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The Fight against SARS CoV-2: Natural Phytochemicals and their Potential for the Treatment of Novel Coronavirus Variants

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ABSTRACT

With the emergence of COVID-19, the whole world came to a standstill. WHO declared it a pandemic as of March 11, 2020. The only hope, a vaccine. In this paper, through research and discovery we explore the possible natural phytochemicals and their potential treatment of novel coronavirus variants. By understanding the pathogenesis and mechanism, we targeted receptor molecules with suitable ligands. Studying pre-existing 'solutions' such as Arbidol (Umifenovir), Favipiravir(Avigan), Rotanavir-Lopinavir(Kaletra**)** we studied the molecular docking and processes. Using this as inspiration we further looked into prospective natural remedies to combat the ill-effects of Sars-CoV2. Docking techniques predicted the binding affinities of these natural compounds and COVID 19 related targets like Spike protein, ACE2, 3CLpro, PLpro, and RdRp.Some of the traditional Indian medicine based chemicals like glycyrrhizin, curcumin, withanoids, quarcetin, griffithsin, are briefed based on their action against the virus and their effects.Keeping this perspective in mind a lot of phytochemicals are being explored and evaluated for COVID infection based on in silico techniques in vivo in vitro studies, or their efficacy clinically. Although, other Indian Plant species like Ocimum sanctum, Withaniasomnifera, Tinosporacordiofolia, Azadirachta indica have shown inhibitory action on HIV protease and SARS protease, its action against SARS-COV-2 can only be reported as a result of molecular testings. Besides this a lot of phytoconstituents such as polyphenolic compounds, flavonoids, alkaloids, lectins have been explored, alone or in combination with other western medicines and yet no drug-specific to SARS-COV-2 have been identified.

ABOUT THE DISEASE

COVID-19 emerged in Wuhan, Hubei province of China in late December 2019. Originally considered an outbreak of pneumonia it later turned out to be a deadly disease caused by an unknown strain of virus[1,2]. This unknown strain was sequenced using different genome sequencing technology and the causative agent was found to be a beta coronavirus. The drastic change of events and an exponential increase in its spread and hence deaths have resulted in WHO to declare it a pandemic as of March 11, 2020 [3,4]. As of today, it has resulted in numerous deaths and the number continues to still increase as I write this article.

Coronavirus belongs to the family Coronaviridae. It is divided into four genera(Alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus) based on its genotype and serological characteristics[5,6]. At present, Alpha and beta genera of corona viruses are reported to cause infections in humans[9]. SARS –COV, and SARS-COV-2 both the species are a type of strain of the beta virus. Covid-19 which is a result of SARS-COV-2 infection was found to share 79% similarity with the strain SARS-COV [8]. Although Certain drugs are administered to patients to prevent multiorgan dysfunction or to lower Acute Respiratory Distress Syndrome(ARDS) no drug or vaccines have been developed to combat the virus yet. Unfortunately, the threat of COVID 19 keeps on increasing which is the research and studies to test the efficacy of certain modern antiviral drugs too.

PATHOGENESIS AND MECHANISM OF ACTION

The SARS-COV 2 belongs to a large family of RNA viruses and is categorized under the subgenus Sarbecoronovirus of the genus beta coronavirus. It is a single-stranded enveloped RNA virus with a genome size of 29.9 kb. The virus is spherical with a diameter of about 80-160 nm[7][10]. The body is composed of certain structural proteins that include – the envelope proteins(E), the membrane protein(M), the spike protein(S) along with the nucleocapsid protein(N)[11]. The virus attaches to the host cell by the use of these spike proteins. The spike protein is cleaved by the use of host cell protease called Transmembrane protease serine -2(TMPRSS 2) into two protein domains an S1 and S2subunit,s1 is associated with cell recognition while the other is

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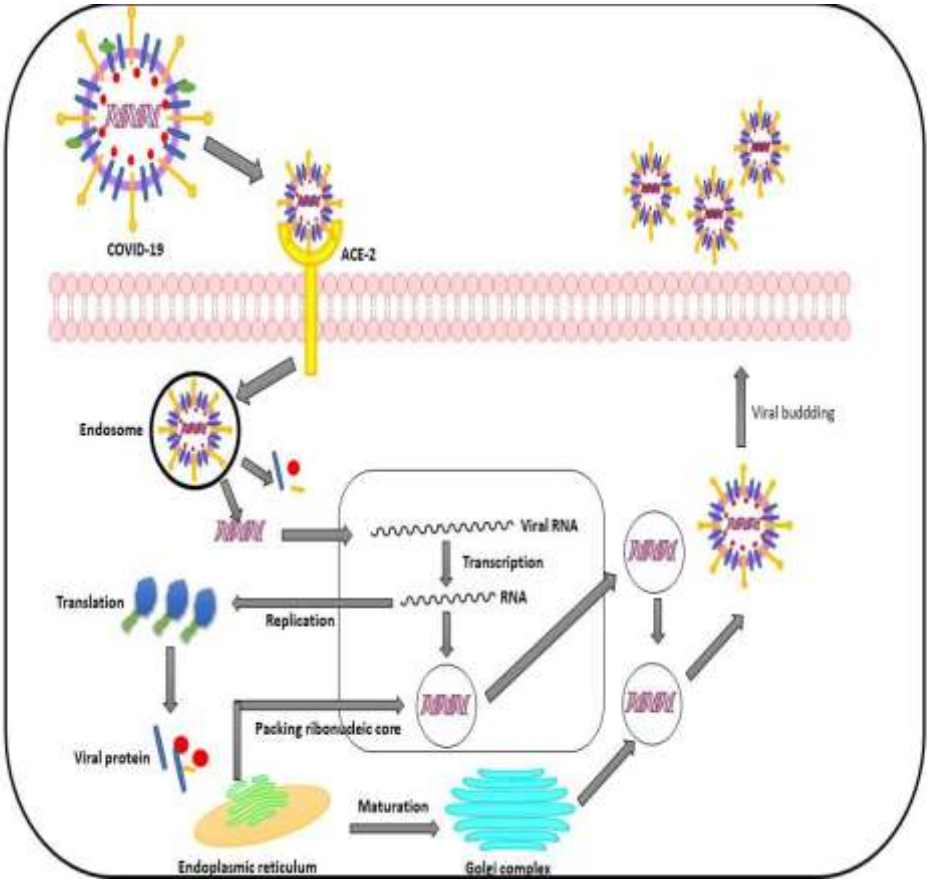
responsible for the fusion of viral and cellular membrane respectively[12,13]. So one of the therapeutic approaches is to develop a vaccine that contains antigen derived from the spike protein which can boost recognition of the virus by the immune cell or develop a monoclonal antibody that binds to the coronavirus spike protein and block the interaction with the human cell. Another potential target is transmembrane protease serine 2(TMPRSS2), which is essential for the entry and spread of the novel coronavirus. Camostat Mesylate is an inhibitory drug that is currently being tested for COVID 19 that works by this mechanism[12,14].

It has been explained that the SARS-COV-2 has an affinity towards the receptor of angiotensin-converting enzyme (ACE 2) and uses these receptors as a mechanism for cell entry and infection into the host[13-18]. One location where ACE2 receptors are highly expressed is Type 2 alveolar cells, which are found in the lungs and hence the virus has an extensive impact on them[19]. So , another potential drug target could be the interaction site of ACE2 of the host and spike protein. Certain computational studies have led to the discovery of one such compound Hesperetin which is a natural flavonoid, it is predicted to interact and bind with the binding interface of the spike –ACE2 complex

The entry of coronavirus into the host is dependent on various protease enzyme including human airway Trypsin- like protease(HAT), Main protease enzyme called the 3- chymotrypsin-like protease(MPro /3CLPro), papain like protease(PLPro), and Transmembrane protease serine 2(TMPRSS2) all of which are responsible for viral fusion and penetration into the host.[18]



After binding to the ACE2 receptors, the virus is brought into the cell in the form of the endosome, by the process of endocytosis. The endosomes then fuse to the lysosome allowing the virus to take over the host lysosomal cell. In the next step, the endosome bursts open to release the endosomes into the cytoplasm, and the uncoating of the viral nucleocapsid(N) begins[20,22]. The viral Rna then takes over the ribosomes and interrupts with the replication /transcription

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complex(RTC). The RTC provides a suitable environment for the viral RNA to replicate and generate a full-length negative-sense RNA.[22,23]

The structural proteins M, S, and E are synthesized in the cytoplasm, incorporated into the endoplasmic reticulum, and further transferred into the endoplasmic reticulum Golgi intermediate compartment(ERGIC). The viral genome or the nucleocapsids are now encapsulated into the ERGIC membrane with the help of Protein for its self-assembly and production of new virions[21,23,24]. These virions are transported out of the cell in smooth-walled vesicles and are released by exocytosis.[21] The continuous process of virion formation in the endoplasmic reticulum results in cell death.

The virions released, initiate an inflammatory response and results in the activation of pathogenic T cells which results in the release of certain granulocyte-macrophage stimulating factors[25].in response to its certain inflammatory monocytes, interleukins, neutrophils, cytokines are also released[25,26]. These uncontrolled responses in different regions of the body result in tissue damage in different regions like the heart, kidney, lungs, and liver. It may also cause respiratory failure, along with multiple organ failure and in severe cases death of the patient suffering from COVID 19. [27]

DRUGS USED FOR THE TREATMENT

At present, the treatment of COVID 19 is done based on previously identified antiviral drugs that somehow positively inhibit this viral strain. The major such mechanism identified includes inhibition of cell entry of SARS-COV-2 by either acting on TMSRSS2 serine protease(drugs like camostatmesilate and nafamostatmesilate), or the main protease enzyme (MPro/CLPro)or inhibiting the angiotensin-converting enzyme receptor on the host. (chloroquine, hydroxychloroquine, selamectin). Certain other drugs used in clinical trials including remdesivir, lopinavir, ritonavir, umifenovir, favipiravir acts by inhibiting either the replication process, the membrane-spike protein fusion or by inhibiting the functional assembly proteins of SARS-COV-2. However, no such drug has been approved yet and the studies to evaluate their efficacy, safety, pharmacological action, and other clinical trials on patients are still underway. Here we mention some of the potential candidate drugs that are being used to treat the patients worldwide.

CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine and hydroxychloroquine have long been used as an antimalarial drug[28]. Along with it CQ/HCQ has shown to have immunomodulatory effects ie, it can inhibit certain immune cell functions which are helpful to treat autoimmune diseases like rheumatoid arthritis[29], lupus, and malaria[30]. It's potential against COVID 19 and its activity as a broad-spectrum antiviral has been demonstrated recently[31-33][36][37]. Hydroxychloroquine acts by alkalinizing vacuole, endoplasmic reticulum, and by increasing the pH level in the lysosome(endosome), that are involved in virus-cell entry, replication, and infection [33][34]. Chloroquine on the other hand inhibits ACE2 receptor terminal phosphorylation, which is responsible for virus attachment to the host membrane[37][40]. The third property of these drugs is that they are zinc ionophores so they allow the influx of zinc into cells and organelles like lysosomes. The rise in the concentration of zinc in the cytosol restricts the activity of RNA-dependent RNA polymerase and essentially prevents the virus from replicating its genetic code[38][39].

When the spike protein of coronavirus binds to the host cell, it gets endocytosed into an endosome and is brought into the cell. The endosome further gets fused to the lysosome where the virus can enter the lysosome and act on it allowing it to infect the cell. Chloroquine acts here, it blocks this process by entering into the cell and permeating into the lysosomes allowing it to alkalinize the endosome(lysosome)which in turn increases the ph of the organelles. The alkalization of these organelles hampers the normal functioning and replication of the virus in the host cell. Further it causes the inhibition of proton pump ATPase and hence the process of endocytosis as a whole is stopped or slowed down[33][34]. Hydroxychloroquine gets metabolized into chloroquine, in vivo. This chloroquine inhibits the very early stage of viral entry into the host. It interferes with the Angiotensin Converting Enzyme(ACE2) receptor of the host and prevents its fusion with the viral spike proteins[40].In vitro results of the efficacy of chloroquine phosphate against SARS-COV strain has already been reported.[41]

Altogether, it has shown potential results against covid19 in certain in vivo, in vitro studies as well as in clinical trials but yet its use without the proper medical recommendation is not

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advisable, due to the lack of proper efficacy data and certain toxic effects.

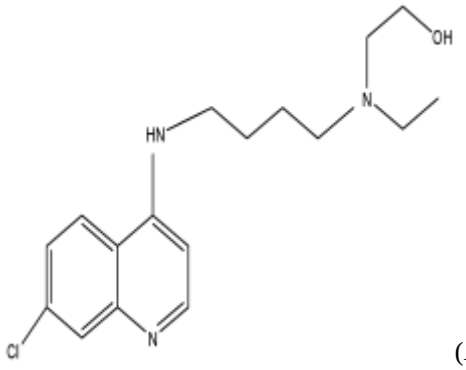
ARBIDOL (UMIFENOVIR)

Arbidol, ethyl-6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2-[(phenylthio)methyl]-indole-3-carboxylate hydrochloride monohydrate) is an Indole derivative and is a broad-spectrum drug used against certain enveloped and non envelopedviruses[42-44]. Arbidol interacts with aromatic amino acids and is reported to inhibit a wide range of viruses by interfering at multiple steps in the virus replication cycle[46,48]. It is done either by direct targeting of viral protein or virus-associated host factors[47,48]. It particularly inhibits the clathrin-mediated endocytosis of the virus, and hence the fusion of host cell cytoplasmic membrane with the viral envelope is inhibited.[45] Studies done on it reported that arbidol efficiently blocked the SARS-COV-2 spike glycoprotein and impedes with its trimerization. Also it acts by interfering with the SARS-COV-2 binding to the host membrane and by hijacking the process of intracellular vesicle formation[46]. Arbidol prevents viral attachment and fusion of the corona virus by itself binding to the lipid membrane and altering the membrane configuration of the cytoplasm or the endosomes.[46,47]. Certain tests are still being done to check its efficacy alone or in combination with other drugs like lopinavir,ritonavir ,chloroquine against COVID 19.[49-53]

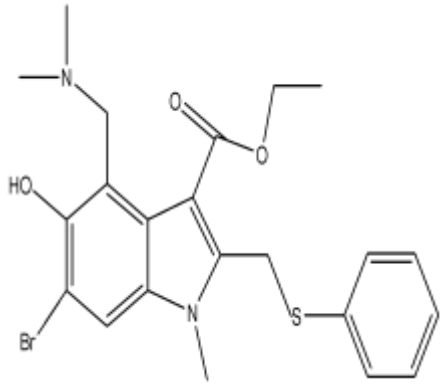
REMDESIVIR

Remdesivir is an antiviral agent but specifically, it's a prodrug of GS441524, i.e.,it is an inactive form of medication and after administration in the body, gets metabolised to its active form[54]. GS441524 is an adenosine analog, which in itself is a nucleoside base that acts as the building block to produce nucleic acid-like RNA and DNA. Remdesivir was originally used to treat ebola virus infection, its activity against certain other single-stranded RNA virus-like pneumovirus, filovirus, paramyxovirus, and MERS-COV has also been reported[55,56].Based on these results, its action against coronavirus was brought into studies.[57,60]

The SARS-COV-2 virus after fusing with the host cell gets endocytosed to take over the host cell(lysosomal) activity and then exit out of it to unravel its genetic code as RNA.once this virus comes in contact with the ribosome it overtakes the complete ribosomal protein synthesis machinery [54,58]. Remdesivir acts by interfering with the activity of RNA-dependent RNA polymerase. After entering it metabolizes into its active form GS1441254, an adenosine analog, this analog further incorporates itself into the viral RNA strand by evading the proofreading process of the RNA dependent RNA Polymerase, so the viral RNA altogether becomes defective and causes the Transcription Replication Process to stop producing new viral RNA after couple more additions to the RNA so we get defective and essentially inactive viral RNA[54]. An In vivo inhuman primate study conducted, revealed EC90 of remdesivir against SARS-COV-2 to be of range 1.76 micro mol[59,60]. Altogether, the drug has not been approved and studies and trials for its consideration as a potential drug against COVID-19 are still underway.



(A)



(B)

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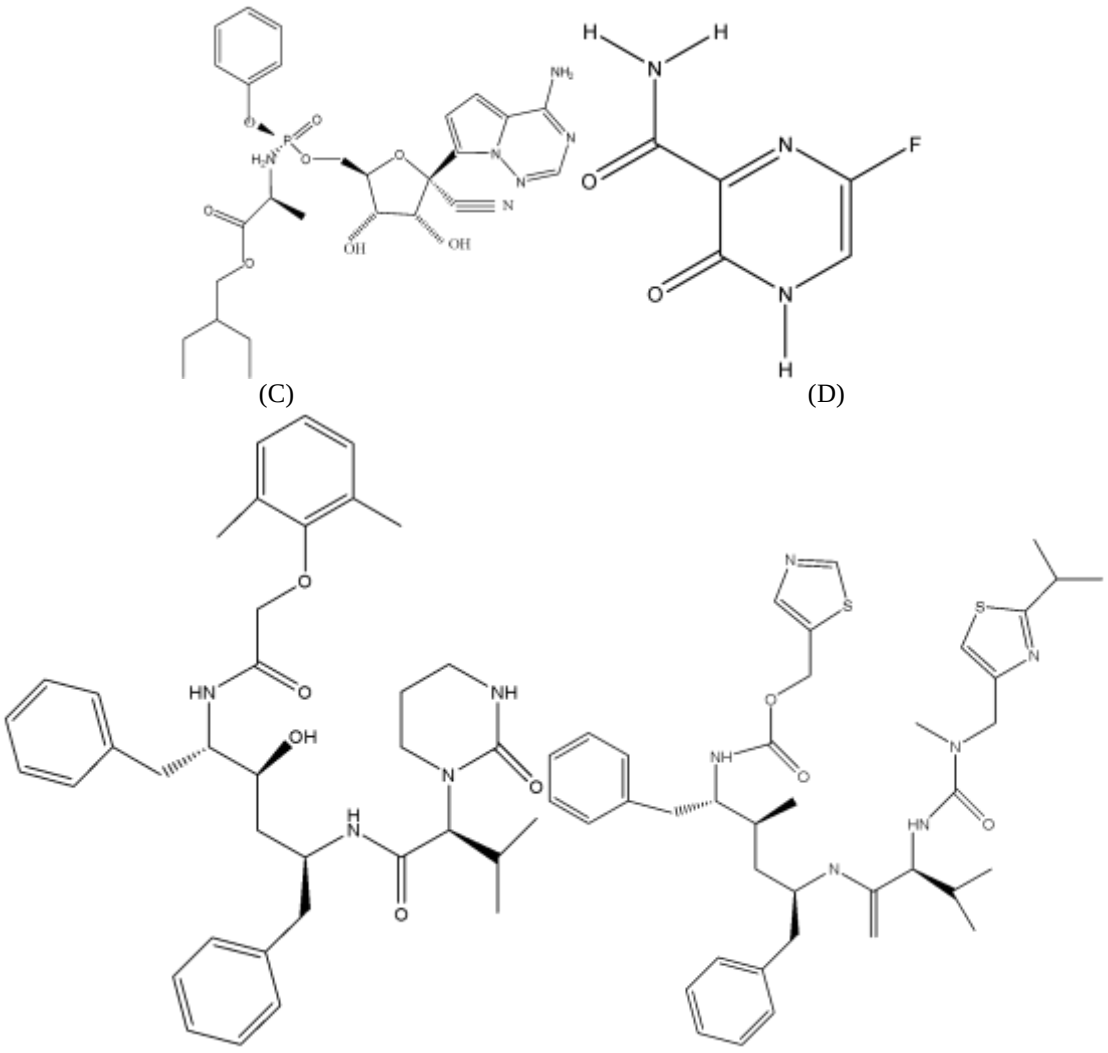

(C) (D)

(E)

Fig: [A]Hydroxychloroquine, [B]Umifenovir [C]Remdesivir [D]Favipiravir [E]Lopinavir -Rotanavir

FAVIPIRAVIR(AVIGAN)

Favipiravir,(6-floro -3-hydroxy-2-pyrazinecarboxamide) is an antiviral drug extensively used to treat viral diseases like the influenza virus[63], ebola virus[65], flavivirus, norovirus.[61,64] It is a guanine analogue with a pyrazinecarboxamide moiety. The antiviral activity of flavipiravir against SARS-COV2 is attributed to its interrupting the nucleotide incorporation process by selectively targeting the catalytic domain of RNA dependent RNA polymerase(RdRp.)[62,66]after the prodrug favipiravir enters the cell it is transformed into its active form favipiravir ribofuranosyl phosphate by the process of ribosylation and phosphorylation which is recognized by the RNA dependent RNA polymerase(RdRp) as its nucleotide, thereby interrupting its activity also this active form competes with the purine nucleotide and altogether disrupts the TRP and hence interfere with viral replication[62,66] .So by blocking the viral RNA it altogether blocks the synthesis of new viral copies in the host. Clinical studies of favipiravir in combination with other potential drugs are being tested for efficacy as anticoronavirus.

ROTANAVIR-LOPINAVIR(KALETRA)

Lopanavir is a majorly an antiretroviral drug which acts as a protease inhibitor[67]. Generally, Lopanavir is formulated in combination with another protease inhibitor, ritonavir. Ritanovir, enhances the bioavailability of lopinavir and also inhibits the metabolizing enzyme cytochrome P450,3A which ultimately increases

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the metabolism of lopinavir and hence its antiviral property[68,69]. Kaletra is the drug formulated consisting of a combination of lopinavir and rotanavir[71,69]. The drug was initially used against HIV infections based on its ability to block gag-pol polyproteins. [72] Based on certain positive in vitro test against SARS and MERS[70], it's potential against COVID 19 was tested, using computational methods such as docking and molecular tests. It was reported that these drugs effectively bind to coronavirus endopeptidase C30 more thereby disrupting the reproductive cycle of the virus. Also, it has an inhibitory action on 3CLPro, a protein involved in viral replication[73,74]. Although the drug has shown positive results in hospitalized COVID patients The use of these drugs as an anti-SARS-COV-2 is not yet established and its activity is yet to be determined.

NATURAL HERBAL REMEDIES

Initially, we summarized the list of drugs being used to somehow inhibit the viral disease. But apart from those drugs, certain traditional drugs are being screened for its activity against the virus. various molecular studies and docking results revealed the potential action of certain phytochemicals such as polyphenols(myricetin, quercetin, scutellarein), lectins, flavonoids (hesperetin, luteolin, tomentinA, B, C, kaempferol), xanthones, alkaloids(lycorine, tylophorine, Jubanine) triterpenes, diaterpenes, saponin(glycyrrhizin, saikosaponin A, B2), diarylheptanoid(curcumin) and ethanolic extracts(bavachinin, neobavaisoflavone, isobavachalcone, 4′-O-methylbavachalcone, psoralidin) on the various target sites of the virus. Docking techniques predicted the binding affinities of these natural compounds and COVID 19 related targets like Spike protein, ACE2, 3CLpro, PLpro, and RdRp.Some of the traditional Indian medicine based chemicals like glycyrrhizin, curcumin, withanoids, quarcetin, griffithsin, are briefed based on their action against the virus and their effects.

1.GLYCERRHIZIN(GLYCYRRHIZA GLABRA)

Glycyrrhizin is a triterpene saponin derived from the roots of glycyrrhiza glabra, also known as Liquorice in English and mulethi herb in Indian medicine. It is a perennial herb belonging to family Fabacecae, and it is effectively used as a therapeutic agent for the treatment of jaundice, arthritis, bronchitis, gastritis, as antiviral, antibacterial, antimicrobial and is known to have various immunostimulating effects[75][79]. Its activity is attributed to its binding to the human ACE2 receptors with a binding energy of -7.o kcal/ mol along with other receptors like 3CLPro(3-chymotrypsin like protease), spike protein, and RdRp with different binding energies of (-6.9,-6.5,-7.2 kcal/mol respectively)[77,78,80]. As the virus typically binds with the ACE2 receptor for its further entry and replication, targeting ACE2 with some potential chemical like glycerrhizin might inhibit the adsorption and penetration of the virus and show positive results. Although the binding energy with the key targets is a result of the in silico docking mechanism, in vitro tests yet to be confirmed. But since it shows an effect on SARS-COV and inhibits immune hyperactivation and cytokine storm in the patient's body[81], this herbal compound might as well be considered more or less effective against COVID 19.

2.QUERCETIN(ALLIUM CEPA)

Quercetin is an organosulphur compound obtained from plants belonging to the genus Allium, like Allium cepa(onion), Allium Sativum(garlic), and Allium Porrum(leek)[82]. It is a polyphenolic flavonoid compound with a wide range of biological activities including anti-inflammatory, antioxidant, and anti-enzymatic, antiallergic, anticancer actions[83-85]. Besides this, recent in silico studies have reported its activity as an antiviral against SARS-COV-2 similar to its counterpart SARS[83,89]. It has a significant potential to inhibit SARS-COV protease(3CLPro).[86-88].Also, it has an inhibitory effect on ACE2 receptors to which the virus attaches. Nguyen .at.al in his in vitro studies reported that quercetin and inhibited the protease of SARS-COV with an IC50 of 73 micromol.[86] Also, Corona virus utilizes certain cellular unfolded proteins (UPR) in different stages of its infection life cycle in the host. These UPR can be modulated by the use of quercetine. Based on this mechanism Nabirotchin.S suggested the use of quercetine as an anticorona viral. [90]

Activity testing and docking results of quercetine on SARS-COV-2 suggested that quercetine not only binds with the 3CLpro with a binding energy of 5.6kcal/mol but also binds to the other targets like spike proteins, ACE2, RdRp, and PLproeffectly[**91**]. Further assays and research on the potential of quercetin against COVID -19 are underway.

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3.GRIFFTHSIN

Griffthsin is an amino acid lectin obtained from red algae, griffithsia. It is demonstrated to have potent HIV inhibitory action.[92] It acts as an entry inhibitor and is known to bind and inactivate a wide range of viruses by blocking the glycan structures present on the surface of the virus.[93] although its activity against SARS-COV-2 is not yet confirmed its biological activity is attributed to the inhibition of surface-exposed S glycoprotein of SARS-COV and SARS-COV-2 which are composed of glycans and are common to both thus preventing viral binding[93,94]. CPE assay done on certain viral strains of SARS-COV confirmed the EC50 of it to be 0.61 micromol. [94]

4.AGGLUTININS(UTRICA DIOCIA)

Aggutinins another type of lectin extracted from the rhizome of utrica dioica has been traditionally used because of its reported effects on cardiovascular, immunity, neurona, and digestive system of the body.[99]Agglutinins of utricadiocia (UDA) have been shown to have an impact on the SARS-COV virus strain in vitro[96,97]. It acts by interrupting the viral attachment to the host in the early stages of the infection cycle[96]. It binds to SARS-COV spike glycoprotein and N – acetylglucosamine like residue on the glycosylated residue. It also inhibits viral replication, by affecting the adsorption and penetration stages of the virus.[95] The antiviral effect of UDA on SARS was assessed using an in vivo c-mouse model assay and Neutral red uptake assay and its EC50 was determined to be 29.9 micromol.[95,98]. On the basis of its action on SARS-COV, its activity on its coequal strain SARS-COV-2 is being studied.

5.CURCUMIN(CURCUMA LONGA)

Curcumin is a natural polyphenolic compound obtained from curcuma longa, referred to as turmeric in English and Haldi in Indian Ayurved and is traditionally used because of its therapeutic, antioxidative, anticancer, antimicrobial, and anti-inflammatory potential on chronic diseases, and certain other viral diseases like hepatitis B infection[100-102]. It might be a potential candidate molecule for SARS-COV-2 since it shows a better binding affinity to the nucleocapsid and ns10, comparable to azithromycin and remedesivir[103]. The nucleocapsid protein is not only responsible for detection, replication, and altogether processing of viral RNA but is also responsible for altering the host cell cycle that further leads to the programmed death of the host cell .Also the inhibition of the nsp10 protein by curcumin would not allow the viral RNA to camouflage with the host eukaryotic RNA which eventually will inhibit the cycle of replication in the host.

Also, curcumin acts as an immunomodulator and therefore decreases the level of inflammatory cytokines [103,105]. curcumin has also been reported to have a binding affinity towards Spike glycoprotein and ACE2 receptors. It binds with a binding energy of -7.9 and -7.8kcal/mol respectively.[104]These results of curcumin show that it might have promising effects on the health of the patients suffering from this infection.

6.WITHANONE(WITHANIA SOMNIFERA)

Withaferin A(Wi-A) and Withanone(WI-N) are the active withanolides obtained from WithaniaSomnifera (Ashwagandha). Certain molecular studies and docking techniques confirmed the inhibitory action of withanolides on the transmembrane protease serine 2[112]. Transmembrane protease serine 2(TMPRSS2) is a type of membrane protein that acts as an activator of S protein by which the viral proteins bind, and thereby undergo fusion, infectivity, and propagation[106,107]. Hence withanolides here act as a protease inhibitor. The withanone has shown to have stronger interaction than withaferin because it induces changes in the allosteric site Of TMPRSS2 similar to its known inhibitor camostatmesylate[108].

These Withanolides have the potential to inhibit the functional activity of SARS-COV-2 (Mpro) main protease[108] The main protease is a key viral enzyme that is essential for the generation of functional polypeptide along with the survival of the virus in the host cell. Studies reported the substrate binding affinity of withanone was equivalent to the efficacy and the binding energy of its claimed inhibitor N3 protease.[109] Also, Withanone significantly decreased the electrostatic binding free energy of ACE2 and spike protein receptor-binding domain(RBD) thereby blocking or weakening viral entry.[110]

So docking results on these withanolides altogether confirm the inhibitory activity not only on the viral(Mpro)protease and on TMPRSS2 protease of the host but also on the ACE2-RBD complex, resulting in restricting the virus life cycle. Additionally, its immunity-boosting property adds to its potential[111].

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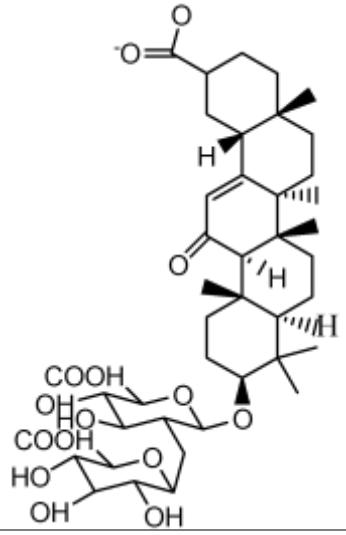
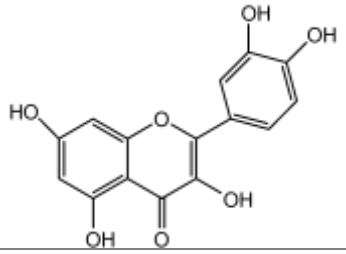
S.No	Natural Herb	Phytochemical	Structural Formula	Effect as Antiviral
1.	 Glycyrrhiza glabra	Glycerrhizin		Inhibits penetration absorption and replication of virus
2.	 Allium cepa	Quercetin		Inhibits main protease enzyme(3CLPro) and potential binds to ACE2 receptors
3	 Griffithsia	Griffthsin		Binds directly to the surface spike glycoprotein.
4.	 Utrica diocia	Agglutinins		Binds to spike glycoprotein and N-acetyl glucoasamine like residues inhibits viral adsorption and replication.

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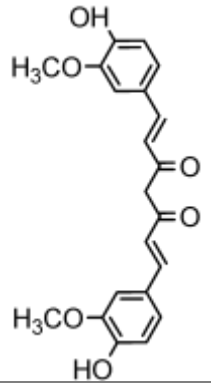
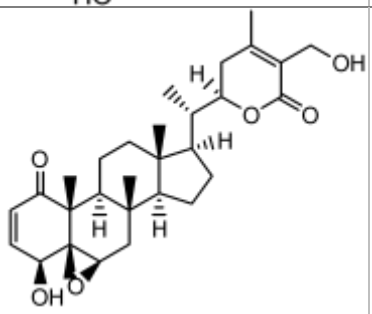
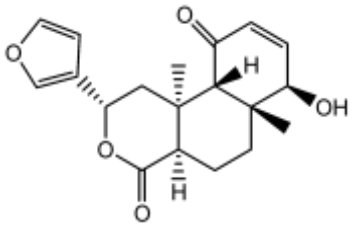
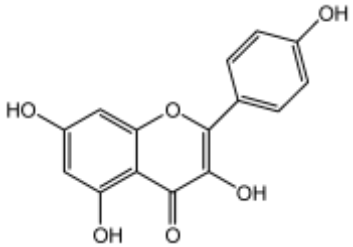
5	 Curcuma longa	Curcumin		Inhibits viral replication and 3CLPro.
6	 	Withanolides		Inhibits transmembrane protease enzyme(TMPRSS2) and MPro.
7		Tinosponone		Binds to spike protein,and inhibits 3CLPro.
8		Kaempferol		Inhibits 3a channel protein along with the main protease enzyme.

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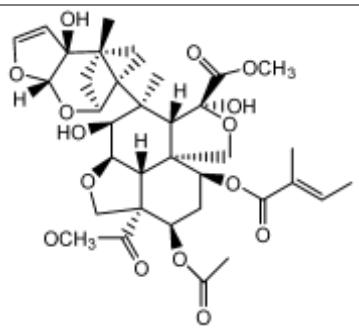
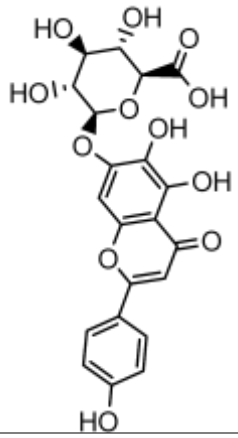
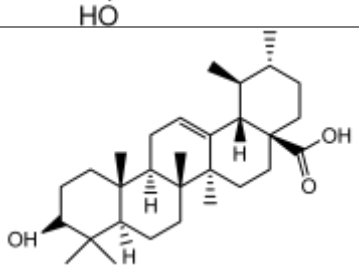
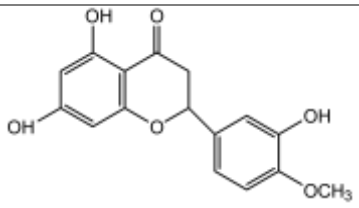
9		Azadirachtin, Nimbin		Prevents assembly of virus by inhibiting spike ,membrane(M)and envelope (E)protein.
10.		Scutellerin		Inhibits 3CLPro IN SARS-COV-2 and ATPase activity of SARS-COV helicase nsP13
11		Ursolic acid		Inhibits RdRp,S protein and main protease enzyme.
12		Hesperetin		Inhibits 3CLPro and RBD spike glycoprotien

7.TINOSPONONE (TINOSPORA CORDIFOLIA)

Tinosponone is a phytochemical derived from Tinospora cordifolia, a native Indian medicinal plant also known as Guduchi, Giloy, or Amrita in Ayurveda. Tinospora has been traditionally used to treat several diseases, because of its antineoplastic, antidiabetic, antioxidant, hypolypedemic, antimicrobial, antiHIV, anti – inflammatory, and antiviral effects along with the

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immunomodulating activity. [113,114]Recently, computational analysis and molecular docking studies have revealed the inhibitory action of tinosponone on the main protease enzyme of SARS-COV-2. Tinosponone along with other phytochemicals like xanosporic acid, cardiofolioside B, tembetarine, and berberine were analyzed and evaluated to test there inhibitory action against SARS-COV-2 main protease(M pro, 3 chymotrypsin-like protease), the results of which revealed the binding affinity of each as,-7.7, -7.5,-7.3,-6.6 and-6.5 kcal/mol[115]. Tinosponone, besides having the highest binding affinity, also possessed better permeability, drugability since it does not interfere with the cytochrome CYP450 of other drugs. Cordifolide A another phytochemical has been depicted to have strong interaction with SARS-COV-2 spike protein and is bound to it with a binding energy of -10.3kcal/mol.[115] further studies revealed the presence of zinc in the stem of Tinosporacordiofolia which has its action somewhat similar to that of hydrochloroquine, both acting as zinc ionophore[118]. Also, tinosporin a diterpenoid present in Tinospora, serves as an effective immunomodulator to improves humoral and cell-mediated immunity, along with selective inhibiting the pathogen to target its macrophages and T4 cells[116,117]. Many studies related to its action are still underway but docking results have suggested its potential against COVID -19.

8.TENUFOLIN AND PAVETANNIN C1 (CINNAMOMUM ZEYALANICUM)

Tenufolin and pavetannin C1 are the phytoconstituent isolated from Cinnamomum zeylanicum(cinnamon), a traditional Indian medicine which has since long been used to treat disorders related to the lungs including pneumonia, respiratory infections along with malignant pleural effusions[119].its use as an immunomodulator along with its actions as antimicrobial, antiviral, antitumor has to lead to it efficacy being tested against SARS-COV-2[120,121]. Phytochemicals isolated from these compounds are being tested to unfold its inhibitory potential against the main protease enzyme and the spike protein, which are essential for the binding and infectious life cycle of the virus.[122]

In silico, testing and docking results revealed the highest binding affinity of tenufolin and pavetannin c1. [124] While tenufolin bound with SARS-COV-2 main protease(6LUL) with a binding affinity of (-8.8kcal/mol), the pavetannin C1 on the other hand bound to the spike protein(6LUZ) of the corona virus with a binding affinity of (-11.1 kcal/mol) [123,124]. Besides them other compounds like 6-Glucopyranosylprocyanidin B1, Cinnamtannin-B1, Kaempferol, PavetanninC1, Proanthocyanidin-A2 and Procyanidin-B7 also interacted moderately with the main protease enzyme with the binding energies of -7.6kcal/mol, -8.4kcal/mol,-8.1kcal/mol, -7.3kcal/mol, -8kcal/mol and -8.2kcal/mol respectively [124]. These in silico docking results along with its additional role in stimulating the immune system suggest cinnamon to be a potential candidate for effective therapy for COVID19.

9.AZADIRACHTIN AND NIMOCIN (AZADIRACHTA INDICA)

Azadirachtin, nimbin, 7-desacetyl-7-benzoylazadiradione, 17hydroxyazadiradione, 7-desacetyl-7-benzoylgedunin, nimbin, nimbiol,nimbolin A, nimocin, nimbidinin, beta amyrin etc are the chemicals derived from Azadirachta indica, a member of Maliaceae family[125,130]. Also known as neem or nimba in the Indian traditional medicine, where it has been in use since ancient times to treat leprosy, jaundice, chicken fox, diabetes, gingitivitis, malaria, and diseases related to heart and liver and as an antimicrobial, antiviral, anti helmintic, anticancer etc [126-128]. Its activity as a free radical scavenger and an immunomodulator has also been reported[130]. Recently, The compounds of Azadirachta were docked for identifying its potential against SARS-COV-2, the results of which revealed its inhibitory action on M (membrane)and E(envelope) protein, which are required for assembly and production of new viruses in the host[131,132]. Nimbolin A displayed strong interaction with the transmembrane of envelope protein with a binding affinity of -11.2 kcal/mol, while the binding affinity with membrane protein was reported highest for nimocin of about -10.2 kcal/mol[132]. Studies of other compounds based on thier interaction with spike glycoprotein[129] and main protease(M Pro) was done along with synthetic antiviral remdesivir and that revealed the highest binding affinity for compounds like kaempferol (-8.4 kcal/mol for spike protein) and azadirachtin B(-7.7 kcal/mol for Mpro) respectively. Certain compounds like azadiradione, nimbolide, nimbiol, nimbinene, and nimbidinine also showed comparative moderate binding affinity for S protein and protease[129,132]. Although in vitro, in vivo

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studies and clinical trials for Azadirachta are yet to be done but these in silico results have portrayed that it might have an ameliorating effect on the propagation and physiology of the virus.

10. SCUTELLARIN AND BAICALIN (SCUTELLARIA BAICALENSIS)

Baicalin and scutellarin are the active compounds found in scutelleriabaicalensis.The plant species has shown to have broad therapeutic effects including anti oxidant, anti platlet, anti inflammatory, anti apoptosis, and many more[133-135].Scientist have successfully demonstrated the potential of baicilin[137] and scutellarin[138] against SARS, ACE receptor on foetal rhesus kidney-4 cell line[136]. The similarity between SARS and SARS-COV-2 has fueled the possibility of their binding to ACE 2 receptor too. Although it has not been tested invivo or in vitro computational studies and docking results reported the binding affinity of scutellarin with ACE2 receptors to be in the range of -14.9 kcal/mol and baicalin in the range of -8.46 kcal/mol[139]. Scutellerin has an additional inhibitory action on the ATPase activity of SARS-COV helicase nsP13[140]. The results of these compounds on SARS –COV make them a worthwhile candidate to be tested Against SARS-COV-2 too.

11.URSOLIC ACID AND METHYL EUGENOL (OCIMUM SANCTUM)

Ursolic acid, oleanoilic acid, methyl eugenol are some of the natural chemicals isolated from Ocimum sanctum, also known as the holy basil or tulsi in the Indian Ayurvedic system[1]. It is a medicinal herb with a broad spectrum of activity ranging from curing skin problems, flu, bronchitis, arithritis, asthma, heart-related diseases to acting as an immunity booster[141-143]. Ursolic acid, oleonilic acid, and methyl eugenol along with other compounds were docked to study their interaction with surface spike glycoprotein, RNA-dependent RNA polymerase and main protease of SARS-COV-2[144]. The result of which unveiled the binding efficacy of methyl eugenol to be around -8.29kcal/mol for spike protein-8.10kcal/mol for RdRp and -8.89kcal /mol for MPro, ursolic acid as -8.37kcal/mol for S protein,-8.01kcal/mol for RdRp and -9.09kcal/mol for MPro and oleanolic acid in the range of -8.27 kcal/mol,--8.00 kcal/mol and-8.95 kcal /mol respectively for Sprotien, RdRp and Mpro[144,145]. The plant is also a rich source of vitamin C and zinc, this adds to its immunomodulatory property[141]. Therefore, it is worthwhile to test Ocimum derived compounds against COVID 19 infection.

12.HESPERETIN (CITRUS SINENSIS)

Hesperetin,3,5,7-trihydroxy-4'methoxyflavanone is a bioflavanoid found abundantly in citrus sinensis and citrus limon[146,147]. It was assayed that hesperitin dose-dependently inhibited the 3CLPro enzyme of SARS-COV with an IC50 of 8.3micromol[148]. These similarities between SARS –COV, and SARS-COV-2 kindled the studies using docking techniques, which reported the potential binding affinity of hesperetin with ACE2 receptors to be around -8.3kcal/mol[149]. Another insight revealed the inhibitory action of hesperetin on RBDspike glycoprotein and the main protease enzyme (3CLPro or MPro)that is responsible for virus replication[149,139]. Citrus fruit is rich in vitamins that contribute to the immunity of the patient[150]. Chemical Studies and evaluation are still being done to discover the new biological potential of these naturally-derived chemicals as anti-COVID.

CONCLUSION AND FUTURE PROSPECTS

From the start of this disease up till today, there is no such FDA approved drug available that is capable of inhibiting or killing this viral strain. With the number of the death toll in rising the evaluation of every chemical that might have the slightest impact on the absorption or replication of the SARS-COV-2 strain has come into play. Chemicals and drugs based on their previous activity on either SARS-COV, MERS, or influenza strain are being tested along with Other previously used broad antiviral drugs like remdesivir, lopinavir, umifenovir, favipiravir, and many more. Besides this, in some countries, the focus of treatment has shifted to traditional medicine guided by their potential antiviral results on various other strain of viruses. Plants and their extracts are the main components of these traditional medicines. Plants based medicine be it the traditional Chinese medicine, the Indian Ayurveda or the south African herbal medicine have always shown promising results not only by having curative action but also by preventing it. These drugs benefit by boosting immunity(immunostimulant) and by altering inflammation, overall restoring vitality in the patient. Indeed it is the results of the computational studies and drug development programs that most of the phytochemicals have been modified and transformed into modern medicine. Keeping this perspective in mind a lot of phytochemicals are being explored and evaluated for COVID infection based on in silico techniques in vivo in vitro studies, or their efficacy clinically. Although,

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Indian Plant species like Ocimum sanctum, Withaniasomnifera, Tinosporacordiofolia, Azadirachta indica have shown inhibitory action on HIV protease and SARS protease, its action against SARS-COV-2 can only be reported as a result of molecular testings. Besides this a lot of phytoconstituents such as polyphenolic compounds, flavonoids, alkaloids, lectins have been explored, alone or in combination with other western medicines and yet no drug-specific to SARS-COV-2 have been identified.

S.NO	PHYTOCHEMICAL	Molecular Docking Binding energy( )[kcal/mol]			
		ACE2	Spike	RdRp	3CLPro
1.	Glycerrhizin	-7.0	-6.5	-7.2	-6.9
2	Baicalin	-7.9	-6.5	-6.9	-6.4
3	Hesperetin	-8.8	-6.5	-6.9	-7.0
4	Kaempferol	-6.9	-6.4	-6.3	-5.4
5	Quercetin	-7.3	-6.5	-7.2	-5.6
6	Curcumin	-6.4	-5.5	-7.6	-5.1
7	Tenufolin	-	-8.7	-	-8.8
8	Pavetannin C1	-	-11.1	-	-7.3
9	Ursolic acid	-	-8.37	-	-9.09
10	Methyl eugenol	-	-8.29	-	-8.89
11	Azadirachtin	-	-6.79	-	-7.72
12	Remdesivir	-	-7.69	-	-
13	Lopinavir	-	-	-	-6.97

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