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Herbs, natural products and bioactive compounds against COVID -19 from South Asia and Africa

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Abstract

Novel Severe Acute Respiratory Syndrome Coronavirus-2 was discovered in 2019 in patients with severe pneumonia in Wuhan, China. This virus infects the respiratory tract of humans, showing symptoms nil or mild to lethal. It spreads via human-to-human contact or via air droplets. Finding a cure to combat this global pandemic is a need of the hour, and unfortunately, no single drug has been approved against COVID-19. Thus, researchers worldwide are screening natural compounds having potent antiviral effects against COVID-19. As nature has been a significant source of drugs for human beings since ancient times, pharmacists have been investigating several therapeutic herbs, their extracts and the secondary metabolites like flavonoids, stilbenoids, fatty acids, tannins, terpenes and alkaloids against COVID-19, virtually via *in-silico* methods as well as, via *in vitro* techniques. Several molecules extracted from natural sources like stilbene, isoflavones, quercetin, terpenoids etc., have been found to have potential antiviral efficacy against COVID-19. This chapter intends to discuss the structure, virology, various target sites of the SARS-COV-2 and review several potent antiviral herbs, their extracts and molecules extracted from them that are effective against COVID-19. The efficacy, required concentrations, side effects and challenges associated with their future developments are also discussed. This study will help provide new ideas for a therapeutic intervention that can selectively target the novel SARS-COV-2.

Keywords: Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2), MERS-CoV, Antiviral herbs, In Silico methods, Phytochemicals, Molecular targets, COVID-19, Antiviral activity.

1. INTRODUCTION

The emerging coronavirus poses a severe threat to the community, healthcare and especially everyone in proximity with a SARS-COV-2 patient. Viruses have been responsible for various infections and diseases ever since time. However, the recent novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV and SARS-COV-2) has spread to 185 countries- infecting more than 236 million people and killing over 4.8 million globally, according to data compiled by Johns Hopkins University on 8th October 2021 [1]. There are four genera for classifying Coronaviruses: α, β, γ, and δ, and these viruses are detected in a wide range of animal species, including humans [2] **(Figure 1)**. The α coronaviruses include the strand 229E and OC43. The β coronaviruses include the strands NL63 and HKU1. Figure 1 represents the taxonomical classification of the coronavirus. NL63 and 229E from human α-coronaviruses, and HKU1 and OC43 from β-coronaviruses, are the common viruses that majorly cause mild upper respiratory diseases [3].

Due to the rising rates of foreign travellers and globalization, the novel COVID-19 has been a global concern wherein the health of ordinary people is in danger. Therefore, it becomes crucial to find drugs or other therapeutic interventions to combat this global pandemic as soon as possible. Scientists have been working to find the potential cure via screening through antiviral herbs and their natural products. This chapter covers various natural products which have been explored against COVID-19. Before discussing the antiviral property of the herbs, authors have discussed a little background about the COVID-19 virus so that the usefulness of the research performed can be easily grasped. Following are the details about the emergence and history of the virus, its virology, molecular targets from coronavirus, methods of discovering antiviral drugs and various researches that have identified antiviral activities of herbs, natural products and their bioactive compounds against COVID-19.

2. EMERGENCE AND HISTORY

As of October 2021, more than 236,059,900 cases have been reported worldwide, with nearly 4,820,691 people losing their lives to COVID-19 [4]. This has affected people across the world and shook humankind to its core, being a global pandemic. SARS CoV-2 is the seventh human coronavirus discovered in Wuhan, China, associated with severe pneumonia with a high fatality rate [5]. It is one of the most infectious coronavirus diseases, after SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [6].

Coronavirus related diseases have affected individuals since the 1960s, but massive outbreaks of the disorders, tracing back to this virus, have been reported in the last two decades [7]. The first-ever case of SARS CoV was reported in 2002, China. Since then, the outbreak has spread across the globe and caused severe complications in several individuals [8]. In June 2012, a brand-new human coronavirus (CoV) was discovered in Jeddah, Kingdom of Saudi Arabia (KSA) [9].

The suspect virus was quickly recognized as Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) and has been a threat to humans. It sickened over 7500 persons and killed more than 700 of them. Research suggested that this was not due to the activity of SARS-CoV of 2002-2003. A newer virus had emerged in the scene that made vaccine development and studies pertaining to

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coronaviruses suffer a halt. That virus is now known as Mideast metabolism Syndrome Coronavirus (MERS-CoV). The novel MERS-CoV was 1st determined in several countries together, mainly Asian countries [10].

In Dec 2019, a unique coronavirus that gets transfers from human to human inflicted severe ill-health was confirmed from China. The virus was named SARS-CoV-2, and therefore, the disease it caused was Coronavirus malady 2019 (abbreviated "COVID-19"). At an early stage, many of the patients were found to have some contact with a massive market of food and animals at the epidemic centre in the metropolis in Hubei Province (China), implying the animal-to-person transmission of Covid-19. Afterwards, it started to spread in an increasing variety of patients who had no access to animal marketplaces, indicating transmission from person to person [11]. Later, SARS-CoV-2 spread like wildfire across all the major nations and caused a near-global shut down; alerts were declared, businesses were temporarily out of service, a strict lockdown was declared in majority places, food and other essential supplies were not regulated judiciously and above all thousands of people lost their livelihood in affected countries. This pandemic has been a low blow to the global economy [12].

3. VIROLOGY OF COVID-19

3.1. *Structure and genetic composition*

Epidemiological studies revealed that the incubation period of SARS-COV-2 was estimated to be 1-14 days duration. A respiratory emissions model found that droplets of size as small as 1 micron can carry the virus. Human sneezing can create a turbulent cloud of gas, in which a virus can travel great distances (7-8 m) and lead to community transmission [13].

It belongs to a class of enveloped, positive-sense single-stranded RNA viruses. The virus particle shape is round or oval and has a diameter of 60-100 nm. It consists of a nucleocapsid that possesses the RNA genome and the phosphorylated nucleocapsid (N) protein. The phospholipid bilayer covers the nucleocapsid, and two types of spike proteins surround the bilayers. The two spike proteins are the spike glycoprotein trimmer (S), which exists in all CoVs, and the other is hemagglutinin – esterase (HE) that some CoVs share. The membrane (M) protein and the envelope (E) protein are located among the spike proteins of the enveloped virus.

SARS-CoV-2 virion has a genome of size 29.9 kB. Genome-wide phylogenetic analysis of SARS-CoV-2 indicates 79.5% and 50% sequence similarity with SARS-CoV and MERS-CoV, respectively. Its genome has 5' and 3' terminal sequences typical of beta-coronavirus. The 5' terminal consists of 265 nucleotides and the 3' terminal consist of 229 nucleotides. The order of gene follows 5'- replicase open reading frame (ORF) 1ab-S-envelope(E)-membrane(M)-N-3'.

The predicted S, ORF3a, E, M and N genes of SARS-CoV-2 are 3822, 828, 228, 669 and 1260 nucleotides in length. SARS-CoV-2 carries many similarities with the SARS-CoV. There is a 96.4% sequence similarity between the seven replicase domains in ORF1ab of SARS-CoV-2 and SARS-CoV. Also, it carries a predicted ORF8 gene between the M and N ORF genes, identical to SARS-CoV [14].

3.2. *Pathophysiology*

SARS-COV-2 spreads mainly through respiratory droplets and human-to-human contact and may also have potential through the faecal-oral route, which is yet to be confirmed [15]. Recently, WHO has assured that the disease might be borne through the air, and several researchers have reinforced this statement

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through their findings [16]. Blood tests of the infected person showed average or lower WBC count (25%) and lymphopenia (65%) [17]. The virus causes infection in the mucosal epithelium of the upper respiratory tract, such as the nose and pharynx, where it infects, that is, the nasal and pharynx. Further reproduction occurs in the lower respiratory tract and gastro-intestinal mucosa, giving rise to mild symptoms [18]. Most of the time, the infections remain asymptomatic or get controlled till this stage. Covid-19 has been supposed to be a self-limiting infectious disease, and most mild cases recover in 1-2 weeks [19].

As ACE2 functions as a receptor of the SARS-CoV-2 in the human body and it is expressed in several parts such as stomach, bladder, nasal mucosa, bronchus, heart, kidney, oesophagus, and lung, ileum and so SARS-CoV-2 poses a risk to all these human organs [20]. In severe patients, non-respiratory symptoms like liver and heart injury, kidney failure and diarrhoea have also been reported indicating multiple organ infections in high-risk patients. Recently, the risk to testicular tissues has been proposed by physicians, suggesting fertility issues in young patients [14].

3.3. *Molecular targets from COVID-19 and host*

SARS-CoV-2 consists of RNA as the genomic material that transcribes into spike glycoprotein, nucleocapsid protein, envelope protein, membrane protein, and other functional and non-functional proteins. Single nucleotide variants are found in many patients affected with COVID-19. (Figure 3)

3.3.1 Proteins involved in inoculation

Spike protein is a glycoprotein present within the bilayer of the viral structure and mediates the entry of the virus into the host cell. It recognizes the angiotensin-converting enzyme 2 in the host receptor [21]. On the other hand, transmembrane protease serine 2 (TMPRSS2) from the host cells comes under the serine protease transmembrane family type 2 and activates the spike protein on the virus surface to facilitate entry of the virus into the host cell. Therefore, TMPRSS2 could act as an excellent target for designing drugs against COVID-19 [22]. The S protein mediates virus entry through the RBD in the S1 subunit and fusion of viral and host membranes through the S2 subunit. Thus, RBD of SARS-CoV-2 S protein may act as a possible target for inhibitors.

3.3.2 Proteins involved in replication and transcription

The replication of viral RNA of SARS-CoV-2 involves a range of functional proteins in the polyprotein. The essential enzymes include the zinc-binding helicase (HEL, Nsp13), RNA-dependent RNA polymerase (RdRp, Nsp12), enzymes required for mRNA capping (Nsp14, Nsp16), and RNA proofreading (Nsp14) as mentioned in Figure 4. The RNA-dependent RNA polymerase catalyzes the manufacture of a complementary RNA strand using the viral RNA as a template. The function of these enzymes is further regulated by several non-structural proteins (Nsp7-Nsp-10), which are necessary for all the processes related to transcription and replication [24]. These proteins can be used as potential drug targets as they are essential for life function.

Nsp1 enhances the virus's replication process, suppresses the host gene expressions, restricts innate immunity in infected cells, and is a significant CoV virulence factor [25]. Further, the nucleocapsid protein protects the viral RNA by packing it into a helical ribo nucleocapsid and interacts with the membrane M protein for packaging and genome condensation [23].

Nsp3 is a papain-like protease protein of 200 kDa size, the most prominent protein encoded

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by the coronaviruses. This papain-like protease domain releases NSP1-3 from the N- terminal of polyproteins 1a and 1ab. Thus, it has an essential role in removing the proteases required for viral replication [21].

3C Like protease ($3CL^{pro}$) is an enzyme-specific protein that helps in replicating the genome in viruses. $3CL^{pro}$ found in SARS-CoV-2 is 96.08% similar to SARS-CoV. Inhibiting such proteins prevents the inoculation of the virus [26]. It cleaves different sites in polyproteins, including the N and C terminal [27].

The pp1a and pp1ab are expressed from the ORF1a and ORF1b, which are present in the genomic RNA of the virus, get translated by the host ribosomal cell [28][29]. The cleavage of these polyproteins follows this to produce structural proteins for RNA Replicase-Transcriptase Complex (RTC), which is responsible for viral RNA replication and transcription. Viral nucleocapsids are assembled and budded from the lumen of the endoplasmic reticulum Golgi intermediate compartment (ERGIC). The replication cycle is completed when viral nucleocapsids wrap viral RNA to generate new coronavirus virions [30].

Main Protease (M^{pro}) is a viral non-membrane bound protein associated with regulating transcription and further replication of the viral genome. M^{pro} is reportedly associated with the substrate-recognition pocket of the viral particle and is responsible for initiating viral replication. The inhibition of the pocket region in M^{pro} or M^{pro} would lead to controlled viral replication and the level of infection in the host [32].

3.3.3 Protein required for host immune suppression

PL^{pro} has been found to suppress the host's innate immunity by targeting interferon production. It targets interferon production by inhibiting IRF3 phosphorylation, dimerization, nuclear translocation and NF-κB signalling pathways [33]. Thus, this protease can act as a potential target for drug delivery against SARS-CoV-2.

3.3.4 Protein required for multiple purposes

NSP5 is the 3-chymotrypsin-like protease $3CL^{pro}$ or the main protease M^{pro}. It plays a vital role in immune regulation and cleaves the polyproteins pp1a and pp1ab in 11 different sites to yield the non-structural proteins [21]. Functional proteins like RNA polymerase, exoribonuclease, and endoribonuclease are also generated by polyprotein cleavage [22]. Therefore, it is recognized as a promising target for COVID-19 therapy as it is involved in processing viral proteins and targeting it will also enhance the innate immune response of host cells [34]. It could act as an attractive target to screen different small molecules that inhibit viral replication and stop the infection [22].

3.4 *Host targets used for COVID-19 drug discovery*

SARS-CoV-2 takes entry into the host body mainly through its spike glycoprotein that binds to the Angiotensin-converting enzyme 2 (ACE2) receptor present in the host cells and is primed by the transmembrane protease/serine subfamily member 2 (TMPRSS2) present in the host airway and alveolar cell. Thus, TMPRSS2 and ACE2 can target drug delivery against COVID-19 by inhibiting viral entry by blocking these two host targets. Host cell proteases such as furin and cathepsin prime the viral structural proteins and aid in membrane fusion can also be studied as a host target for drug design. Also, the coronaviruses may hijack the autophagy pathway used by them for viral vesicle formation and replication. Therefore, the blocking of autophagy mechanisms may also be evaluated as a possible antiviral therapy.

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Another aspect of COVID-19 infection is the excessive inflammatory responses and cytokine storm that leads to an increase in the severity of the disease. From the host side, Furin is a protease that converts inactive precursor proteins into physiologically active forms. It cleaves viral envelope proteins, i.e. the S protein in SARS-CoV-2, into syncytium form. By inhibiting the activity of Furin, viral entry, as well as its replication, could be inhibited [35]. Naphthofluorescein and DEC-RVKR-CMK (decanoyl-RVKR-chloromethyl ketone), along with furin inhibitors, have been well studied [36].

In humans, the primary receptor of SARS-CoV-2 and SARS-CoV viruses has been identified as ACE2(Angiotensin-converting enzyme 2), which converts angiotensin II into angiotensin or its derivatives. Its principal function is to maintain blood flow in vessels, mostly observed in hypertension and dietetic patients. The virus enters the host cell by the renin-angiotensin system via ACE2, an analog to ACE with a similarity of 42% [37] [38].

In humans, PIKFYVE kinase (Phosphatidylinositol 3-phosphate 5-kinase) produces phosphoinositides necessary for early endosome development. Their primary function is the regulation of endocytosis, which is the mode of entry for viruses. It was revealed that PIKFYVE activity is required for SARS-CoV-2 infection of human cells via endocytosis. Apilimod and YM201636, two PIKFYVE inhibitors, were shown to decrease SARS-CoV-2 entry dramatically [39].

TMPRSS2 cleaves both ACE2 and the S protein. It is suspected that cleavage of ACE2 promotes viral uptake, whilst cleavage of S Protein on the membrane fuses with the host cell. The study conducted by Hoffman et al. (2020) suggests TMPRSS2 enzyme activity is required for SARS-CoV-2 lung cell infection. When cells are treated with camostat mesylate, an inhibitor with therapeutic uses in other routes, viral entrance is reduced [40].

4. IDENTIFYING NATURAL DRUGS AND/OR TARGETS EXPERIMENTALLY

The ideal choice for drugs against SARS-CoV-2 needs to have low cytotoxicity, fewer side effects, good bioavailability and undoubtedly antiviral properties.

Generally, drugs having antiviral properties are tested through the *in-vitro* approach on cell lines accompanied by cytopathic effect assay (CPE) but since coronaviruses require a biosafety level 3 lab certain investigations are carried out on pseudotyped viruses that are unable to replicate. Also, molecular docking software has been used extensively to screen the natural molecules against SARS-CoV-2. To determine the mechanism of action, molecular docking simulation software is often the choice because it precisely identifies the potential molecules. For example, Lung et al. (2020) recently observed that theaflavin could act as a potential inhibitor against SARS-CoV-2 using *in-silico* techniques. It showed good binding affinity in the catalytic pocket of the SARS-CoV-2 RNA-dependent RNA polymerase [33]. Several compound classes such as stilbenoids, terpenoids, and quercetin compounds also screened using docking methods demonstrated promising antiviral compounds against SARS-CoV-2 targets.

Similarly, *in vitro* methods are used to determine the anti-covid activity of several traditional herbal medicines or natural compounds, used as single or combined ingredients with regular medication against COVID-19 patients. Different types of *in-vitro* techniques like cytopathic effect inhibition, plaque reduction assay, and PCR techniques are being used widely to investigate drug efficacy against SARS-CoV-2.

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Experts have suggested single herbs or mixtures of different herbs to treat the disease in relevance to its infectious stage. For instance, traditionally used, Lianhua Qingwen (LH), a Chinese formulation. Lianhua Qingwen is composed of 13 herbs that have broad-spectrum antiviral effects and immune regulatory properties against a series of influenza viruses. It is widely used to treat fever, cough, fatigue, pneumonia, and early stages of measles were studied for its anti-SARS-COV-2 efficiency using the cytopathic effect inhibition and plaque reduction assays in Vero E6 cells. The herbal formulation was shown to inhibit SARS-CoV-2 replication in a dose-dependent manner, with its IC_{50} being 411.2 µg/ml. The effect of LH treatment on cell lines incubated with SARS-CoV-2 strain was analysed with electron microscopy. It showed that some viruses on the surface of LH treated cells presented sharp spindle structures in contrast to the typical spherical shape of coronaviruses. Also, LH could reduce the level of IL-6, CCL-2/MCP-1, TNF-α, and CXCL-10/IP-10 in a concentration-dependent manner. The findings suggest that LH treatment significantly inhibits virus replication, changes virus morphology, and exhibits anti-inflammatory effects indicative of a novel strategy to treat COVID-19 [41].

In another study, the ethanol extract of *Sambucus javanica* subspecies stem exhibited potential anti-human coronavirus (NL63) effects with IC_{50} value ranging between 1.17 (virus yield) to 15.75 µg/ml. The extract significantly decreased virus yield, plaque formation, and virus attachment [33].

There is some good evidence about ancient natural herbs being good sources for antiviral compounds. **Glycyrrhizin**, an active component of liquorice roots, has shown antiviral activity against SARS-CoV *in vitro*. Still, the EC50 for the inhibition of viral infection is very high (300 mg/ml) [42].

Plant extracts of ***Lonicera japonica Ginsenoside-Rb1, eucalyptus,*** and one of the phytoactive active components of **Panax ginseng,** have also been reported to show activity against the SARS-CoV [43]. The compounds extracted from *Lycoris radiata*, *Artemisia annua, Pyrrosia lingua*, and *Lindera aggregate* have also been identified to show antiviral activity against SARS-CoV *in vitro,* using Vero cell line, using CPE/MTS assay. Structure and activity studies further have identified that lycorine is a bioactive phenanthridine alkaloid of L. *radiata*. It has anti-SARS-CoV-2 activity with an IC_{50} value of 0.878 ± 0.022 µM [127]. In addition, docking simulation (AutoDock Vina) showed that lycorine interacts with SARS-CoV-2 RdRp at the Asp623, Asn691, and Ser759 residues through hydrogen bonding, at which the binding affinities of lycorine (−6.2 kcal/mol) were higher than those of remdesivir (−4.7 kcal/mol) [128].

5. HERBS AS THERAPEUTIC AGENTS

Medicinal plants used in traditional practices provide various options against various old or emerging diseases. It becomes more important when the options are unavailable, and multidrug resistance increases for many emerging and re-emerging bacterial or viral infections [44]. Herbal medications and their products provide a resource for identifying antiviral drugs and immunomodulatory herbal remedies [45].

5.1 Classification of phytochemicals

Plants have naturally occurring chemical molecules which provide nutritional as well as, therapeutic properties for humans. These molecules are known as phytochemicals [46]. In plants, these molecules help fight against environmental stress and maintain their colour, flavour, aroma [47]. More than 50 thousand

phytochemicals have been identified in the kingdom Plantae [48]. These are divided into the following five categories on the basis of their chemical characteristics: carotenoids, organosulfur compounds, alkaloids, nitrogen-containing compounds, and phenolics (**Figure 4**) [49].

Carotenoids are the organic tints mainly observed in families of plants, algae, bacteria, and fungi [49]. These act as antimicrobial substances for direct and indirect defence mechanisms of plants [47]. In recent years, there has been an increase in demand for β-carotene, lycopene, astaxanthin, lutein, zeaxanthin, cryptoxanthin, and fucoxanthin in the pharmaceutical industry [50].

Organosulfur Compounds are subclasses of sulfur-containing natural chemicals [49]. These reduce inflammatory mediators thus, helping to avoid various human disease progressions, including chronic inflammation [51]. These pose non-antioxidant benefits such as antiplatelet, fibrinolytic, anti-inflammatory, immunomodulatory, anti-ageing and antioxidant properties. Therefore, used to treat various pathological conditions, including cardiovascular disease, cancer, neurological disorders, and diabetes [52].

Alkaloid compounds contain heterocyclic nitrogen atoms and are usually basic and bitter. It was derived from the word" alkaline", which is used to designate any nitrogen-containing base. Since the dawn of advancement, plants containing alkaloids have been used as dye, spices, medicines, and poisons. Antihypertensive effects (indole alkaloids), antiarrhythmic effects (quinidine), antimalarial activity (quinine), and anti-cancer effects (dimeric indoles, vincristine, vinblastine) are the therapeutic activities of alkaloids [47].

Nitrogen-containing Compounds are the subclasses of nitrogen-containing natural chemicals [49]. Plants subjected to salt stress develop a variety of nitrogen-containing compounds. Amino acids, amides, imino acids, proteins, quaternary ammonium compounds (QAC), and polyamines are most often accumulated with them [53].

Phenolics family of chemical compounds that include a hydroxyl group (OH) are directly linked to an aromatic hydrocarbon group. These are also known as "defensive molecules" due to their anticancer, cytotoxic, antimicrobials and vasodilating properties [47]. These are categorized into two major subclasses: Flavonoids and Non-flavonoids. Compounds such as phenolic acids, stilbenes, tannins, coumarins are part of non-flavonoids. Flavonoids can be defined as a plant's secondary byproducts which possess therapeutic properties [48].

6. ANTIVIRAL HERBS

There can be many potential ways wherein the drugs can inhibit or destroy a virus. These could be done by inhibition of viral entry, viral uncoating, inhibition of reverse transcription, viral genome integration, inhibition of viral genome replication, interference with transcription, inhibition of protein expression and inhibition of virus particle assembly and last but not the least- release of virus from the host cell. We need to identify antiviral herbs that can specifically inhibit these mechanisms of the viral life cycle to stop its probation. Scientists have been exploring the old literature to identify herbs against other viruses and experimenting to check if they can also inhibit COVID 19.

In a particular study, glycyrrhizin obtained from *Glycyrrhiza radix* extract showed inhibitory action on the nosocomially derived CoVs against positive control ribavirin. 3-chymotrypsin like proteases, the papain-like proteases, RNA-dependent RNA polymerase and helicase proteins have been identified as the primary

targets for producing RNA synthesis, and replication inhibitors [54]. In addition, spike protein activated by transmembrane protease serine type-2 (TMPRSS2) which helps in virus cell-membrane fusion making it a significant domain was found to be targeted by the antiviral compounds. Herbal extracts against COVID-19 should target multiple protein pathways via mediating anti-viral, anti-pyretic, immune-modulatory, anti-complement, anti-inflammatory, and analgesic responses [55].

6.1 *Tinospora cordifolia*

In India, it is called AMRUTA, Guduchi in Sanskrit and Gurjo in Nepali. It is indigenous to India, Myanmar, China and some other regions of southeast Asia. Apart from that, it is also found in North-western and South Africa [56]. Tinospora is home to several phytochemicals, including alkaloids, fatty acids, aromatic compounds, diterpenoids, phenolics, etc. making it a herb with innumerable benefits [57]. Compounds from Tinospora including 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordioside, and syringin are known for their immunomodulatory potential. They are reported to enhance the macrophage and neutrophil action [58]. A recent *in-silico* study has given proof for the anti-COVID-19 activity of Tinospora. Berberine, β-sitosterol, coline and octacosanol are bioactive compounds that showed the highest binding affinity for $3CL^{pro}$ [59]. Another study showed the binding potential of a few alkaloids, steroids and terpenoids with the human ACE2 protein and the main viral protease (M^{pro}). The docking potential, hydrogen bond interactions and ADMET analysis showed that these compounds could have an excellent inhibitory action on the virus and disease prognosis [60].

6.2 *Glycyrrhiza glabra*

It is the botanical name of Liquor **ice,** also called Yashtimadhu in Sanskrit and Jerstimadhu in Nepali. It is native to North Africa, Europe and some regions of Asia. It has been a part of traditional medicine in significant areas of Egypt, China and India [61]. The plant is commonly used to treat the common cold, sore throat, vomiting, acidity, gout, weakness, joint pain, ulcers, and skin-related diseases. In Ayurveda and traditional medication, liquorice has effectively treated cough, colds, flu, bronchitis, sore throat, and laryngitis [62]. It is considered as an antiviral herb in the various official publications or the monographs of medicinal plants. It inhibited HRSV, mainly by internalization, stimulating the secretion of interferon (IFN) and preventing viral coupling [14]. Several studies have reinforced the evidence that bioactive compounds glycyl-serine and glychromic acid are suitable inhibitors for several viral activities, including Hepatitis A9 and C and Herpes Zoster [63]. Researchers have explored Liquorice for its anti-COVID-19 potential. A molecular docking study revealed bioactive compounds from Liquorice like Glycyrrhizic acid, Liquiritigenin and Glabridin showed the highest binding affinity for M^{pro} [64].

Another study emphasised the usage of Liquorice extract for the treatment and immunomodulatory benefits in people suffering from COVID-19. Due to the presence of spironolactone (SP) and of glycyrrhizin (GI), which show excellent binding potential to spike protein as well as the ACE2 protein along with having several other health benefits. Moreover, widely available and popular Liquorice extracts make it a good alternative medicine candidate [65].

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6.3 *Swertia chirata*

It is commonly named **Chirata**, Kirata, Kirataka, Kiratatikta in Sanskrit and Chiraito or Tito in Nepali. It is native to Himalayan regions and other parts of south-east Asia and has been an essential part of their ancient medical culture [66]. It is used in traditional medicine to treat numerous diseases, and it has a wide range of pharmacological properties [23].

There have been several studies on Chirata, and potential has been found against lethal viral infections. The raw extract (1 gm/ml) to dilution 1:64 showed antiviral properties against the simple herpes virus type 1 (HSV-1). Infected cell cultures treated with extract at various times and test intervals showed no amplification up to 72 hours against HSV Type-150. The tissue culture technique reduction rates in an average plate of active compounds Mangiferin and Isomangiferin against HSV-I were 56.8% and 69.5%, respectively [21]. Amarogentin and Amaroswerin are two bioactive compounds from *Swertia* that showed excellent binding affinity towards M^{pro}, proving the potential anti-COVID-19 action [67].

A few other studies stressed the antipyretic potential of *Swertia*. They proposed that it can be used as a symptom curbing agent and immunomodulatory agent in asymptomatic patients and moderately affected individuals [68] [69].

6.4 *Ocimum sanctum L.*

Popularly known as Basil and called Surasa in Sanskrit and Tulsi in Nepal. Genus *Ocumimum* includes 30 species found in tropical and subtropical regions. The herb is native to the Indian subcontinent and other parts of southeast Asia. It has been an essential part of several regions' traditional medication schemes, and its uses trace back to prehistoric times [70]. It has been utilized in Ayurvedic medicine since time immemorial to treat several stomach ailments, flu-like symptoms, headache, skin conditions and several other mild to moderate conditions [22].

This versatile herb houses several phytochemicals including a few volatile oils, fatty acids, triterpenoids, flavonoids and tannins. These compounds have been studied for their anti-inflammatory, anti-microbial, anti-cancer, ulcer preventive and antioxidant potentials. Moreover, herbal extracts from the leaves of this plant are utilized for their wound-healing effects as well [71].

Given the abundance of basil and its easy availability in surroundings or at the comfort of our garden, this plant could be well exploited for its antiviral potential and future research pertaining to drug development and alternative medication. Anti Covid-19 potential of *Ocumimum* was reported in a recent docking study, with phytochemicals Vicenin, Isorientin 4′-*O*-glucoside 2″-*O*-*p*-hydroxybenzoate and Ursolic acid showing the highest binding affinities with M^{pro} [72].

Apart from being a direct inhibitor of the viral prognosis, extracts from this herb have also been reported to curb disease symptoms and exhibit immunoprotective action in people suffering from COVID-19. Pain reduction, fever management and reducing diarrhoea are some of the reported benefits of this herb in patients of COVID-19 [73].

6.5 *Zingiber officinale Roscoe*

It is a herb commonly known as **Ginger** and Sunthi in Sanskrit and Aduwa in Nepali. It is abundantly grown in Southeast Asia and cultivated in several other African and European regions. It is used as a taste enhancer in several

beverages and a flavouring agent in meal preparations [74]. From an ayurvedic perspective, ginger is a superfood, especially for digestion, breathing, and joints. Ginger has always been used to cure colds and current throat infections and is essential to Ayurvedic formulations [75].

This natural herb is a hub of several bioactive compounds, which exhibit several medical benefits. The presence of compounds like shogaol, gingerol, zingerone and several other phenolic compounds and volatile oils, make ginger an excellent immunomodulatory and therapeutic agent [76].

Phytochemicals or raw ginger extract can be effective against different viruses. It may be helpful in the coronavirus, either inhibiting them directly or stimulating the immune system and necessary for specific mechanistic information. Docking studies for bioactive compounds from ginger for their action against COVID-19 have given significant insight into their drug-development potential. Compounds like Rhoifolin and Gingerol showed the highest binding affinity for the spike protein of the virus [77].

Another *in-silico* experimental study accounted for the good binding affinity of compounds including gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone to the main protease complex. While geraniol, shogaol, zingiberene, zingiberenol, and zingerone showed good binding potential to the ACE2 protein [78].

6.6 *Curcuma longa L*

The famous herb is **Turmeric,** also called Haridra in Sanskrit and Haledo/Besar in Népal. In Ayurvedic medicine, turmeric is a well-documented treatment for various gyawali and respiratory - opinions on Ayurvedic medicinal herbs. This herb is native to the Indian subcontinent and other regions of southeast Asia. Moreover, it has been utilised for its medical potential since time immemorial. Prehistoric texts and ancient religious writings also account for the usefulness of this herb [79].

Several studies account for the anti-oxidant, anti-microbial and anti-inflammatory activity of this magical herb. Moreover, this plant's wound healing and cold-curbing potential have been exploited in several world regions [80].

Curcumin extracts have traditionally been used to prevent sexually transmitted infections such as HPV and treat cervical dysplasia [55]. Several researchers have reported the inhibitory action of curcumin on the entry of the Chikungunya Virus in their work [81]. Curcumin has also been evaluated for a serious activity of acute respiratory syndrome (SARS-VOCs) with coronavirus activities (SARS-VOCs) using a cellular assay exhibited with strong anti-SARS-COV effects [82]. It has been known for many years to have excellent therapeutic potential against various diseases. It can also help improve the immune health system for coronavirus recovery and is a good candidate for antiviral activities. *In-silico* docking studies on bioactive compounds from turmeric have given proof for their anti-COVID-19 activity. Phytochemicals like Curcumin and cyclocurcumin have shown an excellent binding affinity for viral protease receptors (PDB ID 5R82), further solidifying the medicinal potential of turmeric [83].

Another study gave an account for curcumin being beneficial for preventing lung tissue damage by inhibiting the NF-κB signalling. It was also reported to regulate the secretion of inflammatory cytokines; with fulminant hypercytokinemia being the primary factor behind the deaths due to COVID-19, curcumin could prove to be a potential therapeutic [84].

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6.7 *Allium sativum L*

It is popularly known as **Garlic** and Lashunam in Sanskrit and Lasun in Nepali. Native to central and southeast Asia, Egypt and other regions of West Africa, the utilisation of this herb can be traced back to medieval times and way back in some other areas. Predominantly used as a taste enhancer, it has also been utilized for its medicinal potential for centuries. The former Chinese and Indian medicinal scheme suggests the usage of garlic to help to breathe. Ayurvedic practitioners most often use garlic as tea, powder, fruit juice and medication. Ayurveda recognizes the effect of garlic on the respiratory system and rejuvenating herbs with several other uses [85].

This versatile herb has proven to be beneficial for several cardiovascular disorders, liver malfunctioning, skin disorders and gastro-oesophageal disorders, to name a few [86], further aiding the complications associated with COVID-19.

S-allyl cysteine (SAC), S-allylmer Captocysteine (SAMC), Allicin, and Selenium are garlic antioxidant compounds. Volatile garlic oil consists of diallyl, allyl methyl, and mono-hexalfur dimethyl [87]. The few studies on the antiviral properties of the garlic compounds exhibited an *in vitro* activity against influenza A and B have long been claimed for a long time as having qualities that prevent various diseases, including colds and influenza and scientists [88]. A few bioactive compounds from garlic, including Allin and Ajoene, showed moderate to good binding affinity for the spike protein of the COVID-19 virus, showing antiviral potential against this virus [89].

Moreover, garlic's immunoprotective and infection-preventive potential have been well researched and exploited about the COVID-19 pandemic. Phytochemicals from this plant have been reported to inhibit and suppress the expression and release of proinflammatory cytokines responsible for significant complications. Also, garlic extract has shown several dietary and gut-regulatory properties, which are crucial to good recovery in people suffering from COVID-19 [90].

6.8 *Withania somnifera (L.)*

This is famous as **Ashwagandha** in Sanskrit and Nepal. It is native to the Indian subcontinent, Southeast Asia and certain regions of Africa. It is also known as Indian Ginseng due to its versatility. Due to several bioactive compounds, Ashwagandha is reported to exhibit anti-diabetic, anti-inflammatory, anti-tumour and neuroprotective properties, to name a few [91].

Withanolides are compounds isolated from Ashwagandha, which is known to show excellent antimicrobial and anti-protozoan activity [92]. Moreover, this herb has known benefits for disorders like arthritis, skin cancer, anxiety and depression [93]. Plant roots of *Withania somnifera* are famous for helping individuals maintain good homeostasis by many immunomodulatory actions, regulating digestion, providing strength, increasing individual abilities to withstand external environmental pollutants, and imparting a general sense of mental well-being [94]. Due to all these medicinal benefits, researchers performed docking experiments of compounds from this herb with several viral and protein targets concerning COVID-19. Withanoside V and Somniferine were reported to show moderate to good binding affinity to central protease unit M^{pro} [72].

Another study recorded the binding potential of Withanolides A and B with the spike protein of SARS-CoV-2 and the main ACE2 protein complex. They concluded that these compounds could be considered for the

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preparation of future antivirals against coronaviruses [95].

6.9 *Cinnamomum zeylanicum*

It is a very famous herb known to be put in hot drinks like tea. It is also called Thwack in Sanskrit and Dalchini in Nepal. Native to southeast Asia and significant regions of the African continent, cinnamon has been utilised for several health benefits for a very long time. Besides being an excellent taste enhancer, cinnamon has been used for its medical significance, which can be traced to prehistoric times [96]. The herb has been reported to regulate blood glucose levels, curb cholesterol levels, regulate blood pressure, exhibit antioxidant properties and even helps treat neuropathic conditions [97].

Cinnamon consists of various resin compounds, including cinnamaldehyde, cinnamon, cinnamic acid, and many essential oils [98]. Spicy flavour and aroma are caused by cinnamaldehyde's presence and occur because of oxygen [99] absorption [100].

Cinnamon has been considered to be an excellent therapeutic alternative to curb the symptoms and comorbidities of COVID-19. It is a known immunomodulator and helps in the prevention of infections. Cinnamon extracts have been utilized for the immunity-boosting and purifying benefits [101].

6.10 *Trifolium pratense*

It is the botanical name for Red Clover, also called wild clover or bee bread, native to Western Asia, Northwest Africa, and certain parts of Europe. It has traditionally been used for the treatment of menopausal symptoms [102]. Apart from that, red clover extracts have been reported to exhibit excellent antioxidant and anti-inflammatory actions [103]. Red clover is a hub to a number of bioactive compounds collectively termed Isoflavones [104]. Isoflavones have been widely explored for their antiviral potential; with inhibitory actions on HSV, Influenza virus and even HIV induced cytopathic effects [105]. Isoflavones have been discussed in detail later in section 7.2.

6.11 *Nigella sativa* *Nigella sativa*, native to south and southwest Asia and certain regions of Europe, is a herbal medicine used across the globe to treat several disorders. It belongs to the Ranunculaceae family, and its seeds are consumed for treating several health problems. A study reported that the administration of Nigella could enhance immune responses and even cytokine expression. The same research showed inhibitory

effects of Nigella on the Influenza (H9N2) virus [106].

Molecular docking studies were done on the PDB derived molecular structure of the COVID-19 chimeric receptor binding domain and the host cell receptor (PDB ID: 6VW1) and *N. sativa* chief constituents. The *N.sativa* compounds accessed for docking were 4-Terpineol, dithymoquinone (DTQ), Carvacrol, Carvone, p-cymene, t-anethole, thymohydroquinone (THQ), Thymol (THY), and Thymoquinone (TQ). Results showed that DTQ exhibited a high affinity of -8.6 kcal/mol followed by Chloroquine with the affinity of -7.2 kcal/mol against the receptor. Molecular dynamic simulation of 100 ns revealed strong stability of DTQ at the binding pocket [107].

7. NATURAL PRODUCTS EFFECTIVE AGAINST VIRUSES

Herbal medication and its natural compounds have been a valuable source for developing antiviral drugs with the discovery of their mechanism to replicate, enter, bind to a specific host and their life cycle [108]. Major compounds responsible for suppressing the activity of viruses include phenolic acids, terpenes,

flavonoids, coumarins, lignans, alkaloids, and proteins [109]. As mentioned above, the pure compounds can be derived from species such as cinnamon (*Cinnamomum zeylanicum* Blume or *Cinnamomum verum* J. Presl.), ginger (*Zingiber officinale),* basil *(Ocimum sanctum),* etc. [37].

Wild herbs, extracts or their mixtures have not been well accepted in the western world. Instead, single molecule-based therapies have always been preferred. Also, it is needed to research which component of the mix is targeting a particular target during the treatment. The following description discusses studies where a single molecule has been shown to target specific target protein molecules. These studies have been organized according to the chemical group to which they belong. fungal toxins. Resveratrol found in the grape's skin is

7.1 *Stilbenoids as drug candidates*

Stilbenoids are phenolic phyto actives which are derived from plant sources. They are phytoalexins which are being produced by the plants to overcome UV radiation, mechanical aberrations or microbial or of actions such as anti-oxidative, antitumoral, antiviral, anti-inflammatory, and anti-ageing potential [110]. Another resveratrol-based compound named piceatannol also has anticancer and antioxidative properties. Pterostilbene and pinosylvin also have pharmacological benefits similar to resveratrol [111]. A recent study has given evidence for the potential of stilbenoid analogues as antiviral compounds against SARS-CoV-2. For this, molecular docking and molecular dynamic simulation approaches were utilized with the four mentioned stilbenoid analogues against SARS-CoV-2 spike protein and human ACE2 receptor complex (PDB ID: 6VW1) using the AutoDock/vina tool. Almost every compound exhibited a good binding energy (> -7kcal/mol). Results of docked configurations demonstrated that most compounds could bind to the pocket of the S-protein of the receptor molecule with the help of H-bond interactions. Piceatannol and resveratrol were picked up as the most suitable compound among the four compounds used based on their binding affinity values. Further molecular analysis and simulations were performed.

MD simulations were also carried out to understand the interactions and structural annotations of the receptor-ligand complex formed by the top two selected ligands. Results showed fewer fluctuations for resveratrol-protein complex with average RMSF values of 1.19 Å. Lastly, to verify the role of intermolecular chemical reactions in the resveratrol-protein complex MM-PBGBSA assay was done on generated trajectories. According to the docking result, the binding free energies in both MM-GBSA and MM-PBSA exhibited lower energies -23.8889 kcal/mol and -20.2657 kcal/mol, respectively. The whole study indicated that resveratrol is the best stilbenoid derivative that can potentially act as an antiviral against COVID-19 and thus can be studied further for targeted drug delivery against SARS-CoV-2 [112].

7.2 *Isoflavones based natural compounds as potential drug candidates*

Isoflavones are the phenolic subclass of flavonoids having a 3-phenylchromen-4-one backbone. They are naturally present in several herbal species and plant products [113]. Their antioxidant properties, which are because of their radical scavenging nature, have widely been reported [114].

Several studies have accounted for the antiviral potential of isoflavones. Puerarin, an isoflavone derived from the roots of *Pueraria lobata, has* been extensively studied for its antioxidant, anticancer and most recently, antiviral properties. Both *in-silico* and wet lab experimentations have proved the inhibitory

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effects of puerarin on neuraminidase (NA) enzyme which further restricts the exit of newly formed influenza virus particles from infected cells [115]. Other isoflavones, including Genistein, have also been reported to show strong inhibitory effects on viral activities, specifically in rotavirus [116].

A recent *in-silico* study on isoflavonoids against COVID-19 has provided major insights into the likeliness of these bioactive compounds to possess potential drug-likeness properties. The docking experimentations were conducted on 59 isoflavonoids, and they were made to undergo toxicity analysis based on the FDA rodent carcinogenicity model. Moreover, the binding affinity towards hACE2 (Coronavirus Spike Receptor Binding Domain) (PDB:6LZG) and M^{pro} (PDB: 6LU7) was analyzed using CHARMM-based molecular dynamics (MD). The hydrogen bond interactions of the ligand with the amino acid molecules were also visualised. It was observed that Glisoflavone and Kraussianone 2 showed the best results for hACE2, and Vogelin D and Derrisisoflavone D showed the best results for M^{pro} [105].

7.3. *Study on quercetin as a potential antiviral drug*

Quercetin is a bioactive flavonoid derived from natural plant-based sources such as onion, radish and rose flower etc. It is found in various fruits, herbs and other plant products [117]. Quercetin has widely been regarded as a multipotent ligand and has been explored for its antiviral, antioxidant and anticancer potential. It is reported to potentially regulate the enzyme and non-enzyme dependent antioxidant dependent system. Moreover, it regulates several signalling pathways like MAPK by inhibiting intracellular ROS (Reactive Oxygen Species) formation [118]. The antiviral potential of this bioactive compound has been well studied and recorded through the years. It has been reported to be an excellent inhibitor of neuraminidase (NA) in several viruses, causing severe health issues like common flu and H7N9 viral infection [119]. Quercetin has also been reported to show promising action against Acyclovir-resistant HSV-1 by inhibiting the viral binding domain [120].

Molecular docking experimentations have been performed to study the effect of quercetin as an antiviral drug against COVID-19. For this purpose, the main protease of the virus (PDB ID: 6LU7) was taken as the receptor. Quercetin exhibited the lowest binding energy of -7.5 kcal/mol. It was observed that quercetin was well fitted in the main protease's binding pocket, and the ligand's hydroxyl groups formed hydrogen bonds with Leu 141 and His 163 of the receptor [45].

The *in-silico* approach has determined that at a binding energy of 30,500 J/mol, quercetin is reported to impart partial inhibition up to 50% at a concentration of approximately 7µM [129]. Thus, helping in determining the dosage capacity for its functionality. However, Williamson and Kerimi (2020) observed that oral intake of quercetin is not very effective in disrupting the action of envelope proteins or their interactions with host receptors. However, the formulations given through nasal spray and by means of administration, can directly deliver the potent concentration in the required amount and reactive configuration [121].

7.4 *Study of low-risk terpenoids as antiviral compounds*

Terpenoids are the major secondary metabolites reported in 36,000 plants and microbes, so far. They have comprehensive medicinal properties like antiviral, antibacterial, antitumor, antioxidative, and anti-inflammatory. Isoborneol, a terpenoid derived from plant essential oils, has attracted a lot of researchers for its antiviral potential due to its total inhibitory action on HSV-1 replication. Other

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terpenoids, including α-terpinene, γ-terpinene, 1,8-cineole and α-terpineol, have also been reported to show inhibitory activity on HSV-1 replication [122]. Artesunate, a synthetically prepared analog of naturally occurring terpenoid Artemisinin, is known to exhibit inhibitory effects on the surface antigen unit of Hepatitis B virus when it is administered along with a clinical antiviral Lamivudine [123].

A recent study was conducted to determine the effect of terpenic compounds against the SARS-CoV-2 virus, taking the main protease complex of COVID-19 (PDB ID: 6LU7) [124] as target. Nine terpenoids: thymoquinone, salvinorin a, bilobalide, citral, menthol, ginkgolide A, noscapine, forskolin, and beta-selinene were docked using molegro virtual docker (MVD) software to carry out molecular docking with main proteases of COVID-19. The software detected five conserved regions of the enzymatic flap. Of the five areas, the compounds showed interaction with two conserved pockets, and strong binding was determined with the amino acids Asparagine151, Aspartate153 and Phenylalanine8. Among the nine terpenoids, all exhibited an inhibitory effect on the target during *in-silico* experimentation. Ginkgolide A showed the most potent binding and highest affinity against the COVID-19 main protease complex. Since they are naturally derived herbs and cause fewer side effects, they provide a safe solution against COVID-19 disease and can be screened for further validation [125].

Another research done to screen phytochemicals against the main protease proposed that the natural compounds effective against COVID-19 are glycyrrhizin, tryptanthrin, bicyclogermacrene, β-sitosterol, indigo, indirubin, rhein, berberine, indicant, β-caryophyllene, and chrysophanic acid as screened by docking. Glycyrrhizin showed significant interaction with the reported binding energy to be -8.9 kcal/mol and multiple hydrogen bonds with the residues of amino acid [34].

Another target used for drug targeting research of COVID-19 is the viral spike protein. The active compounds of *N. sativa* were docked against viral spike protein, and ACE2 receptor complex. The study showed that among the seven of the compounds studied (thymoquinone (TQ), thymol thymohydroquinone (THQ), p-cymene, DTQ, 4-terpineol, and t-anethole) DTQ bound with a energy of -8.6 kcal/mol compared to positive control chloroquine with a binding energy of -7.2 kcal/mol [107].

Quercetin is a bioactive flavonoid derived from various natural sources. The *in-silico* approach has determined that binding energy of 30.5 kJ/mol was obtained and it is reported to impart an inhibitory action to 50% extent on both host and viral target proteins at a concentration of approximately 7µm. It has been also observed that oral intake of quercetin is not very effective in disrupting the viral glycoprotein (S) or its interactions with the host receptor. However, other administration means as a nasal spray can directly deliver the potent concentration in the required amount and reactive configuration.

As discussed in the above sections, terpenoid compounds and stilbenoid compounds gave promising results and posed to show inhibitory action with reference to SARS-CoV-2. Molecular docking using AutoDock against COVID19 main protease showed that quercetin, hispidulin, cirsimaritin, sulfasalazine, artemisinin, and curcumin exhibited better potential against these receptors in comparison to the positive control hydroxy-chloroquine. quercetin showed the highest affinity with -7.5 kcal/mol, and hispidulin showed the second-highest binding energy reported to be -7.3 kcal/mol [45].

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8 MAJOR FORMS OF ANTIVIRAL HERBS ADMINISTRATION

Literature review indicates that dietary therapy with herbal medicine can potentially inhibit/cure COVID-19 disease. The researchers have also come upon some possible approaches, which can be used to administer herbal medicines to COVID-19 patients to prevent the disease. These approaches are 1) using herbs or food in the form of diet or supplements to prevent infection and boost immunity; 2) the antiviral agent can be used as a coating on the mask; 3) they can be applied as a sanitizing agent to disinfect the surfaces and surroundings, and 4) can be used as an air-disinfectant to stop transmission through the air.

For years, aromatherapy has been in use to treat various viral and bacterial diseases. Essential oil vapours like eucalyptus, cinnamon and lemongrass etc., are effective against the influenza virus, with the inhibitory mechanism majorly being the inactivation of external proteins. A necessary oil therapy can be used against SARSCoV2 as well; however, the exact concentrations of these oils necessary to induce antiviral effects are not yet known [126].

One of the examples, where the nasal spray is found to be more effective than the oral application is that of quercetin. In this case, oral administration was found to be ineffective in disrupting the interactions between the glycoprotein (S) and the receptor (ACE2). So, it can be easily administered in the correct molecular form via nasal spray. Oral administration of quercetin, in a crude configuration or as a supplement, is undesirable because the breakdown of quercetin requires extensive processing, which further paves the way for a reduced amount of quercetin in the plasma [121].

9. CONCLUSION

Evidence shows that COVID-19 is a β-coronavirus and has a close relationship with the SARS-CoV. Its three significant proteins, the spike protein, the main protease or $3CL^{pro}$ and the papain-like protease, play an essential role in virus transmission, entry and replication in the host cell. With the SARS-CoV-2 becoming a global concern, several scientists and researchers have gone on a quest to identify and search for the best possible solution against fighting COVID-19. Many scientists have found that several natural herbs which cause potent antiviral effects on other viruses are showing promising results for COVID as well via inhibition of genome replication, configurational changes in the receptor protein of the host, inhibition of viral receptor-binding domains and inhibition of viral spike glycoprotein present on the capsule etc.. Many *in-silico* and *in-vitro* approaches have been applied to screen these natural compounds against COVID-19. One of the most promising *in-silico* approaches is molecular docking. Several chemical groups like terpenoid compounds and stilbene compounds, have been analysed for efficacy against a particular target of SARS-CoV-2. Hesperidin, dithymoquinone, ginkgolide etc., have shown relatively higher efficacy against SARS-CoV-2, indicating that natural compounds can further be formulated and analysed for their efficacies. In this difficult situation of the global pandemic, these natural antiviral compounds give us a ray of hope that we can use these herbs/herbal combinations/crude extracts/purified compounds that in the future can be used as a drug against COVID-19. This topic has immense future scope because several herbs have been found to have an antiviral characteristic, so harnessing that potential to help in treating COVID-19 and other emerging viral diseases is a shared interest of many scientists. Many researchers are already working over it, and we hope to find some solution to these global problems with the aid of herbal medicines.

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Table 1: Molecular targets for drugs from COVID 19 and host

Stage	Targeted Site For COVID-19 with PDB Code	Viral Protein Name	Host Cell Protein	Function
Entry/Inoculation	Spike protein receptor-binding domain	S protein & S2 Protein	PIKFYVE	Interacts with the host cell for entry via endocytosis
	Post-fusion core of 2019-nCoV S2 subunit (6M1V)	S Protein & S2 Protein	ACE2 Furin TMPRSS2 TMPRSS4/NRP1	Bind to host membrane via membrane fusion
Replication/Translation/Transcription	Main protease (6LU7	Mpro		Replication of Viral genome
	SARS-Cov-2 RNA-dependent RNA polymerase (6M71)	RdRp		Replication & Transcription

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	SARS-CoV-2 helicase(6ZSL)	nsp13		Separates dsRNA or DNA with polarity using nucleotide hydrolysis energy
		Exoribonu-clease(ExoN) or nsp14		Proofreading 3′–5′ ribonuclease
	NSP15 Endoribonucleas e from SARS CoV-2. (6WWW)	nsp15		Integrative Stress response
	Nonstructural protein ten from SARS CoV-2 (6ZCT)	nsp10		Degradation of viral restriction factor in host
		Nsp14, Nsp16		mRNA capping

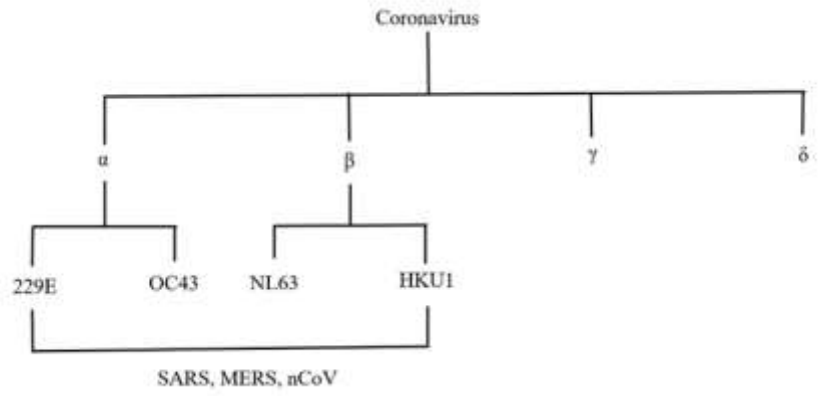

Figure 1: Taxonomy of Coronavirus

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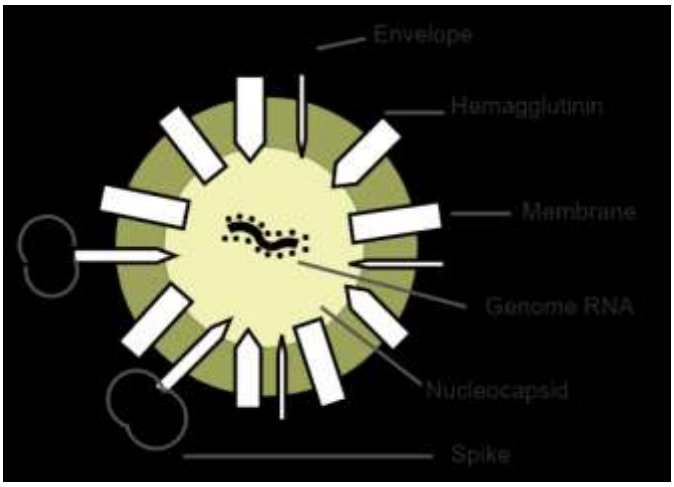

Figure 2: Structure of SARS-CoV-2

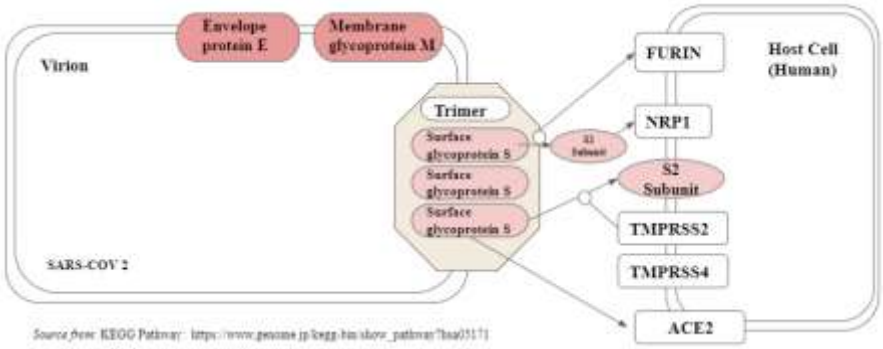

Figure 3: major Protein targets from Covid-19 and host

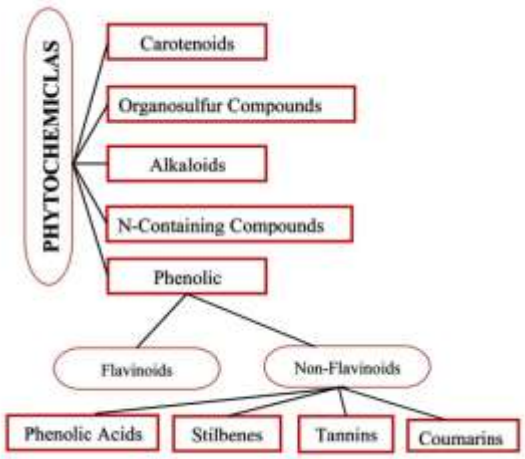

Figure 4: Flowchart depicting classification of phytochemicals

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