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Harnessing Herbal Wisdom against SARS-CoV-2: A Review of Plant-derived Antiviral Agents

Sumaiya[1], Himani Saini[1], Gunjan Panwar[1], Prateeksha[1], Shivani Bahukhandi[1], Urvashi Gaur[1], Ravindra Kumar[1], Shraddha Panti[1], Arun Kumar[1] and Santosh Kumar Karn[2*]

[1]Department of Biotechnology, School of Basic and Applied Sciences, Shri Guru Ram Rai University, Patel Nagar, Dehradun – 248001, Uttarakhand, India

[2]Department of Biochemistry and Biotechnology, Sardar Bhagwan Singh University, Balalwala, Dehradun – 248001, Uttarakhand, India; santoshkarn.sbsu@gmail.com

Abstract

Background: The COVID-19 Pandemic caused by SARS-CoV-2 has exposed a major gap in the global healthcare system. Although vaccines and synthetic antivirals are available, challenges such as emerging variants, limited accessibility, and uneven distribution persist. This has increased in medical plants as alternative therapeutic options. **Aim:** This study aims to evaluate the potential of plant phytochemicals as antiviral agents against SARS-CoV-2 and their role in integrative and future pandemic management strategies. **Methods**: Our systematic review of literature from 2020 to 2025 was included using databases such as PubMed, Web of Science, and Google Scholar. Focusing on antiviral, immunomodulatory and anti-inflammatory properties of medical plants and their bioactive compounds was analysed, including *in silico*, *in vitro* and clinical evidence. **Results:** Some phytochemical such as glycyrrhizin, curcumin, withanolides, andrographolide, baicalein, and resveratrol, demonstrated important antiviral potential. These compounds act through multiple mechanisms, including spike-ACE2 inhibition, RdRp suppression, protease inhibition, and cytokine storm regulation. *In vitro* and computational studies confirmed their efficacy, while emerging clinical evidence supports their role as adjuvant therapies. Nanocarrier systems and bioenhancers like piperine further improve their bioavailability and therapeutic effectiveness. **Conclusion:** Plant-based antiviral compounds are a promising and low-cost way to treat SARS-CoV-2 and other viral infections. However, challenges include standardisation, bioavailability, and regulation.

Major Findings: Plant phytochemicals show multi-target antiviral activity against SARS-CoV-2 via inhibitor RdRp suppression and immunomodulation. Nanotechnology improves their efficacy, but clinical validation and standardisation are still needed.

Keywords: Antiviral Agents, COVID-19, Herbal Medicine, Immunomodulation, Medicinal Plants, Nanotechnology, Phytochemicals, SARS-CoV-2

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1. Introduction

Global health and socioeconomic systems have been profoundly and unprecedentedly impacted by the COVID-19 pandemic, which was brought on by the new coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2)[1]. Following its first appearance in Wuhan, China, in December 2019[2], the virus quickly spread around the world, overwhelming medical facilities and killing millions of people[3]. As of September 2020, there were over 31 million confirmed COVID-19 cases, with an estimated 960,000 fatalities, according to the World Health Organisation (WHO)[4], highlighting the need for efficient treatment and prevention measures. While remarkable progress has been made in vaccine development and deployment, the

*Author for correspondence

search for accessible, affordable, and complementary therapeutic agents continues, especially considering emerging variants, uneven vaccine distribution, and limited access in low-resource settings.

Coronaviruses (CoVs) are members of the genus Coronavirus, order Nidovirales, and family Coronaviridae[5]. According to coronavirus phylogenetic analysis, SARS-CoV-2 shares 96% whole genome identity with the bat-SARS-like coronavirus (Bat-SL-CoV). There are 15 ORFs in the SARS-CoV-2 genome, which code for 29 different proteins. ORF1ab and ORF1a, which encode the 1ab and 1a polypeptides that are proteolytically broken into 16 distinct non-structural proteins (NSPs), are located in the 5′ terminal of the genome. Nine auxiliary proteins (3a, 3b, 6, 7a, 7b, 8b, 9a, 9b, and orf10) and four structural proteins (spike, envelope, matrix, and nucleocapsid) are represented by the 3′ terminal of the genome[6]. Moreover, among Bat and Pangolin, the highest similarity was found against the pangolin based on phylogenetic analysis. These results suggest that SARS-CoV-2 transfers from bats to humans through pangolins[7]. Like its predecessors, SARS-CoV-2 likely crossed species barriers through wildlife trade or close animal-human interactions, emphasising the importance of zoonotic surveillance and ecological preservation in pandemic prevention[8]. Aerosols and respiratory droplets are the main ways that the virus spreads. Coronaviruses enter target cells more easily thanks to the spike (S) protein. Viral attachment to the surface of target cells is decreased when the S protein's surface unit, S1, binds to a cellular receptor, allowing entry. Furthermore, S protein priming by cellular proteases is necessary for entry. To enter a host cell, the SARS-CoV-2 spike (S) protein must be activated through a specific two-step cleavage process. This protein follows a specific structural nomenclature: The S1 subunit, which contains the receptor binding domain (RBD) for docking onto the ACE2 Receptor, and the S2 subunit, which contains the site of fusion peptide (FP) and Heptad Repeats (HR1/2) required for membrane merge. Activation begins when the cellular protease furin splits the S1/S2 sites, priming the virus for entry. The final molecular trigger occurs at the S2' site where the host TMPRSS2 performs a secondary cleavage that reveal fusion peptide. This specific and S1/S2 and S2' processing allows the S2 subunit to drive the fusion of the viral and cellular membrane, successfully releasing the viral genome into the cell[9].

Once the virus enters the body, it takes over the host's cellular machinery to make copies of itself, which in turn sets off a chain reaction in the immune system. In more serious conditions, this can lead to acute respiratory distress syndrome (ARDS), an excessive immune response often called a cytokine storm, and even failure of multiple organs. Understanding processes helps guide treatment methods, which mainly focus on stopping the virus from multiplying, controlling the immune response and reducing inflammation[10].

The absence of targeted antiviral therapies presented a major obstacle in the early phases of the epidemic. Although certain repurposed medications, including dexamethasone, hydroxychloroquine, favipiravir, and remdesivir, were used with differing degrees of success, none proved to be a cure-all[11]. A significant scientific achievement was the quick generation of vaccines employing platforms like inactivated virus (Sinopharm, Covaxin), viral vectors (AstraZeneca, Johnson and Johnson), and mRNA (Pfizer-BioNTech, Moderna)[11-13]. However, issues including vaccine reluctance, supply-chain constraints, breakthrough infections, and the ongoing appearance of novel viral variations make it necessary to investigate adjunct and alternative therapy alternatives[14].

Considering this, interest in traditional medical systems and plant-based treatments has increased globally. The use of therapeutic plants and their bioactive components is known as phytotherapy. Since ancient times, ethnomedicine (such as *Ayurveda, Unani*, Traditional Chinese Medicine, and European Traditional Medicine) has employed medicinal plants to treat a variety of illnesses. The integration of herbal wisdom into pandemic responses has been led by plants, which are a rich source of different phytoconstituents with antidiabetic, anticancer, antibacterial, antihypertensive, antioxidant, antihyperlipidemic, cardioprotective, immunomodulatory, and anti-inflammatory properties[15,16].

Wide availability, cultural acceptance, affordability, and multi-targeted modes of action are only a few benefits of herbal therapy. Alkaloids, flavonoids, terpenoids, saponins, polyphenols, and essential oils are among the complex mixes of phytochemicals found in many therapeutic plants.

These compounds have antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties. These

substances may assist control host immunological responses and lessen oxidative stress, or they may obstruct viral entrance, replication, or assembly[17,18]. Crucially, some medications derived from plants, including quinine (from *Cinchona* species) and artemisinin (from *Artemisia annua*), have historically been essential in the management of infectious disorders like malaria, setting the stage for the creation of plant-based antivirals[19].

The potential of medicinal plants to combat SARS-CoV-2 *in vitro* and *in silico* has been the subject of numerous investigations. The spike protein, major protease, RNA-dependent RNA polymerase, and ACE2 receptor are among the important viral targets that compounds including quercetin, curcumin, glycyrrhizin, with none, andrographolide, baicalin, and thymoquinone have demonstrated encouraging results in suppressing[19]. Furthermore, observational research and clinical trials have started to assess the therapeutic and supporting functions of herbal formulations in improving recovery, reducing symptoms, and enhancing immunity in COVID-19 patients. To boost immunity and treat minor COVID-19 symptoms, the Ministry of AYUSH (*Ayurveda, Yoga, Unani, Siddha*, and *Homoeopathy*) in India released recommendations encouraging the use of specific herbs and formulations[20].

Global interest in investigating complementary and alternative medicines has increased because of the COVID-19 pandemic, and plant-derived antiviral drugs are showing promise. Using herbal knowledge provides a multifaceted strategy that supports immune function, reduces inflammation, and has an antiviral effect, all of which are in line with preventive and therapeutic approaches. Phytomedicine can greatly aid present and future attempts to combat viral epidemics by integrating traditional knowledge with modern science. To build the foundation for integrative and holistic healthcare paradigms, this review attempts to emphasise the therapeutic potential, scientific justification, and prospects of specific medicinal plants and phytochemicals in the context of SARS-CoV-2[20,21].

2. Materials and Methods

To systematically evaluate the relevance of plant-derived agents against COVID-19, this review compiles and analyses evidence from ethnobotanical records, pharmacological studies, and modern scientific literature. Between 2020 and July 2025, a systematic review of medicinal plant interventions was conducted using global databases such as PubMed, Web of Science, and Google Scholar. The review focused on identifying herbs with documented antiviral, immunomodulatory, or anti-inflammatory properties, relevant either directly to SARS-CoV-2 or to other closely related viral infections.

2.1 SARS-CoV-2: Structure and Variants

SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus with a genome of approximately 30,000 nucleotide. The SARS-CoV-2 genome encodes 29 proteins: 16 non-structural, 4 structural, and 9 accessory proteins[21]. The distinctive spike proteins on the surface of the spherical viral particle give it the appearance of a crown when seen under a microscope. These spike (S) proteins are essential for viral entry because they bind to the angiotensin-converting enzyme 2 (ACE2) receptors on human cells, particularly in the respiratory system. The spike (S) consists of two subunits: S1, which mediates receptor binding, and S2, which facilitates membrane fusion[22].

The envelope (E) protein, which is involved in viral assembly and release; the membrane (M) protein, which preserves viral form; and the nucleocapsid (N) protein, which encapsulates the viral RNA and facilitates replication, are the three additional structural proteins that SARS-CoV-2 possesses in addition to the S protein[23].

2.2 Viral Structure and Genome

SARS-CoV-2 belongs to the *Coronaviridae* family, characterised by a genomic architecture; a 29.9 kb positive-sense single-stranded RNA genome, the largest among RNA viruses, encoding both structural and non-structural proteins[23,24].

2.3 Structural Components

2.3.1 Spike (S) Glycoprotein

The spike (S) (Figure 1), glycoprotein of beta coronavirus SARS-CoV-2, is a homotrimer class I fusion protein that exists in a metastable conformation for cleavage by host cell proteases furin and TMPRSS2, thereby undergoing substantial structural rearrangement for ACE2 host cell receptor binding and subsequent viral entry by membrane fusion[24].

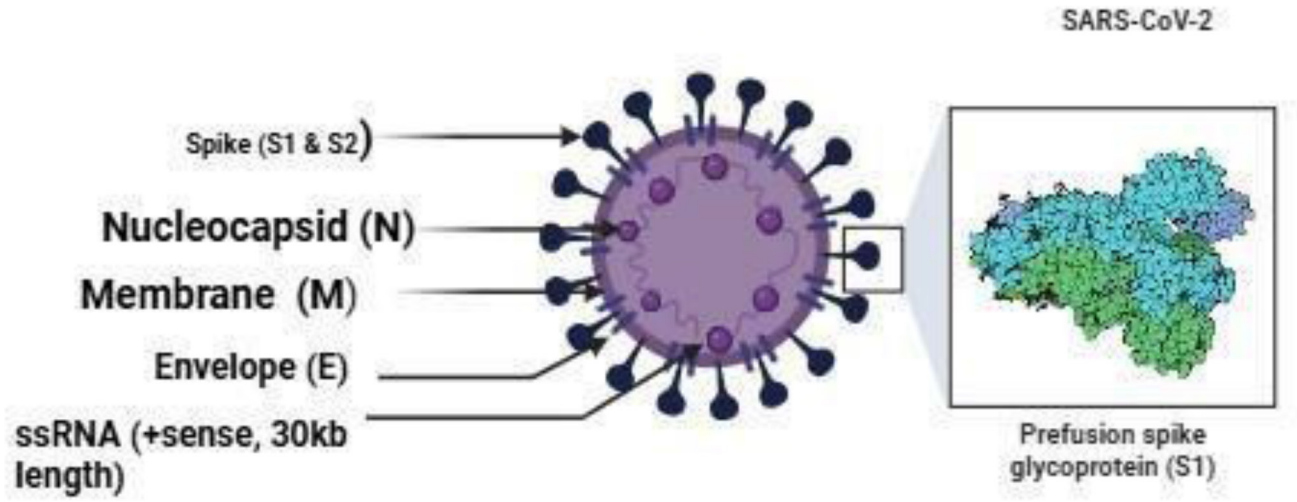


Figure 1. Structural components of SARS-CoV-2 Schematic representation of the SARS-CoV-2 virus structure. The virus is an enveloped, positive-sense single-stranded RNA virus (ssRNA, ~30 kb in length). The major structural proteins include the Spike (S) glycoprotein, which consists of S1 and S2 subunits, the Envelope € protein, the Membrane (M) protein, and the Nucleocapsid (N) protein. The inset shows the prefusion conformation of the S1 subunit of the spike glycoprotein, which is crucial for binding to the host ACE2 receptor.

2.3.2 Membrane (M) Protein

one of the vital components of viral assembly and morphogenesis, contributing to the regulation of replication and packaging of genomic RNA into viral particles[25].

2.3.3 Envelope (E) Protein

The E protein facilitates viral packaging and replication, and its deletion reduces viral pathogenicity. The E protein also possesses ion channel functions, interacts with host proteins, and has the potential to have various structural topologies[26].

2.3.4 Nucleocapsid (N) Protein

The most prevalent and conserved, which is essential for genome packing and nucleocapsid assembly. The N protein can carry out particular tasks, yet it is promiscuous when it comes to RNA recognition[27]. As part of the virus's evolutionary flexibility, the genome also encodes 16 non-structural proteins (nsp1-16) that make up the replication-transcription complex, including the RNA-dependent RNA polymerase (RdRp), which is incapable of proofreading[28]. The World Health Organisation (WHO) classification system identifies VOCs based on demonstrated increases in transmissibility, virulence, or capacity to evade immunity[49].

2.4 Variants of SARS-CoV-2

SARS-CoV-2 has evolved into multiple variants due to genetic mutations. Major variants of concern include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) (Table 1). These variants vary in how easily they spread and how well they can evade the immune system. Notably, the Delta variant showed higher severity, while Omicron exhibited increased transmissibility with relatively lower Severity[29-33]. These variants have emerged through convergent evolution, with mutations frequently occurring in the receptor-binding domain (RBD) of the spike protein, enhancing ACE2 affinity or antibody resistance[34]. The Omicron variant, with its unprecedented spike mutations, represents the most antigenically distinct lineage to date, driving global reinfection waves despite prior immunity from vaccination or infection.

2.5 Transmission Dynamics and Pathogenesis of SARS-CoV-2

Aerosols and respiratory droplets (Figure 2) are the main ways that SARS-CoV-2 spreads throughout the human population. Temperature, humidity, precipitation, air currents, pH, and radiation in the surrounding environment all seem to have an impact on transmission. After exposure, a distinctive set of

Table 1. Key SARS-CoV-2 variants, lineages, mutations, and epidemiological impact

Variant	Lineage	Key Mutations	Epidemiological Impact	References
Alpha	B.1.17	N501Y, P681H	Increased transmission	[29]
Beta	B1.351	E484K,K417N	Significant antibody escape	[30]
Gamma	P.1	K417TE484K	Immune evasion and higher risk of reinfection	[31]
Delta	B1.617.2	L452R , P681R	Increasedtransmissibility doubled hospitalization risk and Deaths	[32]
Omicron	B.1.1529	S371K, K417N	Antibody escape/resistance	[33]

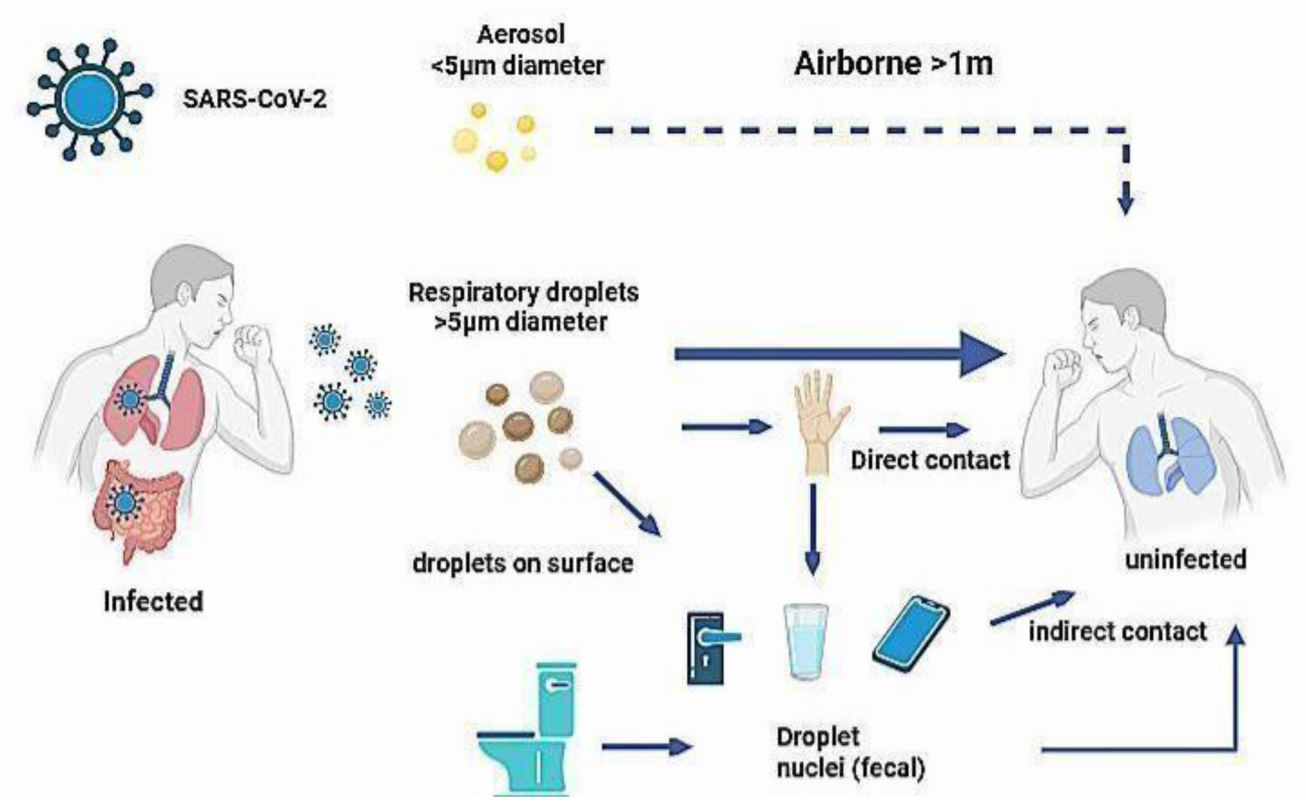


Figure 2. Transmission routes of SARS-CoV-2.

events leads to the development of viral pathogenicity. In addition to increasing replication in the lower respiratory tract and systemically, which can result in severe disease, more effective binding to ACE2 can also boost replication in the upper respiratory tract, which can facilitate more effective transmission[35].

Illustration of various transmission modes of SARS-CoV-2. The virus can spread through respiratory droplets (>5 µm) during coughing or sneezing, as well as via aerosols (<5 µm) over longer distances (>1 µm). Surface contamination from droplets can lead to indirect contact transmission. Direct contact with infected individuals or contaminated surfaces (e.g., door handles, utensils, mobile phones) is another common route. Additionally, faecal oral transmission via droplet nuclei is also a potential, though less common pathways.

As the infection spreads to the lower respiratory tract, it can cause serious pulmonary problems in about 20% of cases. In the worst situations, viremia causes systemic viral dispersion, which frequently results in multi-organ involvement. Increased levels of IL-6,

TNF-α, and other proinflammatory cytokines that cause endothelium damage and encourage coagulopathy are often indicative of a hyperinflammatory state that results from this development[35,36]. The cytokine storm syndrome is the cause of the progression to acute respiratory distress syndrome (ARDS) and explains why patients with underlying metabolic diseases like diabetes or cardiovascular disease experience a disproportionately high level of symptoms[37]. These patho-physiological insights continue to guide the development of targeted therapies and inform public health strategies against emerging variants (Table 2).

3. Phytochemicals as Potential SARS-CoV-2 Inhibitors: Mechanisms of Action

A wide variety of plant-derived substances with multifaceted potential for treating SARS-CoV-2 illness can be found in nature's pharmacy. By blocking the interaction between the spike protein and ACE2 receptors (as seen with glycyrrhizin from liquorice) or by inhibiting host protease like (like theaflavins from black tea), these bioactive plant compounds can stop the virus from entering cells. They can also interfere with replication by targeting key enzymes needed for the virus to multiply. They also target RNA-dependent RNA polymerase, for example, (Barberine from barberry)to slow viral replication. At the same time, compound resveratrol from grapes and curcumin from turmeric help to control too much inflammation by reducing cytokine storms, while botanicals such as *Ashwagandha* and *echinacea* can boost immune responses by enhancing natural killer cell activity[41].

Because these plant-based compounds act in multiple ways at once, they can address different stages of COVID-19 progression, not like single target synthetic drug. Their structural diversity may also help maintain efficacy against emerging variants, and they're generally good at safety profiles to support their use as supportive therapies. Ongoing research is further improving effectiveness through advanced delivery systems like nanoparticle formulation[42]. This approach composites modern pharmacology within traditional herbal knowledge, targeting the virus at the overall level of entry, replication, and immune response. While not a substitute for standard treatments, a photochemical-rich diet or well-formulated supplements may offer additional protection by creating a multi-layer defence and reducing the risk of resistance[43].

Table 2. Comprehensive analysis of SARS-CoV-2 transmission dynamics and pathogenic mechanisms

Category	Characteristics	Clinical/Public Health Implications	References
Transmission Routes	Respiratory droplets (>5μm) Aerosols (≤5μm) Fomites (minor role)	Socialdistancing reduces droplet spread Improved ventilation mitigates aerosoltransmission	37
Viral Entry and Spread	ACE2-mediated nasal infection Upper respiratory replication Potential lower respiratory progression	Nasal vaccines may block entry Early antiviral treatment may prevent progression	38
Severe Disease	Cytokine storm (IL-6, TNF-α) Endothelial damage Coagulopathy	Immunomodulators for cytokine storm Anticoagulants forthrombotic complications	39
Risk Factors	Advanced age Diabetes -cardiovascular disease	Targeted protection for high-risk groups Prioritisation forbooster vaccinations	40

3.1 Viral Entry Blockade (Spike-ACE2 Interference)

Plant-derived compounds show strong potential in blocking SARS-CoV- 2 entry by targeting key steps like viral attachment and fusion[44]. Phytochemicals such as baicalein and quercetin can bind ACE2 receptors, protecting the spike protein from attaching. Similarly, Glycyrrhizin from liquorice interferes with ACE2 Infraction by linking to the protein's receptor binding domain. Compounds like curcumin and Epigallocatechin gallate (EGCG) from green tea can also change the spike protein structure, reducing its ability to fuse with host cells[45].

To prepare the spike protein for cellular entrance, host proteases such as TMPRSS2 are inhibited, which is another crucial process. Theaflavins and luteolin, which are present in black tea and parsley, respectively, have shown strong TMPRSS2 inhibitory action in biochemical tests[46]. These multitargeted strategies may lessen the chance of immune evasion by new virus types in addition to decreasing viral infectivity[47]. According to new clinical research, formulations that incorporate these phytochemicals with zinc or other bioavailability enhancers may enhance treatment results in cases of early infection. The potential of plant-based therapies to prevent SARS-CoV-2 entry is demonstrated by the available data, although more study is required to confirm these results in human trials[47].

3.2 RdRp Inhibition and Viral Replication Suppression

Antiviral phytochemicals target the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 since it is an essential enzyme for viral replication[48]. Certain compounds, such as berberine, which comes from *Berberis vulgaris*, intercalate viral RNA and disrupts its synthesis, while embelin, which comes from *Embelia ribes*, interferes with RNA elongation. Apigenin, which is present in parsley and chamomile, has been demonstrated to bind the active site of RdRp, decreasing the effectiveness of viral replication[49]. Beyond inhibiting RdRp, several phytochemicals also target viral accessory proteins. For example, the skullcap's baicalein inhibits endoribonuclease, which further suppresses the processing of viral RNA[50]. Plant-derived chemicals are highly useful in the fight against SARS-CoV-2 because of their multimechanistic effects, especially considering the remarkable conservation of RdRp across variations. Clinical efficacy should be improved by increasing bioavailability through nanoparticle formulations or synergistic combinations with traditional antivirals, even though preclinical data are encouraging.

3.3 Anti-inflammatory Modulation of Cytokine Storm

IL-6, TNF-α, and NF-κB activation are among the hyperinflammatory responses that are frequently associated with severe COVID-19. Compounds originating from plants provide a natural way to control this dysregulated immune response[51]. Clinical investigations have shown that curcumin, the key ingredient in turmeric, lowers IL-6 levels and suppresses NF-κB activation, as seen by lower CRP in hospitalised patients[52]. Similarly, *Ashwagandha*'s withanolides and grapes' resveratrol reduce lung damage by blocking pro-inflammatory pathways[53]. Sulforaphane, which is present in cruciferous vegetables, inhibits pyroptosis and the production of cytokines by targeting the NLRP3 inflammasome[54]. Through their inhibition of leukotriene production, Frankincense's boswellic acids further reduce inflammation. These substances prevent endothelial damage and coagulopathy, which are frequent side effects of severe COVID-19, in addition to reducing cytokine storm. Integrating these phytochemicals into adjuvant therapy may enhance outcomes for patients in critical condition due to their pleiotropic effects. Recent delivery method such as liposomal encapsulation and nano formulation is needed to improve their low bioavailability[55].

3.4 Immunomodulatory Effects on Host Defence

More than directly fighting the virus, many medicinal plants also improve the body's immune system, offering a double line of defence against SARS-CoV-2[56]. For example, *Echinacea* spp.[57] boosts interferon production,*Andrographis paniculata* enhances CD4+ T-cell activity[58], *Astragalus membranaceus*[59] (Table 3) stimulates macrophage, and *Ashwagandha* increases natural killer cell activity. These effects are especially helpful for high-risk groups like the aged and immunocompromised. While proper standardisation and dosing are still needed, studies suggest that regular

use may reduce severity. Combining these botanicals and vaccine could also improve long-term immune protection, making them a promising part of future combined therapies[60].

4. Promising Medicinal Plants Against COVID-19: Evidence from Ethnopharmacology and Modern Research

The new coronavirus SARS-CoV-2, which produced the COVID-19 pandemic, has presented the world's public health and healthcare systems with previously unheard-of difficulties[61]. Despite developments in vaccines and antiviral medications, finding affordable and efficient treatments is still crucial, especially in areas with limited resources. Traditional medicine provides a wealth of possible therapeutic agents because of its long history of treating infectious diseases. Because of their ethnopharmacological significance and bioactive chemicals with antiviral, anti-inflammatory, and immunomodulatory qualities, medicinal plants have drawn attention[62].

Plants traditionally used to treat fever, inflammation, and respiratory infections that are closely linked to COVID-19 can be identified using ethnopharmacology. Plants with antiviral and immune-stimulating properties, like *Artemisia annua* (sweet wormwood), *Glycyrrhiza glabra* (liquorice), and *Zingiber officinale* (ginger) (Table 3), have long been used. Recent studies have started to support these assertions, showing that bioactive substances such as gingerols, glycyrrhizin, and artemisinin, among others, have mechanisms of action related to SARS-CoV-2, such as preventing viral entry and reproduction and regulating hyperinflammatory reactions. Phytochemicals produced from plants can target important proteins in SARS-CoV-2, including the spike protein and protease, while also reducing cytokine storms, which are a crucial factor in the severity of COVID-19 (Table 4)[63].

4.1 *Withania somnifera* (*Ashwagandha*): Withanolides as ACE2 Modulators

Ashwagandha, a key herb in *Ayurvedic* medicine, has gained attention for COVID-19 management due to its unique withanolide compound. These bioactive steroidal lactones, especially withaferin A and withanolide(Table 3), show multi-target activity against SARS-CoV-2. They can modulateACE2 receptor expression, potentially reducing viral entry while maintaining its normal function and inhibit the protease TMPRSS2, which is needed for spike protein activation[64,65]. Beyond its antiviral effect, *Ashwagandha* has a strong immunomodulatory property. It includes CD4+ T-cell responses and natural killer cell activity, both crucial for clearing viral infections. It also helps control inflammation by lowering through inflammatory cytokines like TNF- α and IL-6 Which are linked to severe disease outcome[66-68]. Current clinical trials are exploring *Ashwagandha* as both a preventive and therapeutic option, with early findings suggesting improved recovery rates and reduced symptom severity[69,70]. Its adaptogenic nature may also help ease post-COVID fatigue and stress, adding to its overall benefits. However, proper standardisation of its active compound and optimisation of dosage are still important challenges for its clinical use[71,72].

Table 3. Key phytochemicals, their natural sources, molecular targets, and proposed antiviral mechanisms against SARS-CoV-2

Phytochemical	Source	Target	Mechanism
Glycyrrhizin	Licorice root (*Glycyrrhiza glabra*)	Spike protein	Competitive ACE2 binding
Andrographolide	Kalmegh (*Andrographispaniculata*)	nsp10-nsp16 complex	Methyltransferase inhibition
Curcumin	Turmeric (*Curcuma longa*)	NF-κB, IL-6	Cytokine storm suppression
Baicalein	Chinese Skullcap (*Scutellarabaicalensis*)	RdRp, nsp15	RNAsynthesis inhibition
Withaferin A	*Ashwagandha(Withaniasomnifera)*	TLR4, IFN-γ	Th1 immune polarization
Sulforaphane	Cruciferous vegetables	Nrf2 pathway	Antioxidant gene upregulation
Emodin	Rhubarb (*Polygonum cuspidatum*)	nsp13 helicase	ATPase activity inhibition
Theaflavin-3-gallate	Black tea (*Camellia sinensis*)	TMPRSS2	Serine protease inhibition

4.2 *Curcuma longa* (Turmeric): Curcumin's Dual Antiviral, Anti-inflammatory Action

Curcumin, the active compound in turmeric, has shown strong potential against COVID-19 due to its dual action. It's straight inhibiting SARS-CoV-2 replication by targeting key viral componentslike RNA-dependent RNA polymerase and the main protease (3CLpro), and its flat structure allows it to interact with viral RNA, further disrupting replication[73]. At the same time, curcumin applies powerful anti-inflammatory effects by suppressing the NLRP3 inflammasome and NF-κB pathway, helping reduce cytokine storm and viral load. Clinical studies also reported decreased inflammatory markers such as CRP and IL-6 in treated patients, linked to better outcomes[74].

However, the low bioavailability remains a drawback which is being addressed through methods like nanoparticle encapsulations, phospholipid complexes and co-administration with piperine, improving adsorption up to 20-fold. Ongoing research is also examining its role in managing long COVID, particularly pulmonary fibrosis and endothelial dysfunction. Despite its strong safety profile and availability, Larger clinical trials are still needed to establish a standardised treatment protocol[75,76].

4.3 *Glycyrrhiza glabra* (Liquorice): Glycyrrhizin's Broad-spectrum Antiviral Activity

Liquorice root, long used in traditional medicine, contains glycyrrhizin A bioactive compound with notable activity against SARS-CoV-2[77]. It works through our triple action mechanism; blocking spikes ACE2 binding, inhibiting viral proteases (PLpro and 3CLpro) needed for replication and increasing antiviral defences by increasing interferon production. It also helps decrease lung inflammation by limiting prostaglandin synthesis and neutrophil infiltration[78-80]. Proof from past coronavirus outbreaks and current studies supports its antiviral potential, with some reports suggesting synergy with remdesivir. It may also reduce post COVID complications like pulmonary fibrosis via TGF-β modulation[80,81]. However, careful dosing is needed due to possible mineralocorticoid effects, especially in hypertensive patients. Its multi-target action makes it a promising option against rising variants[82-84].

4.4 *Azadirachta indica* (Neem): Nimbolide's Protease Inhibition Potential

Traditional Indian medicine called neem the "village pharmacy" because it has nimbolide, a strong limonoid chemical that performs very well against SARS-CoV-2[85]. The principal mechanism of action of nimbolide is the reduction of the viral main protease (Mpro), which breaks down viral polyproteins necessary for replication[86].

Molecular docking experiments show strong binding to the active site of Mpro[87] with binding energies equivalent to those of synthetic protease inhibitors. Nimbolide also lowers the number of places where viruses can enter by stopping the ACE2 receptor from being made in respiratory epithelial cells[88]. In addition to their direct antiviral effects, neem compounds also have strong immunomodulatory effects. They do this by blocking the NF-κB and COX2 pathways, which stop hyperinflammatory responses[89].

The plant's broad-spectrum antimicrobial properties could prevent secondary bacterial infections that occur frequently in severe COVID-19[90-92] . Neem bark extracts look to be able to stop thrombotic problems by decreasing D-dimer and platelet aggregation levels[92]. Even though the results *in vitro* are strong, it is still hard to make extracts that are the same and to make nimbolide more bioavailable. Neem is especially useful for minimising the systemic effects of COVID-19 because it has extra hepatoprotective and antioxidant properties. However, more clinical data is needed to find the best dosing regimens and confirm their effectiveness in human trials.

5. *In Silico* and *In Vitro* Validation of Plant-derived Bioactives

Due to their broad-spectrum biological activity, plant-derived bioactive chemicals have emerged as attractive therapeutic possibilities as the COVID-19 pandemic has heightened the quest for new antiviral medicines. *In vitro* and *in silico* methods have advanced recently, speeding up the process of finding and validating natural compounds that target SARS-CoV-2. Quercetin, curcumin, and berberine are examples of phytochemicals that have been shown to have substantial binding affinities to important viral proteins, including the spike protein, major protease

Table4. Plants with documented antiviral properties

Plant Name	Target Virus	Active Compound	References
Camellia sinensis	HBV	Epigallocatechin-3-gallate	93
Capparis spinosa	HSV-2, HIV-1	Protein (partiallyknown)	94
Cassine xylocarpa	HIV	Pentacyclic lupanetypetriterpenoids	95
Cistusincanus	Influenza(avian and human), HIV-1/2	Polyphenols	96,97
Curcuma longa	HSV-1	Curcumin	98
Cyperus rotundus	HSV-1, HBV	Various sesquiterpenes	99,100
Daphne gnidium	HIV	Daphnetoxin, gnidicin, gniditrin	101
Diospyros kaki	Human rotavirus	Various flavonoids and glycosides	102
Ficus benjamina	HSV-1, HSV-2	Rutin, kaempferol derivatives	103
Leucojum vernum	HIV-1	Homolycorine, acetyllycorine	104
Lilium candidum	HSV-1, HSV-2	Kaempferol	105
Magnolia officinalis	Dengue virus Type 2	Honokiol	106
Maytenus cuzcoina	HIV	Pentacyclic lupanetype triterpenoids	107
Panax ginseng	Human rotavirus	Various flavonoids and polysaccharides	108
Panax notoginseng	Influenza A virus	Unknown	108
Phyllanthus acidus	HBV	Sesquiterpenoids	109
Phyllanthus emblica	Influenza A H3N2, HBV	Sesquiterpenoid glycosides	110,111
Tuberaria lignose	HIV	Ellagic acid derivative	112
Viola diffusa	HBV	Friedelolactones	112
Vitis labrusca	Rotaviruses	Resveratrol and others	113
Vitis macrocarpon	Rotaviruses	Various flavonoids	113
Zataria multiflora	HSV-1	Rosmarinic acid	114

(Mpro), and RNA-dependent RNA polymerase (RdRp), through computational studies using molecular docking and dynamics simulations[115]. The antiviral properties of plant extracts and isolated molecules have been demonstrated *in vitro*, supporting these *in silico* predictions. As an example, andrographolide *of Andrographis paniculata* and thymoquinone of *Nigella sativa* indicate a strong anti-viral entry and replication effect in cell-based studies, along with a reduction in inflammatory responses associatedwith severe COVID-19[116,117]. Likewise, immunomodulatory effects have been demonstrated by bioactive compounds of *Tinosporacordifolia* and *Ocimum sanctum*, which provide immunity against cytokine storms[118,119]. Although these findings support the therapeutic potential of plant-based bioactive compounds, preclinical and clinical research is needed to verify the effectiveness, safety and pharmacokinetics. A combination of *in silico* and *in vitro* allow solid framework to develop antibiotics from plants and screen them within a short time, and the prospect of natural products in the fight against COVID-19 and other viral pandemics.

5.1 Molecular Docking Studies Targeting Viral Proteins

Computational methods, especially molecular docking, have been essential in finding chemicals derived from plants that have a high affinity for binding SARS-CoV-2 proteins. RNA-dependent RNA polymerase (RdRp), papain-like protease (PLpro), main protease (3CLpro/Mpro), and spike protein (RBD) are among

the major viral targets that these *in silico* studies use to evaluate phytochemicals[120]. For example, the ACE2 interface of the spike protein is strongly bound by glycyrrhizin (liquorice) and curcumin (turmeric), which may prevent viral entrance[121]. Baicalein (skullcap) and berberine (barberry) also have a strong affinity for RdRp, which prevents viral replication[122]. Molecular dynamics simulations further validate these interactions by assessing binding stability over time. While these predictions are promising, they require experimental validation. Nevertheless, *in silico* screening accelerates drug discovery by prioritising the most potent phytochemicals for further study.

5.2 Cell-based Antiviral Assays (Vero E6/ Calu-3 Models)

The antiviral properties of plant chemicals are confirmed by *in vitro* experiments employing Vero E6 (kidney epithelial) and Calu-3 (lung epithelial) cell lines[123,124]. The tests measure host cell viability, cytopathic effects and viral load reduction. As an example, quercetin (apples and onions) reduces SARS-CoV-2 replication by 70%[125] in Vero E6 cells. As EGCG (green tea) blocks the entry of viruses in Calu-3 cells[126]. Also, time-of-addition assays help to identify compounds that prevent entry (early) infection or late (replication) infection. These studies will give mechanistic information and dose-response correlations, which will inform the subsequent preclinicaldevelopment. Nevertheless, the findings should be approached with great care because cell models might not be able to completely mimic the respiratory infection dynamics of humans.

5.3 Synergistic Effects with Conventional Antivirals

Compounds derived from plants may improve the performance of standard antivirals (e.g., remdesivir, molnupiravir, nirmatrelvir) as well as decrease the likelihood of resistance[127]. Studies show that curcumin can help fight fibrosis in COVID-19 patients when used with angiotensin-converting enzyme (ACE) and angiotensin II receptor blockers (AT1)[128] and Glycyrrhizin. It has been demonstrated that (GR) and boswellic acids (BAs) work very well against COVID-19, thereby making it simpler for the body to get rid of the virus[129]. In addition to Paxlovid (nirmatrelvir/ritonavir), berberine can reduce dosage requirements, consequently reducing side effects[130]. Combination index (CI) models are used to measure synergy. A CI value of less than one shows potentiation. These results highlight the potential for the development of phytochemical adjuvant therapies; however, clinical trials are necessary to validate their efficacy and safety in humans.

6. Translation Challenges and Opportunities

Herbal antivirals exhibit potential against viral pathogens by various mechanisms, which include blocking viral entry, replication, protease inhibition, and host immune response modulation. However, to convert those bioactive phytochemicals used in conventional settings to clinically testable therapeutics, several challenges must be addressed. They include increasing bioavailability and pharmacokinetics, ensuring that each consignment can be standardised against previous consignments of live constituents, and negotiating different regulatory systems of herbal drug therapy. The subsections below explain some of the important strategies and considerations that would ensure one overcomes those limitations[131].

6.1 Bioavailability Enhancement Strategies (Nanocarriers, Piperile Adjuvants)

Most herbal phytochemicals, including curcumin and andrographolide, are not water soluble, are not stable in the gastrointestinal tract and are highly metabolised, and this severely restricts their therapeutic use. There have been reported instances of drug-drug interactions with curcumin, andrographolide and other herbal phytochemicals. Delivery systems based on nanotechnology, like liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), phytosomes and nanoemulsions, can address these limitations through enhanced solubility, stability, absorption in the intestines and general pharmacokinetics of herbal constituents[132,133].

6.2 Standardisation of Active Phytoconstituents

Natural extracts regularly exhibit variability in their phytochemical composition because of factors including plant species, harvest region, cultivation situations, and extraction techniques. So, standardisation is necessary

to make sure that active phytochemicals stay the same, pure, and strong all the time[134,135]. The use of modern analytical techniques, such as chemometric procedures, DNA barcoding, fuel chromatography mass spectrometry (GC–MS), liquid chromatography mass spectrometry (LC–MS), high-performance liquid chromatography (HPLC), and microscopic inspection, is essential for implementing standardised great control practices. The protection and effectiveness of natural goods may be jeopardised by adulteration, substitution, and the presence of contaminants (such as pollution or heavy metals) that can be found using these techniques[136]. The World Health Organisation (WHO) and other regulatory bodies additionally mandate batch-to-batch consistency and compliance with good production practices (GMP) to ensure that the pleasant requirements of medicinal herbal products are maintained[137].

6.3 Regulatory Considerations for Herbal Antivirals

6.3.1 European Union (EU)

The EU's Directive 2004/24/EC (Conventional Herbal Medicinal Products Directive) added a streamlined registration pathway for classic natural drug treatments. Products need to demonstrate a minimum of 30 years of conventional use, consisting of 15 years in the EU and observe top manufacturing practice (GMP) standards. Protection is classified through present clinical literature (scientific/preclinical/bibliographic); efficacy claims rely upon conventional use in place of new scientific trials. Moreover, pharmacovigilance necessities, user facts, and network monographs are mandatory[137].

6.3.2 Global Perspective and WHO

In 2006, the European Agency for Health and Consumers released the Global Regulatory Cooperation for Herbal Drugs (IRCH) to help make international standards for natural remedies more consistent. As of 2025, IRCH has forty-nine member countries. These countries collaborate to make sure that safety is tracked and that high standards are met. India has been an active participant, hosting the 2025 IRCH workshop to foster global collaboration[138].

6.3.3 Analytical and Quality Protocols

Regulatory submissions typically require a lot of documentation, such as detailed production methods, standardised extract profiles, identity and purity testing, toxicology data, and proof of scientific or conventional use. Those requirements build on the major management ideas[138].

7. Conclusion

Modern medicine cannot adequately handle the complicated problems presented by quickly changing viral pandemics, as the COVID-19 catastrophe has confirmed. Synthetic drugs and vaccines remain necessary, but their downsides due to reduced efficacy against variations and the challenge in obtaining them in resource-scarce regions are subjects to complement. The medicinal herbs have a promising but underutilised source of antiviral, anti-inflammatory, and immunomodulatory compounds. The traditional systems have long recognised their extensive medicinal qualities. The evidence discussed in this study indicates that phytochemicals such as curcumin, glycyrrhizin, baicalein, withaferin A, and andrographolide prevent viral entry (spike–ACE2 interaction), replication (RdRp and protease inhibition), and hyperinflammatory responses (NF- 0 B and IL- 6 suppression). It is through these pleiotropic molecules that enhance host immunity and reduce the pathogenicity of the virus, unlike single-target synthetic medicines. They are even more attractive options to frontline therapy or adjunct therapy due to their historical acceptance and excellent safety profiles.

Nevertheless, there are considerable challenges in translation that should be overcome to deliver the promise. The use of nanotechnology-based delivery systems, strict quality control and standardised international regulatory systems is required to solve the problems of low bioavailability, discrepancy in phytochemical content and lack of standardised clinical information. Plant-based antivirals should be formulated in concerted research that cuts across the borders of molecular biology, ethnopharmacology, and clinical trials. In the future, a better and more developed healthcare paradigm can be developed by incorporating phytomedicine in pandemic preparedness. By leveraging the potential of modern innovations and the pharmacopoeia of nature, people can create solutions to COVID-19 and other viral attacks in the future and make them sustainable. Consequently, phytotherapy

is no longer merely an adjunct therapy, but a major constituent of egalitarian, readily available, and versatile defences in the face of health crises across the world.

8. References

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020; 55(3):105924. https://doi.org/10.1016/j.ijantimicag.2020.105924 PMid: 32081636 PMCid: PMC7127800.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020; 382(13):1199-1207. https://doi.org/10.1056/NEJMoa2001316 PMid: 31995857 PMCid: PMC7121484.
3. Muralidar S, Ambi SV, Sekaran S, Krishnan UM. The emergence of COVID-19 as a global pandemic: understanding the epidemiology, immune response and potential therapeutic targets of SARS-CoV-2. Biochimie. 2020; 179:85-100. https://doi.org/10.1016/j.biochi.2020.09.018 PMid: 32971147 PMCid: PMC7505773
4. Nasajpour M, Pouriyeh S, Parizi RM, *et al*. Internet of things for currentCOVID-19 and future pandemics: an exploratory study. J Healthc Inform Res. 2020; 4:325–364. https://doi.org/10.1007/s41666-020-00080-6 PMid: 33204938 PMCid: PMC7659418.
5. Pal M, Berhanu G, Desalegn C, Kandi V. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus. 2020; 12(3):e7423. https://doi.org/10.7759/cureus.7423
6. Al-Qaaneh AM, Alshammari T, Aldahhan R, Aldossary H, Alkhalifah ZA, Borgio JF. Genome composition and genetic characterization of SARS-CoV-2. Saudi J Biol Sci. 2021; 28(3):19781989. https://doi.org/10.1016/j.sjbs.2020.12.053 PMid: 33519278 PMCid: PMC7834485.
7. Raza S, Rasheed MA, Zahir W, Navid MT, Diwan RA, Awais M, *et al*. Structural and genetic analysis of coronavirus spike proteins suggest pangolin as a proximate intermediate host of SARS-CoV-2 (COVID-19). 2020.
8. Dhama K, Patel SK, Sharun K, Pathak M, Tiwari R, Yatoo MI, *et al*. SARS-CoV-2 jumping the species barrier: Zoonotic lessons from SARS, MERS and recent advances to combat this pandemic virus. Travel Med Infect Dis. 2020; 37:101830. https://doi.org/10.1016/j.tmaid.2020.101830 PMid: 32755673 PMCid: PMC7396141.
9. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, *et al*. SARS-CoV2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2):271-280. https://doi.org/10.1016/j.cell.2020.02.052 PMid:32142651 PMCid: PMC7102627.
10. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, *et al*. COVID-19 infection: an overview on cytokine storm and related interventions. Virol J. 2022; 19:92. https://doi.org/10.1186/s12985-022-01814-1
11. Srivastava K, Singh MK. Drug repurposing in COVID-19: a review with past, present and future. Metab Open. 2021; 12:100121. https://doi.org/10.1016/j.omx.2021.100121
12. Leong KY, Tham SK, Poh CL. Revolutionizing immunization: a comprehensive review of mRNA vaccine technology and applications. Virol J. 2025; 22:71. https://doi.org/10.1186/s12985025-02645-6
13. Bok K, Sitar S, Graham BS, Mascola JR. Accelerated COVID-19 vaccine development: milestones, lessons, and prospects. Immunity. 2021; 54(8):1636-1651. https://doi.org/10.1016/j.immuni.2021.07.017 PMid: 34348117 PMCid: PMC8328682.
14. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020; 586(7830):516–527. https://doi.org/10.1038/s41586-020-2798-3 PMid:32967006
15. Ansari P, Reberio AD, Ansari NJ, Kumar S, Khan JT, Chowdhury S, *et al*. Therapeutic potential of medicinal plants and their phytoconstituents in diabetes, cancer, infections, cardiovascular diseases, inflammation and gastrointestinal disorders. Biomedicines. 2025; 13(2):454. https://doi.org/10.3390/biomedicines13020454 PMid: 40002867 PMCid: PMC11853317.
16. Ang L, Song E, Lee HW, Lee MS. Herbal medicine for the treatment of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis of randomized controlled trials. J Clin Med. 2020; 9(5):1583.
17. Munot NM, Jadhav NY, Phuge AN, Dawange SD, Jain KS. Enhancing immune responses to combat viral infections: a phytoconstituents approach. Biosci Biotechnol Res Asia. 2025; 22(1):73-94. https://doi.org/10.13005/bbra/3342
18. Mani JS, Johnson JB, Steel JC, Broszczak DA, Neilsen PM, Walsh KB, Naiker M. Natural product-derived phytochemicals as potential agents against coronaviruses: A review. Virus Res. 2020; 284:197989. https://doi.org/10.1016/j.virusres.2020.197989 PMid: 32360300 PMCid: PMC7190535.
19. Attia YA, Alagawany MM, Farag MR, Alkhatib FM, Khafaga AF, Abdel-Moneim AME, *et al*. Phytogenic products and phytochemicals as a candidate strategy to improve tolerance to coronavirus. Front Vet Sci. 2020; 7:573159. https://doi.org/10.3389/fvets.2020.573159 PMid: 33195565 PMCid: PMC7606864.
20. Krishnamurthy V, Sankaramourthy D. COVID-19, its prevention and treatment in the light of AYUSH medicines. Pharmacol Res - Nat Prod. 2024; 3:100040. https://doi.org/10.1016/j.prenap.2024.100040

21. Bai C, Zhong Q, Gao GF. Overview of SARS-CoV-2 genome-encoded proteins.Sci China Life Sci. 2022; 65(2):280-294. https://doi.org/10.1007/s11427-021-1964-4 PMid: 34387838 PMCid: PMC8362648.
22. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARSCoV-2 spike protein: potential antiviral drug development for COVID-19. Acta Pharmacol Sin. 2020; 41(9):1141. https://doi.org/10.1038/s41401-020-0485-4 PMid: 32747721 PMCid: PMC7396720.
23. Naqvi AAT, Fatima K, Mohammad T, Fatima U, Singh IK, Singh A, *et al*. Insights into SARSCoV-2 genome, structure, evolution, pathogenesis and therapies: structural genomics approach. Biochim Biophys Acta Mol Basis Dis. 2020; 1866(10):165878. https://doi.org/10.1016/j.bbadis.2020.165878 PMid:32544429 PMCid: PMC7293463.
24. Sternberg A, Naujokat C. Structural features of coronavirus SARS-CoV-2 spike protein: targets for vaccination. Life Sci. 2020; 257:118056. https://doi.org/10.1016/j.lfs.2020.118056 PMid:32645344 PMCid: PMC7336130.
25. Gorkhali R, Koirala P, Rijal S, Mainali A, Baral A, Bhattarai HK. Structure and function of major SARS-CoV-2 and SARS-CoV proteins. Bioinform Biol Insights. 2021; 15:11779322211025876.
26. Agarwal A, Steed AL. Advances in understanding the envelope protein in coronavirus infection. J Immunol Sci. 2024; 8:1-7. https://doi.org/10.29245/2578-3009/2024/1.1256
27. Bezerra PR, Almeida FC. Structural basis for the participation of the SARS-CoV-2 nucleocapsid protein in the template switch mechanism and genomic RNA reorganization. J Biol Chem. 2024; 300(11):107834. https://doi.org/10.1016/j.jbc.2024.107834 PMid:39343000 PMCid: PMC11541846.
28. Davies NG, *et al*. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021; 372(6538).
29. Bayarri-Olmos R, Johnsen LB, Idorn M, Reinert LS, Rosbjerg A, Vang S, *et al*. The alpha/B.1.1.7 SARS-CoV-2 variant exhibits significantly higher affinity for ACE-2 and requires lower inoculation doses to cause disease in K18-hACE2 mice. eLife. 2021; 10:e70002. https://doi.org/10.7554/eLife.70002 PMid:34821555 PMCid: PMC8635972.
30. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, *et al*. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell. 2021; 184(9):23482361.
31. Pecoraro V, Pirotti T, Trenti T. Evidence of SARS-CoV-2 reinfection: analysis of 35,000 subjects and overview of systematic reviews. Clin Exp Med. 2023; 23(4):1213-1224. https://doi.org/10.1007/s10238-022-00922-0 PMid:36289100 PMCid: PMC9607758.
32. Salimović-Bešić I, Dedeić-Ljubović A, Zahirović E, Hasanović M, Šehić M, Vukovikj M, *et al*. The SARS-CoV-2 Delta (B.1.617.2) variant with spike N501Y mutation in the shadow of Omicron emergence. Heliyon. 2022; 8(12). https://doi.org/10.1016/j.heliyon.2022.e12650 PMid: 36590492 PMCid: PMC9789543.
33. Chakraborty C, Bhattacharya M, Sharma AR, Mallik B. Omicron (B.1.1.529) – A new heavily mutated variant: mapped location and probable properties of its mutations with an emphasis on Sglycoprotein. Int J Biol Macromol. 2022; 219:980-997. https://doi.org/10.1016/j.ijbiomac.2022.07.254 PMid:35952818 PMCid: PMC9359758.
34. Bhardwaj S, Verma R, Gupta J. Challenges and future prospects of herbal medicine. Int Res Med Health Sci. 2018; 1(1):12-15. https://doi.org/10.36437/irmhs.2018.1.1.D
35. Zhou L, Ayeh SK, Chidambaram V, *et al*. Modes of transmission of SARS-CoV-2 and evidence for preventive behavioral interventions. BMC Infect Dis. 2021; 21:496. https://doi.org/10.1186/s12879-021-06222-4 PMid: 34049515 PMCid: PMC8160404.
36. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol. 2022; 23(1):3-20. https://doi.org/10.1038/s41580-021-00418-x PMid: 34611326 PMCid: PMC8491763.
37. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, Tousoulis D. Inflammatory mechanisms contributing to endothelial dysfunction. Biomedicines. 2021; 9(7):781. https://doi.org/10.3390/biomedicines9070781 PMid: 34356845 PMCid: PMC8301477.
38. Nie J, Zhou L, Tian W, Liu X, Yang L, Yang X, Zhang Y, Wei S, Wang DW, Wei J. Deep insight into cytokine storm: from pathogenesis to treatment. Signal Transduct Target Ther. 2025; 10(1):112.
39. Leite DRB, Mantovani KM, Cordeiro SP, Maia FB, Betim FCM, de Bona Sartor E, *et al*. RNA-dependent RNA polymerase (RdRp) natural antiviral inhibitors: a review. Med Chem Res. 2022; 31(12):2089-2102. https://doi.org/10.1007/s00044-022-02963-2 PMid:36193545 PMCid: PMC9520115.
40. Peter AE, Sandeep BV, Ganga Rao B, Lakshmi Kalpana V. Calming the storm: natural immunosuppressants as adjuvants to target the cytokine storm in COVID-19. Front Pharmacol. 2021; 11:583777. https://doi.org/10.3389/fphar.2020.583777 PMid: 33708109 PMCid: PMC7941276.
41. Choe K, Park HY, Ikram M, Lee HJ, Park TJ, Ullah R, Kim MO. Systematic review of the common pathophysiological mechanisms in COVID-19 and neurodegeneration: the role of bioactive compounds and natural antioxidants. Cells. 2022; 11(8):1298. https://doi.org/10.3390/cells11081298 PMid:35455977 PMCid: PMC9031507.
42. Mouhid L, Corzo-Martínez M, Torres C, Vázquez L, Reglero G, Fornari T, Ramírez de Molina A. Improving *in vivo* efficacy of bioactive molecules: an overview of potentially antitumor phytochemicals and currently available lipid-based delivery systems. J Oncol. 2017; 2017:7351976.

https://doi.org/10.1155/2017/7351976 PMid:28555156 PMCid: PMC5438845.
43. Navabhatra A. Molecular mechanisms of envelope protein inhibitors from traditional herbal medicines. In: Traditional and herbal medicines for COVID-19. CRC Press; 2025. pp. 162-178.
44. Pan B, Fang S, Zhang J, Pan Y, Liu H, Wang Y, *et al*. Chinese herbal compounds against SARS-CoV-2: puerarin and quercetin impair the binding of viral S-protein to ACE2 receptor. Comput Struct Biotechnol J. 2020; 18:3518-3527. https://doi.org/10.1016/j.csbj.2020.11.010 PMid:33200026 PMCid: PMC7657012.
45. Tolah AM, Altayeb LM, Alandijany TA, Dwivedi VD, El-Kafrawy SA, Azhar EI. Computational and *in vitro* experimental investigations reveal antiviral activity of licorice and glycyrrhizin against severe acute respiratory syndrome coronavirus 2. Pharmaceuticals. 2021; 14(12):1216. https://doi.org/10.3390/ph14121216 PMid: 34959616 PMCid: PMC8703534.
46. Chourasia M, Koppula PR, Battu A, Ouseph MM, Singh AK. EGCG, a green tea catechin, as a potential therapeutic agent for symptomatic and asymptomatic SARS-CoV-2 infection. Molecules. 2021; 26(5):1200. https://doi.org/10.3390/molecules26051200 PMid:33668085 PMCid: PMC7956763.
47. Kaul R, Paul P, Kumar S, Buesselberg D, Dwivedi VD, Chaari A. Promising antiviral activities of natural flavonoids against SARS-CoV-2 targets: systematic review. Int J Mol Sci. 2021; 22(20):11069. https://doi.org/10.3390/ijms222011069 PMid: 34681727 PMCid: PMC8539743.
48. Singh J, Malik D, Raina A. Computational investigation for identification of potential phytochemicals and antiviral drugs as potential inhibitors for RNA-dependent RNA polymerase of COVID-19. J Biomol Struct Dyn. 2022; 40(8):3492-3507. https://doi.org/10.1080/07391102.2020.1847688 PMid: 33200678 PMCid: PMC7684842.
49. World Health Organization. International Regulatory Cooperation for Herbal Medicines (IRCH). 2006. https://www.who.int/medicines/areas/traditional/irch/en/
50. Chen Z, Ye SY. Research progress on antiviral constituents in traditional Chinese medicines and their mechanisms of action. Pharm Biol. 2022; 60(1):1063-1076. https://doi.org/10.1080/13880209.2022.2074053 PMid:35634712 PMCid: PMC9154771.
51. Silva MJA, Ribeiro LR, Gouveia MIM, Marcelino BDR, Santos CSD, Lima KVB, Lima LNGC. Hyperinflammatory response in COVID-19: A systematic review. Viruses. 2023; 15(2):553. https://doi.org/10.3390/v15020553 PMid: 36851766 PMCid: PMC9962879.
52. Ghandadi M, Sahebkar A. Curcumin: an effective inhibitor of interleukin-6. Curr Pharm Des. 2017; 23(6):921-931. https://doi.org/10.2174/1381612822666161006151605 PMid:27719643.
53. Saha P, Ajgaonkar S, Maniar D, Sahare S, Mehta D, Nair S. Current insights into transcriptional role(s) for the nutraceutical *Withania somnifera* in inflammation and aging. Front Nutr. 2024; 11:1370951. https://doi.org/10.3389/fnut.2024.1370951 PMid:38765810 PMCid: PMC11099240.
54. Zhou Z, Dong J, Qiu Y, Zhang G, Wei K, He L, Sun Y, *et al*. Sulforaphane decreases oxidative stress and inhibits NLRP3 inflammasome activation in a mouse model of ulcerative colitis. Biomed Pharmacother. 2024; 175:116706. https://doi.org/10.1016/j.biopha.2024.116706 PMid: 38713944.
55. Al-Yasiry ARM, Kiczorowska B. Frankincense—therapeutic properties. Adv Hyg Exp Med. 2016; 70. https://doi.org/10.5604/17322693.1200553 PMid: 27117114.
56. Anand AV, Balamuralikrishnan B, Kaviya M, Bharathi K, Parithathvi A, Arun M, Senthilkumar N, *et al*. Medicinal plants, phytochemicals, and herbs to combat viral pathogens including SARSCoV-2. Molecules. 2021; 26(6):1775. https://doi.org/10.3390/molecules26061775 PMid:33809963 PMCid: PMC8004635.
57. Declerck K, Novo CP, Grielens L, Van Camp G, Suter A, Vanden Berghe W. *Echinacea purpurea* (L.) Moench treatment of monocytes promotes tonic interferon signaling, increased innate immunity gene expression and DNA repeat hypermethylated silencing of endogenous retroviral sequences. BMC Complement Med Ther. 2021; 21(1):141. https://doi.org/10.1186/s12906-021-03310-5 PMid:33980308 PMCid: PMC8114977.
58. Rajanna M, Bharathi B, Shivakumar BR, Deepak M, D'Souza P, Prabakaran D, Vijayabhaskar T, Arun B. Immunomodulatory effects of *Andrographis paniculata* extract in healthy adults—an open-label study. J Ayurveda Integr Med. 2021; 12(3):529-534. https://doi.org/10.1016/j.jaim.2021.06.004 PMid:34376353 PMCid: PMC8377179.
59. D'Avino D, Cerqua I, Ullah H, Spinelli M, Di Matteo R, Granato E, Capasso R, *et al*. Beneficial effects of *Astragalus membranaceus* (Fisch.) Bunge extract in controlling inflammatory response and preventing asthma features. Int J Mol Sci. 2023; 24(13):10954. https://doi.org/10.3390/ijms241310954 PMid:37446131 PMCid: PMC10342042.
60. Tharakan A, Shukla H, Benny IR, Tharakan M, George L, Koshy S. Immunomodulatory effect of *Withania somnifera* (*Ashwagandha*) extract—a randomized, double-blind, placebo-controlled trial with an open label extension on healthy participants. J Clin Med. 2021; 10(16):3644. https://doi.org/10.3390/jcm10163644 PMid:34441940 PMCid: PMC8397213.
61. Filip R, Gheorghita Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global challenges to public health care systems during the COVID-19 pandemic: a review of pandemic measures and problems. J Pers Med. 2022; 12(8):1295. https://doi.org/10.3390/jpm12081295 PMid: 36013244 PMCid: PMC9409667.
62. Dar RA, Shahnawaz M, Ahanger MA, Majid IU. Exploring the diverse bioactive compounds from medicinal plants:

A review. J Phytopharm. 2023; 12(3):189-195. https://doi.org/10.31254/phyto.2023.12307
63. Trivedi P, Abbas A, Lehmann C, Rupasinghe HV. Antiviral and anti-inflammatory plant-derived bioactive compounds and their potential use in the treatment of COVID-19related pathologies. J Xenobiot. 2022; 12(4):289-306. https://doi.org/10.3390/jox12040020 PMid:36278757 PMCid: PMC9589987.
64. Singh M, Jayant K, Singh D, Bhutani S, Poddar NK, Chaudhary AA, *et al*. *Withania somnifera*(L.) Dunal (*Ashwagandha*) for the possible therapeutics and clinical management of SARS-CoV-2 infection: plant-based drug discovery and targeted therapy. Front Cell Infect Microbiol. 2022; 12:933824. https://doi.org/10.3389/fcimb.2022.933824 PMid:36046742 PMCid: PMC9421373.
65. Kalra RS, Kumar V, Dhanjal JK, Garg S, Li X, Kaul SC, *et al*. COVID-19-inhibitory activity of withanolides involves targeting of the host cell surface receptor ACE2: insights from computational and biochemical assays. J Biomol Struct Dyn. 2022; 40(17):7885-7898. https://doi.org/10.1080/07391102.2021.1902858 PMid: 33797339 PMCid: PMC8022344.
66. Kumar V, Dhanjal JK, Bhargava P, Kaul A, Wang J, Zhang H, *et al*. Withanone and withaferin-A are predicted to interact with transmembrane protease serine 2 (TMPRSS2) and block entry of SARS-CoV-2 into cells. J Biomol Struct Dyn. 2022; 40(1):1-13. https://doi.org/10.1080/07391102.2020.1775704 PMid: 32469279 PMCid: PMC7309304.
67. Press Information Bureau (Government of India). India to host WHO–IRCH workshop on herbal medicine safety and regulations from August 6: three-day technical meet to feature hands-on training, case studies, and global regulatory dialogues. 2025 Aug 5.
68. Saini D, Kesharwani RK, Keservani RK. Nutraceuticals in respiratory and pulmonary diseases. CRC Press; 2025.
69. Joshi MK. *Ashwagandha*—an herbal product used as a neuroprotective agent [master's thesis]. Adelphi University; 2024. https://doi.org/10.1016/j.jbc.2024.106768
70. Ramli S, Wu YS, Batumalaie K, Guad RM, Choy KW, Kumar A, Gopinath SCB, *et al*. Phytochemicals of *Withania somnifera* as a future promising drug against SARS-CoV-2: pharmacological role, molecular mechanism, molecular docking evaluation, and efficient delivery. Microorganisms. 2023; 11(4):1000. https://doi.org/10.3390/microorganisms11041000 PMid:37110423 PMCid: PMC10142625.
71. Biswal BM, Sulaiman SA, Che Ismail H, Zakaria H, Musa KI. Effect of *Withania somnifera* (*Ashwagandha*) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. Integr Cancer Ther. 2013; 12(4):312-322. https://doi.org/10.1177/1534735412464551 PMid: 23142798.
72. Vachaspati A. Clinical study on efficacy of *Ashwagandhavati* and *satvavajaya chikitsa* in the management of *chittodvega* in premenstrual syndrome. 2017.
73. Ferreira LLC, Abreu MP, Costa CB, Leda PO, Behrens MD, Dos Santos EP. Curcumin and its analogs as a therapeutic strategy in infections caused by RNA genome viruses. Food Environ Virol. 2022; 14(2):120-137. https://doi.org/10.1007/s12560-022-09514-3 PMid: 35352306 PMCid: PMC8963406.
74. Saeedi-Boroujeni A, Mahmoudian-Sani MR, Bahadoram M, Alghasi A. COVID-19: a case for inhibiting NLRP3 inflammasome, suppression of inflammation with curcumin? Basic Clin Pharmacol Toxicol. 2021; 128(1):37-45. https://doi.org/10.1111/bcpt.13503 PMid: 33099890.
75. Sadeghi N, Mansoori A, Shayesteh A, Hashemi SJ. The effect of curcumin supplementation on clinical outcomes and inflammatory markers in patients with ulcerative colitis. Phytother Res. 2020; 34(5):1123-1133. https://doi.org/10.1002/ptr.6581 PMid: 31802559.
76. Tabanelli R, Brogi S, Calderone V. Improving curcumin bioavailability: current strategies and future perspectives. Pharmaceutics. 2021; 13(10):1715. https://doi.org/10.3390/pharmaceutics13101715 PMid:34684008 PMCid: PMC8540263.
77. Zhang QH, Huang HZ, Qiu M, Wu ZF, Xin ZC, Cai XF, *et al*. Traditional uses, pharmacological effects, and molecular mechanisms of licorice in potential therapy of COVID-19. Front Pharmacol. 2021; 12:719758. https://doi.org/10.3389/fphar.2021.719758 PMid: 34899289 PMCid: PMC8661450.
78. Ahmad S, Waheed Y, Abro A, Abbasi SW, Ismail S. Molecular screening of glycyrrhizin-based inhibitors against ACE2 host receptor of SARS-CoV-2. J Mol Model. 2021; 27(7):206. https://doi.org/10.1007/s00894-021-04816-y PMid:34169390 PMCid: PMC8225399.
79. Joseph JN, Shrivastava A, Benny B, Baig MY, Georgine SA, Saral AM. Antiviral properties of various bioactive components present in the root of *Glycyrrhiza glabra*. Curr Nutr Food Sci. 2023; 19(2):166-175. https://doi.org/10.2174/1573401318666220411125333
80. Umarov A, Djabborov BI, Rakhmatova MR, Durdiev NK, Yuldashev JI, Suyunov A, *et al*. A systematic review of antioxidant and antimicrobial activities in the different extracts of licorice as a valuable plant for ameliorating respiratory infectious disorders. Caspian J Environ Sci. 2025; 23(1):269-280.
81. Richard SA. Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetinic acids. Mediators Inflamm. 2021; 2021:6699560.
82. Lee SA, Lee SH, Kim JY, Lee WS. Effects of glycyrrhizin on lipopolysaccharide-induced acute lung injury in a mouse model. J Thorac Dis. 2019; 11(4):1287. https://doi.org/10.21037/jtd.2019.04.14 PMid:31179071 PMCid: PMC6531684.

83. Jiang X, Lu Y, Ding Y, Liu Y, Zhao Z, Liu P, *et al*. Potential of phytomedicine in benefiting both long COVID and acute coronary syndromes: a state-of-the-art review. Explor Res Hypothesis Med. 2025; 10(2):97-105.
84. Wetche JL, Schmedes AV, Sjøgren A, Bergmann ML, Fly LH, Madsen JS, *et al*. High plasma 18βglycyrrhetinic acid levels are associated with more intensive antihypertensive treatment, resistant hypertension and apparent mineralocorticoid excess in patients with type 2 diabetes. J Nutr. 2025.
85. 85.Bhattacharyya D, Das Sarma J. The pleiotropic anti-cancer, antiviral, and anti-neuroimmunomodulatory role of methanolic neem bark extract. J Nat Med. 2025; 79(4):951-966. https://doi.org/10.1007/s11418-025-01924-4.
86. Saha O, Siddiquee NH, Akter R, Sarker N, Bristi UP, Sultana KF, *et al*. Antiviral activity, pharmacoinformatics, molecular docking, and dynamics studies of *Azadirachta indica* against Nipah virus by targeting envelope glycoprotein: emerging strategies for developing antiviral treatment. Bioinform Biol Insights. 2024; 18:11779322241264145. https://doi.org/10.1177/11779322241264145 PMid:39072258 PMCid: PMC11283663.
87. Muhammed D, Odey BO, Alozieuwa BU, Alawode RA, Okunlola BM, Ibrahim J, *et al*. Azadirachtin-A, a bioactive compound from *Azadirachta indica*, is a potential inhibitor of SARS-CoV-2 main protease. AROC Pharm Biotechnol. 2021; 1(1):1-8.
88. Pooladanda V, Thatikonda S, Bale S, Pattnaik B, Sigalapalli DK, Bathini NB, *et al*. Nimbolide protects against endotoxin-induced acute respiratory distress syndrome by inhibiting TNF-α mediated NF-κB and HDAC-3 nuclear translocation. Cell Death Dis. 2019; 10(2). https://doi.org/10.1038/s41419-018-1247-9 PMid: 30692512 PMCid: PMC6349848.
89. Patil K, Nangare S, Shete M, Shelke M, Shaikh M, Potdlar M, *et al*. Immunomodulation property of antioxidants. In: Antioxidants as nutraceuticals. Apple Academic Press. 2025. pp. 95-124.
90. Eze MO, Ejike CE, Ifeonu P, Udeinya IJ, Udenigwe CC, Uzoegwu PN. Anti-COVID-19 potential of *Azadirachta indica* (neem) leaf extract. Sci Afr. 2022; 16:e01184. https://doi.org/10.1016/j.sciaf.2022.e01184 PMid:35434432 PMCid: PMC8990437.
91. Wylie MR, Merrell DS. The antimicrobial potential of the neem tree,*Azadirachta indica*. Front Pharmacol. 2022; 13:891535.
92. Batra N, De Souza C, Batra J, Raetz AG, Yu AM. The HMOX1 pathway as a promising target for the treatment and prevention of SARS-CoV-2 of 2019 (COVID-19). Int J Mol Sci. 2020; 21(17):6412. https://doi.org/10.3390/ijms21176412 PMid: 32899231 PMCid: PMC7503392.
93. Maregesi SM, Pieters L, Ngassapa OD, Apers S, Vingerhoets R, Cos P, *et al*. Screening of some Tanzanian medicinal plants from Bunda district for antibacterial, antifungal and antiviral activities. J Ethnopharmacol. 2008; 119(1):58–66. https://doi.org/10.1016/j.jep.2008.05.033 PMid: 18582554.
94. Karamese M, *et al*. Preventive effects of epigallocatechin-3-gallate on hepatitis-B virus DNA replication. Asian Pac J Cancer Prev. 2015; 16(10):4199–4202. https://doi.org/10.7314/APJCP.2015.16.10.4199 PMid:26028072.
95. Lam SK, Ng TB. A protein with antiproliferative, antifungal and HIV-1 reverse transcriptase inhibitory activities from caper (*Capparis spinosa*) seeds. Phytomedicine. 2009; 16(5):444–450. https://doi.org/10.1016/j.phymed.2008.09.006 PMid: 19019643.
96. Callies O, *et al*. Isolation, structural modification, and HIV inhibition of pentacyclic lupane-type triterpenoids from *Cassine xylocarpa* and *Maytenus cuzcoina*. J Nat Prod. 2015; 78(5):1045–1055. https://doi.org/10.1021/np501025r PMid: 25927586.
97. Droebner K, *et al*. CYSTUS052, a polyphenol-rich plant extract, exerts anti-influenza virus activity in mice. Antiviral Res. 2007; 76(1):1–10. https://doi.org/10.1016/j.antiviral.2007.04.001 PMid:17573133.
98. Brijesh S, Daswani PG, Tetali P, Antia NH, Birdi TJ. Studies on the antidiarrhoeal activity of *Aegle marmelos* unripe fruit: validating its traditional usage. BMC Complement Altern Med. 2009; 9:47. https://doi.org/10.1186/1472-6882-9-47 PMid: 19930633 PMCid: PMC2788518.
99. Nair MS, Huang Y, Fidock DA, Polyak SJ, Wagoner J, Towler MJ, Weathers PJ. *Artemisia annua* L. extracts inhibit the *in vitro* replication of SARS-CoV-2 and two of its variants. J Ethnopharmacol. 2021; 274:114016. https://doi.org/10.1016/j.jep.2021.114016 PMid:33716085 PMCid: PMC7952131.
100. Ehrhardt C, *et al*. A polyphenol-rich plant extract, CYSTUS052, exerts anti-influenza virus activity in cell culture without toxic side effects or the tendency to induce viral resistance. Antiviral Res. 2007; 76(1):38–47. https://doi.org/10.1016/j.antiviral.2007.05.002 PMid: 17572513.
101. Xu HB, Ma YB, Huang XY, Geng CA, Wang H, Zhao Y, *et al*. Bioactivity-guided isolation of anti-hepatitis B virus active sesquiterpenoids from the traditional Chinese medicine: rhizomes of *Cyperus rotundus*. J Ethnopharmacol. 2015; 171:131–140. https://doi.org/10.1016/j.jep.2015.05.040 PMid: 26051832.
102. Moradi MT, Rafieian-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(5):506–515. https://doi.org/10.22038/ajp.2016.6567

103. Gyuris A, Szlavik L, Minarovits J, Vasas A, Molnar J, Hohmann J. Antiviral activities of extracts of *Euphorbia hirta* L. against HIV-1, HIV-2 and SIVmac251. In Vivo. 2009; 23(3):429– 432.
104. Alfajaro MM, Kim HJ, Park JG, Ryu EH, Kim JY, Jeong YJ, *et al*. Anti-rotaviral effects of *Glycyrrhiza uralensis* extract in piglets with rotavirus diarrhea. Virol J. 2012; 9:310. https://doi.org/10.1186/1743-422X-9-310 PMid:23244491 PMCid: PMC3547719.
105. Szlavik L, Gyuris A, Minarovits J, Forgo P, Molnar J, Hohmann J. Alkaloids from *Leucojum vernum* and antiretroviral activity of Amaryllidaceae alkaloids. Planta Med. 2004; 70(9):871–873. https://doi.org/10.1055/s-2004-827239 PMid:15386196.
106. Yarmolinsky L, Zaccai M, Ben-Shabat S, Mills D, Huleihel M. Antiviral activity of ethanol extracts of *Ficus benjamina* and *Lilium candidum in vitro*. New Biotechnol. 2009; 26(6):307–313. https://doi.org/10.1016/j.nbt.2009.08.005 PMid:19703599.
107. Lam SK, Ng TB. A protein with antiproliferative, antifungal and HIV-1 reverse transcriptase inhibitory activities from caper (*Capparis spinosa*) seeds. Phytomedicine. 2009; 16(5):444–450. https://doi.org/10.1016/j.phymed.2008.09.006 PMid:19019643.
108. Parsania M, Rezaee MB, Monavari SH, Jaimand K, Mousavi Jazayeri SM, Razazian M, *et al*. Antiviral screening of four plant extracts against acyclovir-resistant herpes simplex virus type-1. Pak J Pharm Sci. 2017; 30(4 Suppl):1407–1411.
109. Choi JG, Jin YH, Lee H, Oh TW, Yim NH, Cho WK, *et al*. Protective effect of *Panax notoginseng* root water extract against influenza A virus infection by enhancing antiviral interferon-mediated immune responses and natural killer cell activity. Front Immunol.2017; 8:1542. https://doi.org/10.3389/fimmu.2017.01542 PMid:29181006 PMCid: PMC5693858.
110. Lv JJ, Yu S, Wang YF, Wang D, Zhu HT, Cheng RR, *et al*. Anti-hepatitis B virus norbisabolane sesquiterpenoids from *Phyllanthus acidus* and the establishment of their absolute configurations using theoretical calculations. J Org Chem. 2014; 79(12):5432– 5447. https://doi.org/10.1021/jo5004604 PMid:24824117.
111. Lv JJ, Yu S, Xin Y, Cheng RR, Zhu HT, Wang D, et al. Anti-viral and cytotoxic norbisabolane sesquiterpenoid glycosides from Phyllanthus emblica and their absolute configurations. Phytochemistry. 2014; 105:175-186. doi:10.1016/j.phytochem.2014.06.011.
112. Soleimani Farsani M, Behbahani M, Isfahani HZ. The effect of root, shoot and seed extracts of the Iranian *Thymus* L. (Lamiaceae) species on HIV-1 replication and CD4 expression. Cell J. 2016; 18(2):255–261.
113. Bedoya LM, Abad MJ, Sanchez-Palomino S, Alcami J, Bermejo P. Ellagitannins from *Tuberaria lignosa* as entry inhibitors of HIV. Phytomedicine. 2010; 17(1):69–74. https://doi.org/10.1016/j.phymed.2009.08.008 PMid: 19748255.
114. Dai JJ, Tao HM, Min QX, Zhu QH. Anti-hepatitis B virus activities of friedelolactones from *Violadiffusa* Ging. Phytomedicine. 2015; 22(7–8):724–729. https://doi.org/10.1016/j.phymed.2015.05.001 PMid:26141758.
115. Azeem M, Mustafa G, Mahrosh HS. Virtual screening of phytochemicals by targeting multiple proteins of severe acute respiratory syndrome coronavirus 2: molecular docking and molecular dynamics simulation studies. Int J Immunopathol Pharmacol. 2022; 36:03946320221142793. https://doi.org/10.1177/03946320221142793 PMid:36442514 PMCid: PMC9716588.
116. Tania M, Asad A, Li T, Islam MS, Islam SB, Hossen MM, *et al*. Thymoquinone against infectious diseases: perspectives in recent pandemics and future therapeutics. Iran J Basic Med Sci. 2021; 24(8):1014.
117. Adiguna SP, Panggabean JA, Atikana A, Untari F, Izzati F, Rosyidah A, *et al*. Antiviral activities of andrographolide and its derivatives: mechanism of action and delivery system. Pharmaceuticals. 2021; 14(11):1102. https://doi.org/10.3390/ph14111102 PMid:34832884 PMCid: PMC8619093.
118. Yates CR, Bruno EJ, Yates ME. *Tinospora cordifolia*: a review of its immunomodulatory properties. J Diet Suppl. 2022; 19(2):271-285. https://doi.org/10.1080/19390211.2021.1873214 PMid:33480818.
119. Yadav I, Kumar R, Fatima Z, Rema V. *Ocimum sanctum* (Tulsi) as a potential immunomodulator for the treatment of ischemic injury in the brain. Curr Mol Med. 2024; 24(1):60-73. https://doi.org/10.2174/1566524023666221212155340 PMid:36515030.
120. Ganjewala D, Bansal H, Mittal R, Srivastava G. Unraveling of inhibitory potential of phytochemicals against SARS-CoV-2 using in-*silico* approach. In: Herbal medicines. Academic Press; 2022. pp. 471-500.
121. Barnes J. Herbal medicines and the European Union's Traditional Herbal Medicinal Products Directive. Planta Med. 2008; 74(6):639–645. https://doi.org/10.1055/s-2008-1074518 PMid:18446673
122. Chen Z, Ye SY. Research progress on antiviral constituents in traditional Chinese medicines and their mechanisms of action. Pharm Biol. 2022; 60(1):1063-1076. https://doi.org/10.1080/13880209.2022.2074053 PMid:35634712 PMCid: PMC9154771.
123. Dighe H, Sarkale P, Patil DY, Mohandas S, Shete AM, Sahay RR, *et al*. Differential cell line susceptibility to the SARS-CoV-2 Omicron BA.1.1 variant of concern. Vaccines. 2022; 10(11):1962. https://doi.org/10.3390/vaccines10111962 PMid:36423057 PMCid: PMC9696227.
124. Sa-ngiamsuntorn K, Thongsri P, Pewkliang Y, Wongkajornsilp A. Cell culture models for SARS-CoV-2 infectivity and systemic complications. Pharm

Sci Asia. 2022; 49(4).292-303. https://doi.org/10.29090/psa.2022.04.22.058
125. Ghidoli M, Colombo F, Sangiorgio S, Landoni M, Giupponi L, Nielsen E, Pilu R. Food containing bioactive flavonoids and other phenolic or sulfur phytochemicals with antiviral effect: can we design a promising diet against COVID-19? Front Nutr. 2021; 8:661331. https://doi.org/10.3389/fnut.2021.661331 PMid: 34222300 PMCid: PMC8247467.
126. Stannard H, Koszalka P, Deshpande N, Desjardins Y, Baz M. Pre-clinical evaluation of the antiviral activity of epigallocatechin-3-gallate, a component of green tea, against influenza A (H1N1) pdm viruses. Viruses. 2023; 15(12):2447. https://doi.org/10.3390/v15122447 PMid:38140688 PMCid: PMC10747412.
127. Sharma S. Medicinal plants as a source of novel antiviral compounds: challenges, opportunities, and future perspectives. 2024.
128. Babaei F, Nassiri-Asl M, Hosseinzadeh H. Curcumin (a constituent of turmeric): new treatment option against COVID-19. Food Sci Nutr. 2020; 8(10):5215-5227. https://doi.org/10.1002/fsn3.1858 PMid:33133525 PMCid: PMC7590269.
129. Gomaa AA, Abdel-Wadood YA, Gomaa MA. Glycyrrhizin and boswellic acids, the golden nutraceuticals: multitargeting for treatment of mild–moderate COVID-19 and prevention of postCOVID cognitive impairment. Inflammopharmacology. 2022; 30(6):1977-1992. https://doi.org/10.1007/s10787-022-01062-3 PMid:36136251 PMCid: PMC9493173.
130. Smith DJ, Bi H, Hamman J, Ma X, Mitchell C, Nyirenda K, *et al*. Potential pharmacokinetic interactions with concurrent use of herbal medicines and a ritonavir-boosted COVID-19 protease inhibitor in low and middle-income countries. Front Pharmacol. 2023; 14:1210579. https://doi.org/10.3389/fphar.2023.1210579 PMid: 37502215 PMCid: PMC10368978.
131. Meyer CT, Wooten DJ, Paudel BB, Bauer J, Hardeman KN, Westover D, *et al*. Quantifying drug combination synergy along potency and efficacy axes. Cell Syst. 2019; 8(2):97-108. https://doi.org/10.1016/j.cels.2019.01.003 PMid:30797775 PMCid: PMC6675406.
132. Dewi MK, Chaerunisaa AY, Muhaimin M, Joni IM. Improved activity of herbal medicines through nanotechnology. Nanomaterials. 2022; 12(22):4073. https://doi.org/10.3390/nano12224073 PMid: 36432358 PMCid: PMC9695685.
133. Aqil F, Munagala R, Jeyabalan J, Vadhanam MV. Bioavailability of phytochemicals and its enhancement by drug delivery systems. Cancer Lett. 2013; 334(1):133–141. https://doi.org/10.1016/j.canlet.2013.02.032 PMid:23435377 PMCid: PMC3815990.
134. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998; 64(4):353–356. https://doi.org/10.1055/s-2006-957450 PMid: 9619120.
135. Lindenmaier MP, Bernart M, Brinckmann JA. Advanced methodologies for the quality control of herbal supplements and regulatory considerations. Phytochem Anal. 2025. https://doi.org/10.1002/pca.70000 PMid:40555399.
136. Balekundri A, Mannur V. Quality control of the traditional herbs and herbal products: a review. Future J Pharm Sci. 2020; 6:67. https://doi.org/10.1186/s43094-020-00091-5
137. Wang H, Chen Y, Wang L, Liu Q, Yang S, Wang C. Advancing herbal medicine: enhancing product quality and safety through robust quality control practices. Front Pharmacol. 2020; 11:602789 https://doi.org/10.3389/fphar.2020.602789.
138. Kim D, *et al*. The architecture of SARS-CoV-2 transcriptome. Cell. 2020; 181(4):914921.e10.

Author Contribution

Arun Kumar, Santosh Kumar Karn provided support and guidance, conceptualised, methodology, data curation, formal analysis and drafted the manuscript; Sumaiya, Himani Saini, Gunjan Panwar, Prateeksha, Shivani Bahukhandi, Ravindra Kumar, Urvashi Gaur, Shraddha Panti, edited and provided critical review of the manuscript. All authors have read and agreed to the published version of the manuscript.