

An Overview of COVID-19 and the Potential Plant Harboured Secondary Metabolites against SARS-CoV-2: A Review

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Abstract

The SARS-CoV-2 virus causes COVID-19, a pandemic disease, and it is called the novel coronavirus. It belongs to the Coronaviridae family and has been plagued the world since the end of 2019. Viral infection to the lungs causes fluid filling and breathing difficulties, which leads to pneumonia. Pneumonia progresses to ARDS (Acute Respiratory Distress Syndrome), in which fluid fills the air sac and seeps from the pulmonary veins. In the current scenario, several vaccines have been used to control the pandemic worldwide. Even though vaccines are available and their effectiveness is short, it may be helpful to curb the pandemic, but long-term protection is inevitable when we look for other options. Plants have diversified components such as primary and secondary metabolites. These molecules show several activities such as anti-microbial, anti-cancer, anti-helminthic. In addition, these molecules have good binding ability to the SARS-CoV-2 virus proteins such as RdRp (RNA-dependent RNA polymerase), Mpro (Main Protease), etc. Therefore, these herbal molecules could probably be used to control the COVID-19. However, pre-requisite tests, such as cytotoxicity, *in vivo*, and human experimental studies, are required before plant molecules can be used as potent drugs. Plant metabolites such as alkaloids, isoquinoline β -carboline, and quinoline alkaloids such as skimmianine, quinine, cinchonine, and dictamine are present in plants and used in a traditional medicinal system.

Keywords: COVID-19, SARS-CoV-2, Alkaloids, Flavonoids, Coumarins, Plant Secondary Metabolites, Mpro

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INTRODUCTION

The emergence of new viruses and their diseases has become common in the last few decades, and this problem is a severe threat to the global population. COVID-19 was first reported in the month of December 2019 at Wuhan (China) when treating patients who showed pneumonia-like symptoms. It is a pandemic that appeared after the influenza epidemic of 1918. Initially, the virus was identified as a 2019 novel coronavirus, after which name changed to acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO)¹. COVID-19 became widespread in more than 100 countries in just 2 months. To tackle these problems, countries need a robust public health system a collective response². On the month of March 11, 2020, the World Health Organization (WHO) declared COVID-19 as pandemic³. The COVID-19 pandemic affects depression in 25% of people, which is 7 times higher than the 3.44% in the global pool of people with global depression in 2017⁴.

Coronavirus belongs to the family RNA viruses, comprises a large RNA genome, i.e., positive-sense single-stranded RNA. It contains helical nucleocapsids and a huge RNA genome, and it regulates the structural and non-structural viral proteins. The entire coding sequence is essential to form a new viral particle, and some sequences are folded into a stable structure and controls the coronavirus life cycle. Subgenomic mRNAs regulate and form protein and form new virions⁵. The viral particle's entry and infection mainly were mediated by the ACE-2 (Angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane protease serine 2) protein structures, as well as other features including binding sites and mutation points. The methylation of ACE-2 gene, DNA methylation, and post-translational histone modifications shows differences in viral infection patterns of biological age, sex-biased patterns and host tissue⁶. In addition, advanced nanotechnology products such as face masks and personal protection equipment (PPE) to specific diagnostic tools can help reduce the spread and impact of COVID-19⁷. Remdesivir is an antiviral medication that targets the SARS-CoV-2 RdRp (RNA-dependent RNA polymerase) enzyme, which is responsible for RNA replication and is one of the virus's main therapeutic targets. The mechanism of

RdRp inhibition by nucleotide inhibitors is revealed by studying the RdRp complex (substrate RNA and Remdesivir), and it provides a molecular blueprint for developing RdRp-targeting medicines⁸.

Plant secondary metabolites (PSM) in plants help combat biotic stresses (microorganisms, insects, parasites) and abiotic stresses (temperature, pH, water activity, heavy metals). In addition, these PSMs are also useful for humans, so plant and plant parts are used as nutraceuticals, drugs, and foodstuffs⁹⁻¹¹. Plant secondary metabolites (PSMs) exhibiting antiviral activities by disturbing the viral particle constituents such as protein, lipid envelope, and genetic materials such as DNA or RNA of a virus particle. The lipid envelope of viruses is disturbed by lipophilic terpenoids of essential oils, membrane-bound viral proteins, and the viral particle's inside the host tackled by phenols and polyphenols of plants. Moreover, free virus particles are more susceptible than the virus present in the host cell to both phenolics and essential oils of plants¹².

Furthermore, DNA intercalators such as berberine, β -carboline, emetine, isoquinoline alkaloids, sanguinarine, and quinoline alkaloids such as cinchonine and quinine skimmianine, as well as dictamen also effectively inhibit the viral genome replication¹². By blocking viral proteins and blocking virus entry into the host cell, perhaps PSMs play a key role in preventing COVID-19 from spreading. *In vitro* research using pomegranate peel extracts revealed an interaction between the spike glycoprotein of SARS-CoV-2 and the ACE-2 (Angiotensin-Converting Enzyme 2) receptor that prevents and inhibits the virus's 3CL protease activity¹⁰.

In this present review, an overview of coronavirus, also known as COVID-19, as well as its symptoms, disease progression, infection mechanism, virus replication, control measures, treatments, and immunization were covered. The virtual drug screening (*in silico*) methods including molecular docking and molecular dynamics simulation studies are also covered. Moreover, the ability of plant secondary metabolites to be active against COVID-19 *in vitro* and *in vivo* studies has also been documented.

COVID-19 Symptoms

COVID-19 exhibits various symptoms from

mild illnesses to chronic and multi-organ failure, leading to older age patients. The most common COVID-19 symptoms include fever, cough, lung auscultation/oxygen saturation; however, this data may be used to rule out patients with COVID-19 or select for further tests. In addition, there are 27 signs and symptoms of COVID-19, which fall under 4 categories: systemic, respiratory, gastrointestinal, and cardio-vascular¹³. In another study, COVID-19 symptoms such as cough (50-80%), fever (85%), fatigue (69.6%), dyspnoea (20-40%), URI (Upper Respiratory Infection) symptoms (15%), and GI (Gastrointestinal) symptoms such as nausea, vomiting, and diarrhoea (10%) have all been described¹⁴. However, some COVID-19 patients were complicated to diagnose because of not showing fever or radiological symptoms initially 15. In addition, symptoms such as dyspnoea- 55% and lymphopenia-63% were found in COVID-19 patients¹⁶.

Coronavirus classification and mechanism of cell entry

The International Committee on Virus Taxonomy states coronavirus belongs to the family Coronaviridae and the order Nidovirales. According to their phylogenetic relationships and genomic structures, the Coronavirinae subfamily is divided into Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. Both Alphacoronavirus and Betacoronavirus infect mammals. Further, birds infected by Gammacoronavirus and Deltacoronavirus, however, sometimes also infect mammals. The MERS or camel flu, SARS, and SARS-CoV-2 are Betacoronavirus members. They were further divided into the subgenera Hibecovirus, Sarbecovirus, Embecovirus Nobecovirus, and Merbecovirus¹⁷⁻¹⁹.

Complete and near-complete genetic analyses of SARS-CoV-2 showed several deletions as well as mutations on coding and non-coding regions, indicating the virus's genomic variety and fast evolution²⁰. Furthermore, a 4 per cent difference in genomic nucleotide variation was found between SARS-CoV-2 and another coronavirus related to SARS, such as bat's SARS-linked coronavirus (SARSr-CoV, RaTG13)²¹.

The SARS-CoV-2 spike binds to human ACE-2 (hACE2), a receptor by its RBD (receptor-binding domain), and proteolytic reactions activate

proteases. Furthermore, the pseudovirus entry test revealed that RBD of SARS-CoV has lesser binding compatibility than SARS-CoV-2 RBD with hACE2. In addition, the spike of SARS-CoV-2 is shorter than the SARS-CoV, which is helpful in binding hACE2 and also useful to minimize exposure to cell defence. Furthermore, the high hACE2-binding affinity to RBD, spike's furin preactivation, and hidden RBD present in SARS-CoV-2 spike are potentially helpful in evading the immune system and successful cell entry²².

Enzymes play a crucial part in the development of the disease, and they are also possible therapeutic hotspots. Four key enzymes of SARS-COV-2, such as RdRp, 3CLp, papain-like protease, helicase, and ACE-2; and transmembrane serine protease (Host factors), play an essential role in disease establishment. Interestingly, α -glucosidase in the endoplasmic reticulum is a promising target for exploring anti-SARS- CoV-2 medicines²³.

Variants of CoV-2

In the United Kingdom, a novel SARS-CoV-2 variety (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7) developed with many changes toward the end of December 2020. Furthermore, scientists discovered in January 2021 that variation B.1.1.7 had a greater mortality risk compared to other variants. Another potential SARS-CoV-2 (20H/501Y.V2 or B.1.351) emerged from B.1.1.7 strain in South Africa²⁴. A thorough examination of the whole-genome sequences of 837 Indian SARS-CoV-2 strains revealed the presence of 33 distinct mutations, 18 of which were unique to India. There are S glycoprotein (6/33) mutation, NSP3 (5/33) mutation, RDRP / NSP12 (4/33) etc., were found²⁵. In India, SARS-CoV-2 variants such as Delta (B.1.617.2) and Kappa (B.1.617.1) were reported and become a dominant strain causing infection in a large population across more than 50 countries²⁶. According to outbreak information, B.1.617.2 strain has a 36% variant of concern and significant threatening strain in India²⁷. A study revealed that SARS-CoV-2 strain B.1.617.2 reported to have hallmark mutations in receptor-binding domain (RBD) and spike protein D111D, G142D, L452R, E484Q, D614G, and P681R. The SARS-CoV-2 strains B.1.617.1 and B.1.617.2 were cause second wave in India and whole genome or next generation sequence analysis of

viral RNA revealed mutations at residue positions 452, 484 and 681 compared with other globally circulating lineages²⁸.

Immunology of COVID-19

Humoral and cell-mediated immunity of both types of immune responses is particularly prominent when COVID-19 infection occurs. However, cell-mediated immunity is prime and effective against viral infections²⁹. In COVID-19 patients, abnormal lymphocyte distribution, an increase in mature natural killer cells (NK), and a decrease in T cells have been identified. NK cells overexpressed T-cell immunoglobulin, mucin-3 domain (TIM-3), and CD69, as well as CD8+ T cells, were also reported. NK cell exhaustion was identified by increased PD-1 (Programmed Cell Death Protein 1) frequencies in positive cells, NKG2D DNAM-1 frequencies were decreased [Natural Killer Group 2 D (NKG2D)-DNAX accessory molecule-1 (DNAM-1)], and Siglec-7 (sialic acid-binding Ig-like lectin 7) expressing NK cells, and interferon (IFN) secretion ability reduced. Further, interferon (IFN) γ secretion ability also reduced observed, and serum IL-6 levels were higher in deceased patients than in survivors³⁰. Plasma levels of interleukins 2, 7, and 10, GSCF, MIP1A, IP10, MCP1, and TNF were higher in ICU admissions patients than in non-ICU patients, indicating that the severity of the disease had increased¹⁶.

A gradual decrease in viral load and increased antibodies have been reported in patients after one week of infection. According to the study, the viral load was highest during the first week and dropped by the second week. Furthermore, antibodies such as IgG and IgM are often detected 10 days after viral infection, and these play an essential role in neutralizing the SARS-CoV-2 virus^{31,32}.

Further, antibodies produced from coronavirus variant 501Y.V2 are also effective against the previously reported coronavirus variants. Therefore, the vaccine from the 501Y.V2 variant can be used against a variety of coronavirus strains³³.

Mode of transmission of SARS-CoV-2

The transmission of SARS-CoV-2 occurs by contact and droplet transmission, airborne transmission, fomite transmission, and other modes of transmission, such as faecal-oral contamination,

blood-borne transmission, transmission from mother to child, and transmission from animals to humans^{34,35}.

COVID-19 protective measures

According to the WHO guidelines, wash or clean the hands frequently or often, while coughing or sneezing use the bent elbow, touching of eyes, nose, and mouth with hands, avoid social gatherings and crowded places, make a suitable distance from the sick, disinfect, and clean touched objects and surfaces³⁵. Furthermore, WHO recommendations suggest identifying suspicions early and testing them as soon as feasible and isolating sick people in appropriate facilities. As early as possible, identify and quarantine all intimate contact with infected people, and will be tested and take appropriate actions for those who show symptoms. Fabric masks are used in public areas and to provide physical separation where there is a risk of communicable disease transmission. Health workers should be taken care of not to contact and droplets formed by COVID-19 patients, and aerosol production avoided. Health workers advise continuous usage of a medical mask throughout the shift for all normal activities. Hygiene at all times, physical separation, avoidance of crowded areas, close-contact situations, and cramped and enclosed rooms with poor ventilation are all recommended³⁴.

Vaccines for COVID-19

There are several vaccine candidates used today, and a mass vaccination program started in several countries. Vaccines such as Johnson & Johnson's, Moderna, AstraZeneca, Pfizer-BioNTech, Janssen, Covaxin, Covishield, etc., are widely used in mass vaccination programs around the world. The types of vaccines used for COVID-19 are mRNA vaccines, protein subunit vaccines, and vector vaccines. It usually takes several weeks after vaccination for the organism to produce T and B lymphocytes. Therefore, it is possible for humans to get an infection and become sick from a virus just before or after vaccination due to didn't have time for protection. The immunization induces Macrophages, B-lymphocytes, and T-lymphocytes are responsible for immunity development³⁶. In India, vaccines such as Covishield[®] and Covaxin[®] are permitted emergency use authorization by Central Drugs Standard Control Organization (CDSCO). Covishield comprised inactivated

adenovirus with segments of Coronavirus, Aluminum Hydroxide Gel, L-Histidine, L-Histidine Hydrochloride Monohydrate, Magnesium Chloride Hexahydrate, Polysorbate 80, Ethanol, Sucrose, Sodium Chloride, and Disodium Edetate Dihydrate (EDTA). Further, Covaxin comprised inactivated Coronavirus, Aluminum Hydroxide Gel, TLR 7/8 Agonist, 2-Phenoxyethanol, and Phosphate Buffered Saline [NKA1]³⁷. Further, there are 7 vaccines like Covaxin (Bharat Biotech), Serum Institute of India Covishield (Oxford/AstraZeneca formulation), AZD1222 (Oxford/AstraZeneca), Ad26.COVS.2 Janssen (Johnson & Johnson), Sputnik V (Gamaleya), mRNA-1273 (Moderna), and ZyCoV-D (Zydus Cadila) are approved for use in India. Moreover, in India 13 vaccines are under clinical trials³⁸.

PSMs against COVID-19

In the evoked of the second wave of COVID-19, medicines are used for a short time so far, no particular medicine is not available for this disease, and the drug discovery process is ongoing. The plants are well-known producers of many low molecular weights based on the inferred functions classified into primary and secondary metabolites and hormones. Plant growth relies heavily on primary metabolites; hormones helpful in organism activities and metabolism; secondary metabolites play an essential role in plant-environment interactions, plant defence, etc. Interestingly, the boundary of activity of these metabolites is not fully known, so a comprehensive study on the effect of the activity of these molecules needs to be conducted³⁹. The diverse phytochemicals such as terpenoids, organosulfur compounds, flavonoids, sulphides, limonoids, lignans, alkaloids, polyenes, polyphenolics, coumarins, saponins, thiophenes, chlorophyllins, furyl compounds, peptides, and proteins exhibit antiviral activities against a wide array of viruses⁴⁰. Table 1 lists prospective phytochemicals and their inhibitory effect on SARS-CoV-2, whereas Table 2 lists medicinal plants and their prospective phytochemicals that are effective against SARS-CoV-2. The protein sequences of SARS-CoV-2 3CLpro and SARS-CoV 3CLpro were 99.02 per cent identical. According to molecular docking and molecular dynamic simulation studies, about 9 active phytochemicals suggested as SARS-CoV-2

antiviral molecules based on their docking score and binding affinity⁴¹.

Artificial or virtual natural drug molecules screening methods for SARS-CoV-2

Bioactive compounds are constantly being investigated in creating novel bioactive molecules with industrial uses, gaining attention from the scientific community due to their pharmacophore-like structures, pharmacokinetic qualities, and chemical space⁴². Computational approaches have revolutionised the identification of novel specific bioactive compounds by evaluating vast structural libraries *in silico* against a bioreceptor or biological system, lowering the cost, facilities, and time to identify new compounds^{42,43}. Machine learning-based models trained on specific proteins have provided affordable and quick-to-implement approaches for the development of successful viral treatments in the recent decade. These models can forecast inhibitor candidates in a structural-based way given a target biomolecule^{44,45}. Artificial intelligence (AI) uses reasoning, representation of knowledge and solution-oriented search; however, machine learning (ML) play a key role in this. ML is a type of machine learning that employs algorithms to detect patterns in a set of data that has been further categorised. Deep learning (DL) is a branch of machine learning that uses artificial neural networks (ANNs) which are mimicking of human neurons kind^{45,46}. With the low cost various *in silico* methods helpful to analyze the virtual chemical gaps considering with ligand interaction and structure in drug discovery process. To choose a lead molecule, drug design methods such as coulomb matrices and molecular fingerprint recognition analyse the physical, chemical, and toxicological characteristics^{47,48}. Various AI tools such as DeepChem, Deep Neural Net QSAR, DeltaVina, AlphaFold, ORGANIC etc., are using in the drug discovery method, protein folding, ligand interaction study⁴⁵.

A virtual drug screening comprises mainly library preparation and suitable computational techniques. Library preparation consists of structure of compounds obtaining and convert them into readable formats like SMILES, SDF and MOL2 (simplified molecular-input line entry system, structure data file and MDL Molfile). The computational techniques includes both

Table 1. List of Phytochemicals and their inhibitory effect against SARS-CoV-2

No.	Compound	Inhibitory Concen./ IC ₅₀ or LD ₅₀	Cell lines used/ Animal model/Molecular Docking	Standard Used	Ref.
I Flavonoids					
1.	Baicalein	IC ₅₀ =10µM	SARS-CoV-2 in Vero E6 cells.	Staurosporine	75
2.	Baicalin	IC ₅₀ =0.39µM (SARS-CoV-2 3CLpro)	SARS-CoV-2 in Vero E6 cells.	Remdesivir	76
3.	Scutellarin	IC ₅₀ =5.8µM (SARS-CoV-2 3CLpro)	Molecular Docking study	baicalein analogue flavonoids (baicalein)	77
4.	Quercetin	LD ₅₀ =159 mg/kg	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
5.	Naringin	LD ₅₀ = 2300 mg/kg	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
6.	Catechin	LD ₅₀ = 10,000 mg/kg	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
II Phenols					
1.	Oleuropein	Mpro and 3CLpro protease	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
2.	Hydroxytyrosol	Mpro and 3CLpro protease	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
3.	Gallic acid	LD ₅₀ =2260 mg/kg	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
4.	Psychotrine	LD ₅₀ = 480 mg/kg	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
5.	Curcumin	LD ₅₀ =4000 mg/kg	Molecular Docking study	Hydroxychloroquine Chloroquine and methyl 4-sulfamoylbenzoate	78
III Terpenoids					
1.	Asiatic acid	IC ₅₀ = 9 µM	HIV-1; EV-7	-	79
2.	β-Aescin	IC ₅₀ = 6 µM	For SARS-CoV-1	-	79
3.	Maslinic	IC ₅₀ = 9 µM	HIV-1	-	79
4.	Ursolic acid	IC ₅₀ = 10 µM	HIV-1	-	79
5.	Pachymic acid	IC ₅₀ = 18.607 µmol L ⁻¹	SARS-CoV-2 main protease (M ^{pro})	Standard Pachymic acid	80
IV Saponins					
1.	Ellagic acid	- 8.4 kcal/mol (Dock score)	SARS-CoV-2 main protease (M ^{pro})	Remdesivir, Dexamethasone, N3Inhibitor	65
2.	Arjunic acid (-8.1 kcal/mol)	- 8.1 kcal/mol (Dock score)	SARS-CoV-2 main protease (M ^{pro})	Remdesivir, Dexamethasone, N3Inhibitor	65
3.	Theasapogenol B	- 8.1 kcal/mol (Dock score)	SARS-CoV-2 main protease (M ^{pro})	Remdesivir, Dexamethasone, N3Inhibitor	65
4.	Euscaphic Acid	- 8.0 kcal/mol (Dock score)	SARS-CoV-2 main protease (M ^{pro})	Remdesivir, Dexamethasone, N3Inhibitor	65
V Alkaloids					
1.	Anisotine	-7.9 kcal/mol (Dock score)	SARS-CoV-2 main protease (M ^{pro})	Lopinavir and Darunavir	81
2.	Berberine	EC ₅₀ = 9.1 µM	SARS-CoV-2 in Vero E6 cells.	0.1% DMSO as negative control	68
3.	Obatoclax	EC ₅₀ = 67 nM	SARS-CoV-2 in Vero E6 cells.	0.1% DMSO as negative control	68

Table 2. List of Plants and their Phytochemicals effective against SARS-CoV-2

No.	Plant	Compound	Standard Used	Ref.
1.	<i>Psoralea argyrea</i>	5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone	Nelfinavir, Prulifloxacin and Colistin	41
2.	<i>Myrica cerifera</i>	Myricitrin	Nelfinavir, Prulifloxacin and Colistin	41
3.	<i>Hyptis atrorubens</i> <i>Poit</i>	Methyl rosmarinate	Nelfinavir, Prulifloxacin and Colistin	41
4.	<i>Phaseolus vulgaris</i>	3,5,7,3',4',5'-hexahydroxy flavanone-3-O-beta-D-glucopyranoside	Nelfinavir, Prulifloxacin and Colistin	41
5.	<i>Phyllanthus emblica</i>	(2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside	Nelfinavir, Prulifloxacin and Colistin	41
6.	<i>Fraxinus sieboldiana</i>	Calceolarioside B	Nelfinavir, Prulifloxacin and Colistin	41
7.	<i>Camellia sinensis</i>	Myricetin 3-O-beta-D-glucopyranoside	Nelfinavir, Prulifloxacin and Colistin	41
8.	<i>Glycyrrhiza uralensis</i>	Licoleafol	Nelfinavir, Prulifloxacin and Colistin	41
9.	<i>Amaranthus tricolor</i>	Amaranthin	Nelfinavir, Prulifloxacin and Colistin	41
10.	<i>Anemarrhena</i> <i>Rhizoma</i>	3 Antiviral compounds	-	82
11.	<i>Anisi Stellati Fructus</i>	3 Antiviral compounds	-	82
12.	Carthami Flos	3 Antiviral compounds	-	82
13.	Daturae Flos	3 Antiviral compounds	-	82
14.	Black Tea	Theaflavin	-	83
15.	<i>Echinacea purpurea</i>	Several active compounds	-	55,56
16.	<i>Olea europaea</i>	phenols (oleuropein and hydroxytyrosol) and terpenoids (oleanolic, maslinic and ursolic acid).	-	84
17.	<i>Scutellaria baicalensis</i>	Scutellarin	baicalein analogue flavonoids (baicalein)	77
18.	<i>Ampelopsis japonica</i>	Dihydromyricetin,	baicalein analogue flavonoids (baicalein)	77
19.	<i>Eriocaulon buergerianum</i>	Quercetagetin	baicalein analogue flavonoids (baicalein)	77
20.	<i>Polygoni avicularis</i>	Myricetin	baicalein analogue flavonoids (baicalein)	77
21.	<i>Poria cocos</i>	Pachymic acid	Standard Pachymic acid	80
22.	<i>Boerhavia diffusa</i> <i>Linn.</i>	Biorobin, Bioquercetin, Boerhaversterol, kaempferol, Boeravinone J, Quercetin, Liriodendrin, Trans – caftaric acid, 2–3-4 beta-Ecdysone	-	85

SBVS- structure-based virtual screening or LBVS- ligand based virtual screening. After the library preparation, computational techniques employed and finally *in silico* results validating by *in vitro* and *in vivo* assays⁴². The majority of machine learning drug discovery studies of SARS-CoV-2 focused on viral proteins such as spike (S) protein, MPro, 3CLPro etc., protein ligand interaction, binding efficiency, and binding free energy are also considered in the process^{44,49,50}. The studies on SARS-CoV-2 drug discovery focused on the sequence of target proteins such as 3CLPro, S protein, ACE-2, Main Protease, RdRP and host TMPRSS2 protease ACE2 receptor are considered. Later by adapting the deep docking, QSAR etc., are using to identify the protein inhibitors from available databases like FDA approved drugs, ZINC database etc. In majority of studies 3CLPro of SARS-CoV-2 is target protein, Deep learning model and molecular dynamic simulation methods approached to finalise the highest hit compound to target protein like 3CLPro of SARS-CoV-2^{42,44,49-53}.

Some of the extracts of litchi seeds, *Houttuynia cordata*, Chinese Rhubarb extracts, *Isatis indigotica* plants (beta-sitosterol) root extract can inhibit the SARS enzymatic activity⁵⁴. In addition, immune-modulating supplements such as *Echinacea purpurea* consumption may prevent the infection^{55,56}. Around 219 plants from 83 families showed antiviral activity and screened the major plant secondary metabolites (PSMs) from 149 plants of 71 families for the COVID-19 pandemic⁵⁷. The computer simulation (*in silico*) studies come out with phytochemicals such as glycyrrhizic acid, 7-deacetyl-7-benzoylgedunin, limonin, maslinic acid, obacunone, corosolic acid, and ursolic acid are effective against some proteins of SARS-CoV-2. These studies majorly focused on viral proteins such as PLpro, SpG-RBD, 3CLpro, RdRp, and ACE-2⁵⁸.

Plants ubiquitously have a diversified flavonoid known as natural health products and chemically showed a 15-carbon skeleton of C6-C3-C6 with different subclasses based on structural configuration. The major subclasses of flavonoids are flavanols or catechins, flavones, flavonols, flavanones, anthocyanins, and isoflavones⁵⁹.

Flavonoids could be efficacious as antiviral chemicals that have an essential function in modulating signalling pathways, which is

critical for COVID-19 survival, especially on inflammation and immunity. Some flavonoids also inhibit essential proteins such as PLpro (papain-like protease), 3CLpro (3C-like protease), NTPase/helicase, which was instrumental in the formation of COVID-19⁶⁰. In addition, modulation of the immune system by flavonoids through inflammatory intermediaries like endothelial activation inhibition, NOD-, LRR-, and pyrin domain-containing 3 (NLRP3) inflammasome, toll-like receptors (TLRs) or BRD4, and Nrf2 (nuclear factor erythroid-derived 2-related factor 2) activation are helpful to cytokine regulation for COVID-19 infection. Furthermore, flavonoids inhibit DPP4, neutralize 3CLpro (3-chymotrypsin-like protease) and ACE-2 (angiotensin-converting enzyme 2) in SARS-COV-2⁶¹.

Triterpenoids are large group of phytochemicals, which are metabolites of isopentenyl pyrophosphate oligomers⁶². Triterpenoids are naturally found in Oleanolic, betulinic, and ursolic acid forms, and they exhibit a broad spectrum of antiviral, antitumor, and anti-inflammatory activities⁶³.

In a study, among selected plant secondary metabolites, superior molecule triterpenoids exhibited lower binding energy (> 50%) and firmly interacted with the viral receptor-binding domain of spike protein. Further, flavonoids and glycosides exhibited > 32% of interaction with the human transmembrane serine protease active site. The lower binding energy was exhibited by flavonol glycosides and anthocyanidins with > 16% of the viral main protease active site. Interestingly, the glycoside of flavonol interacts very firmly with viral RNA-dependent RNA polymerase (>13%). Some Triterpenoid plant secondary metabolites, including Coagulins, Withanolides, Pseudojervine, and others, can actively inhibit the AARs of spike protein, which interacts with hACE2, blocking host cell detection by SARS -CoV-2⁶⁴.

Saponins are the glycosides of triterpenes and steroids that occur naturally in non-volatile and surface-active glycosides and exhibit various pharmacological activities. Saponins have antiviral action and perhaps be used as vaccine adjuvants in mammals because of their capacity to stimulate and activate the immune system⁶⁵.

Alkaloids are significant plant secondary metabolites with a nitrogen atom or elements

like amino or amido groups in their structure, which results in alkalinity. Alkaloids are cyclic structure ones based on a structure divided into isoquinolines, pyrrolizidines, quinolines, pyridines, isoquinolines, pyrrolidinostrypanes, indoles, and terpenoids and steroids⁶⁶.

Alkaloids from medicinal plants of Africa may interrupt cell entry of SARS virus by attaching with spike glycoprotein, human cell receptor ACE-2 blocking and inhibiting the host cell serine protease TMPRSS2⁶⁷. The *in vitro* study of alkaloids such as Berberine and Obatoclax effectively inhibited replication of SARS-Cov-2 in human nasal epithelial cells. However, efficacy tests are required for further usage as potential antivirals. It is interesting to note that Obatoclax showed its effectiveness at early steps in the life cycle of a virus, such as entry processes. On the other hand, berberine was more active in the later phases of the viral life cycle, suggesting that it may limit the infectivity of newly generated virions⁶⁸.

A polyphenolic colourless crystalline oxygenated heterocyclic compound is called Coumarins. Coumarins are naturally found in free forms, and their 800 derivatives are reported from 600 genera of several plants' families⁶⁹. Coumarins used as therapeutic agents and a molecular docking study showed that coumarin analogues such as toddacoumaquinone and synthesized coumarin analogue (1 m) had 7.8 kcal/mol to be the binding energy and -7.1 kcal/mol, respectively⁷⁰.

Methyltransferase (MTase), Endoribonuclease (endoU), and ADP ribose Phosphatase are required for the survivability of SARS-CoV-2 Main Protease enzymes (Mpro). Coumarins showed inhibits these proteins and exhibited antiviral activity, i.e., showed in *in silico* studies, -9.00 to -7.97, -8.42 to -6.80, -8.63 to -7.48 and -7.30 to -6.01 kcal/mol, of docking score recorded against Methyltransferase, Endoribonuclease, and Main Protease components of virus⁷¹.

Food ingredients and other active products

Food is a vital component of life. Meanwhile, it supports the organism free from infection by improving or boosting their immunity. In addition, lipids, which are found in foods, are essential in the virus's suppression. Unsaturated fatty acids like arachidonic acid (AA), icosapentenoic

acid (EPA), and docosahexaenoic acid (DHA) help reduce the inflammation, in addition to this promote wound healing, enhance macrophage and another immune cell phagocytosis, and reduce microbial load, may these activities affect the virus and acts as antiviral molecules. Perhaps after validation, oral or intravenous administration of these will increase the resistance and recovery from SARS-CoV-2⁷².

Nutraceuticals include Ferulic acid, Lipoic acid, Spirulina, N-Acetylcysteine, Selenium, Glucosamine, Yeast Beta-Glucan, Zinc, Elderberry recommended to control coronavirus and influenza. For instance, these enhance the response of type 1 interferon to RNA viruses⁷³. In addition, the docking studies revealed that Phycocyanobilin, Riboflavin, Cyanidin, Daidzein, Genistein are bioactive components of food that potentially inhibit Mpro and RdRp in the SARS-CoV-2 virus⁷⁴.

CONCLUSION

The plant extracts showed inhibitory action against pathogens. Bio-active components such as primary and secondary metabolites play an essential role in viral inhibition. The structure of these molecules may interrupt the attachment to the host, entry of virus particle, arrest the virus replication mechanism, interact with their genome and inhibit the disease establishment. Herbal medicine is an ancient medicine technique that exists from human existence, and nature provides many valuable molecules to human beings through plants. Plants and their products are used as food, and some are used as medicinal plants; these possess secondary metabolites protecting human beings from several diseases by improving immunity. Several plant-based components showed excellent binding capacity toward SARS-COV-2 virus proteins such as Mpro and other proteins compared with standard synthetic drugs used today. Therefore, still effective medication comes to COVID-19, the herbal-based components are a golden token to control the disease. However, the proper validation with thorough *in vitro*, *in vivo* and clinical trials of plant compounds is essential to confer before use as a drug.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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