

Effects of Plant Metabolites on the Growth of COVID-19 (Coronavirus Disease-19) Including Omicron Strain

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Abstract

According to recent reports out of India, a new strain of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) B.1.1.529 Omicron virus has emerged. In comparison to the Wuhan (WHU) strain and the delta variant, this variant showed a far stronger effect on the angiotensin converting enzyme2 (ACE2) receptor. There are several medicinal compounds in plant metabolites, and their diverse chemical structures make them ideal for the treatment of serious illnesses. It's possible that some of these could be useful alternative pharmaceuticals, as well as a starting point for the repurposing of existing medications and new chemical discoveries. SARS-CoV-2 infection triggered a worldwide epidemic of the severe acute respiratory syndrome (SARS). There have been trials for different therapies for SARS-CoV-2 and so also there are recent announcements of extensive research into the development of viable medicines for this global health calamity. After a thorough examination of plant-derived treatments for COVID-19, investigators in the current study decided to focus on plant-derived secondary metabolites (PSMs). According to some researchers, new MDR (Multi-Drug Resistant) antibiotics may one day be developed due to the adaptability of secondary metabolites. Identifying plant metabolites that can treat a wide range of viral infections was one of the study's aims. Many natural medications that could be recommended for the treatment of COVID-19 were discovered as a result of this research, including remedies from plant families, viral candidates that are susceptible, antiviral assays, and mechanisms of therapeutic action. The findings of this study will inspire further research and speed up the development of new antiviral plant-based medications.

Categories: Preventive Medicine, Infectious Disease, Nutrition

Keywords: covid-19, antiviral activity, metabolites, medicinal plants, medication, therapeutic medicine

Introduction And Background

Conferring to the WHO, the SARS-CoV-2 B.1.1.529 Omicron strain was discovered in Botswana and first reported in India on December 24 [1-8]. When compared to the WHU strain and the delta variation, this variant had stronger angiotensin converting enzyme2 (ACE2) receptor connections. Strain-specific immunological protection is a pipe dream in contexts where present vaccination coverage, cross-protection, and herd immunity are unsolved, making strain-specific immunological protection impossible [B.1.1.529]. Between days 189 and 217, SARS-CoV-2 titers increased by 54.4-fold (Ancestral), 21.9-fold (Alpha), 24.5-fold (Beta), 24.4-fold (Delta), and 20.1-fold (Delta), respectively (Omicron) [3-9].

A comparison of the anti-rS IgG activity of the same SARS-CoV-2 strains was made at the same time points across the same period of time [10-11]. The recently discovered Omicron strain (B.1.1.529) poses such a big threat, everyone is wondering when this epidemic will come to an end [12-14]. Discovered on November 11, 2021, the substantially changed Omicron strain originated in Botswana and South Africa. The substantial number of mutations that have occurred in Omicron's spike protein compared to the original Wuhan strain have reduced its binding efficacy to the ACE2 receptor. The hot-spot interaction between B.1.1.529 and hACE2 has been shifted from its prior location in this release. Humans, bats, and other mammals are infected with noroviruses, which spread through the respiratory tracts. the 2019 new coronavirus (2019-nCoV), a rapidly spreading respiratory infection that was first discovered in the Chinese city of Wuhan, is now known as the Coronavirus Disease 2019 (COVID-19) [15-17]. The World Health Organization (WHO) has declared it a global pandemic because it has spread to 216 countries and killed more than 0.5 million people.

So far, human coronaviruses have been discovered in seven different forms, including the human coronavirus (HCoV) OC43, the HCoV-229E, the human coronavirus (HC) VHKU1, the HCVHKU2, the HCVHKU3, the SARS-CoV-2, the Middle East Respiratory Syndrome coronavirus (MERS-CoV), and the newly discovered virus in 2019 [18-20]. The viruses MERS-CoV, SARS-CoV-2, and novel coronavirus (nCoV), to name just a few, have sparked the interest of virus scientists all around the world. As a result of a SARS outbreak in Guangdong in 2003, 8,000 individuals were infected and 800 people died throughout 26 different countries [20-24]. Only a decade later, another coronavirus wreaked havoc around the world, leading to the MERS pandemic, which sickened 2,494 people and claimed the lives of 858 [25-27]. When it came to the outbreak of the COVID-19 pandemic caused by the SARS CoV-2 virus, the results were devastating. China

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was the first country to be infected with SARS CoV-2 [28-30]. First, the virus spread to several countries outside of the United States. Then it spread to the United Kingdom. Patients with COVID-19 have a higher risk of death and morbidity because of pathobiology components such as the viral response and hyperbolic host reaction. With Brazil, Mexico, and Peru serving as new SARS CoV-2 hotspots in Latin America, the virus has spread to the region [51]. In severe COVID-19, cytokine levels (IL-6, IL-10, and TNF- α), lymphopenia (in both CD4⁺ and CD8⁺ T cells), and decreased interferon (IFN) synthesis in CD4⁺ T cells are all related to higher cytokine levels, which are all life-threatening. A specific drug, vaccine, or other certified therapeutic treatment for SARS-CoV-2 has not been developed, resulting in substantial morbidity and mortality among persons who have been exposed to the virus [32-33]. As a result of their healing capabilities, medicinal plants have been essential to human health since the beginning of time [34-35]. Medical plants and herbs are used therapeutically by more than 80% of the global population, according to the World Health Organization [36-39]. Antiviral compounds produced from a wide variety of plants have been used in numerous studies, all of which have been found to be effective [40]. Chemicals developed from antiviral plant secondary metabolites (PSMs) and compounds generated from medicinal plants are being tested around the world to avert this global catastrophe. Papain-like and 3CL proteases, as well as ACE2 protein fusion, have been shown to interfere with CoV replication by plant metabolites according to National Cancer Institute research. Researchers are currently using PSMs to screen for new compounds produced by medicinal plants that could be useful to treat a variety of diseases, including COVID-19 [41-44].

As a result, the current review deals with all available plant-derived antiviral metabolites which are available as an alternative approach against COVID-19. In order to create targeted treatments for newly found diseases, researchers must first understand the structure, life cycle, pathogenicity, cell signaling, epidemiology, pharmaceutical targets, and drug discovery process of these viruses [45-46].

Review

Epidemiology, molecular organization, and life cycle of the SARS CoV-2 virus

There has been an outbreak of SARS CoV-2 in China's Wuhan seafood market in December 2019, making it the most damaging virus epidemic since SARS CoV and MERS [47-49]. It has been found that the virus can spread by close contact with infected people or exposure to coughing, sneezing, and respiratory droplets. According to reports, it has spread to 216 countries and killed about 0.5 million people. Over 11 million people have been infected with SARS CoV-2 in the United States and its allies like Russia and the European nations of France, Italy, Germany, Spain, and the United Kingdom before it [50-55]. An RNA genome of between 26.4 and 31.7 kb, and a crown-like glycoprotein on its surface, characterizes SARS CoV-2, which can be pleomorphic. SARS CoV is more closely linked to MERS than MERS is to SARS CoV. The RNA genome of CoV-2, on the other hand, is considered to be one of the largest among RNA viruses. One or more of the remaining four open reading frames (ORFs), including the envelope glycoprotein or spike protein (S), envelope (E), membrane (M), and nucleocapsid, encodes non-structural proteins, whereas the other four ORFs encode structural proteins. Host cell membrane permeability and virus-host cell interaction are mediated by the S and E proteins, respectively, respectively [56-64]. The nucleocapsid (N) protein is generally engaged in the processing of the helical rib nucleocapsid complex, which contains various auxiliary proteins, while the M protein is known as the coronavirus assembly's principal organizer [61-63, 65]. The SARS CoV-2 genome has been shown to include six different mutations, three of which have been found in the 1ab gene and two in the S gene. According to the results of a proteomic investigation, SARS CoV-2 and SARS CoV are quite similar, but two proteins are not. Upon entering the body, SARS CoV-2 attaches to the receptor-binding domain (RBD) via the virion's surface glycoprotein (Spike-protein), which then tries to activate the hACE2 receptor in order to complete its life cycle. For the SARS CoV-2 to enter the body, it requires the viral receptor, ACE2, as well as the cellular transmembrane serine protease 2 (TMPRSS2). However, the virus's envelope and capsid are destroyed when the SARS CoV-2 virion particle merges with the host cell membrane. For translation of ORF1a and ORF1ab polypeptides into the host cell's cytoplasm, the virus injects its genetic material (RNA), which functions as an mRNA. There are 16 non-structural proteins (NSP) that are involved in replication and transcription after 3CLpro removes them from the polypeptides. After being taken over by SARS CoV-2, infected cells begin to synthesize proteins. SARS CoV-2 is assembled into new virion particles by the immune system in this circumstance. Assembled viral nucleic acids and proteins are subsequently transported into the ERGIC lumen and expelled from the cells through exocytosis. The virions produced by infected cells spread to other types of human cells. All stages of SARS can be divided into three: asymptomatic, non-severe symptomatic, and severe infection [66,67].

Elevated levels of cytokines and chemokines have been observed in SARS CoV-2 patients; cytokines are especially high in patients admitted to intensive care units (ICU's). A patient's serious condition is brought on by these unnaturally high levels [68-70]. There are two forms of spike glycoprotein, the primary mediator of SARS CoV-2, and the enzyme 3CLpro of SARS-CoV-2 shares 99.02 percent sequence identity with 3CLpro of SARS-CoV, which is also quite similar to bat SARS CoV 3CLpro. A greater affinity for the host cell receptor is seen in SARS CoV-2 than in SARS CoV itself (194). The substrate-binding site of bat SARS CoV-2 has undergone significant strategic changes, and SARS CoV-2 has 12-point mutations compared to SARS CoV. Major hydrogen bonds are disrupted and the receptor binding site is altered by SARS-CoV-2 3CLpro mutations (RBS). SARS CoV-2 vaccine development is complicated by the fact that recurrent mutations can

lead to new strains with different pathogenicity [71].

The main drug targets of SARS CoV-2

Multi-viral infections can be successfully treated by interfering the human host-virus interactions. Anti-COVID-19 drugs may find easy targets in the key structural proteins of SARS CoV-2. There is a total of 16 NSPs that can be examined as well. SARS CoV-2 vaccine/drug development is hampered by the occurrence of repetitive recombination events. Although SARS-CoV-2 and CoV identify the same receptor (ACE2) in humans, there is a considerable difference in antigenicity between SARS-CoV and SARS-CoV2, which has important implications for the development of therapeutic alternatives against this rapidly expanding virus. As with SARS-CoV, the spike protein of SARSCoV-2 has a higher affinity for the ACE2 receptor than does that of SARS-CoV, but the RBD (Receptor Binding Domain) of SARS-CoV-2 is less compatible with hACE2. TMPRSS2 and MPRSS2 are two of the most important SARS CoV-2 enzymes, which are responsible for S-protein activation and are interesting targets for COVID therapy [72-74].

Effective therapeutics and SARS-CoV-2

Vaccines and pharmaceutical compounds against SARS-CoV-2 are being researched extensively, although no cures have yet been found. It's also possible to manage COVID-19 by using interferon treatments, monoclonal antibodies, oligonucleotides and small-molecule medications and vaccines. Coronavirus epidemics can be treated with existing drugs, but this is not the only option for eliminating the sickness. There's been a great deal of attention paid to developing therapeutic drugs for the COVID-19 outbreak. Researchers from a variety of fields are working together to come up with new therapeutic options. In contrast, testing ideas for systematic drug recombination may be difficult due to the high costs and long lead times associated with experiments resulting from drug recombination [75].

Control of SARS COV-2 with synthetic drugs

Licensed, repurposed drugs are currently being used in clinical trials, but focused antiviral treatments and vaccines are still urgently needed in the marketplace [75-76]. Bioengineered and vectored antibodies, cytokines, and nucleic acid-based medicines that target virus gene expression have all been discovered as promising treatments for coronavirus infections. Repurposing medications such as favipiravir, remdesivir, lopinavir, ritonavir, nebulized-interferon, chloroquine, hydroxychloroquine, ribavirin, and interferon (IFN) have been demonstrated to be beneficial in the treatment of COVID-19, as well. Also being examined in clinical trials are additional drugs, including a peptide vaccine (mRNA-1273) and antibody treatment [77]. When it comes to the treatment of COVID-19, plasma therapy has recently shown promising outcomes [76]. A number of immunoinformatic approaches are being used by researchers throughout the world in an effort to identify some of the most promising treatment and vaccine candidates against this deadly virus. There is therefore an urgent requirement for COVID-19 therapies/drugs that are safe, effective, and reasonably priced with low side effects. As a source of natural antiviral chemicals, PSMs have the potential to be a viable alternative to standard pharmaceuticals, however, some PSMs can also be dangerous and expensive. Plant-based medications are becoming more and more popular on a daily basis. Crude plant extracts can be beneficial or dangerous depending on the amount employed; if processed correctly, higher activity may be demonstrated [78-80]. Crude extracts have also been shown to target numerous locations within a virion particle at the same time, according to the research. SARS-CoV-2 has not been tested for this. PSMs can disrupt intermediate metabolisms, interfere with DNA/RNA synthesis and function, obstruct normal cell communication (quorum sensing), and cause clotting of cytoplasmic constituents. SARS CoV antiviral activities are found in several plant metabolites [68]. The pathogenic process is influenced by plant-based compounds in a number of ways. When it comes to the human body's redox status, protein kinases, and transcription factors as well as adhesion molecules and cytokines, curcumin, for example, has anti-cancer and anti-proliferative capabilities. SARS CoV-2 anti-SARS CoV PSMs may be a valuable therapeutic target, according to an in-silico investigation. Modern methods for isolating lead compounds from crude extracts include maceration, percolation, decoction, reflux extraction, Soxhlet extraction, pressurized liquid extraction, supercritical fluid extraction, ultrasound extraction, microwave extraction, pulsed electric field extraction, enzyme extraction, hydro distillation, and steam distillation [81]. It is possible to identify new anti-SARS CoV-2 chemicals much more quickly using these techniques. Plant metabolomics is also being utilized to aid in the identification of new plant-based medicines [81-82].

Synthetic drugs and COVID-19 a hope in PSMs

Low molecular weight PSMs are produced by plants to protect themselves from a wide variety of herbivores and microorganisms. The use of these potent natural sources to treat a wide range of human ailments was common prior to the invention of allopathic medications. Plant metabolites, in particular, are being studied as potential lead molecules in the fight against human diseases because of microbial sickness resistance to allopathic treatments. Furthermore, about 35% of the world's medication supply is derived from natural plant or herb sources (worth 1.1 trillion US dollars). Researchers are attempting to produce new and current medicines derived from a variety of herbal therapies in order to overcome this microbial resistance battle. SARS CoV and SARS CoV-2 share significant characteristics (both of them belong to beta family, containing the same genetic material-RNA, and using the same receptor for viral attachment-ACE2, with an 86 percent identity and 96 percent similarity of genome, with almost the same pathogenesis). This means that

previously identified antiviral plant metabolites against SARS CoV can be considered COVID-19 drug candidates. Antiviral medication research is currently constrained by the economic impact of viral infections around the world [83-85]. As opposed to other antiviral capabilities, several PSMs have already demonstrated anti-SARS CoV action. These findings point to the prospect of developing new medications and chemicals that are more customized to the needs of the patient. There is therefore a possibility of utilizing plants in the war against COVID19. Naturally occurring metabolites derived from a wide variety of plant species may be effective in the fight against COVID-19, according to findings from literature [86]. (Table 1)

| Name of the plant | Active metabolite | Action | Dosage |
|-------------------|-------------------------|---|---------------------------------------|
| Asvagandha | Withaferin A | Anti covid 19 activity, Anti pyretic, Anti microbial, Antibacterial, Antioxidant, Immunomodulator, | Powder 3-6 gm |
| Guduchi | Tinosporin | Anti pyretic, Antioxidant, Immunomodulator | Fresh juice-10 -20 ml; Powder -2-6 gm |
| Kalamegha | Andrographolide | Antiviral, Antipyretic, Antiperiodic, Immune Enhancement, Hepatoprotective | Power 1-3 gm; fresh juice 5-10 ml |
| Tulasi | Bornylacetate, Cadinene | Anti viral, Antifungal, Antibacterial, adaptogenic (anti stress) | Fresh juice 10-20 ml |
| Tvak | Cinnamaldehyde | Anti complement activity, anti allergic activity | Powder 1 -3 gms |
| Adaraka | Alpha curcumene | Anti bacterial, Anti histaminic, Anti oxidant, Anti inflammatory | Fresh juice 5-10 ml; powder 1-2gm |
| Vasa | Vascine | Brochodilator activity, Haemostatic, advantages in attenuating the critical inflammatory stages of Covid 19 | Leaf juice 10-20 ml |
| Sathi | Hedychenone | Anti bacterial, anti fungal, Anti inflammatory, Hypoglycaemic, 34 Vasodilator, relieves paraxysmol attack of dyspnoea, Tranquillizer | Powder : 1-3 gm |
| Puskaramula | Alantolactone, | Anti pyretic, Anti fungal, Anti microbial, Bacteriostatic, Fungistatic, Anti inflammatory, Anti histaminic, effective against bronchospasm, Hypoglycaemic, Anti anginal, hypolpidemic | Powder 1-3 gm |

TABLE 1: Name of the plants and the active metabolites used for COVID 19 treatment protocol

Action and structure of PSM

An antiviral component can be found in many different plant species. HIV, Dengue, Simian, and human rotavirus flavonoid molecules are widely disseminated low molecular weight phenolic HIV, Dengue, Simian, and bovine viral molecules. SARS CoV, Influenza virus, hepatitis B virus (HBV), herpes simplex virus (HSV), hepatitis C virus (HCV), vesicular stomatitis virus (VSV), and the Newcastle disease virus were all successfully treated with this compound, which demonstrated significant antiviral activity (NDV). Apigenin and quercetin, flavonoid-type medications, inhibited Mpro enzymes and were effective against SARS CoV virus particles, with IC50 values of 38,4 2.4 M and 23.8 M, respectively. SARS CoV-2 Mpro can be suppressed by flavonoid medications, according to an in-silico study. The heterocyclic ring structure of alkaloids is what distinguishes them from other naturally occurring chemical molecules. Some of them include tropanes (pyrrolidines), is quinoline purines, imidazole's, quinolizidine's and indoles (piperidines), as well as pyrrolizidines. There is a lot of promise in alkaloids for treating HIV-1, HSV-1, HSV-2, DNV, VSV, and influenza viruses (NDV). It was discovered that anti-SARS alkaloids such as emetine and 7-methoxy cryptolerance inhibit protease enzymes, RNA synthesis, and protein synthesis. SARS Cove's nucleic acid intercalating agent is tetrandrine, factionalize, catharanthine, and lycorine, which degrade nucleic acids and block spike and nucleocapsid proteins. SARS CoV and SARS CoV-2 antiviral activity was found in 10Hydroxyusambarensine and Crypto quindoline, two alkaloid compounds extracted from African medicinal plants. Chloroquine, an alkaloid derivative, has been found to have anti-SARS CoV-2 activity. Alkaloids in the form of PSMs could therefore serve as potential treatment targets for COVID-19. Saponins (amphipathic glycosides) are another class of PSMs found in plants that have antiviral activity against Newcastle disease virus (NDV), Simian (SA-11) virus, Murine norovirus (MNV), Feline calicivirus (FCV), RSV, VSV, HSV-1, HSV-2, HIV-1, Epstein-Barr virus (EBV), (SA-11), and human rotavirus (HCR3). Five terpenes derived from plant-produced carbon isoprene make up the most diverse and biggest class of PSM. Sesterterpenes, hemiterpenes, and sesquiterpenes are all types of terpenes [87-88]. The following viruses were shown to be resistant to them: In addition to HSV-1, poliovirus type 2, and vesicular stomatitis virus (VSV), bovine viral diarrhea virus, HSV-1, and HIV-1, HIV-2, SIV mac 251, SARS-CoV, and Influenza A and B viruses. There were ten diterpenes, two sesquiterpenes, and two triterpenes with IC50 values of 3-10 M. The terpene Ginkgolide A

has been shown to have a strong inhibitory effect on the SARS CoV-2 protease enzyme in computer simulations [84]. Human Rotavirus, influenza A, HSV, Coxsackie B3, and VSV have been shown to be inhibited by carbohydrates (monosaccharides, disaccharides, polysaccharides, and oligosaccharides) [87]. Acyclovir is a Food and Drug Administration (FDA)-approved antiviral medication derived from *Carissa edulis* [88]. Herpes simplex virus, chickenpox, and shingles are among the most prevalent illnesses treated by this medication. It is possible to establish the group basic structure of a number of significant chemicals.

Obstacles in the way of future drug development insights

"Drug discovery from plant metabolites" refers to the extraction and purification of active components from conventional medications [89]. The chemical structures of natural plant products are complex and vary widely among species. Some PSMs are responsible for the biological activity of herbal medications whereas others belong to a different category altogether (see below). The molecular targets of PSMs are diverse. In the search for targets, researchers may turn to a variety of molecules, including enzymes, mediators, transcription factors, and even DNA. An in-depth knowledge of the chemical composition of plants allows for a more accurate appraisal of their potential and medical worth. There are many factors that contribute to the success of the transition of a bioactive molecule into a commercially viable pharmaceutical in recent decades [90,91]. This can be done with the help of cutting-edge technology and well-established techniques. The screening of natural items for the creation of new medications has been hastened by modern technology. High-throughput methods such as gas chromatography-mass spectrometry (GC-MS), nuclear magnetic resonance (NMR), infra-red (IR), high performance liquid chromatography (HPLC), and high-performance thin-layer chromatography (HPTLC) are essential for the development of strong and prudent lead compounds that can be progressed from a screening hit to a therapeutic candidate through structural elucidation and structure recognition confirmation. Innovative technology allows us to conduct research on novel compounds by leveraging computer programs and databases to identify common items as an important source for medication discovery. Innovative new technology is reshaping the study of herbal medicine and how it can be used [92,93].

However, a number of elements play a role in the translation of an intriguing chemical into a useful treatment alternative. These characteristics include the compound's exceptional pharmacokinetic profile, availability, bioavailability, and intellectual property. In vivo testing is critical before moving further with animal experiments or clinical trials in the future. Even if a medication shows promise in vivo, a poor pharmacokinetic profile may render it ineffective in animal model experiments. Target compounds are kept in close touch with cells when tested in humans, but in animal models, they may lose some of their bioactivity as a result of many processes [94,95]. The bioavailability of curcumin, for example, has prevented it from being commercialized as a medicine despite its numerous health benefits. Epigallocatechin gallate (EGCG), another fascinating medicinal candidate, has showed antioxidant, antihypertensive, anticancer, antibacterial, and anti-inflammatory potential but, like curcumin, has failed to obtain pharmacological classification for the same reason [96-99].

Researchers throughout the world are coming up with new approaches to deal with these issues. The bioavailability of a drug can be improved by administering it in a different way [99]. Andrographolide, an anti-inflammatory chemical, has a twofold increase in bioavailability when given intravenously rather than orally [100]. Adjuvant systems, drug delivery systems, nano-formulation of a medicine, and structural analogy change are further methods for increasing a target chemical's bioavailability [100,101]. Pharmacokinetic characteristics, such as absorption, distribution, metabolism, and excretion, can potentially be altered to improve a substance's potential to be used as a therapeutic agent. It is critical that the World Health Organization (WHO), FDA, European Medicines Agency (EMA), World Trade Organisation (WTO), International Conference on Harmonization (ICH), World Intellectual Property Organization (WIPO) collaborate on the development of specific protocols for the discovery of novel bioactive compounds [101,102]. Indeed, there is an urgent need for specific protocols for the discovery of novel bioactive compounds, and related organizations, companies, and agencies must collaborate on this effort. A wide range of serious illnesses brought on by lethal viruses have already showed promise in the treatment of plant-derived medicines, which should be tested against SARS-CoV-2.

SARS CoV-2 has been shown to have seven major pharmacological targets. Molecular docking can save both time and money when screening PSMs for drug establishment. MERS has been shown to be effectively vaccinated against using animal models, target antigens, and vaccine candidates generated using computational biology [103,104]. There is, however, a lack of in-depth research on PSMs as an alternative to pharmaceuticals. SARS-CoV-2 druggability investigations have become a time-saving method by recommending possible antiviral plant metabolites or screening. Without a clinical trial pathway in place, many promising candidates would not be able to move forward. PSMs will never be developed into modern medicines and will remain in journals or herbal concoctions. In the fight against antibiotic resistance, the plant is unquestionably an underappreciated source of new bioactive chemicals. As the amount of plant metabolites increases, PSM decryption progresses slower. SARS-CoV-2 secondary metabolites can be produced in a timely and ecologically safe manner using a biotechnological technique [105]. Secondary metabolic pathways require an in-depth knowledge of the genes and proteins involved. In food and drug research, omics approaches (transcriptomics, proteomics, and metabolomics) are essential. Genetic engineering of plant metabolites can assist in the manufacturing of a particular medication [106, 107]. The

quality of natural products must also be monitored. Consequently, laboratory assistance, qualified employees, and financing are all necessary for the discovery of natural resource-based drugs.

Conclusions

The review puts a light on how researchers from all around the world are analyzing the B.1.1.529 Omicron strain of SARS-CoV-2, about its discovery in Botswana and reporting in India. Many plants secondary metabolites are mentioned in our review and may be considered for high-quality IRB-approved clinical research RCTs. These compounds interfered with the essential machinery involved in the pathogenesis and reproduction cycle of the coronavirus. In vitro, in vivo, and in silico, numerous anti-SARS CoV and anti-SARS CoV-2 plant-derived compounds have been discovered. Antiviral bioactive substances can be found in abundance in plants. Plants with potential antiviral efficacy against SARS CoV and MERS may be an attractive treatment option for SARS CoV-2. We have reported here on nine plants that have antiviral activity against a variety of DNA/RNA viruses. The possible effects of such alternatives should be subjected to rigorously designed clinical research trials before being incorporated into practice

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Bedoya LM, Abad MJ, Sánchez-Palomino S, Alcami J, Bermejo P: Ellagitannins from *Tuberaria lignosa* as entry inhibitors of HIV. *Phytomedicine*. 2010, 17:69-74. [10.1016/j.phymed.2009.08.008](https://doi.org/10.1016/j.phymed.2009.08.008)
2. Al-Thibaut SA, Zaid IMA: Phytochemistry and pharmaceutical evaluation of *Balanites Egyptiac*: an overview. *J Exp Biol Agric Sci*. 2018;455-65. [10.18006/2018.6\(3\).453.465](https://doi.org/10.18006/2018.6(3).453.465)
3. Andleeb R, Ashraf A, Muzammil S, et al.: Analysis of bioactive composites and antiviral activity of *Iresine herbstii* extracts against Newcastle disease virus in ovo. *Saudi J Biol Sci*. 2020, 27:335-40. [10.1016/j.sjbs.2019.10.002](https://doi.org/10.1016/j.sjbs.2019.10.002)
4. Shakeri F, Gholamnezhad Z, Mégarbane B, Rezaee R, Boskabady MH: Gastrointestinal effects of *Nigella sativa* and its main constituent, thymoquinone: a review. *Avicenna J Phytomed*. 2016, 6:9-20.
5. Benassi-Zanqueta É, Marques CF, Valone LM, et al.: Evaluation of anti-HSV-1 activity and toxicity of hydroethanolic extract of *Tanacetum parthenium* (L.) Sch.Bip. (Asteraceae). *Phytomedicine*. 2019, 55:249-54. [10.1016/j.phymed.2018.06.040](https://doi.org/10.1016/j.phymed.2018.06.040)
6. Bonvicini F, Lianza M, Mandrone M, Poli F, Gentilomi GA, Antognoni F: *Hemidesmus indicus* (L.) R. Br. extract inhibits the early step of herpes simplex type 1 and type 2 replication. *New Microbiol*. 2014, 41:187-94.
7. Jannat K, Paul AK, Bondhon TA, et al.: Nanotechnology applications of flavonoids for viral diseases. *Pharmaceutics*. 2021, 13:10.3390/pharmaceutics13111895
8. Brian DA, Baric RS: Coronavirus genome structure and replication. *Curr Top Microbiol Immunol*. 2005, 287:1-30. [10.1007/3-540-26765-4_1](https://doi.org/10.1007/3-540-26765-4_1)
9. Brindley MA, Widrechner MP, McCoy JA, et al.: Inhibition of lentivirus replication by aqueous extracts of *Prunella vulgaris*. *Virology*. 2009, 6:8. [10.1186/1743-422X-6-8](https://doi.org/10.1186/1743-422X-6-8)
10. Callies O, Bedoya LM, Beltrán M, et al.: Isolation, structural modification, and HIV inhibition of pentacyclic lupane-type triterpenoids from *cassine xylocarpa* and *maytenus cuzcoina*. *J Nat Prod*. 2015, 78:1045-55. [10.1021/np501025r](https://doi.org/10.1021/np501025r)
11. Cao YG, Hao Y, Li ZH, Liu ST, Wang LX: Antiviral activity of polysaccharide extract from *Laminaria japonica* against respiratory syncytial virus. *Biomed Pharmacother*. 2016, 84:1705-10. [10.1016/j.biopha.2016.10.082](https://doi.org/10.1016/j.biopha.2016.10.082)
12. Chen C, Zuckerman DM, Brantley S, Sharpe M, Childress K, Hoiczky E, Pendleton AR: *Sambucus nigra* extracts inhibit infectious bronchitis virus at an early point during replication. *BMC Vet Res*. 2014, 10:24. [10.1186/1746-6148-10-24](https://doi.org/10.1186/1746-6148-10-24)
13. Cavanagh D: Coronavirus avian infectious bronchitis virus. *Vet Res*. 2007, 38:281-97. [10.1051/vetres:2006055](https://doi.org/10.1051/vetres:2006055)
14. César GZ, Alfonso MG, Marius MM, et al.: Inhibition of HIV-1 reverse transcriptase, toxicological and chemical profile of *Calophyllum brasiliense* extracts from Chiapas, Mexico. *Fitoterapia*. 2011, 82:1027-34. [10.1016/j.fitote.2011.06.006](https://doi.org/10.1016/j.fitote.2011.06.006)
15. Chen F, Yang L, Huang Y, Chen Y, Sang H, Duan W, Yang J: Isocorilagin, isolated from *Canarium album* (Lour.) Raeusch, as a potent neuraminidase inhibitor against influenza A virus. *Biochem Biophys Res Commun*. 2020, 523:183-9. [10.1016/j.bbrc.2019.12.043](https://doi.org/10.1016/j.bbrc.2019.12.043)
16. Chen SG, Leu YL, Cheng ML, et al.: Anti-enterovirus 71 activities of *Melissa officinalis* extract and its biologically active constituent rosmarinic acid. *Sci Rep*. 2017, 7:12264. [10.1038/s41598-017-12388-2](https://doi.org/10.1038/s41598-017-12388-2)
17. Chen Y, Peng H, Wang L, Zhao Y, Zeng L, Gao H, Liu Y: Infants born to mothers with a new coronavirus (COVID-19). *Front Pediatr*. 2020, 8:104. [10.3389/fped.2020.00104](https://doi.org/10.3389/fped.2020.00104)
18. Chiu LC, Zhu W, Ooi VE: A polysaccharide fraction from medicinal herb *Prunella vulgaris* downregulates the expression of herpes simplex virus antigen in Vero cells. *J Ethnopharmacol*. 2004, 93:63-8. [10.1016/j.jep.2004.03.024](https://doi.org/10.1016/j.jep.2004.03.024)

19. Cho WK, Kim H, Choi YJ, Yim NH, Yang HJ, Ma JY: Epimedium koreanum nakai water extract exhibits antiviral activity against porcine epidermic diarrhea virus in vitro and in vivo. *Evid Based Complement Alternat Med.* 2012, 2012:985151. [10.1155/2012/985151](https://doi.org/10.1155/2012/985151)
20. Choi JG, Jin YH, Lee H, Oh TW, Yim NH, Cho WK, Ma JY: Protective effect of Panax not ginsengroot water extract against influenza a virus infection by enhancing antiviral interferon-mediated immune responses and natural killer cell activity. *Front Immunol.* 2017, 8:1542. [10.3389/fimmu.2017.01542](https://doi.org/10.3389/fimmu.2017.01542)
21. Choi JG, Kim YS, Kim JH, Chung HS: Antiviral activity of ethanol extract of Geraniin herba and its components against influenza viruses via neuraminidase inhibition. *Sci Rep.* 2019, 9:12132. [10.1038/s41598-019-48430-8](https://doi.org/10.1038/s41598-019-48430-8)
22. Churqui MP, Lind L, Thörn K, Svensson A, Savolainen O, Aranda KT, Eriksson K: Extracts of equisetum giganteal and copier reticulate ducked show strong antiviral activity against the sexually transmitted pathogen herpes simplex virus type 2. *J Ethnopharmacol.* 2018, 210:192-7. [10.1016/j.jep.2017.08.010](https://doi.org/10.1016/j.jep.2017.08.010)
23. Karimi A, Rafeian-Kopaei M, Moradi MT, Alidadi S: Anti-Herpes Simplex virus type-1 activity and phenolic content of crude ethanol extract and four corresponding fractions of quercus brantii l acorn. *J Evid Based Complementary Altern Med.* 2017, 22:455-61. [10.1177/2156587216676421](https://doi.org/10.1177/2156587216676421)
24. Danciu C, Muntean D, Alexa E, et al.: Phytochemical characterization and evaluation of the antimicrobial, antiproliferative and pro-apoptotic potential of Ephedra alateDecyne. hydroalcoholic extract against the MCF-7 breast cancer cell line. *Molecules.* 2018, 24: [10.3390/molecules24010013](https://doi.org/10.3390/molecules24010013)
25. Derksen A, Kühn J, Hafezi W, Sendker J, Ehrhardt C, Ludwig S, Hensel A: Antiviral activity of hydroalcoholic extract from Eupatorium perfoliatum L. against the attachment of influenza A virus. *J Ethnopharmacol.* 2016, 188:144-52. [10.1016/j.jep.2016.05.016](https://doi.org/10.1016/j.jep.2016.05.016)
26. Donalisio M, Cagno V, Civra A, et al.: The traditional use of Vachellia nilotica for sexually transmitted diseases is substantiated by the antiviral activity of its bark extract against sexually transmitted viruses. *J Ethnopharmacol.* 2018, 215:403-8. [10.1016/j.jep.2017.11.039](https://doi.org/10.1016/j.jep.2017.11.039)
27. Erdelmeier CA, Cinatl J Jr, Rabenau H, Doerr HW, Biber A, Koch E: Antiviral and antiphlogistic activities of Hamamelis virginiana bark. *Planta Med.* 1996, 62:241-5. [10.1055/s-2006-957868](https://doi.org/10.1055/s-2006-957868)
28. Ghoke SS, Sood R, Kumar N, et al.: Evaluation of antiviral activity of Ocimum sanctum and Acacia arabica leaves extracts against H9N2 virus using embryonated chicken egg model. *BMC Complement Altern Med.* 2018, 18:174. [10.1186/s12906-018-2238-1](https://doi.org/10.1186/s12906-018-2238-1)
29. Fahmy NM, Al-Sayed E, Moghannem S, Azam F, El-Shazly M, Singab AN: Breaking down the barriers to a natural antiviral agent: antiviral activity and molecular docking of erythrina speciosa extract, fractions, and the major compound. *Chem Biodivers.* 2020, 17:e1900511. [10.1002/cbdv.201900511](https://doi.org/10.1002/cbdv.201900511)
30. Fehr AR, Perlman S: Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol.* 2015, 1282:1-23. [10.1007/978-1-4939-2438-7_1](https://doi.org/10.1007/978-1-4939-2438-7_1)
31. Ghazal EA, Khamis IMA, Elaw MHM: Chemical constituents of Capparis sinicalVeil. plant and its antimicrobial effects. *Middle East J Appl Sci.* 2015, 5:411-22.
32. Das K: Herbal plants as immunity modulators against COVID-19: a primary preventive measure during home quarantine. *J Herb Med.* 2022, 32:100501. [10.1016/j.hermed.2021.100501](https://doi.org/10.1016/j.hermed.2021.100501)
33. Glatthaar-Saalmüller B, Fal AM, Schönknecht K, Conrad F, Sievers H, Saalmüller A: Antiviral activity of an aqueous extract derived from Aloe arborescens Mill. against a broad panel of viruses causing infections of the upper respiratory tract. *Phytomedicine.* 2015, 22:911-20. [10.1016/j.phymed.2015.06.006](https://doi.org/10.1016/j.phymed.2015.06.006)
34. Gyuris A, Szlávik L, Minárovits J, Vasas A, Molnár J, Hohmann J.: Antiviral activities of extracts of Euphorbia hirta L. against HIV-1 and SIVmac251. *In Vivo.* 2009, 23:429-32.
35. Haasbach E, Hartmayer C, Hettler A, et al.: Antiviral activity of Ladanina067, an extract from wild black currant leaves against influenza A virus in vitro and in vivo. *Front Microbiol.* 2014, 5:171. [10.3389/fmicb.2014.00171](https://doi.org/10.3389/fmicb.2014.00171)
36. He W, Han H, Wang W, Gao B: Anti-influenza virus effect of aqueous extracts from dandelion. *Virology.* 2011, 8:538. [10.1186/1743-422X-8-538](https://doi.org/10.1186/1743-422X-8-538)
37. Helfer M, Koppensteiner H, Schneider M, et al.: The root extract of the medicinal plant Pelargonium sidoides is a potent HIV-1 attachment inhibitor. *PLoS One.* 2014, 9:e87487. [10.1371/journal.pone.0087487](https://doi.org/10.1371/journal.pone.0087487)
38. Heymann DL, Rodier G: Global surveillance, national surveillance, and SARS. *Emerg Infect Dis.* 2004, 10:173-5. [10.3201/eid1002.031038](https://doi.org/10.3201/eid1002.031038)
39. Hirano T, Murakami M: COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. *Immunity.* 2020, 52:731-3. [10.1016/j.immuni.2020.04.003](https://doi.org/10.1016/j.immuni.2020.04.003)
40. Haque MI, Chowdhury AB, Shahjahan M, Harun MG: Traditional healing practices in rural Bangladesh: a qualitative investigation. *BMC Complement Altern Med.* 2018, 18:62. [10.1186/s12906-018-2129-5](https://doi.org/10.1186/s12906-018-2129-5)
41. Hsieh CF, Chen YL, Lin CF, et al.: An extract from Taxodium distichum targets hemagglutinin- and neuraminidase-related activities of influenza virus in vitro. *Sci Rep.* 2016, 6:36015. [10.1038/srep36015](https://doi.org/10.1038/srep36015)
42. Wajid H, Kashif SH, Ibrar K, Isfahan T, Sadia Q, Bilal A, Muhammad NR: Medicinal plants: a repository of antiviral metabolites. *Future Virology.* 2017, 12:6. [10.2217/fvl-2016-0110](https://doi.org/10.2217/fvl-2016-0110)
43. Ibrahim AK, Youssef AI, Arafa AS, Ahmed SA: Anti-H5N1 virus flavonoids from Capparis sinaica Veill. *Nat Prod Res.* 2013, 27:2149-53. [10.1080/14786419.2013.790027](https://doi.org/10.1080/14786419.2013.790027)
44. Romero-Pérez GA, Egashira M, Harada Y, et al.: Orally administered Salacia reticulata extract reduces h1n1 influenza clinical symptoms in murine lung tissues putatively due to enhanced natural killer cell activity. *Front Immunol.* 2016, 7:115. [10.3389/fimmu.2016.00115](https://doi.org/10.3389/fimmu.2016.00115)
45. Ismail MM, Tang AY, Saif YM: Pathogenicity of turkey coronavirus in turkeys and chickens. *Avian Dis.* 2003, 47:515-22. [10.1637/5917](https://doi.org/10.1637/5917)
46. Darshani P, Sen Sarma S, Srivastava AK, Baishya R, Kumar D: Anti-viral triterpenes: a review. *Phytochem Rev.* 2022, 1-82. [10.1007/s11101-022-09808-1](https://doi.org/10.1007/s11101-022-09808-1)
47. Jassim SA, Naji MA: Novel antiviral agents: a medicinal plant perspective. *J Appl Microbiol.* 2003, 95:412-27. [10.1046/j.1365-2672.2003.02026.x](https://doi.org/10.1046/j.1365-2672.2003.02026.x)
48. Javed T, Ashfaq UA, Riaz S, Rehman S, Riazuddin S: In-vitro antiviral activity of Solanum nigrum against Hepatitis C virus. *Virology.* 2011, 8:26. [10.1186/1743-422X-8-26](https://doi.org/10.1186/1743-422X-8-26)
49. Jiang C, Luo P, Zhao Y, et al.: Carolignans from the aerial parts of Euphorbia sikkimensis and their anti-HIV

- activity. *J Nat Prod*. 2016, 79:578-83. [10.1021/acs.jnatprod.5b01012](https://doi.org/10.1021/acs.jnatprod.5b01012)
50. Kanne JP: Chest CT Findings in 2019 Novel Coronavirus (2019-nCoV) Infections from Wuhan, China: Key Points for the Radiologist. *Radiology*. 2020, 295:16-7. [10.1148/radiol.2020020241](https://doi.org/10.1148/radiol.2020020241)
 51. Garber A, Barnard L, Pickrell C: Review of whole plant extracts with activity against herpes simplex viruses in vitro and in vivo. *J Evid Based Integr Med*. 2021, 26:2515690X20978394. [10.1177/2515690X20978394](https://doi.org/10.1177/2515690X20978394)
 52. Knipping K, Garssen J, van't Land B: An evaluation of the inhibitory effects against rotavirus infection of edible plant extracts. *Virology*. 2012, 9:137. [10.1186/1743-422X-9-137](https://doi.org/10.1186/1743-422X-9-137)
 53. Lam SK, Ng TB: A protein with antiproliferative, antifungal and HIV-1 reverse transcriptase inhibitory activities from caper (*Capparis spinosa*) seeds. *Phytomedicine*. 2009, 16:444-50. [10.1016/j.phymed.2008.09.006](https://doi.org/10.1016/j.phymed.2008.09.006)
 54. Lan Jun, Jawan Ge, Jinan Yu, et al.: Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*. 2020, 581:215-20. [10.1101/2020.02.19.956235](https://doi.org/10.1101/2020.02.19.956235)
 55. Lani R, Hassandarvish P, Chiam CW, et al.: Antiviral activity of silymarin against chikungunya virus. *Sci Rep*. 2015, 5:11421. [10.1038/srep11421](https://doi.org/10.1038/srep11421)
 56. Lavoie S, Côté I, Pichette A, et al.: Chemical composition and anti-herpes simplex virus type 1 (HSV-1) activity of extracts from *Cornus canadensis*. *BMC Complement Altern Med*. 2017, 17:123. [10.1186/s12906-017-1618-2](https://doi.org/10.1186/s12906-017-1618-2)
 57. Lee JS, Ko EJ, Hwang HS, Lee YN, Kwon YM, Kim MC, Kang SM: Antiviral activity of ginseng extract against respiratory syncytial virus infection. *Int J Mol Med*. 2014, 34:183-90. [10.3892/ijmm.2014.1750](https://doi.org/10.3892/ijmm.2014.1750)
 58. Lee MH, Lee BH, Jung JY, Cheon DS, Kim KT, Choi C: Antiviral effect of Korean red ginseng extract and ginsenosides on murine norovirus and feline calicivirus as surrogates for human norovirus. *J Ginseng Res*. 2011, 35:429-35. [10.5142/jgr.2011.35.4.429](https://doi.org/10.5142/jgr.2011.35.4.429)
 59. Lin CW, Tsai FJ, Tsai CH, et al.: Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. *Antiviral Res*. 2005, 68:36-42. [10.1016/j.antiviral.2005.07.002](https://doi.org/10.1016/j.antiviral.2005.07.002)
 60. Liu M, Katerere DR, Gray AI, Seidel V: Phytochemical and antifungal studies on *Terminalia mollis* and *Terminalia brachystemma*. *Fitoterapia*. 2009, 80:369-73. [10.1016/j.fitote.2009.05.006](https://doi.org/10.1016/j.fitote.2009.05.006)
 61. Gonçalves JL, Lopes RC, Oliveira DB, et al.: In vitro anti-rotavirus activity of some medicinal plants used in Brazil against diarrhea. *J Ethnopharmacol*. 2005, 99:403-7. [10.1016/j.jep.2005.01.032](https://doi.org/10.1016/j.jep.2005.01.032)
 62. Lu R, Zhao X, Li J, et al.: Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020, 395:565-74. [10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8)
 63. Makau JN, Watanabe K, Mohammed MM, Nishida N: Antiviral activity of peanut (*Arachis hypogaea* L.) skin extract against human influenza viruses. *J Med Food*. 2018, 21:777-84. [10.1089/jmf.2017.4121](https://doi.org/10.1089/jmf.2017.4121)
 64. Mancini DAP, Torres RP, Pinto JR, Mancini-Filho J: Inhibition of DNA virus: Herpes-1 (HSV-1) in cellular culture replication, through an antioxidant treatment extracted from rosemary spice. *Brazilian J Pharm Sci*. 2009, 45:127-33. [10.1590/S1984-82502009000100016](https://doi.org/10.1590/S1984-82502009000100016)
 65. Mukhtar M, Arshad M, Ahmad M, Pomerantz RJ, Wigdahl B, Parveen Z: Antiviral potentials of medicinal plants. *Virus Res*. 2008, 131:111-20. [10.1016/j.virusres.2007.09.008](https://doi.org/10.1016/j.virusres.2007.09.008)
 66. Michaelis M, Doerr HW, Cinatl J Jr: Investigation of the influence of EPs® 7630, a herbal drug preparation from *Pelargonium sidoides*, on replication of a broad panel of respiratory viruses. *Phytomedicine*. 2011, 18:384-6. [10.1016/j.phymed.2010.09.008](https://doi.org/10.1016/j.phymed.2010.09.008)
 67. Maregesi SM, Pieters L, Ngassapa OD, et al.: Screening of some Tanzanian medicinal plants from Bunda district for antibacterial, antifungal and antiviral activities. *J Ethnopharmacol*. 2008, 119:58-66. [10.1016/j.jep.2008.05.033](https://doi.org/10.1016/j.jep.2008.05.033)
 68. Modi M, Nutan, Pancholi B, Kulshrestha S, Rawat AK, Malhotra S, Gupta S: Anti-HIV-1 activity, protease inhibition and safety profile of extracts prepared from *Rhus parviflora*. *BMC Complement Altern Med*. 2013, 13:158. [10.1186/1472-6882-13-158](https://doi.org/10.1186/1472-6882-13-158)
 69. Moradi MT, Rafeian-Kopaei M, Karimi A: A review study on the effect of Iranian herbal medicines against in vitro replication of herpes simplex virus. *Avicenna J Phytomed*. 2016, 6:506-15.
 70. Moses T, Goossens A: Plants for human health: greening biotechnology and synthetic biology. *J Exp Bot*. 2017, 68:4009-11. [10.1093/jxb/erx268](https://doi.org/10.1093/jxb/erx268)
 71. Mushi NF, Mbwambo ZH, Innocent E, Tewtrakul S: Antibacterial, anti-HIV-1 protease and cytotoxic activities of aqueous ethanolic extracts from *Combretum adenogonium* Steud. *Ex A. Rich (Combretaceae)*. *BMC Complement Altern Med*. 2012, 12:163. [10.1186/1472-6882-12-163](https://doi.org/10.1186/1472-6882-12-163)
 72. Namazi R, Zabihollahi R, Behbahani M, Rezaei A: Inhibitory activity of *Avicennia marina*, a medicinal plant in Persian folk medicine, against HIV and HSV. *Iran J Pharm Res*. 2013, 12:435-43.
 73. Gnocchi SR, Companion MVP, De Mello JCP, et al.: Antiviral activity of crude hydroethanolic extract from *Schamusterebinth folia* against herpes simplex virus type 1. *Planta*. 2017, 85:509-18. [10.1055/s-0042117774](https://doi.org/10.1055/s-0042117774)
 74. Ezekwesili-Ofilii Josephine Ozioma and Okaka Antoinette Nwamaka Chinwe Uzoma E, Akaka A. In: Uzoma EJ and Chinwe OAN, editors: *Herbal medicines in African traditional medicine*. IntechOpen. Philip F. Builders (ed): Intech open, London; 2019. 1:1-30. [10.5772/intechopen.80348](https://doi.org/10.5772/intechopen.80348)
 75. Nutan, Modi M, Dezzutti CS, et al.: Extracts from *Acacia catechu* suppress HIV-1 replication by inhibiting the activities of the viral protease and Tat. *Virology*. 2013, 10:309. [10.1186/1743-422X-10-309](https://doi.org/10.1186/1743-422X-10-309)
 76. Özçelik B, Kartal M, Orhan I: Cytotoxicity, antiviral and antimicrobial activities of alkaloids, flavonoids, and phenolic acids. *Pharm Biol*. 2011, 49:396-402. [10.3109/13880209.2010.519390](https://doi.org/10.3109/13880209.2010.519390)
 77. Park JY, Ko JA, Kim DW, et al.: Chalcones isolated from *Angelica keiskei* inhibit cysteine proteases of SARS-CoV. *J Enzyme Inhib Med Chem*. 2016, 31:23-30. [10.3109/14756366.2014.1003215](https://doi.org/10.3109/14756366.2014.1003215)
 78. Patoka J, Navratilova Z: *Achillea fragrantissima*: pharmacology review. *Clin Oncol*. 2019, 4:1601.
 79. Pedersen SF, Ho YC: SARS-CoV-2: a storm is raging. *J Clin Invest*. 2020, 130:2202-5. [10.1172/JCI137647](https://doi.org/10.1172/JCI137647)
 80. Pick A, Ling K, Khoo BF, Seah CH, Foo KY, Cheah RK: Inhibitory activities of methanol extracts of *Andrographis paniculata* and *Ocimum sanctum* against dengue-1 virus. *International Conference on Biological, Environment & Food Engineering*, Bali. 2014, 2014:6.
 81. Karimi A, Moradi MT, Saeedi M, Asgari S, Rafeian-Kopaei M: Antiviral activity of *Quercus persica* L.: high efficacy and low toxicity. *Adv Biomed Res*. 2013, 2:36. [10.4103/2277-9175.109722](https://doi.org/10.4103/2277-9175.109722)

82. Rebensburg S, Helfer M, Schneider M, et al.: Potent in vitro antiviral activity of *Cistus incanus* extract against HIV and Filoviruses targets viral envelope proteins. *Sci Rep*. 2016, 6:20394. [10.1038/srep20394](https://doi.org/10.1038/srep20394)
83. Rehman S, Ijaz B, Fatima N, Muhammad SA, Riazuddin S: Therapeutic potential of taraxacum officinale against HCV NS5B polymerase: in-vitro and In silico study. *Biomed Pharmacother*. 2016, 83:881-91. [10.1016/j.biopha.2016.08.002](https://doi.org/10.1016/j.biopha.2016.08.002)
84. Rothan HA, Zulqarnain M, Ammar YA, Tan EC, Rahman NA, Yusof R: Screening of antiviral activities in medicinal plants extracts against dengue virus using dengue NS2B-NS3 protease assay. *Trop Biomed*. 2014, 31:286-96.
85. Reichling J, Neuner A, Sharaf M, Harkenthal M, Schnitzler P: Antiviral activity of *Rhus aromatica* (fragrant sumac) extract against two types of herpes simplex viruses in cell culture. *Pharmazie*. 2009, 64:538-41. [10.1691/ph.2009.9597](https://doi.org/10.1691/ph.2009.9597)
86. Bhuiyan FR, Howlader S, Raihan T, Hasan M: Plants metabolites: possibility of natural therapeutics against the COVID-19 pandemic. *Front Med (Lausanne)*. 2020, 7:444. [10.3389/fmed.2020.00444](https://doi.org/10.3389/fmed.2020.00444)
87. Rittà M, Marengo A, Civra A, et al.: Antiviral activity of a *Arisaema tortuosum* leaf extract and some of its constituents against herpes simplex virus type 2. *Planta Med*. 2020, 86:267-75. [10.1055/a-1087-8303](https://doi.org/10.1055/a-1087-8303)
88. Lin CW, Tsai CH, Tsai FJ, et al.: Characterization of trans- and cis-cleavage activity of the SARS coronavirus 3CLpro protease: basis for the in vitro screening of anti-SARS drugs. *FEBS Lett*. 2004, 574:151-7. [10.1016/j.febslet.2004.08.017](https://doi.org/10.1016/j.febslet.2004.08.017)
89. Schaal B: Plants and people: our shared history and future. *Plants People Planet*. 2019, 1:14-19. [10.1002/ppp5.12](https://doi.org/10.1002/ppp5.12)
90. Schnitzler P, Schuhmacher A, Astani A, Reichling J: Melissa officinalis oil affects infectivity of enveloped herpesviruses. *Phytomedicine*. 2008, 15:734-40. [10.1016/j.phymed.2008.04.018](https://doi.org/10.1016/j.phymed.2008.04.018)
91. Kaushik S, Dar L, Kaushik S, Yadav JP: Anti-dengue activity of super critical extract and isolated oleanolic acid of *Leucas cephalotes* using in vitro and in silico approach. *BMC Complement Med Ther*. 2021, 21:227. [10.1186/s12906-021-03402-2](https://doi.org/10.1186/s12906-021-03402-2)
92. Shi H, Ren K, Lv B, Zhang W, Zhao Y, Tan RX, Li E: Baicalin from *Scutellaria baicalensis* blocks respiratory syncytial virus (RSV) infection and reduces inflammatory cell infiltration and lung injury in mice. *Sci Rep*. 2016, 6:35851. [10.1038/srep35851](https://doi.org/10.1038/srep35851)
93. Shamsabadipour S, Ghanadian M, Saeedi H, Rahimnejad MR, Mohammadi-Kamalabadi M, Ayatollahi SM, Salimzadeh L: Triterpenes and steroids from *Euphorbia denticulata* Lam. With anti-herpes symplex virus activity. *Iran J Pharm Res*. 2013, 12:759-67.
94. Shetty R, Ghosh A, Honavar SG, Khamar P, Sethu S: Therapeutic opportunities to manage COVID-19/SARS-CoV-2 infection: present and future. *Indian J Ophthalmol*. 2020, 68:693-702. [10.4103/ijo.IJO_639_20](https://doi.org/10.4103/ijo.IJO_639_20)
95. Soltan MM, Zaki AK: Antiviral screening of forty-two Egyptian medicinal plants. *J Ethnopharmacol*. 2009, 126:102-7. [10.1016/j.jep.2009.08.001](https://doi.org/10.1016/j.jep.2009.08.001)
96. Szlák L, Gyuris A, Minárovits J, Forgo P, Molnár J, Hohmann J: Alkaloids from *Leucocjum vernum* and antiretroviral activity of Amaryllidaceae alkaloids. *Planta Med*. 2004, 70:871-5. [10.1055/s-2004-827239](https://doi.org/10.1055/s-2004-827239)
97. Tang LI, Ling AP, Koh RY, Chye SM, Voon KG: Screening of anti-dengue activity in methanolic extracts of medicinal plants. *BMC Complement Altern Med*. 2012, 12:3. [10.1186/1472-6882-12-3](https://doi.org/10.1186/1472-6882-12-3)
98. Shoji M, Woo SY, Masuda A, et al.: Anti-influenza virus activity of extracts from the stems of *Jatropha multifida* Linn. Collected in Myanmar. *BMC Complement Altern Med*. 2017, 17:96. [10.1186/s12906-017-1612-8](https://doi.org/10.1186/s12906-017-1612-8)
99. Theisen LL, Erdelmeier CA, Spoden GA, Boukhallouk F, Sausy A, Florin L, Muller CP: Tannins from *Hamamelis virginiana* bark extract: characterization and improvement of the antiviral efficacy against influenza A virus and human papillomavirus. *PLoS One*. 2014, 9:e88062. [10.1371/journal.pone.0088062](https://doi.org/10.1371/journal.pone.0088062)
100. Tolo FM, Rukunga GM, Muli FW, et al.: Anti-viral activity of the extracts of a Kenyan medicinal plant *Carissa edulis* against herpes simplex virus. *J Ethnopharmacol*. 2006, 104:92-9. [10.1016/j.jep.2005.08.053](https://doi.org/10.1016/j.jep.2005.08.053)
101. Tung NH, Kwon HJ, Kim JH, Ra JC, Ding Y, Kim JA, Kim YH.: Anti-influenza diaryl heptanoids from the bark of *Alnus japonica*. *Bioorganic Med Chem Lett*. 2010, 20:1000-3. [10.1016/j.bmcl.2009.12.057](https://doi.org/10.1016/j.bmcl.2009.12.057)
102. Visintini M, Redko F, Muschietti L, Campos R, Martino V: Cavallaro LV. In vitro antiviral activity of plant extracts from Asteraceae medicinal plants. *Virology*. 2013:245. [10.1186/1743-422X-10-245](https://doi.org/10.1186/1743-422X-10-245)
103. Xu HB, Ma YB, Huang XY, et al.: Bioactivity-guided isolation of anti-hepatitis B virus active sesquiterpenoids from the traditional Chinese medicine: Rhizomes of *Cyperus rotundus*. *J Ethnopharmacol*. 2015, 171:131-40. [10.1016/j.jep.2015.05.040](https://doi.org/10.1016/j.jep.2015.05.040)
104. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA: Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012, 367:1814-20. [10.1056/NEJMoa1211721](https://doi.org/10.1056/NEJMoa1211721)
105. Zandi K, Zadeh MA, Sartavi K, Rastian Z: Antiviral activity of *Aloe vera* against herpes simplex virus type 2 : an in vitro study. *Afr J Biotechnol*. 2007, 6:1770205. [10.5897/AJB2007.000-2276](https://doi.org/10.5897/AJB2007.000-2276)
106. Zhou B, Yang Z, Feng Q, et al.: Aurantiamide acetate from *Baphicacanthus cusia* root exhibits anti-inflammatory and anti-viral effects via inhibition of the NF-κB signaling pathway in Influenza A virus-infected cells. *J Ethnopharmacol*. 2017, 199:60-7. [10.1016/j.jep.2017.01.038](https://doi.org/10.1016/j.jep.2017.01.038)
107. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY: Coronaviruses - drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016, 15:327-47. [10.1038/nrd.2015.37](https://doi.org/10.1038/nrd.2015.37)