Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Based on Principles and Insights of COVID-19 Epidemiology, Genome Sequencing, and Pathogenesis: Retrospective Analysis of Sinigrin and Prolixin^{RX} (Fluphenazine) Provides Off-Label Drug Candidates

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative pathogen of pandemic coronavirus disease 2019 (COVID-19). So far, no approved therapy has been developed to halt the spread of the pathogen, and unfortunately, the strategies for developing a new therapy will require a long time and very extensive resources. Therefore, drug repurposing has emerged as an ideal strategy toward a smart, versatile, quick way to confine the lethal disease. In this endeavor, natural products have been an untapped source for new drugs. This review represents the confederated experience of multidisciplinary researchers of 99 articles using several databases: Google Scholar, Science Direct, MEDLINE, Web of Science, Scopus, and PubMed. To establish the hypothesis, a Bayesian perspective of a systematic review was used to outline evidence synthesis. Our docking documentation of 69 compounds and future research agenda assumptions were directed toward finding an effective and economic anti-COVID-19 treatment from natural products. Glucosinolate, flavones, and sulfated nitrogenous compounds demonstrate direct anti-SARS-CoV-2 activity through inhibition protease enzymes and may be considered potential candidates against coronavirus. These findings could be a starting point to initiate an integrative study that may encompass interested scientists and research institutes to test the hypothesis in vitro, in vivo, and in clinics after satisfying all ethical requirements.

Keywords

SARS-CoV-2, SARS-CoV, MERS-CoV, sinigrin, Prolixin, systematic review

Background

Coronaviruses are a large family of pleomorphic RNA viruses that cause respiratory tract diseases. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third highly pathogenic and large-scale pandemic beta-coronavirus, after the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 that spread throughout in China and the Middle East respiratory syndrome coronavirus (MERS-CoV) that was identified in Saudi Arabia in 2012.[1] On March 11, 2020, the World Health Organization (WHO) officially described the new coronavirus disease 2019 (COVID-19) outbreak as a global epidemic disorder.[2] SARS-CoV-2 is characterized by mutations in nsp1, nsp3, nsp15, and gene S, which are associated with its epidemic behavior.[3] The clinical manifestations of infected cases are varied, from asymptomatic to intensive care hospitalization

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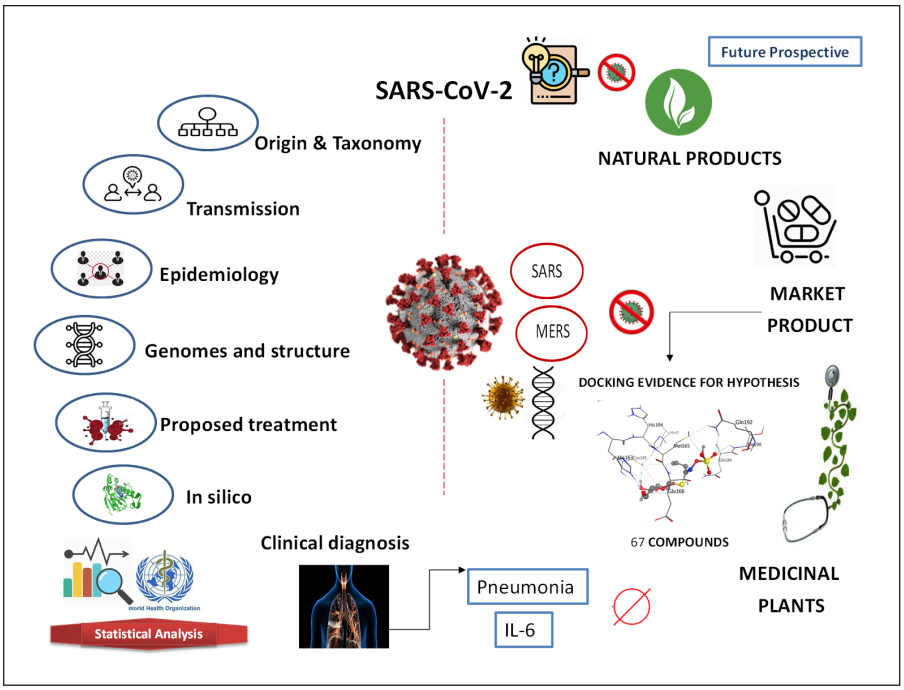

Figure 1. Graphical abstract of systematic review using screening mode design.

states with pneumonia disorder.[4] Reports have indicated that SARS-CoV-2 has the same cell entry receptor angiotensin-converting enzyme 2 (ACE2) and pathological features as acute respiratory distress syndromes (ARDSs) like SARS-CoV.[5] This study aimed to find the similarity between SARS-CoV, MERS-CoV, and SARS-CoV-2 in genomic variation, pathogenesis, and epidemiology, in addition to discussing the theories of SARS-CoV-2 origins and its clinical manifestation, based on insights from COVID-19 genome sequencing and pathogenesis. The research builds a hypothesis and tries to answer a question: Can natural products assist during the COVID-19 crisis?

Method

The following electronic databases were searched: Science Direct, Google Scholar, Web of Science, Scopus, PubMed, and MEDLINE. A literature search was performed using the following key terms: CoV-19/COVID-19/SARS-CoV-2, SARS-CoV, World Health Organization (WHO)/reports, genomic sequence/genetic/origin, mutated protein, difference SARS/MERS/SARS-CoV-2, epidemiology, replication/pathogenesis, transmission, genetic susceptibility/factors affecting, clinical manifestation/clinical radiology/diagnosis, in silico/docking, treatment/FDA, plant remedies/complementary medicine/medicinal plants/natural product/extract/Chinese medicine, severe respiratory syndrome coronavirus/SARS-CoV/plant, Middle East respiratory syndrome coronavirus (MERS-CoV)/plant, plant affect pneumonia virus/RSV/HRV/HMPV/HPV, interleukin6/IL-6/clinical/COVID-19, IL-6/secondary metabolite/compound, review/systematic review.

The screening of search outputs was performed in three stages (**Fig. 1**):

Stage 1: Collecting research and review articles concerning SARS-CoV-2 and statistically monitoring the virus's spread worldwide according to WHO reports.
Stage 2: Searching for natural products of medicinal plants that have previously proved to be a potential antiviral against SARS-CoV, MERS-CoV, and pneumonia virus, in addition to phytoconstituents that inhibit interleukin-6 (IL-6; pathogenesis marker of respiratory failure).
Stage 3: Practical point/hypothesis via virtual screening and docking studies.[6]

Data Analysis

WHO reports for 10-day intervals, from January 20, to June 1, 2020, were entered into Statistical Software Packages (SPSS software version 25; IBM Corp., Armonk, NY) to test the difference between groups using the Kruskal-Wallis test; the results were considered significant at $p < 0.05$. Descriptive and cumulative statistical methods, including percentage and frequency, were used to present confirmed, infected, and recovered cases and deaths in different regions and countries. Graphs were made using Microsoft Excel (2016; Redmond, WA). Charts and tables were used to present medicinal plant studies. In silico and docking simulation was performed using Molecular Operating Environment

(MOE) version 2014.09 (Chemical Computing Group Inc., Montreal, QC, Canada).

Results

Structures of Coronaviruses and Genomic Variation with SARS-CoV-2

Coronaviruses are classified as the largest species of RNA viruses (26–32 kb) as they are about 125 nm in diameter.[1] There are four types of viruses: alpha, beta, gamma, and delta. HCoV-229E and HCoV-NL63 are examples of the alpha type, which are responsible for one-third of the common colds, as they use different host proteins as receptors. SARS-CoV, MERS-CoV, and SARS-CoV-2 are examples of a beta-coronavirus; they have the same genomic structure as coronaviruses[7] and contain an enveloped, single, positive-stranded genome that encodes four major viral structural proteins (spike [S], envelope [E], membrane [M], and nucleocapsid [N] proteins 3–5, that follow the characteristic gene order, 5′-replicase [rep gene], spike [S], envelope [E], membrane [M], and nucleocapsid [N]-3′) with short untranslated regions at both termini. The S protein binds to the host cell receptor and allows its entrance; therefore, it is considered to be the main target of therapy.[8]

It is composed of two functional subunits, S1 for binding to the host receptor and S2 for membrane fusion. The cleavage of S1/S2 subunits occurs by one or more host proteases. Moreover, the activation of the SARS-CoV S protein needs additional cleavage by the endosomal cysteine protease cathepsin L and trypsin-like serine protease. Few enzyme inhibitors affecting these proteins have shown anticoronavirus activity in vitro.[9]

The nonstructural protein is encoded by the rep gene, which represents about two-thirds of the genome at the 5′ end. Open reading frame 1a/b (ORF1a/b) is partially overlapped with the 5′-terminal end, which encodes the large replicase polyproteins 1a (pp1a) and 1ab (pp1ab). Moreover, papain-like cysteine protease (PLpro) and 3C-like serine protease (3CLpro) cleave pp1a and pp1ab to give nonstructural proteins, involving RNA-dependent RNA polymerase (RdRp) and helicase (Hel), which are considered the major enzymes during the process of transcription and replication of coronaviruses. The structural proteins (S, E, M, and N) are encoded by the 3′ one-third of the coronavirus genome, which is important for binding the virus to the receptor host cell assembly of the virion.[10]

Modification of the spike glycoprotein by homologous recombination is a characteristic difference between SARS-CoV-2 and SARS-CoV,[11] in addition to the absence of the 8a protein and the change in the number of amino acids in 8b and 3c proteins.[12] Also, the spike glycoprotein of SARS-CoV-2 has composed a combination of bat SARS-CoV and undetected beta-CoV.[13] On the other hand, a fluorescence study has proved that SARS-CoV-2 utilizes the ACE2 cell receptor and the mechanism of the entrance to host cell as SARS-CoV.[14] The binding affinity of SARS-CoV-2 for ACE2 is increased by the single N501T mutation in the spike protein.[15]

ACE2 is the main cellular receptor for SARS-CoV-2; the virus binds to these receptors by its spike protein, which facilitates its entrance to the host cell, duplicates genomic materials, and synthesizes many different required proteins using the cellular machinery. After that, it produces new virions from the cell surface.[16] Moreover, after the entrance of SARS-CoV-2 through the ACE2, it subsequently downregulates ACE2 expression causing the unchallenged angiotensin II accumulation and local RAAS (renin–angiotensin–aldosterone system) activation, which deranges homeostasis, triggers inflammation, and induces tissue injury in lungs and other organs.[17,18]

Pathogenesis

Life Cycle of SARS-CoV and MERS-CoV in Host Cells. CoVs enter the host cell by exploiting two pathways: the endosomal and cell surface nonendosomal pathways. Low pH and pH-dependent endosomal cysteine protease cathepsins assist the membrane fusion and enosomal CoV cell entry and support endosomal cell entry of coronaviruses.[19] Host proteases such as transmembrane protease serine 2 (TMPRSS2) and TMPRSS11D (airway trypsin-like protease) cleave S into the S1 and S2 subunits to activate S for the entrance of cell surface nonendosomal virus at the plasma membrane. Inhibitors of these proteases can prevent this proteolytic cleavage and partially block cell entry. MERS-CoV is additionally activated by furin, a serine endoprotease that has been involved in the processing of fusion proteins and the entrance of the cells of other RNA viruses, including HIV, avian influenza A/H5N1 virus, Ebola virus, Marburg virus, and flaviviruses.[20] The Furin is included in MERS-CoV S1/S2 cleavage during exit from the infected cell. Monotherapy and/or combinatorial treatment with inhibitors of host proteases concerned with the various cell entry pathways are potent as anticoronaviruses.[21] **Table 1** illustrates the major differences between SARS-CoV, MERS-CoV, and SARS-CoV-2.

Endosomal Pathway of SARS-CoV and MERS-CoV. The S proteins of SARS and MERS bind to two main receptors: cellular receptor ACE2 and cellular receptor dipeptidyl peptidase 4 (DPP4), respectively. After the entrance of the virus into the host cell, the viral RNA is released in the cytoplasm. ORF1a and ORF1ab are translated to produce pp1a and pp1ab, which are then cleaved by the proteases encoded by ORF1a to give 16 nonstructural proteins (RNA replicase–transcriptase complex). The performed complex leads to the production of negative-sense (−) RNA by both

Table 1. Differences between SARS, MERS, and SARS-CoV-2.

	SARS-CoV[16,31,32]	MERS-CoV[31–33]	SARS-CoV-2[16,31,34,35]
First occurrence	November 16, 2002, in Foshan, Guangdong	September 2012	December 7, 2019, in Wuhan, Hubei
Virus type	RNA virus		
Species pathogen	Beta-coronavirus		
Intermediate host	*Paguma larvata*	Dromedary camel	Pangolin, mink, bat (possible)
Definitive host	*Rhinolophus sinicus*	*Tylonycteris pachypus* and *Pipistrellus abramus*	*Rhinolophus sinicus* (possible)
Predominant receptor	Human ACE2	Human DPP4 (or CD26)	Human ACE2
Total DNA sequence length of pathogen	29,751	30,119	29,903
Characteristic gene order	50-replicase ORF1ab, spike (S), envelope (E), membrane (M), and nucleocapsid (N)-30		5′-Replicase ORF1ab-S-envelope (E)-membrane (M)-nucleocapsid (N)-3′; ORF3ab, ORF6, ORF7ab, ORF8, ORF9ab, and ORF10
Transmission rate	More than MERS-CoV but less than SARS-CoV-2	Less than SARS-CoV and SARS-CoV-2	More rapid than MERS-CoV and SARS-CoV
Male–female patient ratio	1.0:1.2	—	2.7:1.0
Clinical symptoms	Fever, cough, myalgia, dyspnea, and diarrhea	High fever, chill, cough, shortness of breath, chest pain, headache, myalgia, sore throat, arthralgia, abdominal pain, anorexia, vomiting, and severe diarrhea (some cases)	Fever, fatigue, and dry cough
Propagation mode	Droplets or close contacts, fomites, fecal transmission, and handling of animals having the virus	Droplets or close contact with infected dromedary camels	Human to human/spread through respiratory droplets from coughs or sneezes; handling of animals having the virus
Diagnostic methods	real-time PCR (RT-PCR), rRT-PCR, RT-LAMP, rRT-LAMP, coronavirus detection kit	Chest radiography, electron microscope, immunofluorescence microscopy, cell culture, enzyme-linked immunosorbent assay (ELISA), and RT-PCR	RT-PCR, rRT-PCR, RT-LAMP, rRT-LAMP, coronavirus detection kit
Treatment	Glucocorticoid and interferon	Interferon, lopinavir/ritonavir, cyclosporin A, chloroquine/hydrochloroquine	Lopinavir/ritonavir, chloroquine
Mortality	9.6%	40.0%	2%–7%
Number of deaths worldwide	916	800	379,941 and rising daily (WHO website, June 3, 2020)

rRT, reverse transcription loop-mediated isothermal amplification; rRT-LAMP, real-time reverse transcription LAMP assay.

replication and transcription. Full-length (−) RNA copies of the genome are produced during replication and used as a template for full-length positive-sense (+) RNA genomes. A subset of seven to nine subgenomic RNAs, included those encoding all structural proteins, is produced by discontinuous transcription.[7,22]

Virion Assembly and Release. Virion assembly occurs in the endoplasmic reticulum–Golgi intermediate compartment (ERGIC) and is coordinated by the M protein. Incorporation of viral proteins into coronavirus virions relies on protein trafficking to protein–protein interactions at the ERGIC. The M, E, and some S proteins have intracellular trafficking signals that are important in their targeting to accumulation beside the budding site.[23,24] The M protein is essential, and homotypic M-M interactions through multiple contact sites are required to drive virus-like particle (VLP) and coronavirus assembly.[25,26] Also, the integration of E, S, and ribonucleoproteins (RNPs) with virions occurs by heterotypic interactions with M proteins at the budding site.[27,28]

Life Cycle of SARS-CoV-2. The virus life cycle starts when S protein binds to the cellular receptor ACE2. After binding, modification in the S protein allows fusion between the viral envelope and the cell membrane through the endosomal pathway. After that, RNA is released into the host cell. Genome RNA is then translated into viral replicase pp1a and pp1ab, which are cleaved into small products by viral proteinases. Groups of subgenomic mRNAs are formed by the polymerase throughout discontinuous transcription and

finally translated into related viral proteins. Following that, viral proteins and genome RNA are aggregated into virions in the ER and Golgi and then transported by vesicles and released out of the cell.[29]

Pathogenic Mechanism of SARS-CoV-2

SARS-CoV-2 and Pneumonia. The viral infection has the ability to produce an excessive immune reaction in the host; in some patients, a "cytokine storm" reaction takes place and leads to extensive tissue damage. IL-6, which is known as the protagonist of this storm, can be produced by activated leukocytes. It allows the differentiation of B lymphocytes and the growth of some groups of cells, and inhibits the growth of others. Additionally, it can stimulate the production of acute-phase proteins and plays a vital role in thermoregulation, bone maintenance, and the functionality of the central nervous system. Moreover, the IL-6 level rises during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases, and some cases of cancer. It is also involved in the pathogenesis of the cytokine release syndrome (CRS), which is characterized by fever and multiple organ dysfunction.[30]

Inhibition of Human Heme Metabolism. Preprint research has reported that viruses target hemoglobin and attack porphyrins where the viral ORF8 and surface glycoproteins form a porphyrin complex. At the same time, ORF1ab, ORF10, and ORF3a proteins could coordinate an attack on the heme on the 1-beta chain of hemoglobin to dissociate the iron porphyrin. This results in a decreasing the number of hemoglobin carrying oxygen and carbon dioxide. Also, the released iron led to the production of reactive oxygen species (ROS); therefore, the lung cells will have vigorous inflammation and damage.[36]

Theories of SARS-CoV-2 Origins

In reviewing the SARS-CoV-2 genomic data sequence, two theories explain the origin of the virus. According to Andersen et al,[37] the viral genesis depends on natural selection in a non-human animal host before zoonotic transfer. Another belief depends on natural selection in humans following a zoonosis transfer; the author reported that analysis of the public genome sequence proved that there is no evidence the virus was made in a laboratory or otherwise engineered.

Several reports record a variable virus origin interpretation, some of which have indicated that most of the coronaviruses in humans are derived from a bat reservoir.[1,38–40] Only one study states that the virus matches with pangolin as a host carrier,[1] while another report shows a similarity with a bovine sequence with a 90% genome identity.[40,41]

Interestingly, upon searching using the SARS term, a reported invention of a novel strain of SARS coronavirus was found. The patent concerned isolation of the virus strain, with diagnostic reagents and vaccine applications thereof. The virus genome was in the form of complementary DNA, a serine codon reported in positions 23220–23222 of protein S or positions 25298–25300 of the ORF3 gene. There was a glycine codon, and an alanine codon in positions 7918–7920 of FORT la or a serine codon in positions 26857–26859 of the protein M gene. The protein S was a membrane glycoprotein (200–220 kDa) that is in the "spike" emerging from the surface of the viral envelope.[42]

The genome sequences of SARS-CoV-2 show ≥70%–79% identity to SARS-CoV.[1,35,43] Additionally, Nezhad et al.[44] indicated that the structural analysis homology percentage is 96% for the envelope and 89.6% for the nucleotide. These findings are consistent with those of Tahir et al.[40] On the other side, Xiaolu et al.[35] signify that the virus is similar to MERS-CoV, with 50% similarity, which is in contrast to the investigation of Tahir,[40] who indicated an 87% resemblance relationship between the two viruses. From the authors' point of view, there is a bit of conflict in the virus origin reports; thus, this research area requires more attention by genomic scientists.

Epidemiology

According to the observed data from the early outbreak in mainland China during January 10–24, 2020, the tendency of incidence largely follows exponential growth, and the mean basic reproduction number (R_0) was estimated to range from 2.24 to 3.58, associated with a two- to eightfold increase in the reported rate. Another estimation based on the data from December 31, 2019, to January 28, 2020, suggested similar findings, with $R_0 = 2.68$ and the epidemic doubling time being 6.4 days. The current estimate of the mean incubation period for COVID-19 is 6.4 days, ranging from 2.1 to 11.1 days, with potential asymptomatic transmission. However, the situation is evolving and further updated data are required to confirm these estimations.[45,46]

Factors Affecting the Prevalence of COVID-19

Sex. In a study of 140 patients in China using single-cell sequencing, it was found that the expression of ACE2 is more predominant in Asian men than women, which might be the reason for the higher prevalence of COVID-19 in men. The data indicate that there might be a sex predisposition to the virus.[47]

Smoking. Because ACE2 has been identified as a receptor for COVID-19, studies have reported that smoking affects the expression pattern of ACE2 in the respiratory tract, causing differences in susceptibility to the virus.[34] Another investigation considered that sex predisposition to SARS-CoV-2 with men might be related to the higher rate of smoking in men than in women in China. Additionally,

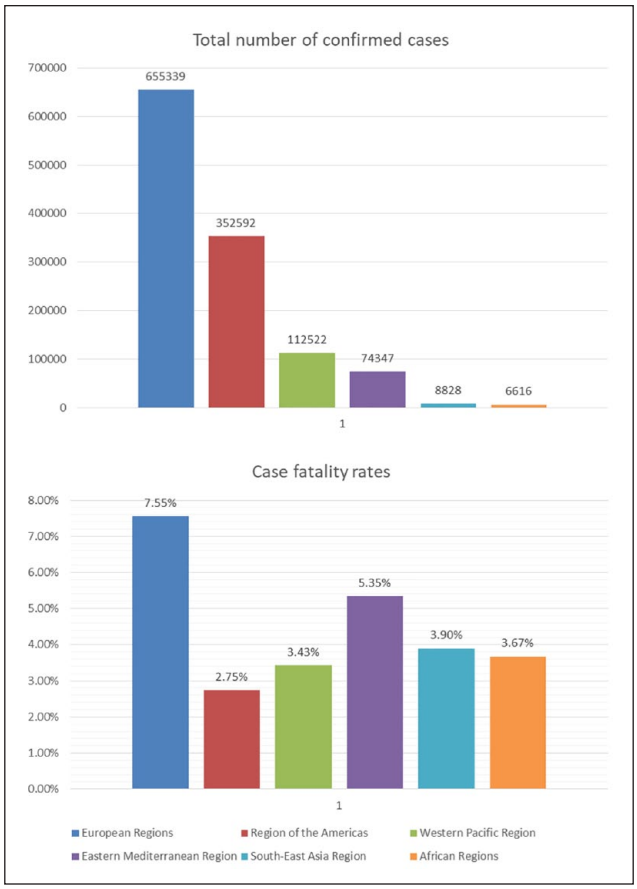

Figure 2. The number of confirmed cases (Kruskal-Wallis H = 34.339, df = 5, $p < 0.001$) and fatality rates (Kruskal-Wallis H = 16.601, df = 5, $p = 0.005$) of different worldwide regions distributed according to WHO reports, represented throughout the study period.

susceptibility was significantly higher in current smokers of Asian ethnicity than in Asian nonsmokers. In a study by Cai and colleagues (11.8% of smokers had nonsevere disease vs 16.9% of smokers with severe disease), a tendency toward an association between smoking and severity of disease was observed, but it was not significant.[47]

Chronic Diseases. The most distinctive comorbidities of nonsurvivors from a group of 52 intensive care unit states were cerebrovascular diseases (22%), diabetes (16.2%–22%), hypertension (19.30%–23.7%), and coronary heart disease (5.8%).[48]

Environmental Factors. Oliveiros et al. reported that the doubling time correlates positively with temperature and inversely with humidity, suggesting a decrease in the rate of virus progression with the arrival of spring and summer in the northern hemisphere. A 20 °C increase is expected to delay the doubling time by 1.8 days. Those variables explain 18% of the variation in disease doubling time; the remaining 82% may be related to containment measures, general health policies, population density, transportation, or cultural aspects.[49]

The intolerance of coronaviruses to heat is due to the presence of a lipid bilayer that can easily be damaged by high temperatures; also, the transmission of these viruses can be affected by humidity in the air.[50] Moreover, SARS-CoV-2, like other respiratory viruses, involves aerial transmissions of respiratory droplets that expose the virus to external environmental conditions. SARS-CoV-2 and SARS-CoV can be viable on surfaces for more than 5 days at temperatures of 11–25 °C and relative humidity of 40%–50%; then it drastically loses its viability as temperatures and humidity increase.[50] Cold temperatures and low humidity can increase the half-life and viability of the virus, the stabilization of the droplet, and its propagation in the nasal mucosa.[51]

Genetic Susceptibility of the Different Populations to Viral (SARS-CoV-2) Infection. To compare the genomic characteristics of ACE2 among different populations, coding region variants in ACE2 and expression quantitative trait loci (eQTL) were systematically analyzed. The findings indicated that no direct evidence was identified to support the existence of coronavirus S protein binding-resistant ACE2 mutants. The data of variant distribution and allele frequency (AF) may contribute to further investigations of ACE2, including its roles in acute lung injury and lung function. The East Asian populations have much higher AFs in the eQTL variants associated with higher ACE2 expression in tissues, which may suggest different susceptibilities or responses to COVID-19/SARS-CoV-2 compared with different populations under similar conditions.[52]

Statistical Analysis of WHO Reports. The differences between the total infected SARS-CoV-2 cases and the number of people who died in different regions (Western Pacific, Eastern Mediterranean, Southeast Asia, African, European, and America regions) according to WHO reports were statistically interpreted from January 20 to May 30. The total number of confirmed cases (Kruskal-Wallis H = 34.339, df = 5, $p < 0.001$), the total death numbers (Kruskal-Wallis H = 31.839, df = 5, $p < 0.001$), and case fatality rates (Kruskal-Wallis H = 16.601, df = 5, $p = 0.005$) throughout the study period were recorded.

The African, Southeast Asia, Eastern Mediterranean, and Western Pacific regions represent a significantly lower number of reported infected cases than the European regions and regions of America. However, the fatality rate did not directly correlate with the confirmed cases of such regions. Hence, the regions of America and Western Pacific regions showed the least fatal cases worldwide (2.75% and 3.43%, respectively). The bars (**Fig. 2**) show that the European region represents a higher total number of confirmed and fatality rates worldwide (7.55%). The Eastern Mediterranean

region represents the second-highest fatality rate, although it represents the fourth level of reported cases worldwide.

From the previous statistical data, we concluded that different factors may contribute to the variation in fatality rate between world regions; for example, genetic susceptibility and lack of widespread systematic testing may be considered the main sources of discrepancy in COVID-19-infected cases. Other predisposing elements are the ratio of men to women infected; complex cases with comorbid disease, especially immunocompromised states; elderly persons who are COVID positive; people's state of immunity, lifestyle, and diet; hospitalization efficiency protocols, and the readiness of respiratory ventilation systems.

The line graphs compare countries in the same region, to represent the most affected (top 10) countries with reported cases of infection and death. The European region (**Fig. 3A**), Spain, Italy, and the United Kingdom, showed a high number of confirmed cases and mortality rates. The Western Pacific region, China, represents a high number of confirmed cases and deaths, with a plateau of patient cases at the end of February. The number of fatalities demonstrated a fluctuation at the end of April; this represents an increase for a short time interval and then reaches a steady state again (**Fig. 3B**). The Southeast Asia region, India and Indonesia, recorded a rise of positive cases of the virus with a remarkably significant number between the cases of the two countries (**Fig. 3C**). In the Eastern Mediterranean region, Iran demonstrated a higher number of COVID-19 patients (about 150,000 cases) and most deaths in the region (more than 7500 persons died) (**Fig. 3D**). In the region of the Americas, the increase in both infected and death instances recorded by the United States skyrocketed compared with other countries in the same region (**Fig. 3E**). In the African region, South Africa, followed by Algeria, had the most cases. While Algeria had a significant number of deaths at the end of March, compared with other countries in the region, South Africa achieved the same level by the end of May (**Fig. 3F**).

Statistical Analysis of Egypt WHO Reports. The infected cases, death numbers, and fatality rate in Egypt compared with the same parameters for the rest of the world were statistically analyzed. The numbers of confirmed cases and deaths in Egypt are in alignment with the world average until March 10 and possesses almost the same level until the end of April, followed by dramatic uplifting. The world case fatality rate was 3%–4% until March 19, which represents a cross section with the line for the death rate in Egypt. Afterward, the mortality rate jumped to an apex on April 19 with a percentage of 7.5, followed by a decline. Afterward, the confirmed case and death numbers surged until the start of June. Continuation in recording cases should be taken into consideration to confirm the passing of the critical phase.

Clinical Manifestation

COVID-19 patients suffer from common symptoms of typical respiratory diseases and other manifestations, like fatigue, diarrhea, and myalgia.[53] Clinical radiology is used to distinguish SARS-CoV-2 from other viral pneumonia. Chest computed tomography (CT) records a high specificity but moderate sensitivity. The detailed imaging features can evaluate the severity and extent of disease and differentiate between four clinical types (early, common, critical, and fatal). The imaging features of the early stage include multifocal patchy shadows or ground-glass opacities located in the lung periphery, subpleural area, and both lower lobes on chest CT scans. The long-axis lesion is mostly parallel to the pleura. Additionally, interlobular septal thickening and intralobular interstitial thickening are manifested. After progression of the disease, an enlarged and increased density of the lesions is observable as consolidated lesions with the air bronchogram sign. Increased density of opacity in the whole lung (white lung) and ground-glass opacities can be completely absorbed by some consolidation lesions that leave fibrotic stripes or subpleural reticulation as a critical sign. In time, multiple lobular involvement of lesion expansions is detected at the disease is exacerbated.[54–57]

Future Prospective: Role of Natural Compounds against COVID-19

Virus mutation is an evolutionary mechanism for adaptation, and the scientific community faces the challenge of finding preventive vaccines and efficient antiviral therapies.[58] The pandemic state of COVID-19 has yielded a globally heavy toll. Researchers are still actively testing various strategies, including new and repurposed drugs, for finding a solution. Hence, there is clear room for the intervention of alternative and complementary medicine as a therapy for SARS-CoV-2 patients, inconsistent with the WHO report, where there is no specific medicine for COVID-19 to date.[59]

Plant and microbial natural products could represent a new prospect for coronavirus treatments.[60,61] Medicinal plants are considered a highly attractive strategy for the economic production of a treatment,[62] and have also been used by ancient nations against viral respiratory infections. The secondary metabolites of plants are characterized by novelty and potency as bioactive biological agents.[63] It is relevant to note that the current clinical guideline in China is to use conventional medicine previously reported to treat SARS and MERS patients. More than 85% of SARS-CoV-2-infected patients in China are receiving traditional Chinese medicine (TCM) treatments, such as *Astragali radix, Glycyrrhizae radix, Saposhnikoviae radix, Atractylodis rhizoma*, and *Lonicerae japonicae*. These plants were

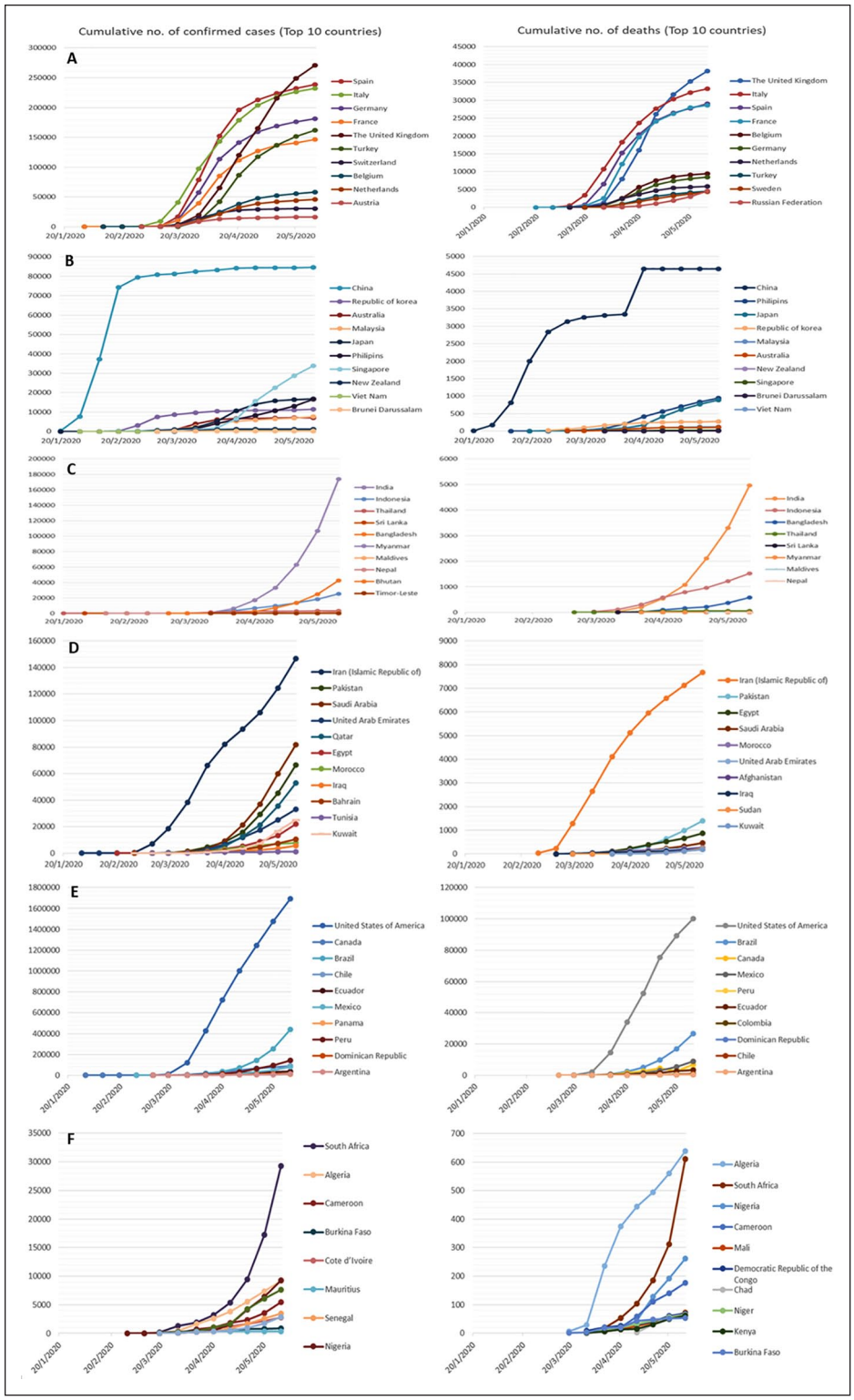

Figure 3. The number of confirmed cases and deaths reported in the (**A**) European region, (**B**) Western Pacific region, (**C**) Southeast Asia region, (**D**) Eastern Mediterranean region, (**E**) region of the Americas, and (**F**) African region according to WHO reports.

recorded as the most frequent plants commonly used in preventive formulae for COVID-19.[59]

Previous reports have indicated the similarity between SARS-CoV-2 and SARS-CoV in genomic sequence (70%–96% in the envelope and nucleotide segment) and pathogenesis pathways[1,10,40,44] and proposed a resemblance with the MERS-CoV human virus by 50%.[35] Based on these factors, there is a general hypothesis that anti-SARS-CoV

Table 2. Reported Plants Affecting Pneumonia Viruses.

Virus	Plants	Reference
HMPV	*Aspidosperma tometosum, Gaylussacia brasiliensis, Virola sebifera, Arrabideaa chica*	58
HPIV	Dahlia, *Glycine max* (L.) Merr, *Phaeseolus aureus* Roxb, *Cossypium herbaceum, Allium sativa*	68
	Mistletoe (*Viscum album* L. spp. *album*)	69
	Ipomopsis aggregate, *Rhus succedanea, Garcinia multiflora, Sanicula europea*	70
RSV	*Alchornea cordifolia, Alchornea floribunda, Nauclea latifolia*	71
	Plantago asiatica, Clerodendrum trichotomum	72
	Ballota glandulosissima	73
	Allium sativa, Markhamia lutea	68
	Potentilla arguta, Sambucus racemose, Eleutherococcus senticosus, Myrcianthes ciplatensis, Rhus succedanea, Garcinia multiflora	70
HRV	*Plectranthus cylindraceus, Pogostemon cablin, Heterotheca grandiflora, Aglaia andamanica, Euodia glabra, Larrea triden tata, Bollata glandulosissima*	73
	Pelargonium sidoides radix	74
	Chrysosplenium tosaense, Calendula arvensis, Eriobotrya japonica Lindl., *Urginea scilla steinh*	68
	Woodfordia fruticose	75

and MERS-CoV natural products would be potential ammunition to fight the lethal virus.

SARS-CoV-2 infects the upper and lower respiratory tract and causes mild or highly acute respiratory syndrome with a consequent release of pro-inflammatory cytokines (IL1β and IL-6). Supportive care to ameliorate a patient's symptoms is the logical option at this time. The pathogenesis of the virus includes binding to the toll-like receptor (TLR) that results in the release of pro-IL-1β, which is a mediator of lung inflammation, fever, and fibrosis. The suppression of IL-1β through IL-37 and IL-38 may have a therapeutic effect, as this strategy has previously inhibited inflammation during viral infections.[64,65]

As a result of the progression of the clinical and radiological speculation regarding severe acute respiratory syndrome (SARS-CoV-2), pneumonia states have been indicated,[66,67] so we postulate that plants previously used to treat pneumonia disease could help to relieve the symptoms. In **Table 2** is a review list of plants that act against different pneumonia viruses: human metapneumo virus (HMPV), human parainfluenza virus (HPIV), respiratory syncytial virus (RSV), and human rhinovirus (HRV).

From all previous concepts, that is why the literature search and review strategy are based on three different scopes: natural products affecting SARS-CoV and MERS-CoV, compounds able to inhibit IL-6, and medicinal plants that relieve pneumonia.

Natural Products Affecting SARS-CoV. *Artemisia annua, Pyrrosia lingua*, and *Lindera aggregata* have been reported to display antiviral activity against SARS-CoV in screening analysis using the Vero cell.[76] *Houttuynia cordata* water extract inhibits 3CL protease enzyme and blocks RNA polymerase activity.[77] Also, leukocytic IFN-α, ribavirin, lopinavir, and rimantadine have been indicated as a prophylaxis or curative agent against the virus.[78] In the investigation of the activities of 15 plants against viruses, lectins compounds such as sugar *N*-acetyl-specific agglutinins and nonspecific agglutinin showed a potent anti-SARS-CoV activity, in particular the mannose type.[79] Moreover, tryptanthrin, myricetin, scutellarin, baicalin, glycyrrhizin, aloe-emodin, hesperetin, sinigrin, lycorine, and amentoflavone are isolated natural compounds that possess activity against SARS-CoV with different action mechanisms.

Natural Products Affecting MERS-CoV. Park et al.[80] demonstrated the inhibitory activity of polyphenol compounds derived from *Broussonetia papyrifera* (broussochalcone B, broussochalcone A, 4-hydroxyisolonchocarpin, papyriflavonol A, 3′-[3-methylbut-2-enyl]-3′,4,7-trihydroxyflavane, kazinol A, kazinol B, broussoflavan A, kazinol F, and kazinol J) against 3-chymotrypsin-like and papain-like MERS coronavirus cysteine proteases. The prenylated quercetin derivative papyriflavonol A was the most potent compound against papain-like proteases. Furthermore, another natural compound having antiviral activity is resveratrol, which is found in grape skin and seeds, where it inhibits MERS-CoV infection and prolongs cellular survival after virus infection through different pathways: (1) reducing the viral RNA expression, (2) blocking the NF-κB pathway, (3) decreasing nucleocapsid (N) protein essential for virus replication, and (4) inhibiting caspase 3 cleavage and apoptosis induced by virus infection. It also decreases the production of nitric oxide in tissue, thereby reducing tissue inflammation.[81] Homoharringtonine (HHT) is a pharmaceutical class of natural alkaloid ester obtained from plant, and *Cephalotaxus harringtonii* is marketed as an omacetaxine mepesuccinate against MERS-CoV. Moreover, natural products like trigocherin, jatropane esters, and

Table 3. Natural Product Candidates Could Be Used against SARS-CoV-2.

Compound	Mechanisms	Reference
Natural products affect SARS-CoV		
Tryptanthrin	RdRp and PLP2 inhibitor Moderates the viral RNA genome synthesis and progeny virus production	83
Myricetin	Interacts with ATP/ADP binding pocket of Hel protein Interacts with critical residues of the ATPase domain (N265, Y269, and R443)	84
Scutellarin, baicalin	Conjugate with chemokines and interfere with their capacity to activate cellular receptors CCR5 and CXCR4	78
Glycyrrhizin	Induces nitrous oxide synthase, which inhibits virus replication	78, 85, 86
Aloe emodin, hesperetin sinigrin	Inhibit cleavage activity of the 3CLpro	83
Lycorine	Unclear how this compound interacts with expressed viral proteins and antigens	76
Amentoflavone	SARS-CoV 3CL protease inhibitor	58
Sugar *N*-acetyl glucosamine and agglutinins	Bind to the ACE2 receptor, resulting in the inhibition of SARS-CoV fusion with the target cell	79
Preparation Echinaforce	Interacts directly with viral envelope proteins	87
Natural agents affect IL-6		
Tocilizumab	Inhibits the binding of IL-6 to its receptor	88
Epigallocatechin-3-gallate	Blocks IL-6 synthesis in IL-1, inhibits p38 pathways, inhibits IL-6–induced apoptosis	88
Curcumin	Inhibits the production of pro-inflammatory cytokines and reduces IL-6/IL-6-soluble receptor (sIL-6R)-induced STAT3 and ERK phosphorylation	89
Celastrol	Reduces levels of IL-6 and IL-1β by inhibition of STAT3 phosphorylation to block the IL-6 receptor signaling pathway	90
Statins	Inhibits the enzyme HMG-CoA reductase and JAK/STAT3 signaling pathway for IL-6-mediated inflammation	91
Bisphosphonate	Inhibits the enzyme FPP synthase and the JAK/STAT3 signaling pathway for IL-6-mediated inflammation; reduces sIL-6R serum levels	
Polyphenolic compounds	Hinder JAK/STAT3 signaling pathway for IL-6-mediated inflammation	
Genistein	Decreases IL-6 production	
Sophoricoside	Arrests IL-6 bioactivity	
Isoflavones	Inhibit production of IL-6	
Eriodictyol	Inhibits expression of inflammatory cytokines TNF-α, IL-6, and IL-1β	92
Luteolin	Reduces TNF-α, KC, ICAM-1, and SOD; activates MAPK and NF-κB	
Quercetin	Diminishes TNF-α, IL1-β, IL-5, and IL-6; NO and COX-2	
Kaempferol	Reduces inflammatory cells; activates MAPK and NF-κB pathways	
Mitraphylline	Lowers IL-1α, IL-1β, IL-17, TNF-α, IL-6, and IL-8	
Asperuloside	Depletes TNF-α, IL-1β, and IL-6 levels	
Callicarpa japonica	Reduces cytokine IL-6	
Sakuranetin	Minimizes eosinophils, TNF-α, IL-5, IL-1β, M-CSF, and RANTES; inhibits NF-κB in lung, MMP-9-positive, and MMP-12-positive cells; increases TIMP-1 expression	
Apigenin	Inhibits eosinophil infiltration in lung tissue and IL-6	
Herbal formula PM014	Lowers IL-6 levels	
Punica granatum	Depletes eosinophils and cytokines IL-1β and IL-5	
Peganum harmale	Inhibits the production of both IL-6 and TNF-α	93
Baicalin	Decreases the induction of IL-1, IL-6, TNF-α, and IFN-γ	
Kaempferia parviflora	Lowers phosphorylation of STAT3, Akt, and the expression of Mcl-1 in response to exogenous IL-6 stimulation	94

harringtonine have shown potent antiviral effects on the MERS-RNA viruses.

Natural products such as alkaloids, flavonoids, phenolics, and terpenoids are reported to inhibit SARS-CoV and also the pathogenic elevation of IL-6 (**Table 3**). Moreover, current market products are available as MERS-CoV and SARS-CoV inhibitors (**Table 4**) according to Jadav et al.[82]

Table 4. Current Available Inhibitors against MERS-CoV* and SARS-CoV.[82]

Drug Classification	Drugs	Probable Mode of Action
Neurotransmitter inhibitor	Clomipramine HCl, chlorphenoxamine HCl, astemizole promethazine HCl, fluphenazine HCl, thiothixene, fluspirilene, benztropine mesylate	Clathrin-mediated endocytosis inhibitors
Antibiotic agent	Anisomycin	Protein processing inhibitor
Antibacterial agent	Emetine $2HCl{\cdot}H_2O$, cycloheximide	Unknown protein synthesis inhibitor
Anticancer agents, antiparasitic agent/ antimalarial	Dasatinib, imatinib, mesylate, chloroquine, $2H_3PO_4$ mefloquine hydroxychloroquine SO_4, amodiaquine $2HCl{\cdot}H_2O$	Inhibition of viral replication
Estrogen receptor inhibitor	Toremifene citrate, tamoxifen citrate	Viral entry inhibitor
Nucleoside analog	Gemcitabine HCl	DNA metabolism inhibitor
Cytoskeleton inhibitors	Nocodazole	Microtubule depolymerization
Ion channel inhibitors	Monensin, salinomycin Na	Blocks the formation of virus particle and eruption

Evidence-Based Hypothesis Using Molecular Docking Study

Our docked library was collected based on the aforementioned data hypothesis of 67 tested candidates, including 24 natural compounds, 22 market products previously reported to act against SARS-CoV and MERS-CoV, and 14 natural compounds previously indicated for inhibition of IL-6. In addition, some recommended treatments for SARS-CoV-2-infected patients were used as reference drugs (seven products). The molecular docking trial has been focused on one of the most promising potential target proteins of SARS-CoV-2: the main protease (Mpro or 3CLpro), which hinders enzyme activity, blocks viral replication, and disturbs the viral life cycle.[95]

Among all the natural compounds, the docking results showed that the top 3 hits are sinigrin, scutellarin, and baicalin based on their docking score (S), number of amino acids that interact, and binding pattern to fit the main protease binding pocket (**Table 5, Fig. 4**).

As shown in **Figure 5**, the first hit, sinigrin, mediates a network of hydrogen bonding interactions with most of the essential amino acids within the active site—Gly143, His163, Glu166, Gln189, and Thr190—in addition to a hydrophobic interaction with the His41 hot residue. Extra hydrogen bonding interactions formed between sinigrin and Gln192, Cys145, and Pro168 might stabilize its binding within the active site. 2D and 3D analysis of the second hit, scutellarin, showed its binding through hydrogen bonding with Phe140, Cys145, His163, and Glu166. Moreover, a hydrophobic interaction was observed with Met165. The third hit, baicalin, interacts through hydrogen bonding with Phe140, Cys145, His163, Glu166, Gln189, and Gln192, and a Pi–H hydrogen interaction with Glu166.

The docking score, which represents the final score for binding energy, could be used to compare the binding affinity of different ligands to the same protein. Our three hits, sinigrin, scutellarin, and baicalin, attained high docking scores of –14.20, –15.29, and –14.75 kcal/mol, respectively. The docking scores of other natural compounds are illustrated in **Table 5**.

Twenty-four different pharmaceutical products previously reported to act against SARS-CoV and MERS-CoV were docked within the main protease binding site. The docking scores of the top candidates ranged from –7.79 kcal/mol to –11.75 kcal/mol (**Table 5**). Analysis of these market product binding modes showed that fluphenazine revealed the best binding pattern and the highest docking score (–11.75 kcal/mol). As shown in **Figure 5**, fluphenazine could mediate hydrogen bonding interactions with Met165, Gln189, Thr 190, and Gln192.

Chloroquine, Remdesivir, oseltamivir, ribavirin, lopinavir, ritonavir, and favipiravir, which are drugs recommended to be received by SARS-CoV-2-infected patients,[10] were also docked within the enzyme binding site as a reference. Chloroquine (docking score = –9.26 kcal/mol) showed a better binding pattern between those recommended medicines. It could bind through hydrogen bonding interactions with Met165, Thr190, and Gln192 residues and hydrophobic interaction with Glu166. Other recommended agents—Remdesivir, oseltamivir, ribavirin, lopinavir, ritonavir, and favipiravir—showed docking scores of –8.99, –8.88, –8.69, –8.64, –8.55, and –6.85 kcal/mol, respectively.

In a comparison of fluphenazine and chloroquine with sinigrin, sinigrin showed an excellent binding pattern with the SARS-CoV-2 main proteinase active site, as illustrated in **Figure 5**. Moreover, it attained a promising docking score compared with fluphenazine and all the SARS-CoV-2-recommended regimens. Sinigrin is one of the previously reported natural compounds that affect SARS-CoV;[83] its docking result reveal it to be a hot candidate for trial against SARS-CoV-2's main proteinase enzyme inhibition.

Table 5. Docking Energy Scores (S) for the Collected Database (in kcal/mol).

Compound	Docking Score	Compound	Docking Score
Natural Compounds		Market Products	
Natural compounds affecting SARS-CoV		Market products affecting SARS-CoV and MERS-CoV	
Scutellarin	−15.29	Fluphenazine	−11.75
Sinigrin	−14.2	Toremifene	−11.72
Hesperetin	−14.19	Amodiaquine	−11.57
Myricetin	−13.92	Mefloquine	−11.42
Baicalin	−12.87	Monensin	−11.26
Aurantiamide	−11.24	Tamoxifen	−11.15
Lycorine	−10.1	Thiothixene	−10.71
Glycyrrhizin	–9.49	Dasatinib	−10.65
Aloe-emodin	–9.37	Resveratrol	−10.41
Tryptanthrin	–9.17	Chlorophenoxamine	−10.34
Natural compounds affecting MERS-CoV		Nocodazole	−10.19
Kazinol F	−12.70	Imatinib	–9.56
Kazinol A	−12.57	Anisomycin	–9.50
4,7-Trihydroxyflavane	−12.41	Cycloheximidine	–9.26
Hydroxyisolonchocarpin	−12.25	Chlomipramine	–9.24
Harringtonine	−12.15	Benzotropine	–9.24
Homoharringtonine	−11.93	Astemizole	–8.51
Kazinol B	−11.84	Emetine	–8.46
Broussoflavan A	−11.71	Fluspirilene	–8.45
Broussochalcone B	−11.58		
Broussochalcone A	−11.43	Promethazine	–8.06
Papyriflavonol A	−11.32	Salinomycin	–7.93
Resveratrol	−10.79	Hydroxychloroquine	–7.90
Gemcitabine	–7.79		
Trigocherin	–8.38	Standard reference regimen	
Natural compounds affecting IL-6		Chloroquine	–9.26
Eriodictyol	−14.72	Remdesivir	–8.99
Quercetin	−14.35	Oseltamivir	–8.88
Kaempferol	−14.13	Ribavirin	–8.69
Epigallocatechin-3-gallate	−13.55	Lopinavir	–8.64
Luteolin	−13.30	Ritonavir	–8.55
Statins	−12.38	Favipiravir	–6.85
Celastrol	−11.98		
Apigenin	−11.81		
Mitraphylline	−11.76		
Genistein	−11.39		
Asperuloside	−11.26		
Sophoricoside	−10.46		
Curcumin	–9.11		
Sakuranetin	–8.69		

Computational Approaches to Estimate Solubility and Permeability of Sinigrin. The bioavailability of the sinigrin compound was assessed using the Molispiration online property calculation toolkit, in particular, compliance with Lipinski's "rule of five," which describes molecular properties important for a drug's pharmacokinetics (ADME) in the human body. Sinigrin obeyed Lipinski's rule,[96] showing no violations: Molecular weight (M.wt) = 359.38 Da; number of hydrogen bond donors (nOHNH) = 5; number of hydrogen bond acceptors (nON) = 10, and calculated octanol/water partition coefficient (c log P) = –3.63. So, it is considered a promising drug candidate.

Practical Points

Drug Research and Development against COVID-19

Even though drugs such as ribavirin, lopinavir, favipiravir, Remdesivir, hydroxychloroquine, Arbidol, and Camostat

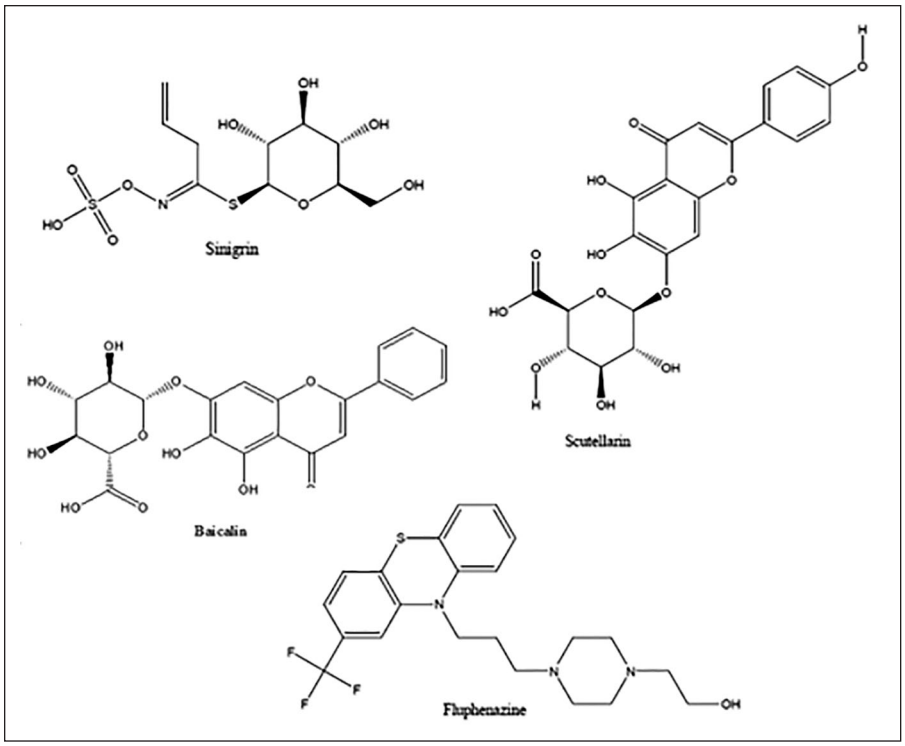

Figure 4. Top 4 hit compounds under docking investigation.

mesylate should be taken into consideration as an urgent measure, we ought to consider the following practical facts about COVID-19:

- SARS-CoV-2 is an RNA beta-coronavirus with mutations in nsp1, nsp3, nsp15, and gene S that are associated with its epidemic behavior. COVID-19 has seven major target proteins (protease, Hel, hemagglutinin, esterase, membrane, envelope, and spike proteins).
- Activation of SARS-CoV (S) protein resulted from sequential cleavage by the endosomal cysteine protease cathepsin L, and another trypsin-like serine protease and drug target could both be essential for virus inhibition.
- Origin sequence and structural analyses of SARS-CoV-2 revealed virus similarity with ≥70%–96% homology with SARS-CoV and 50%–87% homology with MERS-CoV, which prompted the proposal, from the docking analysis results, that sinigrin and fluphenazine (sulfated nitrogenous compounds) may be considered promising COVID-19 protease inhibitors.

Fluphenazine (brand name Prolixin) is an antipsychotic medication used to treat schizophrenia and psychotic symptoms; it has previously reported activity as an SARS-CoV and MERS-CoV inhibitor. Currently, fluphenazine is not recommended for COVID-2 as a management regimen and may be considered a relatively safe candidate with minor common side effects, like lethargy, dizziness, nausea, loss of appetite, sweating, and dry mouth.[97] Sinigrin is an allylglucosinolate present in plants of the Brassicaceae family, such as broccoli and brussels sprouts, and *Brassica nigra* seeds (mustard seeds).[98] The docking score indicated that it is almost twice as potent as products from the reference regimen (Remdesivir, oseltamivir, ribavirin, lopinavir, ritonavir, and favipiravir).

- Statistics from WHO reports for confirmed cases and deaths have revealed that temperature may affect the virus. This investigation is aligned with previously reported data that showed the consequences of different environmental states on coronavirus viability.[49–51] On the other hand, countries in the southern hemisphere with high temperatures and low humidity have recorded an increasing number of infected cases, which may be attributed to the formation of virus aerosol particles and their accumulation in a large diameter as a result of lower humidity. This phenomenon could lead to increasing the risk of transmission via aerosol particles.
- To prevent contagion between individuals, it is advisable to avoid close contact with anyone showing symptoms of respiratory illness, such as coughing and sneezing. Wearing masks and gloves is helpful and could decrease the spread of infection.
- Although the rate of death is relatively low in comparison with old SARS-CoV, the high rate of

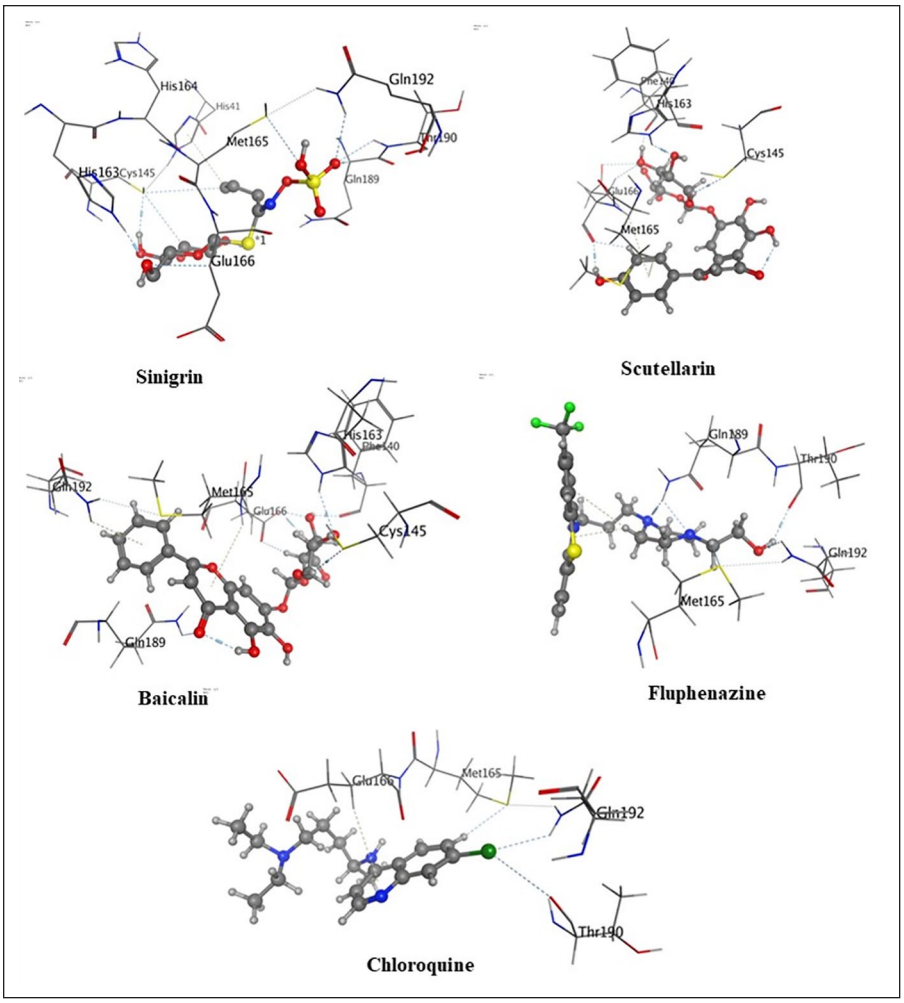

Figure 5. 3D representations of the most promising compounds with the main protease active site of SARS-CoV-2.

transmission leads to pandemic categorization of the virus by the WHO, which consequently may lead to many economic disasters in the event that no treatment or vaccine is found for a long time.

- Ground-glass opacities, glass nodules, pleural effusion, mediastinal lymphadenopathy on CT scan, and x-ray white lung are the main features of clinical radiology for COVID-19.

Proposed Research Agenda

- Further research on all aspects of the disease is needed to elaborate on the mode of infection (especially concerning the rate of asymptomatic patients), different genetic susceptibilities, virus genomic sequence, and beneficial treatments.
- The high prevalence of COVID-19 in some nations compared with others may inform the relationship between people's genetic makeup and disease susceptibility.
- Plant or microbial natural products such as glucosinolate, flavones, and sulfated nitrogenous compounds could be promising for future research against the coronavirus family.

Complementary Treatment Candidates

- *Punica granatum* (pomegranate), *Peganum harmale* (harmel), *Eriobotrya japonica* Lindl. (loquat), *Urginea Scilla steinh* (red squill), *Artemisia annua* (anuual wormwood), *Allium porrum* (leek), *Allium ursinum* (wild garlic), *Allium sativum* (garlic), *Colocasia esculenta* (cocoyam), *Phragmites australis* (common reed), *Morus nigra* (blackberry), *Vitis vinifera* (grape seeds), *Glycine max* (L.) Merr (soybean), *Plantago asiatica* (Chinese plantain), *Clerodendrum trichotomum* (peanut butter tree), *Markhamia lutea* (Nile tulip), and *Eleutherococcus senticosus* (Siberian ginseng) may be contemplated as source materials for scientific and clinical studies,

as they could help in the development of cheap, effective, protective, complementary medicine in the African region. Therefore, we invite curious researchers to carry out detailed studies on nation medicinal plants and food.

- The herbal formula PM014[92] and preparation Echinaforce[87] could be helpful remedies against COVID-19. Clinical trials are recommended on the bases of previous art.

Drugs Need Further In Vitro, In Vivo, and In-Clinic Studies

- Supplemental market products such as fluphenazine, toremifene, amodiaquine, mefloquine, monensin, and tamoxifen may demonstrate supportive effects against COVID-19. Future clinical studies are recommended to investigate their possible role in the prevention and treatment of SARS-CoV-2 respiratory viral infections.
- Our obtained preliminary results from docking analysis revealed that sinigrin, scutellarin, and baicalin could have direct anti-SARS-CoV-2 activity through inhibition protease enzymes and may be considered potential candidates against COVID-19. Interestingly, the ADMET results of sinigrin showed good bioavailability.

General Recommendation

- Additional studies should also test the possibility of combining available recommended treatments with other natural agents or with repurposed standard therapeutics, as a multitarget therapy could help in reducing the risk of generating drug-resistant viruses.
- The authors wish to expand this research area not only for scientific soundness but also for potential druggability.[99]

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