. The words in the blue state are the steps of viral transformation inside the host cell. The activation process begins when the viral glycoprotein attaches to hACE2 and TMPRSS2 receptors. The virus fuses into the cell by endocytosis and starts to enter the cell. Following this cellular entry, the virus undergoes an uncoating process to release its viral genome. Further, structural protein synthesis is followed by RNA packaging, budding, and assembly to form a mature virion. Exocytosis releases a new infectious virion to infect a new cell. The insert box (on the bottom right) illustrates what happens to the host cell resulting in further cell death

virus. This approach fills the empty pocket of the virus, preventing extensive conformational shifts that could cause the virion to disassemble. Therefore, chelating agents, such as a divalent cation, may block the release of RNA from the capsid.

Most inhibitors target the glycoprotein of the virion capsid or viral envelope, inhibiting viral attachment to the receptor. However, positive-stranded viral RNA is translated once the virus has attached and entered the host cell. The viral genomic RNA is released from the viral capsid through an uncoating mechanism, often facilitated by a receptor such as ACE2. Inside the host cell, viral proteins replicate and produce new ones through mRNA synthesis (Fig. 2). The virus strain, host cell type, pH, temperature, and multiplicity of infection influence this process. Typically, a virus requires five to ten hours to replicate in a single cycle [31].

SARS-CoV-2 virus consists of a large membrane glycoprotein called the structural protein (S protein), which includes several proteins such as membrane, spike, envelope, and nucleocapsid. S protein belongs to the class I viral fusion glycoproteins and is responsible for cell entry. Among the sixteen non-structural proteins (nsp1-16), three play a crucial role in the replication, transcription, and host cell recognition processes. These proteins are chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), and RNA-dependent RNA polymerase (RdRp) [33, 39, 43, 44]. Cys-proteases and papain are protein degrading and processing enzymes, especially during the translation process. Chymotrypsin protease (3Cpro) contains Cys-proteases with a sulfhydryl group that cleaves the glutamine-glycine amide bond. 3CLpro is a highly conserved protease and plays a vital role in coronavirus replication by overlapping polyproteins pp 1a (486 kDa) and pp 1ab (790 kDa) in SARS-CoV [31]. Both PLpro and 3CLpro are necessary for replication, transforming polyproteins into non-structural proteins such as RdRp and helicases. 3CLpro and PLpro contain 11 and 3 cleavage sites, respectively. Therefore, 3CLpro is also known as the main protease (Mpro) and an ideal target for developing antiviral drugs [45]. 3CLpro is a highly conserved protease, and its substrate specificity is similar to the 3Cpro of the main picornavirus. Protease inhibitors can block the proteolytic process of viral polyproteins, leading to incorrect viral replication and transcription.

Drugs targeting SARS-CoV-2 spike protein can prevent membrane fusion between the spike and virus, thereby disrupting virus entry into the host cell. The spike protein also contains SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which recognizes the ACE2 receptor [33, 46]. ACE2 is a type I transmembrane metallocarboxypeptidase that plays a crucial role in the physiological renin-angiotensin system by hydrolyzing vasoconstricting angiotensin II into vasodilating angiotensin. During severe COVID-19, ACE2 expression is downregulated, leading to inflammation or cytokine storm and an increase in interleukins and other stimulating factor proteins. Therefore, modulating ACE2 expression may be a potential strategy for controlling COVID-19 symptoms.

Vaccines for COVID-19

A vaccination campaign using emergency-approved vaccines is underway in many countries. According to WHO website, there are current 13 different COVID-19 vaccines from four platforms that have been widely released and administered worldwide. These vaccines include Pfizer/BioNTech Comirnaty (BNT162b2), Moderna mRNA-1273, AstraZeneca AZD1222 and Covishield from the Serum Institute of India, Johnson & Johnson Ad26.COV2.S and Sinopharm COVID-19 vaccine from China etc. Table 2 also shows two versions of the AstraZeneca/Oxford COVID-19 vaccine produced by AstraZeneca-SKBio (Republic of Korea) and the Serum Institute of India as the ChAdOx1-S vaccine as mention on WHO website on 15 February 2021 [15]. The Pfizer/BioNTech COVID-19 (BNT162b2) vaccine is a nucleoside-modified mRNA vaccine that utilizes lipid nanoparticles to encode the prefusion SARS-CoV-2 spike protein [47]. The Ad26.COV2.S vaccine, an alternative to the ChAdOx1S recombinant vaccine produced by the Serum Institute of India, is also a recombinant vaccine that uses a vector to encode the full-length SARS-CoV-2 from incompetent adenovirus serotype 26 (Ad26) [48].

The significant advancement in vaccine development has allowed for the production of effective vaccines against SARS-CoV-2 and the development of herd immunity within the community. However, drugs and therapeutic actions are still necessary to manage and treat COVID-19 cases. Li et al. (2022), and Rehman et al. (2021), reported that majority of the vaccines recently developed use novel techniques such as messenger RNA (mRNA) to stimulate the human immune system [49, 50]. The techniques for applying messenger RNA (mRNA) as a recognizing and reactive component of the virus to create the immune system of the human body have been developed as a significant advancement in public health and vaccine development. Instead of containing a weakened or inactive form of the virus, these vaccines rely on the immune system of the body to recognize and attack the spike protein of the virus. After vaccination, vaccine particles interact with immune system cells, which deliver the mRNA message to create the spike protein in vaccinated cells. The immune system then recognizes the spike protein as foreign and produces antibodies for its

Table 2 List of some approved vaccines

Vaccine	Vaccine platform	Effectivity
SinoVac vaccine (Coronavac)	Inactivated virus	50% effective against P.1 in Brazil [24]; 96.8% efficacy against COVID-19 in Indonesia [51]
Covaxin BBV152 (Bharat Biotech-Indian Council of Medical Research)	Inactivated virus	81% interim efficacy in preventing COVID-19 (SARS-CoV-2 original variant) [52]; 78% effective against the double mutant variant [24]; third dose neutralizes antibody responses against β and Omicron variants (14.70 and 18.53 fold, respectively) [53]
ChAdOx1-S-/AZD1222 (AstraZeneca/University of Oxford)	Viral vector (non-replicating)	70.4% efficacy against α variant [54]. 60–70% efficacy against ancestor and B.1.1.7 variants in UK, Brazil and South Africa, but did not protect against B.1.351 variant [55]
Ad26.COV2.S (Janssen Pharmaceutical)	Viral vector (non-replicating)	Protects over 80% of Syrian hamster and non-human primate SARS-CoV-2 infection models [56]; but 59% effective against COVID-19 hospitalization [57]
SARS-CoV-2 rS (Novavax)	Protein subunit	95.6% effective against SARS-CoV-2 wild type; 85.6% and 60% effective against α and β variants [58]
CVnCoV vaccine (Curevac AG)	Nucleic acid vaccine (RNA based)	Low efficacy [59], up to 47% efficacy against SARS-CoV-2 [60]
mRNA-1273 (Moderna-NIAID)	Nucleic acid vaccine (RNA based)	94% efficacy in preventing COVID-19 illness [61]
BNT162b2 (3LNP-mRNAs) (Pfizer/BioNTech)	Nucleic acid vaccine (RNA based)	95% efficacy against COVID-19 [62, 63]

destruction. This process generates an immune response that continues until all spike proteins have been eliminated, enabling the immune system to fight the virus upon infection.

The COVAX initiative, under the auspices of WHO, has facilitated the development and manufacturing of COVID-19 vaccines, aiming to ensure equitable access worldwide. In order to meet the demands of the pandemic, all recommended drugs and vaccines for SARS-CoV-2 were assessed based on the Emergency Use Listing (EUL) procedure, which ensures safety, efficacy, and quality standards. The EUL relies on a rigorous evaluation of late-phase II and phase III clinical trials, which are independently reviewed by WHO experts and teams.

WHO has emphasized that a vaccine on its own will not end the pandemic [64]. Despite the progress of the vaccination program, numerous cases associated with it have been reported, and doubts remain regarding the its long-term efficacy. The emergence of new coronavirus strains has become a significant challenge that needs to be addressed promptly. Additionally, the preparation required for administering two doses of the vaccine and booster shots is a significant task that medical and health services, pharmaceutical industries, and governments must fulfil [65].

Alerts on several medical products have been issued to the following release of COVID-19 vaccines to increase the public awareness of drugs and vaccine safety. Some rare adverse events related to vaccine use have been reported to inform individuals in making informed decisions about enhancing their immune systems. For instance, Sinovac vaccines have been linked to deafness and cerebral venous thrombosis [66, 67]. Janssen Pharmaceutical R&D team has reported that booster shots enhance immunity and maintain a safety profile of relatively 93.7% efficacy in the US [68]. However, the vaccine has been associated with rare adverse effects such as thrombocytopenia [69] and acute myocarditis [70]. The AstraZeneca vaccine has also been associated with adverse reactions such as thrombosis and blood clots [71–73]. Despite this, the positive benefit-risk profile of the vaccine and its tremendous potential to prevent infections and reduce deaths worldwide have outweighed the adverse effects, and it continues to be used in the public domain. Based on previous studies, Curevac, which uses an unmodified RNA-based vaccine, has low efficacy [59], with an efficacy rate of only 47% against SARS-CoV-2 [60]. Other modified mRNA-based vaccines such as Moderna and Pfizer have demonstrated significant efficacy and have been approved for emergency use during COVID-19 pandemic. In addition, mRNA vaccines are straightforward to manufacture, have a high biosafety profile, and are a safer vector than DNA, with no chance of infectious viruses [74, 75]. The development of modified mRNA-based vaccines has garnered widespread support.

As the public becomes increasingly aware of the safety and efficacy of drugs and vaccines, new natural-based alternatives are being explored. Despite the lack of specific drugs to cure COVID-19, recommendations for treating the disease have emerged from informal trials, including traditional herbal medicine. This has led to a

renewed interest in repurposing or repositioning drugs, including natural products such as medicinal plants and some commercial synthetic drugs that have previously shown antiviral activity.

Repurposing antiviral agents as a potential way of drugs discovery for COVID-19

Several studies have been working to discover drugs to combat coronavirus using various methods. Some of these proposed drugs were discovered through in silico studies involving bio- and immuno-informatics, while others were discovered using conventional organic synthetic chemistry based on the retrosynthetic method [76, 77]. However, all proposed drugs must undergo preclinical and clinical testing, including a series of safety and health considerations, before they can be released commercially. These steps can take over five years to assess the safety of a drugs for consumption. Based on the emergency and pandemic nature of COVID-19, WHO has authorized health sectors and scientists to openly communicate their results and clinical trial assessments for new drugs to combat the virus.

In light of the health concerns surrounding the use of drugs to treat COVID-19 and the time required for their clinical assessment, an approach to repurpose or reposition existing drugs that have previously been recognized as effective antiviral was proposed. This approach is based on certain criteria, including the similarity of the virus type or group, genomic composition, and structure. Examples of some drugs that have been repurposed in this way are shown in Fig. 3, Table 3.

The phylogenetic tree can group viruses that share similar characteristics based on their genomic composition and structure. HCoV is a member of the Coronaviridae group, an RNA virus that causes respiratory tract infections. This means that HCoV viruses have close relationships with each other, as shown in a phylogenetic tree analysis. SARS-CoV-2, as a member of this group, has an 88% similarity in identity to two bat-derived SARS-like coronavirus [20, 21]. Additionally, the viral structure can be used as a critical factor in grouping the virus. For example, SARS-CoV-2 has an enveloped viral design, similar to herpes simplex virus (HSV), human immunodeficiency virus (HIV), retrovirus, flavivirus, and hepatitis B and C virus (HBV/HCV). On the other hand, non-enveloped structures are found in human papillomavirus (HPV), poliovirus, norovirus, and rhinovirus. Respiratory tract infections can be caused by viruses such as rhinoviruses, influenza, parainfluenza, respiratory syncytial virus (RSV), enteroviruses, coronavirus, and certain strains of adenovirus.

Antiviral agents previously used to treat respiratory tract diseases are potential candidates for repurposing as drugs for COVID-19. For instance, resveratrol has been proven to reduce inflammation and levels of interferon-gamma (IFN-γ) in human RSV A2-strain virus infections. This was demonstrated in in vitro assays using 9HTEo and Hep-2 cell lines, as well as in vivo assays using BALB/c nude mice [89, 90]. Therefore, resveratrol is a promising candidate for treating COVID-19 infections.

Baicalin and baicalein from *Scutellaria baicalensis* Georgi have been proposed as potential treatment for COVID-19 due to their inhibitory effects on the activity of HIV-1 reverse transcriptase, which blocks HIV-1 replication [94, 97, 98]. Since HIV is also an enveloped virus like SARS-CoV-2, it is hypothesized that baicalein may also inhibit COVID-19. Su et al. [103] investigated the effects of baicalin and baicalein against SARS-CoV-2 in silico study. The results showed that baicalein interacted with the two catalytic residues of SARS-CoV-2, acting as a shield to prevent further interaction with the substrates or receptors of human cells.

The approach of repurposing drugs based on the nature similarity of the virus is considered a promising technique to identify potential treatment for COVID-19. This method is viewed as a faster alternative to developing new drugs since existing medicines that have been approved as safe for use are repurposed for COVID-19 treatment, thereby eliminating the need for additional safety assessments. Consequently, this approach saves time and expedites drugs release to the public.

The strategy of repurposing drugs is crucial in responding to the emergence of new variants of SARS-CoV-2, which result from natural mutation and evolution of the virus. The high levels of viral transmission have led to the emergence of virus variants associated with increasing viral transmissibility but not disease severity. Clinically tested drugs and vaccines should also cover variant B.1.351, which has been associated with reduced efficacy of some previously recommended ones. Therefore, the scientific response to the rising number of new SARS-CoV-2 variants must adapt quickly to develop practical antiviral activity against these emerging variants. WHO reported that efforts to suppress transmission, protect the vulnerable, and save lives in a comprehensive and coordinated manner needs to be redoubled in response to the welcoming of new variants of SARS-CoV-2 in 2021. Several new variants of SARS-CoV-2 were identified after whole-genome sequencing in samples from Brazil (SARS-CoV-2 (P1) derived from B.1.1.28 lineage, the United Kingdom (SARS-CoV-2 VUI 202012/01, some listed as SARS-CoV-2 VOC 202012/01 from cluster B.1.1.7 lineage), and South Africa (501Y.V2 variant as an N501Y mutation) at the end of 2020 and into the following year. Therefore, the acceleration of access to

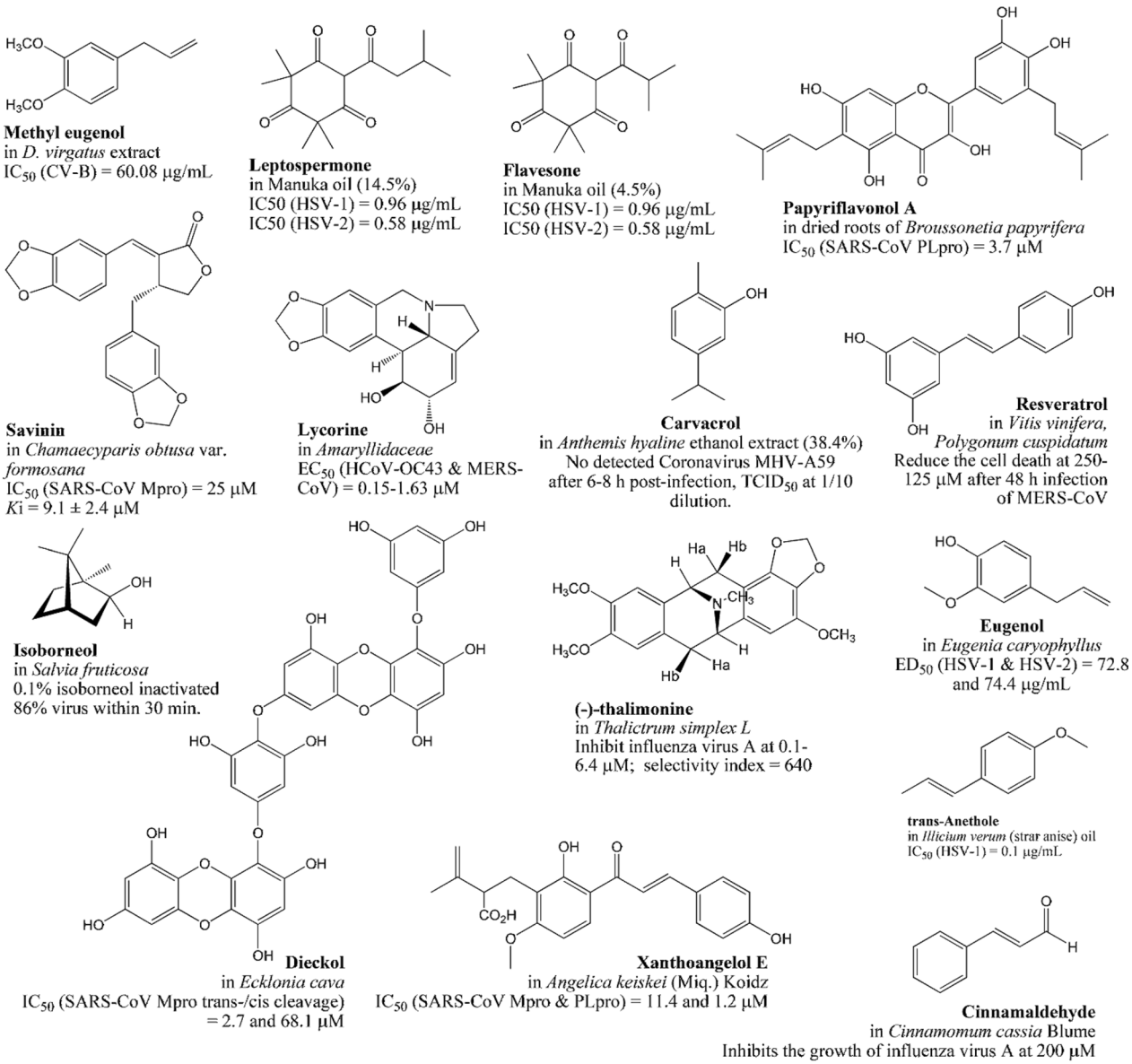

Fig. 3 Some compounds acting as antiviral agents have similarities in the type, genomic composition, and structure of SARS-CoV-2 [78–80, 87, 88]

vaccination campaigns worldwide and the development of drugs discovery are supported.

Repurposing of existing drugs has led to individuals or groups using commercial antiviral agents, such as chloroquine or hydroxychloroquine and ivermectin, without medical prescription. Scientific studies have shown that these FDA-approved drugs, initially developed as antiviral and antiparasitic agents, have potential in inhibiting SARS-CoV-2 in in vitro and in silico assays [105–107]. While the efficacy and risks associated with the use of chloroquine and hydroxychloroquine in COVID-19 treatment have been debated [108–110], they were even proposed as chemoprophylaxis in some countries, with trials conducted in 2020 [111]. In June 2020, WHO announced on their website that hydroxychloroquine should be discontinued as it did not reduce mortality in hospitalized COVID-19 patients [112–114]. Despite this, controversy over the use of hydroxychloroquine remains, and some countries continue to use it as a COVID-19 treatment [104, 111, 115, 116]. It may be a promising candidate for further investigation as a treatment for SARS-CoV-2 [117]. Ivermectin has also demonstrated antiviral activity against SARS-CoV-2 in in vitro studies, with an IC_{50} of approximately 2 µM [118, 119]. Chaccour

Table 3 Antiviral Drugs or Compounds against Viruses have Similarities in the Type/Group, Genomic Composition, and Structure of SARS-CoV-2

Viruses	Compounds	Plant Sources	Assays	Activities	Refs.
Human coronavirus type					
Human coronavirus strains OC43 (HCoV-OC43)	Tetrandrine (TET) Fangchinoline (FAN) Cepharanthine (CEP)	*Stephania tetrandra*	In vitro: in MRC-5 cells	IC_{50} of TET = 0.33 ± 0.03 μM; FAN = 1.01 ± 0.07 μM; CEP = 0.83 ± 0.07 μM	[91]
HCoV-OC43 MERS-CoV HCoV-NL63 MHV-A59	Lycorine (standard)	*Amaryllidaceae*	In vitro: in BHK-21, Vero E6, LLC-MK2, DBT cells In vivo: in mice against HCoV-OC43	EC_{50} = 0.15 – 1.63 μM	[78]
Coronavirus MHV-A59	Essential oils of the ethanol extracts (*Ah* extract) containing carvacrol (38.4%) and α-pinene (30.9%)	*Anthemis hyaline (Ah)*	In vitro using quantitative analysis by enzyme-linked immunosorbent assay (ELISA) in HeLa-CEACAM1a cells	After 6 and 8 h post infections, no detected virus was evaluated with $TCID_{50}$ values at 1/10 dilution of *Ah* extracts	[79]
HCoV-229E	Saikosaponin B_2	*Bupleurum spp., Heteromorpha spp., Scrophularia scorodonia*	In vitro using XTT assay	IC_{50} = 1.7 ± 0.1 μmol/L	[92, 93]
Genomic similarities					
SARS-CoV strains 39,849	Baicalin	*Scutellaria baicalensis* (Huang Qin)	In vitro antiviral susceptibility testing on fRhK4 and Vero-E6 cell lines	EC_{50} in fRhK4 and Vero-E6 cell lines = 12.5 and 100 μg/mL at 48 h	[94]
Recombinant SARS-CoV PLpro	Papyriflavonol A (prenylated quercetin derivative)	*Broussonetia papyrifera* (dried roots)	In vitro using viral protease inhibition assay on SARS-CoV based on the FRET method	IC_{50} = 3.7 μM	[80]
MERS-CoV	Resveratrol	*Vitis vinifera* (grape), *Polygonum cuspidatum* (Huzhang), *Vaccinium macrocarpon* (cranberry)	In vitro using MTT assay, NRU (neural red uptake) assay, and plaque reduction assay in Vero E6 cells	Resveratrol reduced cell death in a range concentration of 250–125 μM for 48 h after infection	[81]
SARS-CoV 3CLpro	Curcumin		In vitro using FRET method	IC_{50} 40 μM	[95]
SARS-CoV 3CLpro	Savinin	*Chamaceyparis obtusa* var. *formosana*	In vitro using FRET method	IC_{50} 25 μM *Ki* = 9.1 ± 2.4 μM	[95]
SARS-CoV 3CLpro and PLpro	Xanthoangelol E	*Angelica keiskei* (Miq.) Koidz (ethanolic leaf extract)	In vitro using cell-free based assay	IC_{50} of 11.4 and 1.2 μM	[82]
SARS-CoV PLpro	Coumestrol, isobavachalcone, and psoralidin	*Psoralea corylifolia* L. (ethanol extract of the seeds)	In vitro using the fluorogenic substrate Ub-AMC	IC_{50} of 4.2; 7.3 and 10.1 μM	[96]
Recombinant SARS-CoV 3CLpro	Dieckol	*Ecklonia cava* (brown algae)	In vitro using FRET method (for cell-free transcleavage assay) and luciferase activity (for Vero cell-based cis-cleavage assay)	IC_{50} of trans- and cis- cleavage inhibitory: 2.7 and 68.1 μM, respectively	[83]
Enveloped viruses					
HIV-1	Baicalin and baicalein	*Scutellaria baicalensis Georgi*	In vitro using ELISA on fresh normal peripheral blood mononuclear cells (PBMC)	IC_{50} = 0.5 μg/mL	[97]
HIV-1	Baicalin	*Scutellaria baicalensis Georgi*	In vitro using quantitative colorimetric assays	IC_{50} = 4 μM	[98]

Table 3 (continued)

Viruses	Compounds	Plant Sources	Assays	Activities	Refs.
Murine cytomegalovirus (MCV)	Black seed oil (BSO) or habatus-saudah	*Nigella sativa*	In vivo using a viral plaque-forming assay of BALB/c mice spleen and liver	Undetected virus at the ratio of the effector to target cells was 20:1	[99]
HSV-1 and HSV-2	Ethanol extracts of flower buds of *E. caryophyllus* containing eugenol	*Eugenia caryophyllus (Spreng.) Bullock & S.G. Harrison*	In vitro using plaque reduction assay on green monkey kidney (GMK)	ED_{50} against HSV-1 and HSV-2: 72.8 and 74.4 µg/mL	[84]
HSV-1	Isoborneol	*Salvia fruticosa*	In vitro using viral plaque assay on Vero cells	0.1% isoborneol inactivated 86% of the infectious virus within 30 min	[85]
HSV-1	Star anise oil (SAO) contains trans-anethole (80%), eugenol, b-caryo-phyllene, eugenol	*Illicium verum* (star anise)	In vitro using plaque reduction assay	IC_{50} SAO = 1 ± 0.1 µg/mL IC_{50} beta-caryophyl-lene = 0.25 ± 0.0 µg/mL	[86]
Hepatitis B Virus (HBV)	Phyacidusin B and phllanthacidoid A1	*Phyllantus acidus* (stem)	In vitro using the cytopathic end-point assay in HepG2.2.2.15 cells	IC_{50} of HBsAg is 11.2 ± 0.01 µM by Phyacidusin B and HBeAg is 57.1 ± 0.02 µM by phllanthacidoid	[100]
HSV-1 (F strain ATCC VR733)	*J. oxycedrus* berries oil containing α-pinene, β-myrcene	*Juniperus oxycedrus ssp.*	In vitro, using visually scoring of the virus-induced cytopatho-genic effect (CPE) for 72 h post-infection on Vero cells	IC_{50}: 200 µg/mL; SI of 5	[101]
Respiratory diseases					
Influenza virus A/Germany/27, str. Weybrigde (H7N7) and A/Germany/34, str. Rostock (H7N1)	(-)-thalimonine (Thl)	*Thalictrum simplex L* (aerial parts)	In vitro in cell cultures of chicken embryo fibroblasts	Inhibit viral reproduction at non-toxic concentration 0.1–6.4 µM with a selectivity index = 640	[87]
Influenza type A (A/Betezda/63/10/H2N2) and type B (B/Lee/40)	Essential oil from fruits contain-ing pinene, limonene, a complex of ethers of octanol and hexanol	*Heracleum L* species, such as *H. aco-nitifolium* Woronow. *H. antasiaticum* Manden., etc	In vivo using intrasanal and oral treatments on mice	LD_{50} of 0.2–0.4 mL	[102]
Influenza A/PR/8/34 (PR8) virus (H1N1 subtype)	Cinnamaldehyde (CA)	*Cinnamomi cortex*	In vitro using plaque reduction assay on MCDK cells In vivo based on therapeutic effi-cacy in mice	CA inhibits all of the virus growth at 200 µM. Application of CA in the airways led to the significant rescue of infected mice	[88]

et al. conducted randomized clinical trials on the use of ivermectin as a COVID-19 treatment [120]. WHO (2021c), recommends that ivermectin should only be used in COVID-19 treatment based on clinical trials as the evidence supporting its efficacy is inconclusive [121]. Doxycycline has also been investigated for its ability to inhibit SARS-CoV-2 in in vitro studies, with an EC_{50} of 4.5 ± 2.9 mM when tested on the IHUMI-3 strain in Vero E6 cells [122].

The use of some commercial medicines has been approved by health and medical ministries to treat COVID-19 (Fig. 4). WHO is conducting solidarity therapeutic trials in over 30 countries, enrolling nearly 12,000 patients, to find effective treatment for the disease. However, after six months of attempting these trials, WHO reported in October 2020 that remdesivir, hydroxychloroquine, lopinavir or ritonavir, and IFN regimens showed little or no effect on patients hospitalized for 28 days. Other drugs, including oseltamivir, azvudine, ribavirin, favipiravir, and auranofin, have been recommended off-label [106, 123–126]. Remdesivir, an adenosine analogue that stops RNA synthesis and acts as a false substrate for RdRp, is one of the primary drugs used to treat hospitalized patients [125, 127, 128]. It is important to note that the effectiveness of these drugs in treating COVID-19 is still being evaluated.

In December 2021, Pfizer released a new oral drugs for COVID-19 called Paxlovid, which contains nirmatrelvir (300 mg) and ritonavir (100 mg) [129–132]. Administered orally twice daily for five days, Paxlovid has demonstrated a significant reduction in COVID-19-related deaths [133]. Nirmatrelvir (PF-07321332) has shown oral activity against SARS-CoV-2 in vitro, and its potency was demonstrated in phase I clinical trials with a tolerable plasma concentration in the cell [134, 135]. The detailed computational analysis of PF-07321332 against SARS-CoV-2 Mpro has been clearly discussed in several studies [136, 137]. In October 2021, Pfizermectin, new drugs for COVID-19 treatment suspected to contain ivermectin, was also developed by Pfizer, but the company has denied repackaging ivermectin inside this new pill and selling it at a higher price than existing commercial

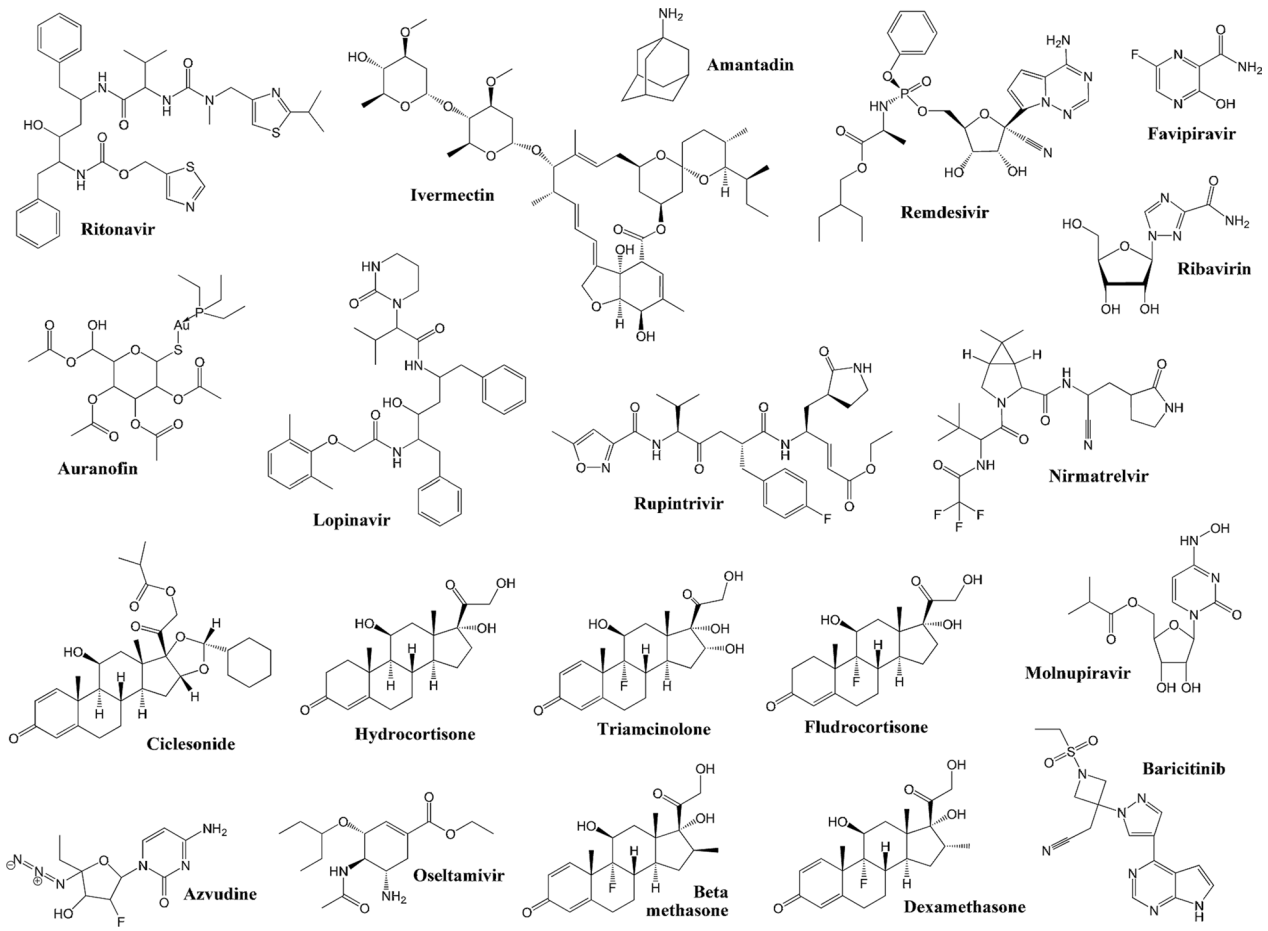

Fig. 4 Some commercial drugs have been recognized and approved to treat COVID-19 patients

ivermectin. It was suspected of containing ivermectin, a protease inhibitor proposed to kill parasites. Molnupiravir has been shown to successfully target the viral RdRp on the Omicron variant [138–140]. In early 2022, WHO recommended two new drugs for COVID-19 patients, baricitinib and sotrovimab [141], while other monoclonal antibodies, such as bebtelovimab and Evusheld (containing tixagevimab and cilgavimab), have also gained attention due to their high efficacy against the virus at mild to moderate levels [142].

Rupintrivir (AG7008) are other drugs being investigated for its potential to treat COVID-19. It contains a lactam ring that mimics Glutamine residues at the P1 position and forms a covalent bond with the active-site cysteine residue of the virus protease [143]. In vitro antiviral assays using H1-HeLa and MRC-5 cells have shown Rupintrivir to have a potent broad-spectrum antiviral activity against 48 HRV serotypes and four related picornaviruses [144]. Ramajayam et al. has proven that the fluorophenylalanine group and isoxazoyl moiety in rupintrivir may hinder its ability to bind to Arg188 in the S2 pocket and hydrophobic residues of SARS-CoV 3CLpro, respectively [143]. Therefore, its efficacy in treating COVID-19 is still being studied in detail. A similar case has also been observed with amantadine, which was previously used to treat influenza. In vitro studies have shown an inhibitory effect of amantadine on SARS-CoV-2 infected Vero E6 cells with an IC_{50} between 83 and 119 μM [145]. The dosage required for in vitro efficacy is not feasible in vivo due to toxicity concerns. Its therapeutic window cannot be offered, suggesting that the oral administration of amantadine appears obsolete. Several studies reported that amantadine could be administered through inhalation, as the infection of human airways by SARS-CoV-2 covers a high concentration in the nasal epithelium until distal pulmonary epithelium [146].

IFN are signaling proteins produced by host cells that have shown therapeutic potential for MERS and SARS-CoV [35, 147], making it a proposed treatment for COVID-19. The EC_{50} of IFN-α and IFN-β treatment on infected SARS-CoV-2 Vero cells is reported to be 1.35 IU/mL and 0.76 IU/mL, respectively [148]. In addition, glucocorticoids such as ciclesonide, dexamethasone, betamethasone, hydrocortisone, fludrocortisone, and triamcinolone are potential candidates for treating inflammation accompanying COVID-19 [149]. Other therapies such as convalescent plasma and anti-interleukin-6 (anti-IL-6) inhibitors have also been explored to combat the pandemic.

Investigations have proven that 25-hydrocholesterol, a type of oxidized cholesterol products found in various human body fluids, has the potential to inhibit COVID-19 with an IC_{50} of 550 nM by blocking membrane fusion [150, 151]. In addition, 25-hydrocholesterol is oxidized cholesterol products found in human peripheral blood, cerebrospinal fluid, colostrum, and milk. Several studies are considering 25-hydroxycholesterol and 27-hydroxycholesterol, which are side-chain oxysterols, as potential inhibitors of respiratory viruses against COVID-19 [152].

Clinical trials have been conducted using a drugs repurposing approach, either with a single-molecule therapy or a combination of therapies, to treat COVID-19. However, one of the studies involving 1206 randomized patients showed no improvement in the recovery of mild to moderate COVID-19 patients using a single treatment of ivermectin [153]. Combination therapies involve the simultaneous repurposing of therapeutic, antiviral, immunotherapeutic, and convalescent plasma therapies. Remdesivir is popular antiviral drugs that has received emergency approval from WHO. A combination of remdesivir and baricitinib, as immunotherapeutic agents, produces better outcomes in hospitalized patients with COVID-19 than the use of only remdesivir. The use of two antiviral drugs, remdesivir and dexamethasone, has resulted in reduced mortality for 30 days. The use of combined antiviral and antibiotic therapies has also been proven to be more effective and safer for early symptomatic patients [154].

The application of repurposed drugs has yielded some promising examples of inhibitors for SARS-CoV-2. Several studies have identified available drugs agents that can inhibit the protein and reproduction cycles of viruses [155–157]. In addition, clinical trials conducted on April 2020 have shown that the combination of natural products, such as honey, and Nigella sativa seeds, improved symptoms and reduced mortality without adverse effects [158]. The Ayurvedic drugs, AYUSH 64, demonstrated improved recovery and reduced hospitalization for mild-moderate symptomatic patients [159]. The potential of these natural compounds as alternative COVID-19 drugs and therapeutic agents is described in detail in the following section of this study.

In-silico study on drugs discovery for COVID-19

Modern drugs discovery relies on in-silico studies involving molecular docking and dynamics. This approach uses bioinformatics and computational modelling to design new lead compounds and enable virtual screening of bioactive metabolites [160]. However, by enabling preliminary screening activities, this technology accelerates the identification and analysis of bioactive compounds, while significantly reducing time and costs associated with laboratory work. Molecular modelling is particularly useful for repurposing existing drugs and natural products, as it predicts the affinity and binding mode of molecules to the active site of a receptor protein.

Computer modelling enables the efficient screening of hundreds and thousands of compounds, in experiments conducted for a brief period. Promising compounds or drugs identified during the process are further subjected to docking studies (Table 4, Fig. 5). In order to understand the mode of action of these compounds or drugs, molecular dynamics (MD) simulations were used to model their interaction with the active site of the virus [161–163]. However, through artificial neural network analysis, medicines are classified based on their primary role in SARS-CoV-2 infection, specifically in viral replication and immune response. This approach differentiates between antiviral agents that prevent virus replication and those modulating immunity to combat the virus without overreacting. Once a potential antiviral candidate is identified, further assays using human and non-human cell lines are necessary.

Viral entry is prevented by targeting the host receptor, ACE2 and other proteins parts of coronavirus, such as spike glycoproteins (including nsp1-16, RdRp) and proteases (Mpro and PLpro), and has been explored as a potential strategy [33, 157, 179–181]. In-silico investigations provide valuable parameters, including RMSD, docking scores, and binding affinities, to assess the effectiveness of antiviral agents.

A notable example of applying the in-silico approach for drugs discovery is the study conducted by Elinger et al. [182]. They successfully generated a small set of

Table 4 Antiviral drugs/compounds that have been assessed using in silico approach against SARS-CoV-2 proteins

Compounds	Antiviral activities	Molecular docking tools	Refs.
40 triterpenoids, flavonol glycosides, anthocyanidins	SARS-CoV-2 Mpro (pdb id: 6LU7), RBD (pdb id: 6M0J), RdRp (YP_009725307.1), human trans-membrane serine protease 2 TMPRSS2 (NP_001128571.1)	AutoDock Vina	[164]
51 alkaloids, terpenoids, polyphenols, peptides	SARS-CoV-2 Mpro (pdb id: 6LU7)	AutoDock 4.2.0	[165]
19 hydrolyzable tannins	SARS-CoV-2 Mpro (pdb id: 6Y84)	Molecular Operating Environment (MOE 09)	[166]
24 natural plant-based compounds, 22 antiviral drugs, 16 anti-malarial drugs	SARS-CoV-2 Mpro (pdb id: 6LU7)	Virtual screening followed with SP and XP docking modes using GLIDE module MD simulations using GROMACS-2019	[167]
Four tropane alkaloids from *Schizanthus porrigens*	SARS-CoV-2 PLpro (pdb id: 6WX4)	Autodock Vina Molecular dynamic simulations using NAMD v.2.14	[168]
21 flavonoids	SARS-CoV-2 Mpro (pdb id: 6YNQ)	AutoDock Vina and Swiss dock Molecular dynamic simulations using CABS Flex 2.0	[169]
66 active flavonoids were selected from 2030 natural compounds	SARS-CoV-2 Mpro (pdb id: 6LU7)	GLIDE module	[170]
80 flavonoids	SARS-CoV-2 Mpro (pdb id: 6LU7)	Molegro Virtual Docker 7	[171]
23 flavonoids and 25 indole chalcones	SARS-CoV-2 Mpro (pdb id: 6YB7), RdRp (pdb id: 6M71), spike protein (pdb id: 6LZG)	AutoDock Vina v.1.1.2	[172]
458 flavonoids	SARS-CoV-2 Mpro (pdb id: 6LU7), RdRp (pdb id: 6M71), spike protein (pdb id: 6VW1)	AutoDock 4.1	[173]
12 triterpenoids isolated from *Calendula officinalis* L	SARS-CoV-2 Mpro (pdb id: 6LU7)	MOE 2019 Suite Molecular dynamic simulation using GROMACS-2019	[174]
14 limonoids and terpenoids	SARS-CoV-2 RBD (pdb id: 6M0J)	AutoDock 4.2 Molecular dynamic simulation using Desmond MD System	[175]
218 coumarins	SARS-CoV-2 Mpro (pdb id: 6LU7), viral methyltransferase (nsp16/10 complex, pdb id: 6W4H), RBD (pdb id: 6M0J), human ACE2 (pdb id: 6VW1)	AutoDock Vina	[176]
78 secoiridoids	SARS-CoV-2 Mpro (pdb id: 6LU7), and S protein (6LZG)	AutoDock Vina Molecular dynamic simulation using Desmond MD System	[177]
6 phenyl propanoids	SARS-CoV-2 Mpro (pdb id: 6Y2F); PLpro (pdb id: 6WX4); RdRp (pdb id: 6M71)	Genetic optimization of ligand docking (GOLD v5.2.2) Groningen machine for chemical simulations (GROMACS v5.15)	[178]

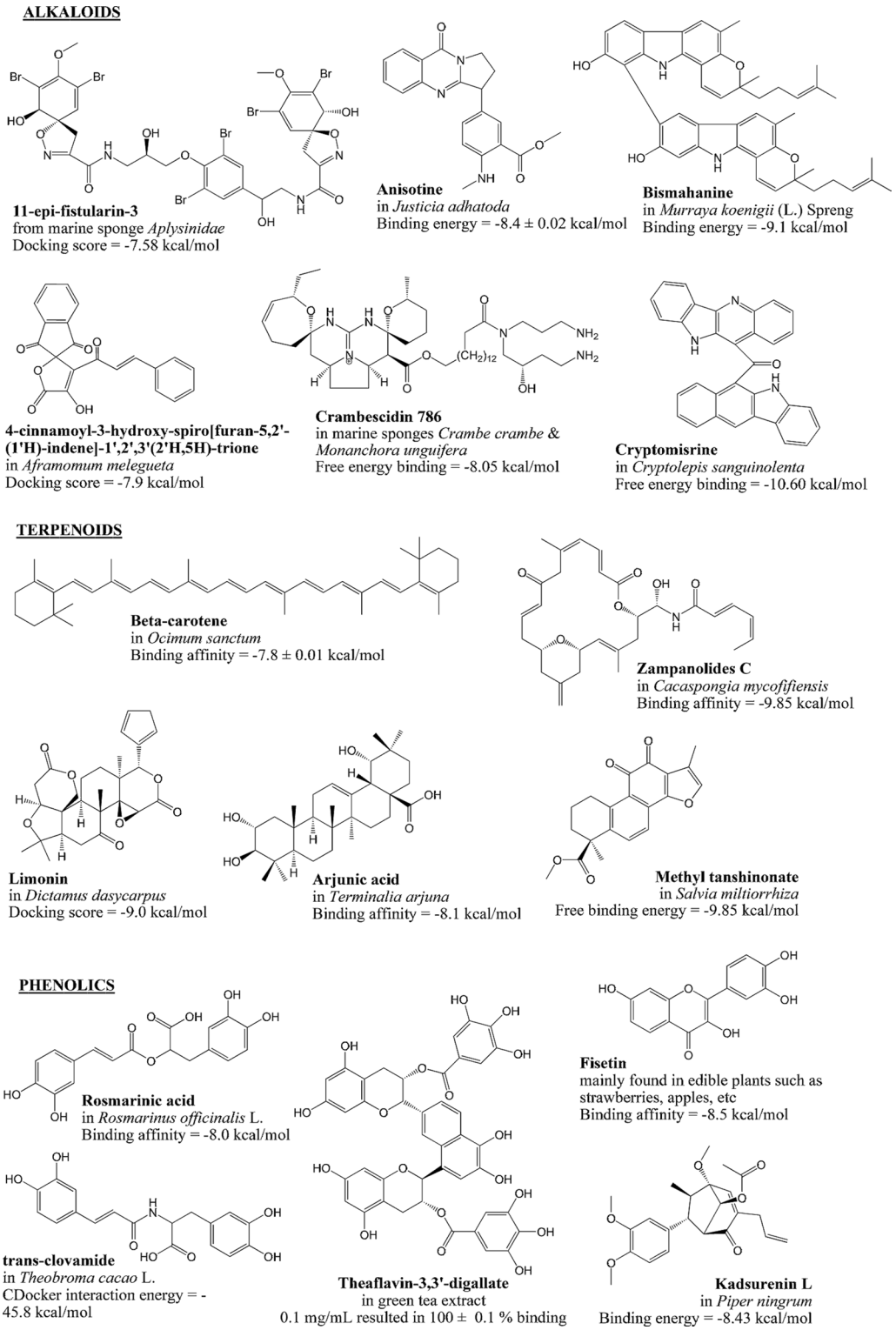

Fig. 5 Interesting compounds with higher activities against SARS-CoV-2 proteins in terms of lower binding affinity or Docking score in recent papers [34, 164, 165, 186–199]

related drugs that exhibited significant activity in terms of IC_{50}. A primary screening assay [183] of 5632 compounds was tested for their ability to inhibit SARS-CoV-2 in human epithelial colorectal adenocarcinoma cells (Caco-2) [184]. After the procedure, 271 compounds were selected based on achieving more than 75% inhibition cut-off, as determined by quantifying cell viability readouts. Subsequently, 184 compounds were further chosen based on their clinical status. Among these, 64 compounds demonstrated an IC_{50} value of less than 20 μM, while 19 exhibited an IC_{50} value of less than 1 μM.. This study highlighted six of the 64 compounds, namely camostat, nafamostat, lopinavir, mefloquine, papaverine, and cetylpyridium. However, 90% of those confirmed compounds have not been reported as SARS-CoV-2 antiviral agents in in vitro cell assays [182, 185]. The names and structures of those compounds were not disclosed in the present study.

The molecular docking-based virtual screening approach using AutoDock Vina was employed to identify potential inhibitors of 3CLpro of SARS-CoV-2 [200]. The top four compounds were selected from a pool of 2000 compounds in the ZINC database, based on their low free energy binding adherence to the Lipinski rule of five, and functional molecular interactions with the target protein. Similarly, Barage et al. utilized AutoDock Tool 1.5.6 to retrieve 3277 compounds from the ZINC database and generate 10 top compounds with the lowest binding energy against RdRp (PDB ID: 6NUR) and Nsp15 (PDB ID: 20ZK). MD simulations performed with GROMACS tools, was used to identify three compounds with the highest affinity to interact with RdRp and Nsp15 namely alectinib, naldemedine, and ergotamine [201].

Potential components of Ayurvedic medicinal plants have been assessed for their repurposing possibility as anti-COVID-19. After screening selected compounds from twelve medicinal plants, molecular docking and dynamic simulations showed that curcumin, gingerol, and quercetin were potential candidates [202]. In another study, fluoro-substituted heterocyclic ring systems were added to quercetin-based derivatives, which were then screened by in silico experiments against SARS-CoV 3CLpro (PDB ID: 6LU7) using Autodock 4.2 software. The compounds L4 (5-fluoro-2H-1,2,3-triazol-4-yl), L8 (2-fluoro-4H-1,3-oxazin-4-yl), and L14 (3-fluoropiperidin-4-yl) showed promising results, with IC values of 0.330, 0.456, and 0.50 uM, respectively. Additionally, a study on marine natural product-based drugs-like small molecules screened 14,492 compounds from the MNP library, of which 7471 compounds fulfilled Lipinski rule of five. After conducting the evaluation process through ADMET descriptor, 2033 compounds were selected for further analysis. Docking analysis and molecular dynamic simulations of 14 compounds led to the identification of six hits of phenyl propanoid compounds, including fasciospongiside A, epolactoena, constanolactone B, constanolatone F, debromo araplysillin I, and maniloside A as potential anti-COVID-19 agents [178].

The Korea Chemical Bank Drugs Repurposing (KCB-DR) database, consisting of 1,865 compounds, was used to propose potential therapeutic agents for COVID-19. GOLD virtual screening identified 149 binders based on their Goldscore and Chemscore. MD simulations were then employed to analyze the binding modes and fundamental interactions, thereby revealing seven top drugs. Based on the binding free energy approaches, ceftaroline fosamil and telaprevir emerged as potential drugs against SARS-CoV-2 with telaprevir raising safety concerns due to its side effects. In order to address this, a substructure search in the PubChem database led to the identification of 11 potential derivatives of telaprevir exhibiting desirable pharmacokinetic properties, particularly lower hepatotoxicity [203]. However, in another study, the molecular interactions and stabilities of 3,639 drugs from the SuperDRUG2 database were analyzed using PyRx and GROMACS v5.1.5. It was observed that colchicine emerged as the top binding compound against SARS-CoV-2 Mpro [204].

Sharma and Kaur investigated the potential of jensenone, a key component of eucalyptus oil, as an inhibitor for COVID-19 infection [205]. The in-silico study revealed that jensenone formed a complex structure with the main viral proteinase/chymotrypsin-like proteinase (Mpro) through hydrophobic, hydrogen bonds, and strong ionic interactions. Paul et al. explored synthetic molecules, peptidomimetic, and small molecules inhibitors targeting viral proteinases to assess its potentials as anti-SARS-CoV Mpro agents through computational approaches [206]. Another study by J. K. R. da Silva et al. [207], investigated the potential of 171 essential oil components in treating SARS-CoV-2 using molecular docking analysis. The findings showed that (E)-β-farnesene exhibited the best normalized docking score, while (E,E)-α-farnesene, (E)-β-farnesene, and (E,E)-farnesol were identified as the best docking ligands. Unfortunately, the docking energies were relatively weak, limiting their applicability to coronavirus interactions.

The Searching off-lAbel drugs aNd NEtwoRk (SAveRUNNER) is an interesting approach for repurposing existing drugs to treat COVID-19. This method evaluates the interaction between drugs and target protein based on their location and position in the same network neighbourhoods. Recent study utilized 14 COVID-19-related diseases to generate 282 repurposing drugs of 1875 FDA-approved drugs from DrugBank v5.1.6. Ruxolitinib has the potential to inhibite JAK and H1-antihistamines that

play a vital role in controlling immune responses [208]. Asides from SAveRUNNER, other in-silico approaches for identifying potential repurposing drugs include network module separation and the RWR algorithm. Both approaches highlight the disease module of H1N1 flu and SARS-CoV-2 infection [209]. The development of network-based mechanisms involves multimodal technology using artificial intelligence, network diffusion, and proximity algorithms. [210], stated that 76 of the 77 drugs achieved viral effects through indirect viral protein binding targets by perturbing the host subcellular network. Molecular docking through computational approaches was used to observe the interaction patterns of binding viral proteins to host targets. Indeed, network-based perturbations is induced by altering the virus ability to enter the cell or replicate within the cell. This advanced approach of in-silico method for drugs repurposing is beneficial in developing a faster and cheaper strategy for drugs discovery schemes.

However, computer modelling is not the only approach for determining drugs as reliable antiviral agents, even when it shows a strong binding mode to the active sites of the virus. Vatansever et al. [211] stated that calculated binding energy does not necessarily correlate strongly with the actual IC_{50} values. Computer modelling is the only approach used to obtain detailed information in relation to predicting the mode of antiviral action. The next crucial step is to conduct in vitro and in vivo assays in preclinical trials. These assessments help to identify a small number of drugs or compounds for further evaluation in clinical trials. As public awareness of health and safety increases and the challenges posed by viral infections persist, there is a growing need for alternative, nature-based medications. This alternative treatment can complement existing approaches and offer potential solutions for viral infections that are difficult to cure or present challenges during treatment.

Natural products for treatment of viral infection

Medicinal plants encompass all plants or herbs whose components exhibit biological activities. These bioactive compounds, when extracted from medicinal plants, can be considered as lead compounds. In recent times, there has been a growing interest in novel natural approaches to treating viral infections, driven by increased public awareness and concern for safety and health issues in comparison to synthetic drugs. The utilization of natural products as remedies for various infectious diseases often stems from the fields of ethnobotany, phytochemistry, and local wisdom, giving rise to ethnopharmacology. However, it is important to note that in many cases, there are insufficient or even lack of scientific evidences to substantiate the health-related information or knowledge associated with these natural remedies.

Discovery of alternative drugs for treating viral respiratory diseases such as COVID-19 has led to repurposing of natural products with new pharmacological properties. Medicinal plants from the Lamiaceae, Cupressaceae, and Zingiberaceae families, as well as isolated natural products such as ritonavir, chloroquine phosphate, arbidol, and ribavirin, have shown potential antiviral activities against some viruses [212]. These natural products have also been found to be beneficial in preventing and relieving the symptoms of COVID-19. Other natural products compounds, such as vitamin D (calcitriol), vitamin C (ascorbic acid), lactoferrin, quercetin, resveratrol, hanfangchin A (tetrandrine), glycyrrhizin, artemisinin, colchicine, and berberine, are current under clinical trials for treatment of COVID-19 [213]. In addition, Panyod et al. [5] stated that the use of immunomodulator foods and herbs containing large amounts of vitamins C and D, flavonoids, and essential oils, helps strengthen the immune system and acts as air disinfectants or sanitizers to prevent aerosol transmission of the virus. The use of rich and bulky spices found in tropical lands, such as cinnamon, cloves, mint, lemon, and balm, also offers possibilities for discovering bioactive natural molecules suitable against viruses [214–219].

Several food sources have been found to play a role in the immunomodulatory system by reducing inflammation. For example, the fruit extract of Embelia schimperi (Myrsinaceae), which contains benzoquinones, has been proven to exhibit potent HCV-PR (hepatitis C virus protease) activity [220]. Pomegranate peel extract (PPE), which contains polyphenols, has also been found to have immunomodulatory effects [221–223]. In addition, Ali et al. [224], and Wen et al. [95], reported that among 221 phytocompounds, some diterpenoids, sesquiterpenoids, triterpenoids, and lignoids were potent inhibitors against SARS-CoV on Vero E6 cells. Other possible sources of natural products active compounds in treating human diseases include endophytes and medicinal plants. [105], stated some molecules obtained from medicinal plants that have been claimed to be effective against SARS-CoV-2 in virtual assays or clinically applied, although there is no scientific proof.

Traditional herbal medicines

Traditional herbal remedies are widely used as complementary or alternative medicines in many countries, particularly in the context of eastern medicine. These remedies consist of traditional medicinal preparations derived from single or combined medicinal plants. Despite the lack of comprehensive studies, these therapies have been employed for centuries in treatment of

various ailments. Traditional Chinese Medicine (TCM), which boasts a history of over 2000 years, and Ayurveda are two prominent herbal remedies enjoying trust and popularity not only within their countries of origin, China and India respectively, but also in other parts of the world.

In a study conducted by Yang et al. [227], various TCM herb formulae and extracts were identified for their potential in treating SARS-CoV infections, along with TCM-derived compounds exhibiting anti-HCoV activities. Notably, the Yin Qiao San formula demonstrated positive therapeutic effects against upper respiratory tract infections, while Ma Xin Gan Shi Tang exhibited anti-SARS-CoV activity. Several TCM compounds were found to possess antiviral properties, particularly against SARS-CoV, MERS, and SARS-CoV-2. These include plant-derived phenolic compounds from *Isatis indigotica* root extract, litchi seed extract, herbacetin, rhoifolin, pectolinarin, quercetin, epigallocatechin gallate, and gallocatechin gallate. Glycyrrhizin from Glycyrrhizae radix, water extract of Houttuynia cordata, and emodin derived from Rheum and Polygonum genera also exhibited antiviral activity (Fig. 6). Yi et al. [228], conducted study on 121 Chinese herbal medicines and reported that tetra-O-galloyl-β-D-glucose and luteolin were two active constituents effective against the wild type of SARS-CoV. Another review reported that TCM is obtained from a single preparation rather than the combination of medicinal plants or Chinese medical formulas. Xi et al. [229], specifically identified components of TCM herbs as potential agents against antiviral pneumonia, while An et al. [225] listed various TCM treatment along with their initial symptoms, outcomes, and effects on antiviral diseases. It is important to note that the evidence supporting TCM treatment relies on clinical evidence obtained from their practical use.

TCM is believed to treat COVID-19 by inhibiting the replication and transcription of SARS-CoV-2 through various mechanisms such as blocking the viral functions of RdRp, 3CLpro, spike protein, and PLpron. Additionally, it can hinder the binding of the virus to host cells by acting on ACE2 and TMPRSS2. TCM also has the potential to reduce cytokine production, prevent immune system impairment, and abnormal blood clotting following SARS-CoV-2 post-infection.

Shuanghuanglian is a popular traditional Chinese patent medicine that is formulated from the extraction of three Chinese herbal medicines, namely Lonicera japonica Thunb, *Scutellaria baicalensis* Georgi, and Forsythia suspense (Thunb.) Vahlv. The key constituents of this medicine are chlorogenic acid, phillyrin, and baicalin. Despite being a traditional medicine, Shuanghuanglian has undergone scientific investigations in China to assess its antiviral activity. Su et al. [45] reported that the inhibitory effect of Shuanghuanglian on SARS-CoV-2 3CLpro is primarily attributed to its significant components,

Fig. 6 Some parts of medicinal plants are used as traditional herbal therapies to alleviate the symptoms of respiratory diseases, and the effectiveness of some of these remedies has been scientifically proven. However, there are other herbal remedies that have not been listed in international monographs [225, 226]. All pictures were obtained from the Google search engine and were not recognized as the author's ownership or copyright

baicalin and baicalein (an aglycone of baicalin). The IC_{50} value for this inhibition was found to be only 0.94 μM. However, it should be noted that these two compounds exhibited less than 50% inhibition activity against SARS-CoV-2 PLpro at a concentration of 50 μM.

The potent inhibitory activity of baicalein against SARS-CoV-2 3CLpro can be attributed to its structural features, including three phenolic hydroxyl groups, a carbonyl group, and a free phenyl ring. These features allow baicalein to form multiple hydrogen bonds and hydrophobic interactions with amino acid residues, both in the main and side chains of the viral active sites. While both baicalein and baicalin demonstrated significant inhibition, antiviral activity of Shuanghuanglian was found to be limited in Vero E6 cells. Su et al. [45], reported that this could be attributed to the low permeability of the cell membrane to the components of the preparation.

Ni et al. [230], reported a case in which a combination of Shuanghuanglian and Western medicine was used to treat three family members suffering from COVID-19, resulting in a positive therapeutic effect. However, the use of this method needs to be approached with caution due to the need for early treatment and potential errors, such as combining antibiotics and antiviral drugs. In addition to health concerns, some TCM herbs contain nephrotoxins and mutagens, such as aristolochic acids found in Aristolochia and related plants [231]. The regulation of these herbs varies among nations, China, Taiwan, and the US are some countries that have unregulated their usage.

Pudilan Xiaoyan Oral Liquid (PDL), another TCM preparation, has been the subject of study for disease enrichment analyses. It has shown promising potential in treating asthma and chronic obstructive pulmonary disease, with similar significance levels to COVID-19 ($p = 2.4E{-}03$ and $p = 2.45E{-}03$, respectively). PDL contains four herbs, including Indigowoad Root (*Isatis indigotica*), Bunge Corydalis (*Corydalis Bungeana*), Mongolian Dandelion (*Taraxacum Mongolicum*), and Scutellaria Amoena (*Scutellaria Baicalensis*) [232]. Interestingly, there is also a commercially available oral liquid in the United States known as Respiratory Detox Shot (RDS), which is a food supplement containing ingredients commonly used in TCM. These ingredients include Panax ginseng, Lonicera japonica, Forsythia suspensa, Glycyrrhiza uralensis, Scrophularia ningpoensis, etc. The effect of RDS on SARS-CoV-2 was investigated, resulting in an IC_{50} value at a 1:40 dilution [233].

Ayurveda, an ancient traditional medicine system dating back to the Vedic period (1500 to 500 BCE), has emerged as a potential remedy for mitigating the severity of COVID-19. Care [234], reported that the Ayurvedic approach, focuses on both preventive and curative aspects, tailored to different stages of the disease. Maurya et al. [235], have virtually screened natural products from Ayurveda to identify compounds capable of modulating the immune system and blocking the entry of SARS-CoV-2. Three plants of critical significance in Ayurvedic medicine, especially in Rasayana therapy, are Whitania somnifera, Tinospora cordifolia, and Asparagus racemosus. These plants contain active steroid compounds such as ashwagandhonolides, whitacoagin, withaferin, and withanone, which have shown potential against various proteins associated with SARS-CoV-2, including spike glycoprotein (RBD), RdRp, and Mpro [236]. Ayush-64, an Ayurvedic formulation used clinically for its anti-malarial, anti-inflammatory, and antipyretic properties, has demonstrated favourable binding energy to Mpro, with values of approximately − 8.4, − 7.5, and − 7.4 kcal/mol, corresponding to molecules akuammicine N-Oxide (from Alstonia scholaris), akuammiginone, and echitaminic acid, respectively [237]. Nimbin and curcumin, active compounds found in Ayurvedic formulations, have exhibited higher binding affinity than nafamostat, a synthetic protease inhibitor [235]. Figure 7 shows some of the active compounds found in traditional Ayurvedic medicines that have demonstrated efficacy against SARS-CoV-2 in in vitro assays.

In Romania, the native flora, including medicinal plants such as dandelion, daisy, and fat grass [238], was utilized as part of traditional medicine during current pandemic [225, 239]. These plants are rich in flavonoids, saponins, tannins, sterols, fatty acids, coumarin, and vitamins. Moreover, the *Fritillaria* species, known for their pharmacological effects on the respiratory system, possess antitussive, expectorant, and antiasthmatic properties. This genus has been included in the Ayurvedic (*Fritillaria roylei*), Korean (four species), and Chinese Pharmacopeia (ten species known as Bei Mu in Chinese), and are also widely used in Tibetan, Mongolian, Miao, Lisu, Tujia, Kazakh, Uighur, Jingpo and De'ang traditional medicine [240]. Other herbal products, Sumac, extracted from the Rhus genus, has demonstrated interactions with viral envelopes and host cell surfaces, exhibiting diverse antiviral activities against influenza A and B, HSV, and HIV. According to Korkmaz [241], it has been suggested as a potential treatment for COVID-19 infection.

Traditional medicines in the form of Jamu have been produced in Indonesia [242–244]. Popular Jamu formulations include *wedhang jahe, jamu kunyit asam, jamu teulawak,* and *jamu beras kencur*, which typically contain rhizomes from the ginger family (*Zingiberaceae*) such as *Zingiber officinale* and *Curcuma longa*. These formulations may also include additional ingredients like *Cinnamomum verum* bark, *Citrus aurantifolia* fruit, and starch fillers.

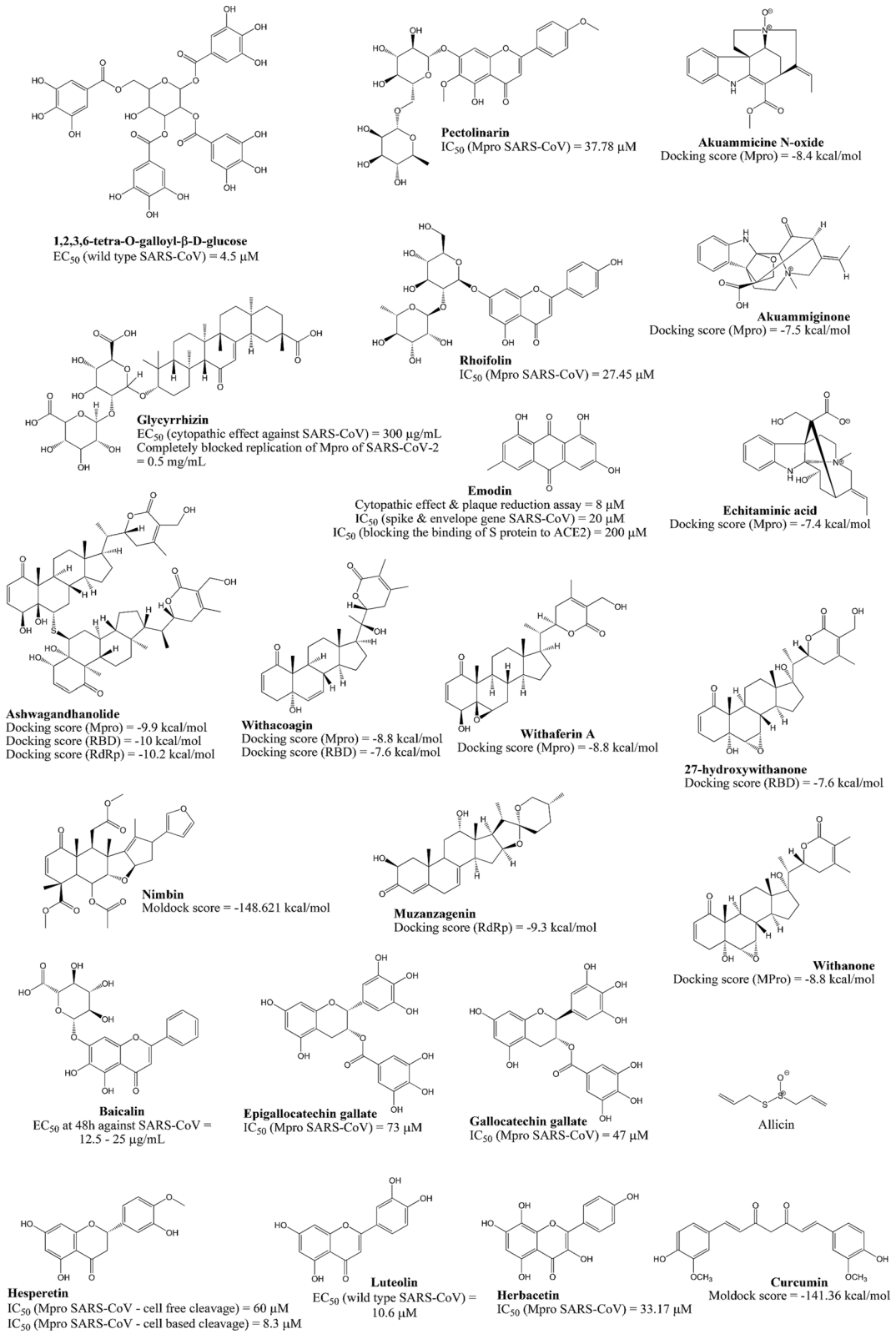

Fig. 7 Chemical structures of active components inside traditional medicines that have been tested by in vitro and in silico analysis against proteins of SARS-CoV and SARS-CoV-2 [94, 228, 235–237, 247–253]

Although the use of *Jamu* is not officially recommended in treatment of COVID-19 patients, it has become a popular alternative among Indonesians as an immunostimulatory agents to prevent symptoms and promote speedy recovery from post-infection symptoms [245]. Another example is the application of virgin coconut oil (VCO) in the local communities as a therapeutic adjuvant to overcome inflammation caused by COVID-19. While no scientific evidence has been presented, clinical trials have been conducted in four hospitals in Yogyakarta caring for hospitalized COVID-19 patients [246]. It is important to note that traditional remedies should not be used as a substitute for medical treatment for COVID-19 and their effectiveness remains unproven.

According to the Committee on Herbal Medicinal Plant Products (EMEA/HMPC/892618/201), consuming the extract of *Eucalyptus globulus* Labill, in the form of dried leaves up to four times a day, is helpful in managing respiratory diseases such as bronchitis and rhinitis. This is because it contains active components such as 1,8-cineol and phenolic compounds. The British Herbal Pharmacopeia recommends the use of garlic products that contain sulfuric compounds, including allicin and mercaptan, amino acids, peptides, terpenes, minerals, and flavone glucosides to treat COVID-19, as it has traditionally been used to manage colds and whooping cough. However, it is important to note that Traditional Herbal Medicine Products (THMP) in Europe are not considered a treatment for COVID-19 as it is a severe, life-threatening illness [226].

The utilization of medicinal plant extracts mentioned earlier has gained widespread popularity worldwide as a recommendation to combat COVID-19, serving as an alternative to drugs provided by WHO and the Ministry of Health in each country. Zhang et al. [254], conducted in silico screening of Chinese herbal medicine and identified 13 active compounds effective against SARS-CoV-2. This method of analysis is beneficial in expediting drugs discovery process based on ethnobotanical reasoning. Exploring traditional medicine and ethnopharmacology presents a potential alternative for drugs discovery in combating COVID-19 pandemic. However, it is crucial to exercise caution regarding the preparation, dosage, and individual health considerations associated with traditional treatment prior to their application. Therefore, conducting a detailed investigation into the extraction of active compounds from traditional herbal medicines would prove advantageous as it focuses on the specific or known combination of active molecules responsible for their bioactivity, eliminating unnecessary or unsafe components that may be consumed.

Polyphenol-based secondary metabolites

Polyphenols are a prominent group of naturally occurring bioactive compounds found in plants that contain at least one substituted phenol ring or several hydroxyl groups on aromatic ring compounds. This group comprises four classes, namely phenolic acids, flavonoids, stilbenes, and lignans. The flavonoid class includes several derivatives such as chalcones, flavones, flavanones, flavonols, isoflavones, anthocyanins, and flavan-3-ols. Polyphenols are known for their broad antiviral activities against various viruses, including influenza A virus (H1N1), HBV/HCV, HSV, HIV, and Epstein-Barr virus (EBV) [255]. Table 5 shows some phenolic compounds that have been explored as antiviral agents, particularly against SARS-CoV-2. In silico and in vitro approaches have been used to study subsites of the virus, including proteins and enzymes related to SARS-CoV-2 and cell receptors in the human body.

Polyphenolic compounds can also act as antioxidants due to their hydroxyl groups, which react with radicals and oxidizing compounds. Resveratrol, a biflavonoid compound with the IUPAC name 3,5,4-trihydroxy-trans-stilbene, is a potent antioxidant that scavenges for reactive oxygen species, such as O_2^- and OH^-, and lipid hydroperoxyl free radicals. Although it has poor oral bioavailability and water miscibility, resveratrol is rapidly metabolized in the body. Abba et al. [282] have stated the role of resveratrol and its action mechanisms in combating viral infections in human and animal cells. Therefore, resveratrol is presumed to have potential therapeutic benefits in treating COVID-19 by enhancing the immunity of infected patients. Quercetin is another popular phenolic compound that has been combined with N-acetylcysteine in the formulation of Quercinex to be directly administered to the deep lung tissue through a nebulizer to treat respiratory problems and multifocal pneumonia in COVID-19 patients [283]. Rutin, another phenolic compound, has been studied for its in-silico binding affinity to interact with the main protease of SARS-CoV-2 in the three-dimensional structures of PDB IDs 6LU7 ([170] and 6YNQ [169].

The polyphenols present in ethanol PPE have exhibited positive in vitro activity in reducing the interaction between SARS-CoV-2 spike glycoprotein and human ACE2, along with the activity of SARS-CoV-2 Mpro. ACE2 and TMPRSS2 gene expression levels were reduced by 30 and 70%, respectively, by applying PPE at 0.04 mg/mL on human kidney-2 cells infected by SARS-CoV-2 Spike pseudotyped lentivirus. Furthermore, PPE displayed the inhibition of Mpro activity by relatively 80% when used at 0.2 mg/mL [223]. It has also been evaluated in three commercial forms, namely pomegranate juice, a concentrated liquid extract, and 93% PP powder extract,

Table 5 Potential polyphenolic compounds as antiviral agents against SARS-CoV-2

Compounds	Plant sources	Antiviral Activities	Assays	IC50/Binding Affinity*	Refs.
Phillyrin (KD-1)	*Forsythia suspensa*	SARS-CoV-2 and HCoV-229E	In vitro using cytopathic effect and plaque reduction assay in Vero E6 cells	IC_{50} against SARS-CoV-2 and HCoV-229E is 63.90 and 64.53 mg/mL	[256]
Phillyrin (KD-1)	*Forsythia suspensa*	SARS-CoV-2 and HCoV-229E	In vitro based on pro-inflammatory cytokine expression levels in Huh-7 cells by RT-PCR assay	Phillyrin reduced the production of proinflammatory cytokines at mRNA levels and reduced the protein expression of p-NF-κB p65, NF-κB p65, and p-IκBα	[256]
Cannabidiol and Δ^9-tetrahydrocannabinol	*Cannabis sativa* L. (Chongsam, leaves)	SARS-CoV-2 (βCoV/KOR/KCDC03/2020)	In vitro using screening assay in Vero cells	IC_{50} of 7.91 mM and 10.25 mM	[257]
Pelargonidin		SARS-CoV-2 Spike protein	In vitro using Spike/ACE2 Inhibitor Screening Assay Kit and using plaque assay in Vero E6 cells	At 50 mM reduces Spike binding to ACE2 by about 40%. Plaque assay reduces virus entry by about 70% at 100 mM	[258]
Juglanin		3a-protein channel of SARS-CoV	In vitro using Voltage-clamp experiments on SARS-3a protein	IC_{50} of 2.3 mM	[259]
Emodin	Genus *Rheum* and *Polygonum*	SNE (spike and envelope gene)-3a protein of SARS-CoV	In vitro using Voltage-clamp experiments on SARS-3a protein	IC_{50} of 20 mM	[249]
Emodin		SARS-CoV spike protein	In vitro using luciferase assay	IC_{50} of 200 mM	[250]
ThE (composed of green tea catechin and epigallocatechin gallate EGCG; total catechins were 85–95% and total EGCG was 65–70%, caffeine < 0.5%)	Product from Mitsui Norin Co. Ltd	SARS-CoV-2	In vivo using clinical trials. Ten patients were treated for 15 days sessions of inhalation plus three capsules per day (total catechin, 840 mg; total EGCG, 595 mg)	Seven of ten patients switched to a negative SARS-CoV-2 nasopharyngeal swab test in a range of 6–13 days	[260]
Curcumin Hesperidin Quercetin hydroxychloroquine	From chemical manufacturers	SARS-CoV-2 from hCoV-19/Egypt/NRC-3/2020 SARS-CoV-2 virus (Accession Number on GSAID: EPI_ISL_430820)	In vitro using plaque reduction assay in Vero E6 cells	IC_{50} values: Curcumin 0.44 mM Hesperidin 13.25 mM Quercetin 18.2 mM Hydroxychloroquine 1.72 mM	[194, 261]
Gallocatechin gallate (GCG) Epigallocatechin gallate (EGCG) Quercetin	From Sigma-Aldrich	Recombinant SARS 3CLpro transformed and expressed in *Pichia pastoris* GS115 based on GenBank accession no. AY274119	In vitro: proteolytic activity based on fluorescence resonance energy transfer (FRET) assay In silico: using Autodock Tools software with a ligand number of 3CLpro is 2ZU5	IC_{50} of: GCG = 47 mM EGCG = quercetin = 73 mM The binding energy of: GCG = − 14.1 kcal/mol, EGCG = − 11.7 kcal/mol, quercetin = − 10.2 kcal/mol SAR: EGCG and CGC have a galloyl moiety at the 3-OH position to interact with the 3CLpro active site pocket	[248]

Table 5 (continued)

Compounds	Plant sources	Antiviral Activities	Assays	IC50/Binding Affinity*	Refs.
Myricetin		SARS-CoV-2 Mpro	In vitro using a proteolytic assay based on FRET In silico: using AMBER18 with ligand number of 3CLpro is 6LZE In vivo: pulmonary inflammation in bleomycin treated mice	IC_{50} 3.684 ± 0.076 μM The binding free energy is -32.98 kcal/mol Myrcetin inhibits the infiltration of inflammatory cells and secretion of inflammatory factors in the lung	[262]
Ginkgolic acid (GA) and anacardic acid (AA)		SARS-CoV-2 PLpro, SARS-CoV-2 CLpro, isolated SARS2-CoV-2 USA-WA1/2020	In vitro using an enzymatic assay based on fluorometric peptide (FRET) assay. Antiviral determination using plaque reduction assay on Vero-E6 cells In silico using Autodock Vina with ligand 6m2n and 6WX4	IC_{50} against PLpro: GA = 16.30 ± 0.64 and AA = 17.08 ± 1.20 mM IC_{50} against 3CL pro: GA = 1.79 ± 0.58 and AA = 2.07 ± 0.35 mM EC_{50} against SARS-CoV-2: GA = 8.3 ± 0.03 mM and AA = 9.0 ± 2.5 mM Inhibition at 7.5 mM: GA = 42% and AA = 13% Binding affinity of GA to 3CLpro and PLpro is -5.3 and -4.9 kcal/mol	[263]
Curcumin, brazilin, and theaflavin-3,3′-digallate		SARS-CoV-2 RBD	In vitro using SARS-CoV-2 Surrogate Virus Neutralization Test Kit	% binding with RBD at 0.1 mg/mL = 100 ± 0.2; 100 ± 0.1; and 100 ± 0.1	[34]
Broussochalcone A (BcA); Papyriflavonol A (PA); 3′-(3-methylbut-2-enyl)-3′,4′,7-trihydroxy flavane (tHF); Broussoflavan A (BfA); Kazinol F (KF); Kazinol J (KJ)	*Broussonetia papyrifera*	SARS CoV-2 Mpro	In silico using AutoDock Vina on SARS-CoV-2 Mpro (6LU7)	Binding affinity (kcal/mol): BcA = − 8.1 PA = − 7.9 tHF = − 8.2 BfA = − 7.8 KF = − 8.1 KJ = − 8.0	[264]
Kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate	From chemical manufacturers	SARS-CoV-2 3CLpro/Mpro and SARS-CoV 3CLpro/Mpro	In silico using Autodock 4.2 with Lamarckian Genetic Algorithm on Mpro (6LU7 and 2GTB)	These listed compounds were ranked by affinities (ΔG)	[265]
Curcumin Hesperidin Quercetin hydroxychloroquine	From chemical manufacturers	SARS-CoV-2: S spike protein and main protease	In silico using MOE 2019.012 suite with S spike protein (6VW1) and Mpro (6LU7)	Binding score to S protein and Mpro: Curcumin − 7.02 and − 7.28 kcal/mol Hesperidin − 7.92 and − 8.37 kcal/mol Quercetin − 6.48 and − 6.23 kcal/mol Hydroxychloroquine -6.60 and − 7.05 kcal/mol	[194]

Table 5 (continued)

Compounds	Plant sources	Antiviral Activities	Assays	IC50/Binding Affinity*	Refs.
Gallocatechin gallate (GCG) Epicatechin gallate (ECG) Epigallocatechin gallate (EGCG) Catechin gallate (CG) Epicatechin (EC) Catechin Gallocatechin (GC) Epigallocatechin (EGC)		SARS-CoV-2 main protease	In silico using AutoDock Vina with Mpro (6LU7)	Three best binding energies: GCG – 9.0 kcal/mol ECG – 8.2 kcal/mol EGCG – 7.6 kcal/mol	[266, 267]
Rutin		SARS-CoV-2 Mpro (6LU7 and 6YNQ)	In silico using Glide module	Docking score: above – 7.0; – 8.7; – 9.16 kcal/mol	[169]–[171]
Calceolarioside B		SARS-CoV-2 Mpro (6LU7), Nsp15 endoribonuclease (6VWW), coronavirus fusion protein (6LXT), SARS-CoV-2 spike ectodomain (6VYB)	In silico using Molegro Virtual Docker	MolDock score: – 191.295 – 164.77 – 141.587 – 153.135	[268]
5-O-D-glucopyranosyl-4′-hydroxy-7-methoxy-4-phenylcoumarin		SARS-CoV-2 Nsp15 endoribonuclease (6WXC)	In silico using windows MOE	Binding energy of – 10.1 kcal/mol	[269]
Luteolin 7-O-β-glucopyranoside (cynaroside), acacetin 7-O-β-rutinoside (linarin) and isoacteoside (isoverbascoside)	*Amphilophium paniculatum* (L.) Kunth (leaves)	SARS-CoV-2 Mpro (7BUY)	In silico using Molecular Operating Environment (MOE) 2019.0102	Energy score of – 9.54, – 8.54, – 8.46 kcal/mol	[270]
Cannabidiol and Δ^9-tetrahydrocannabinol		SARS-CoV-2 (6LU7)	In silico using Autodock and Vina	Binding energy in Autodock is – 10.53 and – 10.42 kcal/mol, while in Vina is – 6.43 and – 7.13 kcal/mol	[257]
Cyanidin, malvidin, pelargonidin, peonidin, petunidin	*Pimpinella anisum* L. (anise)	SARS-CoV-2 3CLpro (6LU7)	In silico using AutoDock Vina	Binding energy: – 8.1; – 8.0; – 8.0; – 7.7; – 7.5 kcal/mol	[271]
Procyanidin b2 and mangiferin	*Chincona pubescenc.* and from mango tree	SARS-CoV-2 3CLpro (6LU7)	In silico using AutoDock Vina	Binding affinity: -9.4 and -8.5 kcal/mol	[272]
Heptafuhalol A		SARS-CoV-2 Mpro (6LU7)	In silico using Vina and Autodock	Average ΔG = – 14.6 kcal/mol	[273]
Oolonghomobisflavan-A		SARS-CoV-2 Mpro (6Y2F)	In silico using GROMACS	Binding free energy on MM-PBSA calculation: -256.875 kj/mol	[274]
Epigallocatechin gallate	Green tea	SARS-CoV-2 Mpro (6LU7), NSP15 endoribonuclease (6VWW), free enzyme Mpro (6Y2E), and 2019-nCoV HR2 domain (6LVN), post fusion core of S2 subunit (6LXT), prefusion spike glycoprotein (6VSB), chimeric receptor-binding domain complexed with hACE2 (6VW1)	In silico using AutoDock	Binding energy (kcal/mol): 6LU7 = – 6.99; 6LVN = – 4.90; 6LXT = – 7.57; 6VSB = – 7.26; 6VWW = – 8.38; 6Y2E = – 9.30; 6VW1 = – 8.66	[275]
Theaflavin digallate		SARS-CoV-2 Mpro (6LU7)	In silico using GLIDE	Docking score: -10.574 kcal/mol	[167]

Table 5 (continued)

Compounds	Plant sources	Antiviral Activities	Assays	IC50/Binding Affinity*	Refs.
Glycyrrhizic acid (GlA) and theaflavin 3,3-digallate (TF3)		SARS-CoV-2 Mpro (6LU7) and ACE2 receptor (IR4L)	In silico using AutoDock Vina	Binding energy to 6LU7: GlA = – 9.3 and TF3 = – 10; and with 1R4L: GlA = – 9.6 and TF3 = – 8.3 kcal/mol	[276]
Theaflavin		SARS-CoV-2 RBD	In silico using SwissDock	Idock score – 7.95 kcal/mol	[277]
Pedunculagin, tercatain, and castalin		SARS-CoV-2 Mpro, catalytic dyad residues: Cys145 and His41 (6Y84)	In silico using MOE 09	S score: – 18.58; – 23.11; and – 14.04	[166]
Hypericin, Amentoflavone, terflavin	*Hypericum perforatum* L. *and Terminalia chebula* Retz. or *T. catappa* L	SARS-CoV-2 Mpro (6LU7)	In silico using AutoDock Vina	Binding energy: – 10.4, – 9.7 and – 9.7 kcal/mol	[164]
Eriodictyol-7-O-rutinoside, narirutin	Flavanone glycoside in lemon and sweet orange	SARS-CoV-2 RdRp protein sequence (YP_009725307.1)	In silico using AutoDock Vina	Binding energy: -9.9 and -9.7 kcal/mol	[164]
Cis-miyabenol C	*Foeniculum vulgare Mill. (fennel)*	SARS-CoV-2 human transmembrane serine protease 2 (TMPRSS2: sequence NP_001128571.1)	In silico using AutoDock Vina	Binding energy: -9.4 kcal/mol	[164]
Ellagic acid	*Prunica granatum*	SARS-CoV-2 Mpro (6LU7)	In silico using AutoDock Vina	Binding affinity and IC: – 8.4 kcal/mol and 0.7 μM	[193]
5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone Myricitrin Methyl rosmarinate	*Psorothamnus arborescens* *Myrica cerifera* *Hyptis atrorubens* Poit	SARS-CoV-2 3CLpro (PMDB ID PM0082635)	In silico using MOE	Binding affinities: – 29.57 – 22.13 – 20.62	[278]
Agathisflavone		SARS-CoV-2 Mpro (pdb id: 6LU7)	In silico using AutoDock 4.1	Binding energy: – 8.4 kcal/mol	[173]
Albireodelphin		SARS-CoV-2 RdRp (pdb id: 6M71) and spike protein (pdb id: 6VW1)	In silico using AutoDock 4.1	Binding energy: – 9.8 and – 11.2 kcal/mol	[173]
Inophyllum G2		SARS-CoV-2 Mpro (pdb id: 6LU7)	In silico using AutoDock Vina	Docking score: – 8.8 kcal/mol	[176]
Daphnorin		SARS-CoV-2 viral methyltransferase (nsp16/10 complex, pdb id: 6W4H) and RBD (pdb id: 6M0J)	In silico using AutoDock Vina	Docking scores: – 9.8 and – 8.2 kcal/mol	[176]
Isodispar B and daphnogirin		SARS-CoV-2 hACE2 (pdb id: 6VW1)	In silico using AutoDock Vina	Docking score: – 8.0 kcal/mol	[176]
Isorhamnetin-3-*O*-rutinoside (narcissin)	*Salvadora persica* L	SARS-CoV-2 Mpro (pdb id: 6LU7)	In silico using AutoDock	Binding energy:– 8.2530 kcal/mol	[279]
Acetoside	(polyherbal formulation	SARS-CoV-2 Mpro (pdb id: 6LU7)	In silico using iGEMDOCK	Binding energy: – 153.06 kcal/mol	[280]
Demethyloleuropein		SARS-CoV-2 Mpro (pdb id: 6LU7)	In silico using AutoDock Vina	Binding energy: -8.90 kcal/mol IC_{50} prediction: 11.58 μM	[177]
Nuzhenide oleoside		SARS-CoV-2 S protein (pdb id: 6LZG)	In silico using AutoDock Vina	Binding energy: – 8.90 kcal/mol. IC_{50} prediction: 6.44 μM	[177]
Myricitrin Quercetin-3-O-glucuronide	*Phyllanthus amarus*	SARS-CoV-2 Mpro (pdb id: 6LU7)	In silico using AutoDock Vina	Binding affinity: – 9.6 kcal/mol, and – 9.4 kcal/mol	[281]
Isorhamnetin-3-O-rutinoside (narcisin)	*Salvadora persica*	SARS-CoV-2 Mpro (pdb id: 6LU7)	In silico using AutoDock Vina	Docking score: – 8.2530 kcal/mol	[279]

* **IC_{50}** (mg/mL and mM): the concentration of particular compound or drug in inhibiting the biological process to half of the maximum. Docking score (kcal/mol): a computational result for particular program and energy to allow in predicting binding free energy and binding affinity, or ranking the complex of ligand and receptor according to specific parameters. Binding affinity (kcal/mol): an expression of the degree of ligand binding with the protein in complex formation. Binding energy (kcal/mol): the energy released due to the bond formation or the interaction of the ligand and protein which is calculated as a sum of all the intermolecular interactions presented in the complex

to demonstrate its anti-influenza activity against PR8 (H1N1), X31 (H3N2), and H5N1 [221].

Dietary intake of polyphenols at high concentrations also regulates ACE2 expression and function, by acting as an antioxidant. Calceolarioside B is an active compound found in *Akebia trifoliata* fruit, which has been suggested as a potential dietary treatment for COVID-19 patients due to its various health benefits, including antimicrobial and anti-inflammatory effects [284]. This caffeic acid derivative is also present in other plants such as *Stauntonia hexaphylla* (leaves), *Scutellaria galericulata* L. (aerial parts), *Forsythiae Fructus* (fruit), and *Mimulus guttatus* (seeds) [285–288]. Figure 8 shows that active phenolic compounds, such as quercetin and vitamin C, have a synergistic effect as adjuncts in treating COVID-19 [289].

Based on this reasoning, it becomes evident that exploring the antioxidant potential of natural phenolic extracts, as well as other forms such as food-based extracts and polyphenol-containing functional foods or nutraceuticals [290–292], can be valuable in managing severe COVID-19 cases with inflammatory conditions like cytokine storm. Further discussion about the correlation between the activities of polyphenolic compounds, especially those with flavonoid structures, against the Mpro of SARS-CoV-2 has been elaborated in subchapter 8.

Alkaloid-based secondary metabolites

Alkaloids are a class of organic nitrogenous base compounds that occur naturally in plants, microorganisms,

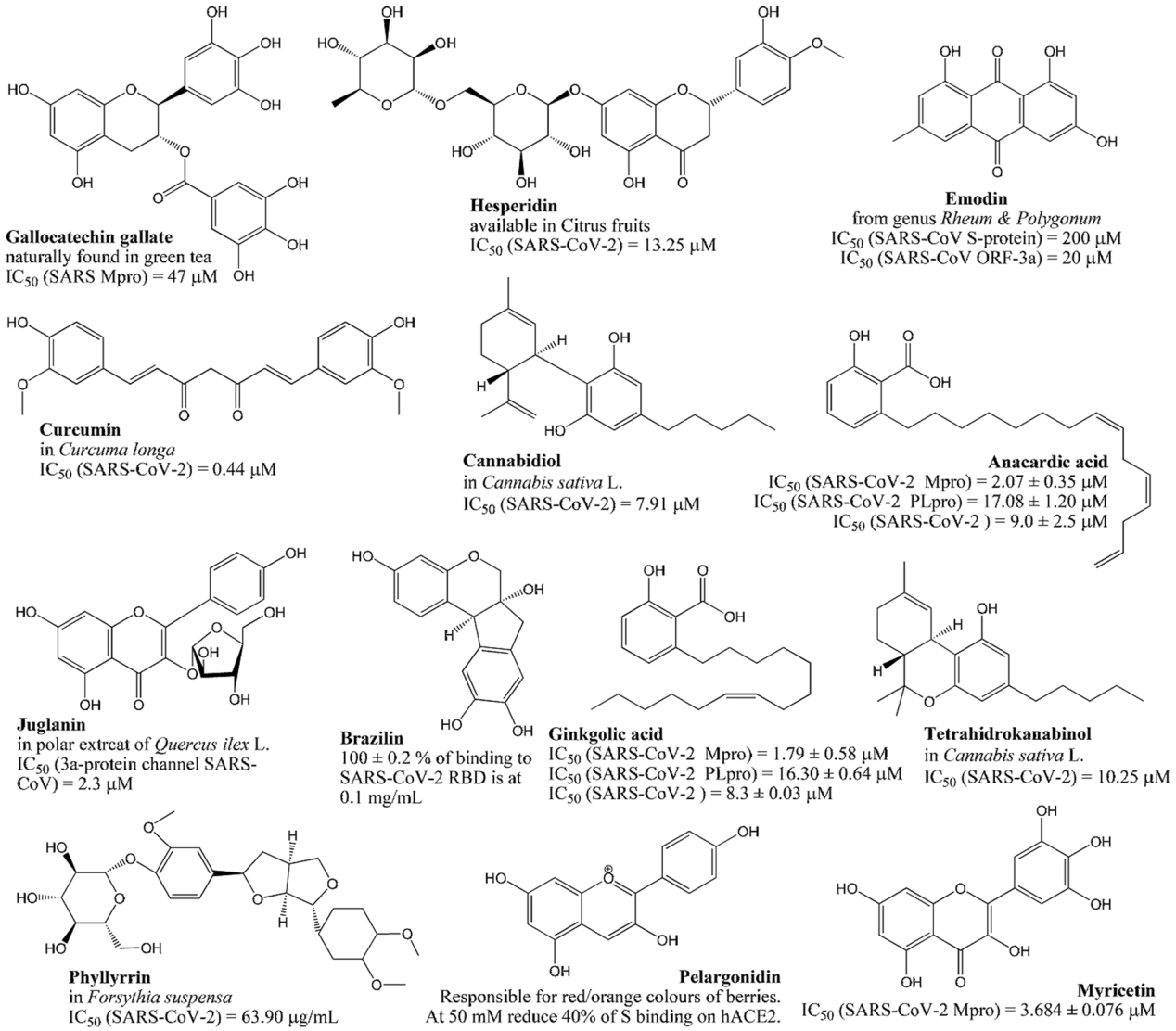

Fig. 8 Structures of some phenolics which have been tested for SARS-CoV-2-related in vitro activities [194, 249, 250, 256–259, 262, 263]

and animals. Their basicity depends on the form of nitrogen they contain, which can be primary, secondary, or tertiary amines. Alkaloids are categorized based on the amino acids that make up their nitrogen content and the structure of their alkaloid skeleton. These secondary metabolites have been found to exhibit a diverse range of biological and pharmacological activities, including antimicrobial, antiparasitic, antiasthma, analgesic, antihyperglycemic, anticancer, psychotropic, and stimulant properties. Some alkaloids have been identified as potential antiviral agents against SARS-CoV-2 through both in silico and in vitro assays, as outlined in Fig. 9, Table 6.

In 1818, quinine was discovered and isolated from *Chincona* bark, which prompted the exploration of other plant alkaloids due to their bioactivities [304]. Recent studies found that quinine exhibited promising activity against SARS-CoV-2 with an effective concentration of EC90 at 38.8 mM [305]. In Northern Chile, *Schizanthus porrigens* Graham, herbaceous species, contains a tropane-derived alkaloid called Schizanthine Z that actively binds to PLpro with docking affinity − 7.5 kcal/mol [168]. Another promising bis-benzylisoquinoline alkaloid, cepharanthine, showed strong activity against SARS-CoV-2 by blocking host Ca + channels and inhibiting virus fusion and entry [306]. Additionally, *Cryptolepis sanguinolenta*, a plant found in West Africa, contains antipathogenic-based alkaloids that could be a promising candidate for SARS-CoV-2 inhibitors [307]. Focus has also been directed to marine products in the search for secondary metabolite contents, particularly alkaloids. Some marine organisms such as sponges from *Cryptotethya crypta*, *Dysidea avara*, *Crambe crambe*, a cyanobacterium from *Nostoc ellipsosporum*, and starfishes from *Fromia monilis* and *Celerina heffernani*, produce a polycyclic guanidine alkaloid skeleton in their secondary metabolites, which act as antiviral agents [190].

The study conducted by Quimque et al. [308] focused on examining 97 antiviral secondary metabolites from fungi. They utilized computational modelling to screen these metabolites and identified Quinadoline B as the top-scoring compound, predicted to exhibit high binding affinity to various proteins associated with SARS-CoV-2, including PLpro, 3CLpro, RdRp, non-structural protein 15 (nsp15), and the spike binding domain to GRP78. Additionally, the ADMET value analysis indicated that quinadoline B is a favourable compound with high absorptive probability in the gastrointestinal tract and low capacity for crossing the blood–brain barrier.

Chowdhury [300] conducted a molecular docking study of five secondary metabolites from *Tinospora cordifolia* (Willd.) Hook.f. & Thomson (*Menispermaceae*) and found that berberine showed the best binding affinity of − 7.3 kcal/mol to 3CLpro of SARS-CoV-2, leading to an inhibition constant of 4.4 μM. Berberine has previously been shown to have antiviral activity against influenza, with a comparable IC50 to the standard drugs oseltamivir [309]. Garg and Roy [302] identified the four best molecules out of twenty antiviral alkaloids for potential scrutiny using Lipinski's rule and docking study based on maximum negative binding energy with Mpro of SARS-CoV-2. Thalimonine, emetine, sophaline D, and tomatidine exhibited binding energies of − 8.39 kcal/mol, − 10.17 kcal/mol, − 8.79 kcal/mol, and − 9.58 kcal/mol, respectively. Thalimonine and sophaline D were recommended for further in vitro studies based on filters, parameters, and mechanisms of virtual bioactivity

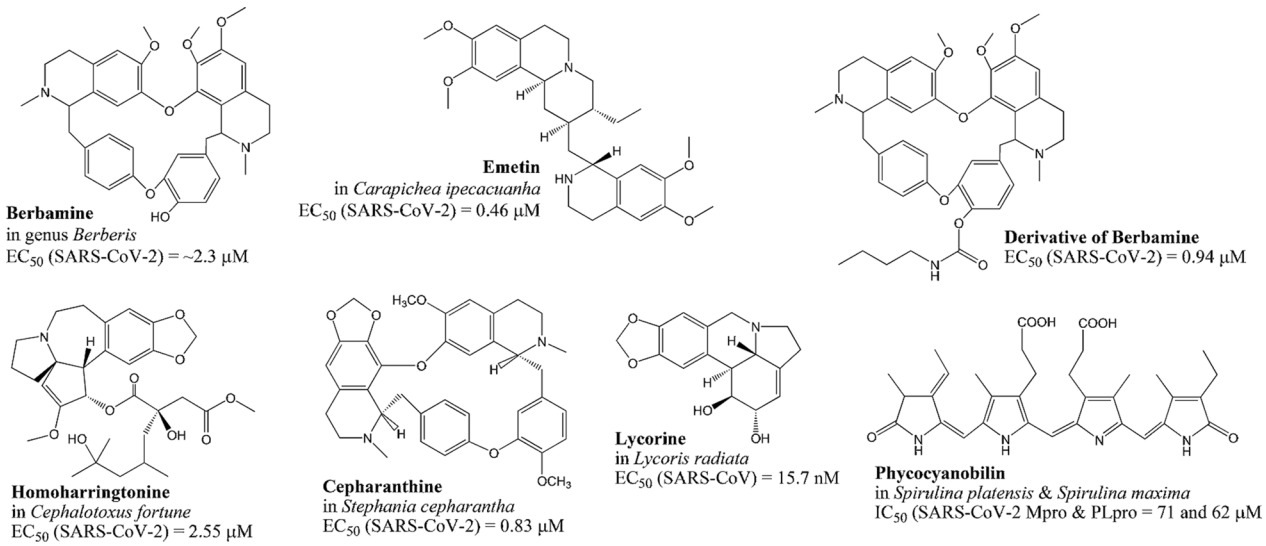

Fig. 9 Some alkaloid structures which have been tested by in vitro and in vivo assays against SARS-CoV-2 proteins [293–296, 298, 305]

Table 6 Potential alkaloid compounds acting as antiviral agents against SARS-CoV-2

Compounds	Plant sources	Antiviral acitivities	Assays	IC_{50}/Binding Affinity*	Refs.
Berbamine	*Berberis*	SARS-CoV-2	In vitro: in Vero cells	EC_{50} = ~ 2.3 mM	[293]
Emetin Homoharringtonine (HHT)	*Carapichea ipecacuanha* and *Cephalotoxus fortune*	SARS-CoV-2 replication step The virus, beta-CoV/Hongkong/VM20001061/2020, was isolated from the nasopharynx aspirate	In vitro: in Vero E6 cells	IC_{50} of emetine and HHT were 0.46 mM and 2.55 mM, respectively A combination of remdesivir at 6.25 mM with emetine at 0.195 mM resulted in 64.9% inhibition in viral yield	[294]
Berbamine (BE12) Derivate of berbamine (BE33)		SARS-CoV-2 envelope protein containing ion permeable channels that regulates electrolyte balance, including potassium, sodium and calcium concentration in serum	In vitro: in Vero E6 cells and other 13 cell lines In vivo: BE-33 was injected into mice, which significantly reduced cytokine secretion	IC_{50} of BE12 and BE33 as: an inhibitor of envelope channels: 111.50 mM and 5.79 mM antivirus; 14.50 mM and 0.94 mM. Selection index of BE12 and BE33: 2.06 and 33.47	[295]
Isolated lycorine EC50 = 15.7 ± 1.2 nM; selective index (SI) > 900	*Lycoris radiata* (steam cortex) *Artemisia annua* (whole plant) *Pyrrosia lingua* (leaf) *Lindera aggregata* (root)	SARS-CoV strain BJ001	In vitro: 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium inner salt (MTS) assay for virus-induced cytopathic effect (CPE)	*L. radiata* extract (EC_{50} = 2.4 mg/mL; SI = 370) *A. annua* extract (EC_{50} = 34.5 mg/mL; SI = 31) *P. lingua* extract (EC_{50} = 43.2 mg/mL; SI = 55) *L. aggregata* extract (EC_{50} = 88.2 mg/mL; SI = 16)	[296]
Phycocyanobilins	*Spirulina platensis* and *Spirulina maxima* [297]	SARS-CoV-2 Mpro and PLpro	In vitro using FRET-based cleavage assay with SARS-CoV-2 Mpro and PLpro	IC_{50} with Mpro and PLpro is 71 mM and 62 mM	[298]
Chloroquine	The bark of *Cinchona* tree	nCoV-2019BetaCoV/Wuhan/WIV04/2019	In vitro using qRT-PCR and immunofluorescence microscopy in Vero E6 cells	EC_{50} = 1.13 µM; CC_{50} > 100 µM, SI > 88.50	[299]
Berberine Beta-sitosterol Octacosanol Tetrahydropalmatine Choline	*Tinospora cordifolia*	3CLpro of SARS-CoV-2	In silico with ligand (6LU7)	Binding affinities in order: − 7.3; − 7.1; − 6.6; − 6.4; − 3.4 kcal/mol Inhibition constant in order; 4.4 × mM; 6.16 × mM; 1.43 × mM; 2.01 × mM; 3.2 × mM	[300]
Schizanthine Z	*Schizanthus porrigens*	PLpro (6WX4) of SARS-CoV-2	In silico using Autodock Vina and PyRx with a ligand of 6WX4	Binding affinity: − 7.5 kcal/mol	[168]
Caffeine and nicotine		Active sites of the S protein in SARS-CoV-2	In silico using AutoDock v4.2 package with a ligand of 6LZG and 6VW1	Binding energy: Nicotine + favipiravir + CTD-ACE2 = − 7.13 kcal/mass Caffeine + ribavirin + RBD-ACE2 = − 6.76 kcal/mol	[301]
Thalimonine Sophaline D Tomatidine Emetine		Mpro of SARS-CoV-2	In silico using AutoDock	Binding energy in order: − 8.39; − 8.79; − 9.58; − 10.17 kcal/mol Inhibition constant in order: 0.706 mM; 0.36266 mM; 0.09544 mM; 0.03535 mM	[302]

Table 6 (continued)

Compounds	Plant sources	Antiviral acitivities	Assays	IC_{50}/Binding Affinity*	Refs.
Phycocyanobilins		SARS-CoV-2 Mpro (6LU7) and PLpro (6WUU)	In silico using AutoDock Vina	Binding energy of Mpro and PLpro is − 8.6 and − 9.8 kcal/mol	[298]
Bismahanine	*Murraya koenigii* (L.) Spreng (leaves)	SARS-CoV-2 spike protein (6M0J)	In silico using AutoDock Vina	Binding energy: − 9.1 kcal/mol	[164]
Quinine	The bark of *Cinchona* tree	SARS-CoV-2 Mpro (pdb id: 6m0k)	In silico using	Binding energy: − 6.2 kcal/mol	[303]

* **IC_{50}** (mg/mL and mM): the concentration of particular compound or drug in inhibiting the biological process to half of the maximum. Docking score (kcal/mol): a computational result for particular program and energy to allow in predicting binding free energy and binding affinity, or ranking the complex of ligand and receptor according to specific parameters. Binding affinity (kcal/mol): an expression of the degree of ligand binding with the protein in complex formation. Binding energy (kcal/mol): the energy released due to the bond formation or the interaction of the ligand and protein which is calculated as a sum of all the intermolecular interactions presented in the complex

against Mpro of COVID-19. Various alkaloids derived from plants have been shown to have potent antiviral activity against various viruses, including coronavirus, as listed by Majnooni et al. [305] and Topcu et al. [304].

Terpenoid and its derivatives

Terpenoids are a diverse group of natural products that are derived from isoprene (1,3-butadiene) units. They are formed by combining carbon skeletons from other acetate and shikimate pathways such as steroidal saponins, cardioactive glycosides, and phytosterols. Terpenoids have many essential applications in the fields of medicine, cosmetics, and food industries. This group of secondary metabolites exhibits biological activities, including antitumor, anti-inflammatory, antibacterial, antiviral, antimalarial, and antidiabetic activities [310]. Some terpenoids have also been studied for their potential bioactivity against SARS-CoV-2 and illustrated in Fig. 10, Table 7.

Tetraterpenes, particularly astaxanthin from the carotenoid class, have been extensively discussed for their potential as an adjunctive supplement in COVID-19 [314]. Triterpene glycosides, such as saikosaponins A, B, C, and D, which can be isolated from *Heteromorpha* spp., *Bupleurum* spp., and *Scrophularia scorodonia*, have demonstrated antiviral activity against HCoV-22E9 [93]. Another saponin, 3-beta-O-(alpha-L-rhamnopyranosyl-(1- > 2) alpha-L-arabino pyranosyl)olean-12-ene-28-O-(alpha-L-rhamnopyranosyl-(1- > 4)-beta-D-glucopyranosyl-(1- > 6)-beta-D-glucopyranosyl) ester, isolated from leaves and stems of *Oreopanax guatemalensis* [315], exhibited the highest binding energy to interact with SARS-CoV-2 S-RBD compared to other terpenes using computer-based molecular simulation [316]. Li et al. [296] reported that extracts from *Artemisia annua*, *Lycoris radiate*, *Pyrrosia lingua*, and *Lindera agregata* were practical for anti-SARS-CoV screening analysis. The aqueous extract of *Houttuynia cordata* showed inhibition of viral 3CL protease and blockade activity of viral RNA-dependent RNA polymerase in SARS-CoV [317].

Glycyrrhizin, also known as glycyrrhizic acid, is a type of terpenoid saponin that is commonly extracted from the roots (*Glycyrrhizae radix rhizoma)* of glycyrrhiza plants, including *Glycyrrhiza glabra* L. and licorice root [251, 328]. The primary compound of glycyrrhizin is a triterpene glycoside, with its aglycone being 18b-glycyrrhetinic acid [329]. Due to its mode of action and characteristics, glycyrrhizin has the potential to be utilized as an anti-SARS-CoV-2 agents [251, 330]. In a case report of a non-hospitalized COVID-19 patient who took diammonium glycyrrhizinate, Ding et al. [331] stated that immune regulation against cytokine storm had improved, and inflammation was reduced.

Derivatives of glycyrrhizin, including the amide form, have been shown to exhibit higher anti-SARS-CoV activity than glycyrrhizin itself. This is due to the addition of amino acid residues on the glycoside part, while preserving the free -COOH function in C30, which appears to be crucial for the anti-SARS-CoV effect [332]. In vitro experiments on antiviral activity of aqueous licorice root extract containing glycyrrhizin against SARS-CoV-2 in Vero E6 cells have demonstrated that glycyrrhizin blocks SARS-CoV-2 replication by inhibiting Mpro, [252].

Terpenoids, specifically monoterpenes and sesquiterpenes, are highly active compounds that may interact more rapidly with the primary site of infection in COVID-19 patients when delivered via aerosol delivery systems such as nebulizers and inhalers. This form of drugs delivery is preferred over oral administration as it allows for direct entry of the terpenoids through the respiratory tract, which increases their bioavailability [255]. The aerosol form of terpenoids contains essential oils, which are volatile oils obtained from different parts of plants including leaves, fruit, flowers, bark, and roots using various extraction methods. Essential oils are classified as terpenoids because they predominantly contain monoterpenes and sesquiterpenes, rather than derivatives of phenyl, propanoid, and aromatic compounds.

According to Javed et al. [333], carvacrol, a phenolic monoterpene found in thyme and oregano, has demonstrated therapeutic properties against various viral diseases such as HSV type 1, bovine diarrhea virus, respiratory syncytial virus, and murine norovirus in vitro. It was proposed that carvacrol could also have potential mechanisms of action against SARS-CoV-2, the virus responsible for COVID-19. Specifically, carvacrol may interfere with ACE2 receptors in host cells, leading to protective effects against inflammation, and potentially hinder the virus's interaction with viral proteases during infection.

Essential oils derived from medicinal plants and their food matrices contain volatile compounds that can be quickly released, making them highly therapeutically potent compared to the original plants or herbs [334]. These essential oils can easily enter the body through inhalation and reach the bloodstream due to their high volatility. However, it is important to assess the duration of essential oil diffusion to ensure that it is safe to inhale and maintain indoor air quality [335].

Boukhatem (2020) conducted a literature review of published study articles and reported antiviral activities of essential oils and isolated compounds. The potential of essential oils from aromatic plants as antiviral compounds against coronavirus have also been explored [3, 207, 336]. Adorjan and Buchbauer [337], as well as Ojah [338], have listed essential oils with antiviral activities

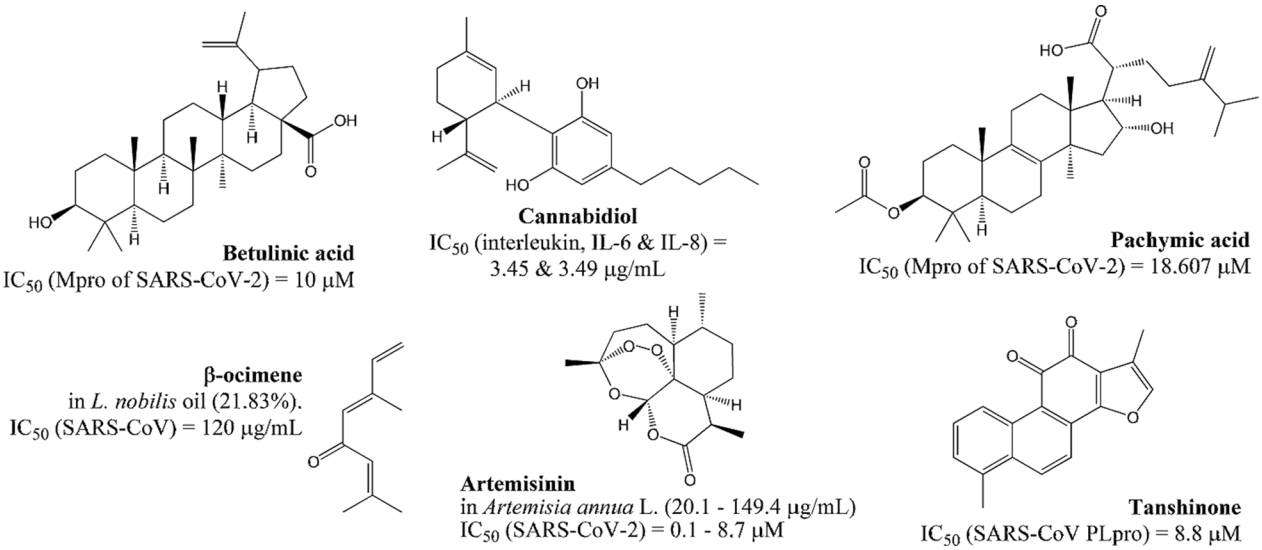

Fig. 10 Chemical structures of terpenoids with their bioactivities against SARS-CoV-2 proteins [95, 101, 311–313]

against human-targeting viruses. Using essential oils as a therapeutic antiviral intervention is a safe alternative due to their natural extract origin. Essential oils directly act on enveloped viruses, such as HSV type-1 and type-2, by binding to viral envelopes and glycoproteins. The plaque development assay supported this statement and showed that essential oils reduced viral load significantly during contact with virions before the adsorption process or during the pre-treatment step, but not when used before HSV-1 and HSV-2 adsorption and attachment [339, 340]. Time-of-addition experiments concluded that essential oils blocked virus adsorption [341]. Thymoquinone and black seed fixed oil were also found to be positively active against avian influenza virus (H9N2) and MCMV infection model 36. *Pelargonium sidoides*, extracted herbal products, has been licensed and marketed for patients with acute bronchitis, reducing rhinovirus infection and interfering with the reproduction of multiple respiratory viruses [163–165].

Essential oils are edible, but their potential toxicity requires caution when ingesting orally. The non-polar properties of essential oils make them easily permeable through skin membranes, leading to whole-body healing. As a result, essential oils can activate specific brain regions, influencing the hypothalamus and providing pain relief, mood enhancement, and improved cognitive function [334]. Due to concerns about their bioavailability, essential oils are recommended for topical application to the skin. Their lipophilic nature enables them to easily penetrate the skin and disrupt the virion envelope, inhibiting host cell attachment. Several essential oils with virucidal activity, such as lemongrass (Cymbopogon citratus) [342], lemon balm (*Melissa officinalis*) [343], peppermint [341], dwarf lavender cotton (*Santolina insularis*) [339], ginger (*Zingiber officinale*), thyme (*Thymus vulgaris*), hyssop (*Hyssopus officinalis*), and sandalwood (Santalum album) [340], have been identified. Table 7 highlights some potential essential oils and common terpenoids with activity against SARS-CoV-2.

The efficacy of natural plant essential oils in reducing virus titers ($TCID_{50}$) against non-enveloped viruses at different temperatures and times was found to be insignificant. Several previous studies have investigated the impact of essential oils on non-enveloped viruses, such as norovirus, rotavirus, adenovirus, and HPV. For instance, Kovac et al. [344] examined the effect of *Hyssopus officinalis* and *Thymus mastichina* essential oils against murine norovirus (MNV-1) and human adenovirus serotype 2 (HAdV-2). Garozzo et al. [345] investigated *Melaleuca alternifolia* essential oil (tea tree oil, TTO) against polio type 1, ECHO 9, and Coxsackie B1. While Cermelli et al. Evaluated eucalyptus oil against adenovirus. In all of these [344, 346], essential oils were unable to mask non-enveloped viruses, indicating that they may not be a viable option for reducing foodborne viruses in the food industry. Conversely, essential oils have shown significant virucidal activity against enveloped viruses due to their ability to disrupt the virus's enveloped proteins and interaction with host cells. Jackwood et al. [347] reported that QR448(a), a blend of botanical oleoresins and essential oils developed by Quigley Pharma, Inc., exhibited virucidal effects against avian infectious bronchitis virus (IBV) in Vero E6 cells, embryonated eggs, and chickens by reacting before virus attachment and entry.

Table 7 Derivates of terpenes potentially act as antiviral agents

Compound/Extract	Plant sources	Antiviral activities	Assays	Activity*	Refs.
Black seed oil (BSO) or habatus-saudah	*Nigella sativa*	Murine cytomegalo virus	In vivo using a viral plaque-forming assay of BALB/c mice spleen and liver	Undetected virus at the ratio of the effector to target cells was 20:1	[99]
Manuka oil		HSV	In vitro using a plaque reduction assay on RC-37 cells (monkey kidney cells)	IC_{50} = 0.96 mg/mL	[318]
Laurus nobilis oil containing β-ocimene, 1,8-cineole, α-pinene, β-pinene	*Laurus nobilis*	SARS-CoV (isolate FFM-1 from Germany)	In vitro using visually scoring of the virus-induced cytopathogenic effect (CPE) for 48 h post-infection on Vero cells	IC_{50}:120 mg/mL; SI of 4.16	[101]
Ethyl acetate and methanol extracts of aerial parts of *D. virgatus*	*Daucus virgatus (Poir.) Maire*	Coxsackievirus B (CV-B)	In vitro using plaque reduction assay on Hep-2 cell line	IC_{50} ethylacetate and methanol extracts = 98.16 and 60.08 mg/mL	[319]
Ethanol extracts	*Mentha piperita* *Desmodium canadense* *Thymus vulgaris*	Avian infectious bronchitis virus (IBV)	In vitro using plaque reduction assay on Vero cells	TCID = 1.83 ± 0.31–3.45 ± 0.21 log_{10} EC_{50} = 0.003–0.076 mg	[320]
Betulinic acid		SARS-CoV 3CL pro	In vitro using FRET method	IC_{50} 10 mM	[95]
The fraction containing high of cannabidiol (F_{CBD})	*Cannabis sativa* strain Arbel	Interleukin: IL-6 dan IL-8	In vitro using enzyme-link immunosorbent assay on A549 cells	IC_{50} of 3.45 and 3.49 mg/mL	[311]
Artemisinin content	*Artemisia annua* L. (dried leaves)	SARS-CoV-2 USA/WA1	In vitro using cytophatic effect assay on Vero E6 cells infected by SARS-CoV-2	IC_{50} of 0.01–0.14 mg	[313]
Cryptotanshinone	*Salvia miltiorrhiza*	SARS-CoV PLpro	In vitro using proteolysis of the fluorogenic substrate	IC_{50} = 0.8 ± 0.2 μM	[321]
Dihydrotanshinone I	*Salvia miltiorrhiza*	SARS-CoV Mpro	In vitro using proteolysis of the fluorogenic substrate	IC_{50} = 14.4 ± 0.7 μM	[321]
Pachymic acid	Dried sclerotia of *Poria cocos (Schw.)*. Wolf	SARS-CoV-2 Mpro recombinant	In vitro using the fluorogenic substrate for inhibition assay	IC_{50}: 18.607 μM	[312]
Garlic essential oil containing 17 organosulfurs		ACE2 protein and main protease of SARS-CoV-2	In silico using MOE 2015.10 on ACE2 protein and 6LU7 (Mpro)	ACE2: diallyl tetrasulfide and allyl disulfide − 14.06 and − 12.84 kcal/mol Mpro: Allyl disulfide and allyl trisulfide − 15.32 and − 15.02 kcal/mol	[322]

Table 7 (continued)

Compound/Extract	Plant sources	Antiviral activities	Assays	Activity*	Refs.
β-farnesene α-farnesene farnesol α-bulnesene		SARS-CoV-2: Mpro (main protease), Nsp15/NendoU (endoribonucleoase), ADRP (ADP-ribose-1′′-phosphatase), rS (binding domain of the SARS-CoV-2 spike protein), RdRp (RNA-dependent RNA polymerase), and hACE2 (human angiotensin-converting enzyme)	In silico using Molegro Virtual Docker v. 6.0.1 on SARS-CoV-2 Mpro (5R7Z, 5R80, 5R81, 5R82, 5R83, 5R84, 6LU7, 6M03, 6Y84), Nsp15/NendoU (6VWW, 6W01, 6W02), rS (6M0J, 6M17, 6VX1, 6VW1), RdRp (6M71)	Docking Score (DS) SARS-CoV-2 Mpro = (*E*)-β-farnesene – 115.4 kJ/mol SARS-CoV Nsp15/NendoU = (*E*,*E*)-alpha-farnesene -107.5 kJ/mol SARS-CoV-2 ADRP = (*E*)-β-farnesene -116.3 kJ/mol SARS-CoV-2 RdRp = (*E*,*E*)-farnesol -89.6 kJ/mol hACE2 = alpha-bulnesene < -100 kJ/mol	[207]
Eucalyptol (1,8-cineole) in eucalyptus oil		MPro/3CLpro of SARS-CoV-2	In silico using 1-click dock and swiss dock tools	DS = – 4.2 ΔG = – 6.04 kcal/mol	[323]
Jensenone in eucalyptus oil		MPro/3CLpro of SARS-CoV-2	In silico using 1-click dock and swiss dock tools	DS = – 5.5 ΔG = – 6.03 kcal/mol	[205]
Cuminal Carvacrol Myrtanol Pinocarveol		Receptor binding domain (RBD) of the S1 glycoprotein (residues 319–541)	In silico using AutoDock Vina on RBD of SARS-CoV-2 S1 subunit (6M07)	Binding affinity (kcal/mol): Cuminal – 4.9 Carvacrol – 4.9 Myrtanol – 5.3 Pinocarveol -5.0	[324]
Lauruside 5	*Laurus nobilis*	SARS-CoV-2	In silico using 1-Click Mcule on SARS-CoV-2 Mpro (6YB4)	Binding energy – 8.2 kcal/mol	[325]
Tanshinone I		SARS-CoV PLpro	In silico using Gold software with PLpro (6WX4)	IC_{50} of 8.8 mM	[92]
3-β-O-(α-L-rhamnopyranosyl-(1- > 2) α-L-arabinopyranosyl) olean-12-ene-28-O-(α-L-rhamnopyranosyl-(1- > 4)-β-D-glucopyranosyl-(1- > 6)-β-D-glucopyranosyl)ester		SARS-CoV-2 S-RBD	In silico using Autodock Vina with ligand 6LZG	IC_{50} of – 11 kcal/mol	[316]
Limonin and scopadulcic acid B	*Dictamus dasycarpus*, and *Citrus orange*	SARS-CoV-2 RdRp (6M71), hACE2 (6M1D), and Spike glycoprotein (2GHV)	In silico using Autodock 4.2	The docking score of limonin against RdRp, hACE2, and spike protein is – 9.0, – 8.9, and – 8.4. While docking score of scopadulcic acid B is – 8.6, – 8.2, and – 8.8	[192]
Carvacrol, anethol, cinnamyl acetate		SARS-CoV-2 RBD S1 subunit of S glycoprotein (6M0J)	In silico using AutoDock Vina	Binding affinities of three of them were – 5.2. kcal/mol	[326]
Coagulin N	*Withania coagulans* (Stocks) Dunal	SARS-CoV-2 spike protein (6M0J)	In silico using AutoDock Vina	Binding energy: – 9.1 kcal/mol	[164]
Glycyrrhizic acid	*Glycyrrhiza glabra* L. (liquorice roots)	SARS-CoV-2 TMPRSS2 (sequence NP_001128571.1)	In silico using AutoDock Vina	Binding energy: – 9.5 kcal/mol	[164]
Glycyrrhizin	*Glycyrrhiza glabra L*	SARS-CoV-2 spike RBD (6M0J)	In silico using AutoDock 4.2	Binding affinity: – 9.47 kcal/mol	[175]

Table 7 (continued)

Compound/Extract	Plant sources	Antiviral activities	Assays	Activity*	Refs.
Ashwagandhanolide, withacoagin, withaferin, and withanone	Ayurveda botanical: *Withania somnifera* (roots)	SARS-CoV-2 Mpro (5R84)	In silico using AutoDock 4.2.6	Docking score: − 9.9, and three other withanolide are − 8.8	[236]
Ashwagandhanolide, withacoagin, 27-hydroxywithanone	Ayurveda botanical: *Withania somnifera* (roots)	SARS-CoV-2 RBD spike glycoprotein (6M17)	In silico using AutoDock 4.2.6	Docking score: − 10, and two others are − 7.6	[236]
Ashwagandhanolide, muzanzagenin	Ayurveda botanical: *Withania somnifera* (roots)	SARS-CoV-2 RdRp (6M71)	In silico using AutoDock 4.2.6	Docking score: − 10.2 and − 9.3	[236]
Arjunic acid, theasapogenol B, euscaphic acid	*Terminalia arjuna* *Camelia sasanqua* *Folium eriobortryde* and *Geum japonicum*	SARS-CoV-2 Mpro (6LU7)	In silico using Autodock Vina	Binding affinities and inhibition constants: − 8.1 kcal/mol and 1.16 μM − 8.1 kcal/mol and 1.16 μM − 8.0 kcal/mol and 1.37 μM	[193]
Crocin, digitoxigenin, β-eudesmol,	*Crocus sativus* L *Nerium oleander* *Lauris nobilis* L	SARS-CoV-2 Mpro (6LU7)	In silico using Autodock 1.5.4	Binding energies: − 8.2, − 7.2, − 7.1 kcal/mol	[327]
Calendulaglycoside A	*Calendula officinalis* L	SARS-CoV-2 Mpro (6LU7)	In silico using MOE 2019 Suite	Binding-free energy: − 72.14 ± 38.78 kJ/mol	[174]

* IC_{50} (mg/mL and mM): the concentration of particular compound or drug in inhibiting the biological process to half of the maximum. Docking score (kcal/mol): a computational result for particular program and energy to allow in predicting binding free energy and binding affinity, or ranking the complex of ligand and receptor according to specific parameters. Binding affinity (kcal/mol): an expression of the degree of ligand binding with the protein in complex formation. Binding energy (kcal/mol): the energy released due to the bond formation or the interaction of the ligand and protein which is calculated as a sum of all the intermolecular interactions presented in the complex

Antiviral mechanism of essential oils may be useful in inhibiting SARS-CoV-2 when the virus has structural similarities to other viruses. One such virus is HSV, an enveloped virus similar to SARS-CoV-2. Eugenol, extracted from *Eugenia caryophyllus* (Spreng.) Bullock & S.G. Harrison, was found to inhibit the replication of HSV standard strains [84] in HSV-1 and HSV-2 viruses [348] and delay the development of herpetic keratitis in HSV-1-infected mice. However, due to its stability concerns, eugenol is better suited for topical treatment rather than internal use. Eugenol in *Syzygium aromaticum* extract has also been evaluated for its ability to inhibit the replication of hepatitis C virus [220]. Another essential oil component, isoborneol from *Salvia fruticosa*, has dual viricidal activity against HSV-1, and inhibits virus replication and viral glycosylation at a concentration of 0.06%. Inactivation of the virus by isoborneol may lead to the interaction of the alcoholic moiety of isoborneol and the lipid in the virus envelope. Clove (*S. aromaticum* L.) has been reviewed as a potential therapeutic agents for anti-COVID-19 due to its essential oil content, with eugenol being a major component [349]. Clove extract has been shown to inhibit HCV replication [220] and exhibit chemopreventive activity [350]. This dried flower bud contains approximately 11–20% of the essential oil, while its dried leaves comprise less than 5% of the oil, with eugenol being a major component (70–90%) [350–353]. Eugenine, an isolated compound from *Syzygum aromaticum* extract, also exhibited anti-HSV potential activity [354]. Manuka oil was found to inactivate HSV before entering the cell, and its virucidal activity is believed to be due to the interference of β-triketones and other terpenes in adsorption and entry into host cells [337].

In an evaluation of coronavirus inhibition in HeLa-CEACAM1a cells, ethanol extracts of *Nigella sativa*, *Anthemis hyalina*, and peel of *Citrus sinensis*, which were presumed to contain essential oil compounds, were. Ulasli et al. [79] reported that *A. hyaline* extract molecules have the potential to treat CoV infections. Additionally, Salem and Hossain [99] noted that BSO from *N. sativa* exhibited a remarkable antiviral effect against MCMV infection.

According to Tkachenko's [102], essential oil extracted from the fruit and roots of *Heracleum L.* species (*Apiaceae*) demonstrated a toxicity LD50 of 0.2–0.4 mL against both Influenza Types A and B. The main constituents of these essential oils were found to be octyl acetate and octyl isobutyrate in the seeds, while the fruits contained monoterpenes such as pinene and limonene, as well as complexes of ethers of octyl and hexyl alcohols. The roots, on the other hand, were found to contain pinene, ocimene, and sesquiterpene derivatives. Hayashi et al. [88] reported that cinnamaldehyde, the primary constituent in *Cinnamomi cortex* (*Cinnamomum cassia* Blume), was able to reduce virus yields in the lungs during an infection with lethal influenza virus-induced pneumonia in the airways of mice.

CBD is a compound belonging to the class of cannabinoids and is typically found in *Cannabis sativa*. CBD has a unique chemical structure consisting of terpenes and phenols, which is commonly referred to as a terpenophenolic compound. Recent study by Anil et al. and Raj et al. [257, 311] suggests that CBD, along with other terpenoid and phenolic compounds, may possess potential activity against SARS-CoV-2. CBD has been detected in the blood plasma of healthy patients at concentrations in the nanomolar range when using approved CBD drugs. Conversely, CBD metabolite, 7-hydroxy-cannabidiol (7-OH-CBD), was found to be in the micromolar range. A study conducted on A549 human lung carcinoma cells expressing exogenous human ACE-2 receptor (A549-ACE2 cells) showed that CBD inhibited the replication of SARS-CoV-2 with an EC_{50} of 1.24, while 7-OH-CBD was 3.6 μM. Additionally, oral administration of CBD with a high-fat meal has been shown to increase the presence of 7-OH-CBD in the blood, which could effectively inhibit SARS-CoV-2 infection. Nguyen et al. [355] also found that CBD therapy resulted in a lower rate of testing positive for COVID-19 in patients. Furthermore, Chatow et al. [356] reported that CBD exhibited a synergistic effect on HCoV-229E-infected human lung fibroblasts when combined with the NT-VRL-1 terpene formulation. Current, CBD is available as a mouth spray under the licensed name Nabiximols, which is intended to reduce and relieve respiratory disease-related pain.

A study by Amparo et al. [357] on molecular docking of certain terpenoids and essential oils against SARS-CoV-2 showed satisfactory results. AutoDock Vina was used to investigate some compounds and the results revealed that (*E*)-α-atlantone, 14-hydroxy-α-muurolene, allo-aromadendrene epoxide, amorpha-4,9-dien-2-ol, aristolochene, azulenol, germacrene A, guaia-6,9-diene, hedycaryol, humulene epoxide II, α-amorphene, α-cadinene, α-calacorene, and α-muurolene have the highest binding energy values for PLpro, 3CLpro, S protein, and RdRp, respectively. Similarly, plant secondary metabolites such as bismahanine, eriodictyol-7-O-rutinoside, glycyrrhizic acid, and hypericin showed the highest binding energy against S protein, RdRp, TMPRSS2, and Mpro, respectively.

Antiviral activity of plant secondary metabolites against SARS-CoV-2 has been discussed, along with the various drugs discovery approaches that can be employed. Polyphenols, alkaloids, and terpenoids are some of the secondary metabolite classes that can serve as antiviral agents. Additionally, Machado et al. [358] and Pisoschi

et al. [359] have suggested other secondary metabolites such as polysaccharides, lipids, vitamins, and animal-derived compounds for the modulation of early inflammatory responses in COVID-19 patients.

Structure–activity relationship (SAR)

SAR is a theoretical concept that links chemical molecules structure or structural-related properties to its biological activity or target properties. This model enables the modification of a molecular structure to alter its bioactivity. Essentially, molecules with identical chemical properties that interact and bind with targets similarly will have similar activities. Therefore, SAR approach involves identifying the properties of molecules, such as geometric and electronic properties, solubility, and certain chemical groups, to predict its physicochemical and biological properties in targeting biological targets. SAR model reduces costs, time, and concerns related to toxicity bioassays.

Earlier studies by Mehaney et al. and Mengist et al. [366, 367] have discussed the detailed mechanism for designing inhibitors for SARS-CoV-2. Ye et al.[199] have also proposed a mechanism for inhibiting SARS-CoV-2 Mpro. The focus of this study is on the impact of flavonol structures on the binding affinities of Mpro to SARS-CoV-2, with Fig. 11 providing illustrations of three forms of flavonols with varying hydroxy substituents in the B ring skeleton of flavonol and glycosides.

Quercetin derivatives, with mono- or di-substituents of the glycoside, exhibited high activity against Mpro. Quercetin-3-O-glucuronide **9**, quercetin-3-O-rutinoside (rutin) **12**, and quercetin-3,5-digalactoside **11** had binding affinities to Mpro of -9.4 kcal/mol, − 9.16 kcal/mol, and − 9.6 kcal/mol, respectively, which were higher than quercetin **2** (− 8.47 kcal/mol). This suggests that the presence of glycoside as a substituent on the quercetin skeleton is important for increasing binding affinity to Mpro. Most glycoside compounds have higher bioavailability in the body than aglycon [164]. However, isoquercitrin or isoquercetin **9**, a monosubstituted quercetin glycoside, showed less binding energy than quercetin. The presence of glucose as the glycoside did not improve binding access to Mpro. Similar to quercetin, myricetin derivatives in a glycoside form also showed high binding affinity to Mpro compared to the lead compound, myricetin **3**. Myricetin-3-O-rhamnoside (myricitrin) **13** and myricetin-3-O-rutinoside **14** are two examples of this. However, myricetin itself did not show a good binding affinity to Mpro, and was not ranked highly in previously reported study, with a binding energy of − 7.311 kcal/mol [164].

Myricetin derivatives have also been tested for their binding energy against the RdRp of SARS-CoV-2, and it has been found that myricetin-3-O-rutinoside (− 9.5 kcal/mol) has a lower binding energy compared to myricetin (− 8.4 kcal/mol). Myricetin has shown promising activity against Mpro in vitro, with an IC_{50} of 3.684 μM [262]. Therefore, it is expected that myricetin derivatives would exhibit better bioactivity against Mpro of SARS-CoV-2 based on in vitro and in vivo analysis.

Kaempferol **1**, quercetin **2**, and myricetin **3** are known structurally similar flavonols, differing only by the presence of hydroxy substituents at positions 3′ and 5′. Based on in silico analysis of their binding energy with Mpro, their relative binding energy values are comparable. The number of hydroxyl substituents on the B ring does not significantly affect their binding activity against Mpro, as they show similar binding activity values of around − 8.4 to − 8.5 kcal/mol, with critical energy data from other literature ranging from − 7.307 kcal/mol [362] to − 9.5 kcal/mol [164]. Quercetin **2** has been identified as crucial molecules [155] in the prophylaxis and treatment of COVID-19 patients due to its anti-inflammatory activity against cytokine storm during severe inflammation. Meanwhile, kaempferol derivatives, such as rhamnoside **4** and glucuronide **5** glycosides, exhibit higher binding affinities to Mpro (− 8.8 and − 9.1 kcal/mol, respectively) than the lead compound kaempferol (− 8.58 kcal/mol). The presence of two di-rhamnosides in the kaempferol skeleton at positions 3 and 7, as kaempferitrin **7**, shows lower binding affinity to Mpro compared to kaempferol.

Based on the previous discussion, the optimal position for the hydroxy group on the B ring of the flavonol skeleton is on the para-substituted benzene ring, as shown in Fig. 12. The meta-position of the hydroxyl substituent does not significantly impact the binding energy, especially when comparing kaempferol **1**, quercetin **2**, and myricetin **3**. When a glycosylated hydroxyl position is present on carbon number 3, compounds 4, 5, 6, 9, 10, 12–15 exhibit better binding affinity against Mpro than the original compounds or aglycon (1, 2, 3). An interesting observation is that compounds 7 and 11 have di-glycosides in their flavonol skeleton, but at different positions. While kaempferitrin 7 has two sugar moieties at positions 3 and 7, which reduces its binding energy against Mpro compared to the aglycon, kaempferol, quercetin-3,5-digalactoside 11 comprises two sugar moieties at positions 3 and 5, enabling it to bind better to the active site of Mpro than its aglycon, quercetin 2. The type of sugar presented as glycosides in molecules is presumed to influence molecules bioactivity against Mpro, with glucuronic acid, rhamnose, and rutinose enhancing and facilitating the binding affinity against Mpro, while glucose does not. This SAR between flavonol derivatives and Mpro may serve as the foundation for the development of a novel drugs compound against Mpro of SARS-CoV-2.

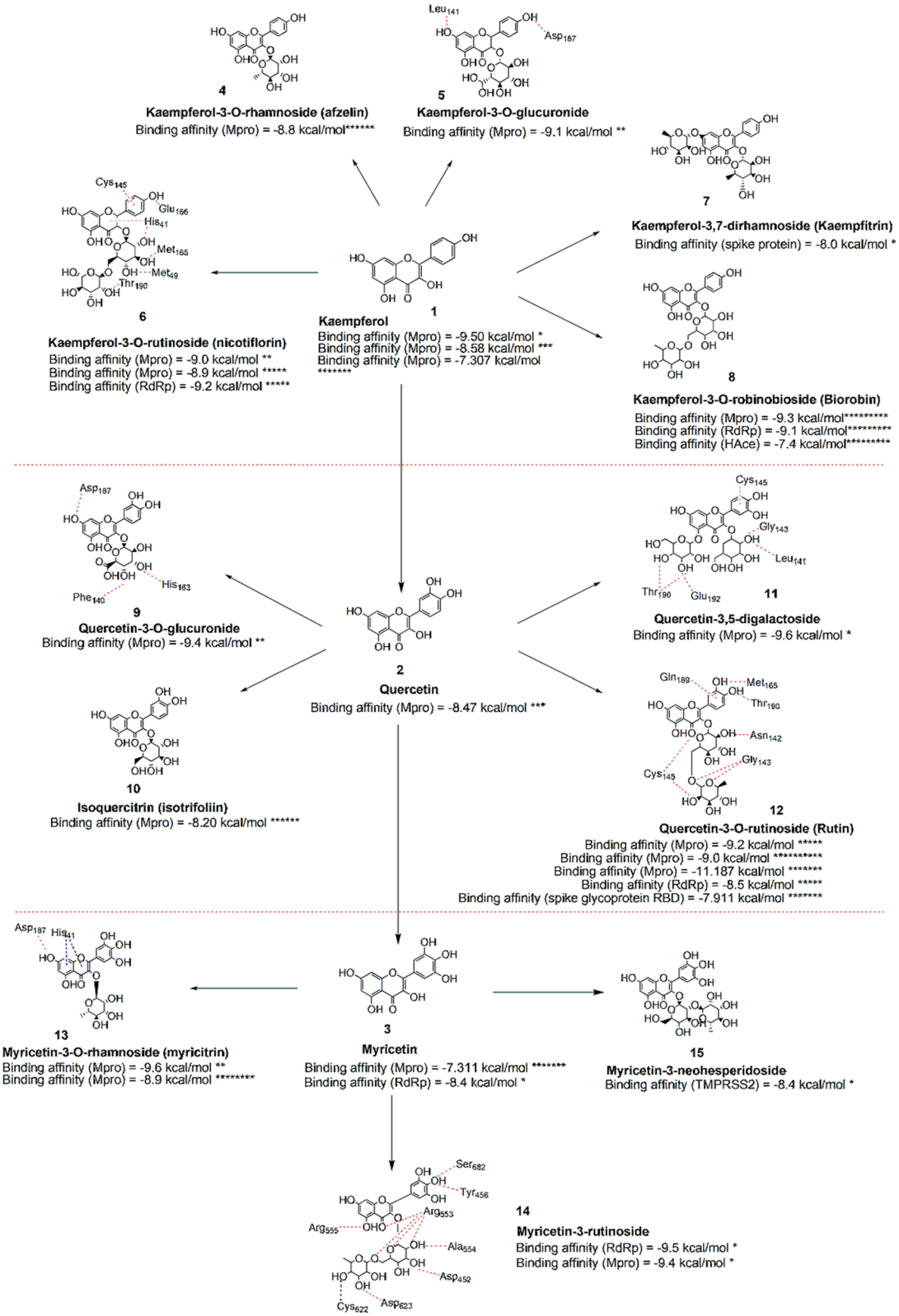

Fig. 11 Correlation of flavonol-based derivatives with their in-silico bioactivities with Mpro of SARS-CoV-2. All docking scores data presented here were obtained from different references, which will be influenced by their own use on (1) docking program, (2) docking algorithm, and (3) system set-up. Refs.: *[164]; **[281]; ***[265]; ****[262]; *****[360]; ******[361]; *******[362]; ********[363]; *********[364]; **********[365]

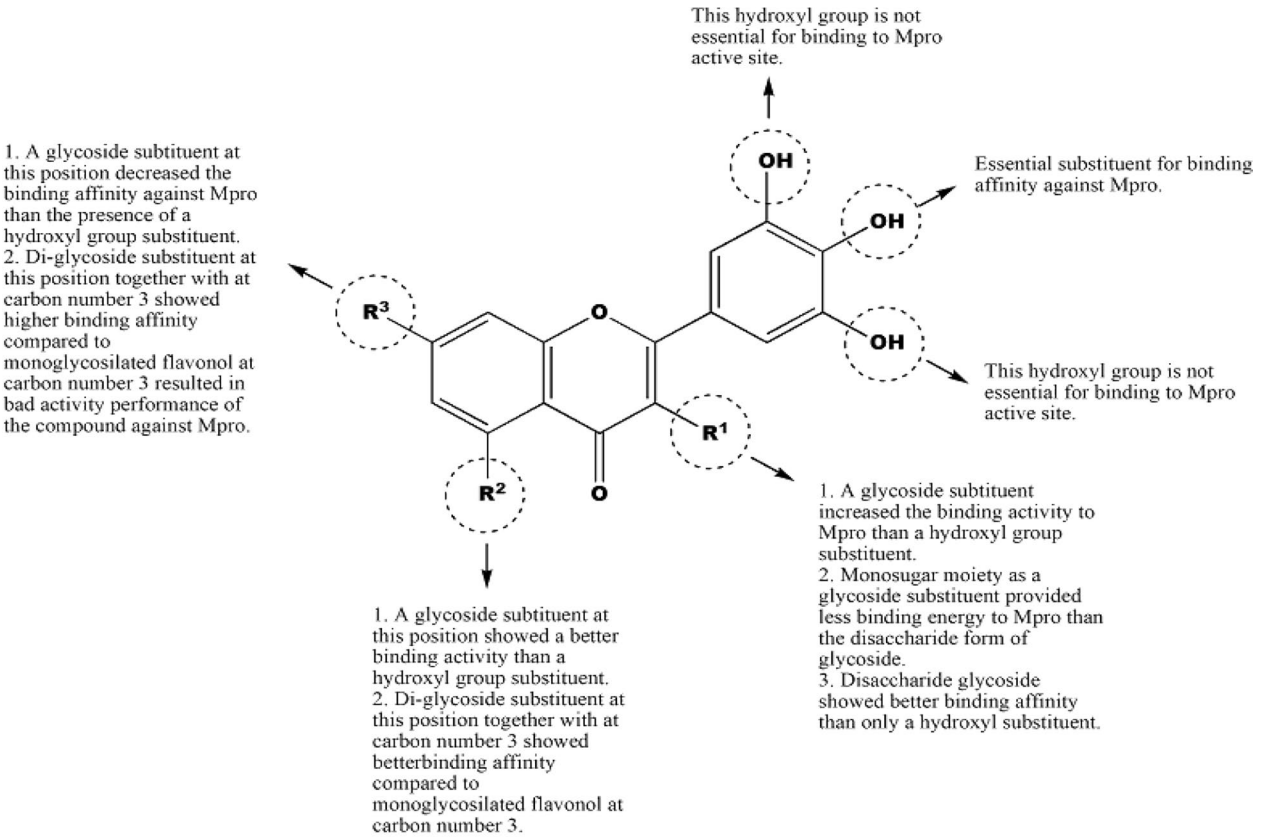

Fig. 12 SAR of flavonol against Mpro of SARS-CoV-2 based on in silico data from previous studies as shown on Fig. 11 [164, 262, 265, 278, 281, 317, 363, 368]

Current challenges against COVID-19

New variants of SARS-CoV-2 have emerged through mutations that increase their transmissibility, severity, and mortality. In the future, significant attention and funding will be given to the study of drugs, with a shift towards vaccine redesign when repurposing drugs is not enough. However, an effective vaccine cannot entirely prevent future mutant attacks, and not all vaccines are suitable for worldwide application due to factors such as environment, geography, and genetic diversity. Each SARS-CoV-2 variant has unique characteristics and infection roles, and current antibodies may not always be effective in neutralizing these variants. Therefore, specific vaccines are needed to enhance human immunity against each variant. The effectiveness of vaccines, such as NVX-CoV2373, varies across different regions and variants. In the UK, it showed 95.6% effectiveness against the original strain of SARS-CoV-2, but its efficacy in South Africa was 60%, and it was only 49.4% effective against the beta variant. Additionally, vaccine effectiveness diminishes over time, with up to a 50% reduction in efficacy observed after ten weeks of a booster dose [2].

After COVID-19 pandemic subsides, a major challenge that remains is increasing immunity to prevent unexpected virus mutations, thereby leading to questions, such as *Should people receive annual vaccinations to prevent unexpected mutants?* Further investigation on vaccine production is ongoing, but the long-term impact of immunization on the human body must also be investigated. Concerns have been raised about the potential carcinogenic effects of vaccination, which may not be detected quickly. Identifying adverse events after vaccination is important, especially for children, who have a longer expected future than older individuals. In some countries, vaccinations are mandatory for children over eight years old to improve their immunity. Therefore, it is important to track the progress in the muscular, cardiovascular, respiratory, and reproductive systems. In the coming years, study on COVID-19 will provide valuable scientific insights into preventing future unexpected viral infections.

Regarding the development of natural products into antiviral drugs, there are some considerations about what kind of challenges and problems researchers facing nowadays. Firstly, the complexity of natural products leads to

time consuming and labour-intensive problems due to the long way of isolation, characterization and synthesis process [4, 6]. Secondly, standardization on the manufacture of the isolate or compound from natural products is difficult to be applied since a broad variation on bioactivity potency from different sources and batches [8]. In addition, formula stability and safety on the use of natural product extracts require specific strategies on the preservation of its efficacy and safety assessments which also to avoid any occurred resistances [10, 12]. The limited sources of natural products are also being an ethical and ecological concerns nowadays. Therefore, interdisciplinary collaborations among researchers in chemistry, biology, pharmacy, and medicine are required to commit in addressing the various scientific, regulatory and ethical challenges that arise.

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Author contributions
IO wrote the first draft of the manuscript, wrote additional sections, and created the figures. IO, MS, MFAB, YUK, and SF created the concept, edited, and revised the manuscript together. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests
The authors declare that they have no competing interests.

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