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Review Article

EXPLORING THE POTENTIAL OF HERBAL THERAPY IN COVID-19

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ABSTRACT

The world has been facing the deadly coronavirus for a stretch of period now and with the innovation and latest research, the development of vaccines has been possible. The initial duration wherein the vaccines were under trials the most opted choice was the use of modern drug like Remdesivir along with other existing daily supplements. This review article describes the various pathogenic mechanism of action by which the virus attacks and replicates inside the body. It briefly gives the role of modern allopathy drugs, the use of traditional Ayurvedic medicines and herbs which act by discrete mechanism. It also focuses on the traditional herbs acting as drugs and supplements which could be prophylactic and hence used for the management of mild to moderate COVID conditions. Herbal agents like *Ocimum sanctum, Curcuma longa, Withaniasomnifera*, *Glycyrrhiza glabra, Andrographis paniculata, Zingiber officinale* etc. can have different antiviral actions which were used during the COVID-19 outbreak and have shown good margin of efficacy. Phytoconstituents like quercetin, fenugreek, liquorice etc. have shown to have activities like anti-viral, anti-inflammatory, immunomodulatory action, which is studied further in *in silico* modelling and by molecular docking. The significant use of these herbs and phytoconstituents which have contributed for preventive action has been described.

Keywords: Remdesivir, Herbal, *In silico*, COVID-19, Anti-viral, Phytoconstituents

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INTRODUCTION

The SARS-COV2 outbreak in 2019 has been one of wildly spread pandemic, raising a threat to human life. The disease has spread worldwide and affected every section of human life. With the existence of different variants, till October 2022, about 62 crore case have been reported. This deadly virus is associated with respiratory disorder, causing breathing issues and dysfunction of the various organs, ultimately leading to death. Previous study reports have indicated that MERS and SARS-CoV have similar mechanisms and symptoms; however, SARS-CoV 2 spreads much faster than MERS [1]. The fast rate of multiplication has led to an awakening of numerous renowned healthcare centres, which led to the development of several healthcare policies related to the pandemic.

Origin of SARS-COV 2

The spark of Covid-19 began from the seafood market of Wuhan, China wherein several patients were detected with respiratory issues. On investigation, the suspected pneumonia patients were kept under observation until the virus was detected. This human respiratory disorder is air airborne disease which can be transmitted via touch of humans and through air droplets [2]. The signs and symptoms include fever, which could be extreme along with chills, shortness of breath, cough and headache. Other minor signs can be body and muscle ache and sore throat. Further, it can have higher chances of pneumonia followed by acute respiratory diseases. This can lead to multiple organ failure and eventually death. The most common symptom experienced by all ages is loss of smell and taste [3].

Pathogenesis of COVID-19

The origin

'Proximal Origin of SARS-CoV-2', a study published by Nature Journal, suggested three theories that could possibly explain the origin of SARS-CoV-2. [1]

1. Natural selection in the animal host before zoonotic transfer: Bats likely served as a reservoir (since bat coronavirus RaTG13 is 96% identical to the humans i.e. SARS-CoV-2) but their spikes or S protein (spike-like glycoprotein on the envelope of the virus) [4] do not bind efficiently to ACE-2. Some Pangolins coronaviruses exhibit strong similarity to SARS-CoV-2 in RBD (Receptor Binding Domain) and the RBD was found to be optimized for binding to human-like ACE-2. Although both coronaviruses have some strong similarity with SARS-CoV-2, neither of them has polybasic cleavage sites as found in the human coronavirus.

2. Natural selection in humans following zoonotic transfer: It may be possible that natural selection took place in favor of SARS-CoV-2 between the initial zoonotic event and acquisition of polybasic furin cleavage, probably a period of unrecognized transmission in humans.

3. Selection during passage in human population: The virus might have acquired the mutations in RBD during adaptation to the passage from one cluster to other in human population.

Characteristic features of SARS-CoV-2 genome

The study also stated some notable features of the virus that might be the reasons we need novel therapies for the infection. Mutations in the Receptor Binding Domain is one of the two key structural peculiarities of SARS-CoV-2. Structural and biochemical studies have proven that the RBD of SARS-CoV-2 has a high affinity for the ACE-2 (angiotensin-converting enzyme-2) receptor. High-affinity binding of S (spike) protein of the novel coronavirus is regarded to be a result of natural selection on a human or homologous ACE-2 enzyme that has ensured a new optimal binding interaction.

This could be explained by computational studies, which showed that the high binding affinity of SARS-CoV-2 for ACE-2 is not an ideal interaction and RBD sequence is different from that of SARS-CoV to be optimal for receptor binding. Researchers evidently thus propose that SARS-CoV-2 is not a product of purposeful manipulation; however, the assumption may be disproved upon appraisal of new theories1. The second characteristic feature is the polybasic furin and O-linked Glycan. Furin aka PACE (paired basic amino acid cleaving enzyme; an endoprotease responsible for recognition of the cleavage site sequence Arg-Xaa-Lys/Arg-Arg, and catalyzing the hydrolysis of the precursors with basic amino acids Arg-Arg or Lys-Arg) allows effective cleavage at the junction of two subunits of S protein i.e. S1 and S2. The S1 domain mediates binding to the cognate host cell receptor and the S2 domain mediates the fusion events, between the viral membrane and host cell membrane [5]. The furin protein with oxygen-linked glycans determines the host range and infectivity of SARS-CoV-2.

The functionalities of SARS-CoV-2-specific-conserved-genes hold considerable significance in its virulence. While the E gene, majority of the which is localized at the site of intracellular trafficking, i.e. the ER, Golgi, and ERGIC, (ER-Golgi intermediate compartment) where it participates in CoV assembly and budding, [6] governs the expression of the envelope protein which is one of the four structural genes of SARS-CoV-2, the RdRp gene (RNA Dependent RNA Polymerase gene) [5] is implicated in RNA polymerization or modification once the viral genome enters the host cell and is a subpart of the long chain of the alliance of 16 protein-expressing genes (NSPs or non-structural proteins) i.e. ORF1ab. Another structural gene, responsible for the expression of nucleocapsid protein is the N gene that keeps the viral envelope stable. Localization of N protein to the endoplasmic reticulum (ER)-Golgi region has advocated a function for it in assembly and budding. It is also encompassed in the coronavirus' replication cycle and host's cellular response to the virus.

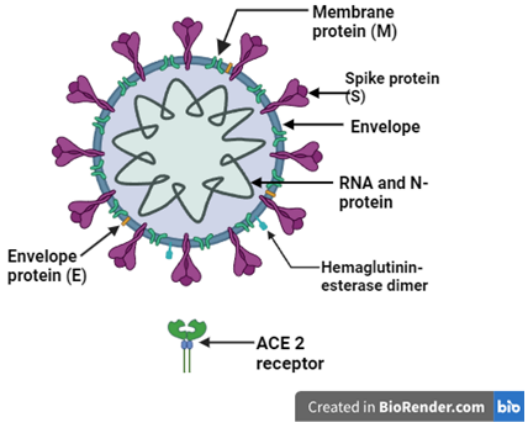


Fig. 1: Structure of SARS-COV 2 virus

SARS-CoV-2 has a genome of about 29.9 kb and shares 79.5% and 96% identity with SARSCoV and bat coronavirus, respectively [3]. The virus is said to exhibit genetic camouflage, preventing its genes being attacked by host genes [7]. It might be molecular mimicry or structural camouflage of proteins and nucleic acid [8]. It was shown by a genomic study that 98 nucleotide mutations at 93 sites in the genome of different SARS-CoV-2 strains. Amongst them, 58 mutations had caused changes in amino acids, pointing it to the side of neutral evolution. According to a study, the elicitation of a heterotypic response blocking S gene-mediated entry of SARS-CoV-2 into host cells accords with the genomic as well as the structural conservation of the spike protein along with the relative glycans shields of both SARS-CoV-2 and SARS-CoV. This insinuates that resistance against one virus of the Sarbecovirus subgenus can plausibly provide immunity against related viruses [4]. The mutations in S glycoprotein might induce its conformational changes, probably leading to alterations in the antigenicity of the virus. Characterization of the amino acids involved in conformational changes of the protein structure might aid in developing a new therapeutic strategy for COVID-19.

Pathophysiology of COVID-19

SARS-CoV-2 was reported to enter cells via binding to ACE2, followed by its priming by TMPRSS2 protease enzyme, just like the SARS-CoV [2, 3]. The entry of the virus into the host cell was initially thought to be involving direct fusion with the plasma membrane. A recent study reveals that the process of entry of SARS-CoV-2 is a pH and receptor-dependent endocytosis process [7]. Translation of viral proteins by the host cell machinery immediately takes place starting with large overlapping open-reading frames ORF1ab. The resulting protein is RdRp, the viral RNA-dependent RNA-polymerase, which along with polymerization, is also involved in generating sub genomic mRNAs. These comprise RNAs encoding the nucleocapsid protein N, the envelope glycoproteins E (small envelope protein), M (membrane protein), the S-protein and 8 proteins of unknown function. The assembly of the viral contents occurs in the ERGIC (ER-Golgi Intermediate Compartment). The E proteins are processed in the ERGIC and transported to the budding compartment. The membrane-protein associates with the helical N, E and S proteins [5, 6]. The release of new viral particles is an endosome driven event. Endosome fuses with acidic intracellular lysosome leading to cell lysis thereby releasing new viral particles.

A study by Chen *et al.* refers to "cytokine storm" that is responsible for the weakening of the adaptive immune system against SARS-CoV-2 infection. The immunological study gave three key finding:

1) T cell depletion and CD4+T cell dysfunction,

2) CD4+and CD8+T lymphopenia (very low in severe conditions), and

3) Increased overproduction of IL-6, IL-2R, IL-10 and (TNF)-α (prominently high in severe conditions). COVID-19 patients asymptomatically spread the illness even before diagnosing themselves as positive for SARS-COV-2 presence due to the delayed emergence of signs and symptoms. The collapse of the anti-viral immunity of the host body further causes respiratory distress and rapid complications that may include fatal pneumonia. This might be one of the several reasons that make SARS-CoV-2, a deadly virus [9].

According to a Chinese study, percentage of cases dealt with mild symptoms (non-pneumonia and mild pneumonia); patients with severe conditions about 14% of cases, experienced dyspnea, a high respiratory frequency ⱷ 30/min, normal rang e: 12-20/min), low blood oxygen saturation (SpO2≤ 93%, normal r ange: 95-100% for healthy lungs), a low PaO2/FiO2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)]<300 (normal: about 500), and/or lung infiltrates>50% within 24 to 48 h [10]. In 14% of cases, patients with critical disease suffered from respiratory failure, septic shock, and/or multiple organ dysfunctions (MOD) or failure (MOF).

Some laboratory abnormalities that were encountered in COVID-19 patients, as reported by a study, precise with other findings, have lymphopenia as the hallmark of the pandemic disease; especially the peripheral CD4 and CD8 T cells are found to be substantially reduced. CD8 cells are also found to contain a considerable number of cytotoxic granules. Neutrophil count, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, cardiac biomarkers, D-dimer, prothrombin time (PT), procalcitonin (because of bacterial superinfection; higher in ICU patients than the ones not in ICU), C-reactive protein (CRP) are found to have elevated values whereas, lymphocyte count (hallmark) and albumin levels are decreased significantly [11].

The symptoms of the disease can take longer to develop. Most infected people show either mild or no symptoms for up to 2 w, which makes it difficult to control the infection and hence for proper surveillance of COVID-19, efficient management strategies are a must.

Allopathy therapy

Antiviral agents are currently being explored in trials. Some of these antivirals work by blocking the entry of the virus into the host cells, some block the viral replication, while some delay the response of the immune system. (12)Antiviral agents may not be a standalone factor to stop the cytokine storm, pulmonary destruction and respiratory distress in COVID-19 patients who present late after infection. Targeted immunomodulation reduces the cytokine storm, which may ameliorate pulmonary inflammation and likely improve mortality.(13) Further studies on viral factors driving immune dysregulation may provide insights into shaping vaccine responses toward defensive immunity. It is still a long go through many phases of clinical trials of different drugs against the standard of treatment until we find a potential therapy to combat the deadly pandemic disease of COVID-19.

The anti-Covid therapy consists of the use of a blend of antiviral drugs like Remdesivir, followed by antibiotic treatment. The extensive use of oxygen and intravenous immunoglobulin therapy is known by all. Since ages supplements have been used for common flu which have also shown efficacy against COVID-19. Data have reported that Vitamins, including Vitamin C and Vitamin D have effectively decreased the risk of symptoms. Some other multivitamin supplements have also been prescribed widely along with Vitamin B12. Hydroxychloroquine which is an anti-malarial drug that exhibited a decrease in the viral activity in patients. The use of a combination of antiviral drugs like Remdesivir and steroids have shown greater efficacy in terms of treatment action. But along with efficacy, they also exhibit adverse and toxic effects on human lives. A recent study for a small group of people with moderate COVID also stated the use of ceftazidime or cefepime in combination with the steroid dexamethasone but data from larger group still needs to be reported.

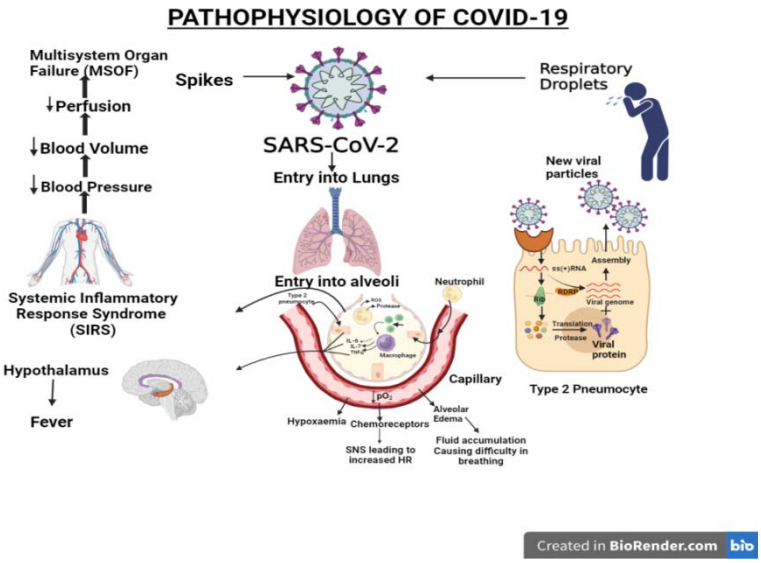


Fig. 2: Pathophysiology of COVID-19

Treatment using vaccines

Despite the use of these existing drugs and supplement combinations, the urge to design vaccines for faster control and action among the population was required. The modern research and fast track studies lead to the development of vaccines based on whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA) that have been introduced in the market. Each of these protects people by producing immunity in a slightly unique way. BNT162b2 (mRNA vaccine) by Pfizer and BioNTech, mRNA-1273 by Moderna, ChAdOx1nCoV19 (Covishield) by the University of Oxford+AstraZeneca and Serum institute of India etc include some of the popular vaccines used.

Herbal drugs: the original remedy

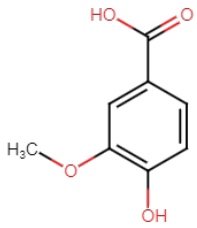
The use of allopathic antiviral agents is accompanied by adverse events and toxicity issues. Herbal drugs have been widely explored for a range of disease conditions. Natural herbal drugs have been used in both Ayurveda and Traditional Chinese medicine for respiratory-related ailments and have shown significant improvement in therapeutic condition. Similar studies have demonstrated the use of different herbal plants and their phytoconstituents for antiviral therapy as well.

Dating back to the time when COVID-19 began the, herbal medicines were highly recommended across China to cease down the number of cases and the extent of spread. And herbal plants also being a part of traditional Chinese medicine were endorsed by the regulatory bodies for prompt use [14]. On similar lines, Ayurveda being the oldest medicinal system in India was opted for treating the respiratory disorder. However, these were recommended for only preventative action and not complete cure. Chinese medicines like Shuanghuanglian which is composed of a mixture of honeysuckle, Chinese skullcaps and forsythia shows antiviral and immunomodulatory action. Even Ayurveda has recommended some of the mixtures which could act by regulating the immune and viral state in patients. Dicoctions made of Ocimum sanctum, Piper nigrum, Zingiber officinale, Cinnamomum verum and Vitis vinifera have been used for boosting immunity for Covid patients [15].

Some of the herbs active against different facets of symptoms of Covid 19 include;

i) *Lonicera japonica* (Japanese Honeysuckle)

Lonicera japonica belongs to the family Caprifoliaceae, which consists of the seeds, fruits and leaves which consist of the important phytoconstituents. The active phytoconstituents of Japanese honeysuckle include hydroxycinnamic acid, isoflavone, and flavanones which are useful in the SARS-coV. It acts by inhibit SARS-COV-2-S protein/ACE2 binding [16]. Itcould inhibit SARS-CoV-2 by inhibiting Mpro activity [17]. It had shown the reduction of toll-like receptor 3 and tank bound kinase 1 caused byrespiratory syncytial viral infection [18].



4-hydroxycinnamic acid

Fig. 3: 4-Hydroxycinnamic acid

ii) *Adhatodavascica* (Vasaka)

It consists of the leaves of the plant *Adhatodavascica,* belonging to the family Acanthaceae.

The main phytoconstituents of vasaka are vasicine, vascinone, vascinolone andadhatodine. It has strong anti-influenza virus activity that can inhibit viral attachment and viral replication. The action is possibly by the blockage of viral attachment through inhibition of viral HA protein, by blocking the viral absorption to

cells, by synergistically binding tothe free virus particles or by blocking the sialic acid receptors to prevent virus entry intothe cells and by inhibiting the replication of influenza virus or virus budding from theinfected Madin-Darby Canine Kidney (MDCK) cells. It shows antitussive and bronchodilatory actions relieving pneumonia-like symptoms which are similar to symptoms seen in COVID patients [19].

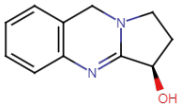
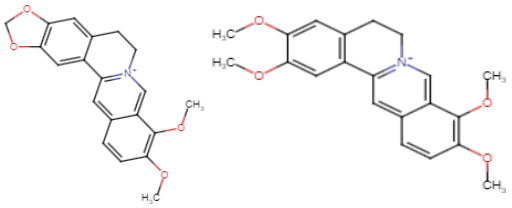


Fig. 4: Vasicine

iii) *Tinospora cordifolia* (Guduchi)

Guduchib belongs to the family Menispermaceae which consists of the whole plant. It is used for its immunomodulatory, anti-inflammatory, and antioxidant effects [20]. Itconsists of berberine, palmatine, tinocordiside, tinocrodifolioside A, cordioside, cordofoliside A, B, C, D, and E, tinospora, tinosporides, jateorine and columbine. It focuses on targeting the main protease (Mpro) of the virus. The two main potential targets are the Virus (Receptor binding motifs-spike (S), envelope (E) and nucleocapsid (N) proteins dependent RNA polymerases and second the Receptor motif on human ACE2 (angiotensin-converting enzyme) and its associated functional proteins like TMPRSS2and B0AT1 [21].



Berberine **Palmitine**

Fig. 5: a. Berberine, b. Palmitine

iv*) Swertia chirata* (Chirata)

Swertia chirata belongs to the family Gentianaceae, is an indigenous herb to the temperate Himalayasand is used in traditional medicine to treat numerous ailments. It shows antiviral properties against the SARS-CoV-2 virus by acting on Mpro and RNA-dependent RNA polymerase (RdRp) targets [22] It consists of methyl swertianin,1-hydroxy-3,5-dimethoxyxanthone, bellidifolin and two triterpenoids, oleanolic acid. β-amyrin targets the spike protein, while amarogentin targetsthe Mproprotein [23].

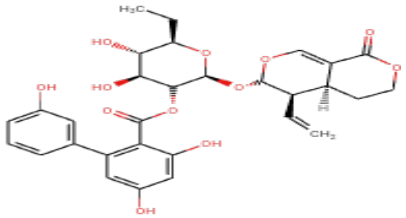
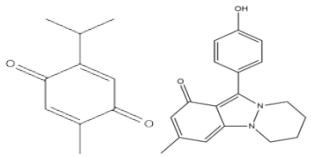


Fig. 6; Amarogentin

v) *Nigella sativa* (Kalonji)

Also known as black cumin or *Nigella sativa*, it is a flowering plant of Ranunculaceae family. The main actives present in the seeds are thymoquinone and nigellidine. Studies based on molecular docking show that it is a potent inhibitor of COVID-19, the extracts exhibit immunosuppressive activity [24]. Nigellidine and α-hederin inhibit the main protease 3CL Pro/Mpro [25]. Thymoquinone binds to the hydrophobic component of SARS-COV-2 and causes activation of virus anti-inflammatory activity. It has immunomodulatory effect which acts by the activation of T cells and helps in the production of IFN-γ. It also has the capability to inhibit main protease MPRO in SARS COV-2.



Thymoquinone **Nigellidine**

Fig. 7: a. Thymoquinone, b. Nigellidine

vi) *Camellia sinensis* (Green tea)

Green tea plant, botanically known as *Camellia sinensis* belongs to the family Theaceae. It consists of several polyphenols like theaflavin, myricetin 3-O-beta-D-glucopyranoside, catechin, epicatechin, epigallocatechin and epigallocatechin gallate. The two major actives present are epigallocatechin gallate and theaflavin. These show potential ability to inhibit matrix metalloproteinase (MMPs) against SARS-CoV-2 main protease [26]. The *in vitro* studies show that EGCG (epigallocatechin gallate) exhibited 85% inhibition of 3clpro at a concentration of 200 µm and had an IC50 value of 73±2 µm [27].

And hence epigallocatechin gallate is a better option in the prophylaxis of COVID-19 due to hydrogen binding. Theaflavin (Tfs) have shown RNA-dependent RNA polymerase (RdRp) inhibition and ACE2 binding activity. Therefore, both EGCG and Tfs are potential antiviral agents [28]. The inhibition effects of EGCG on SARS-COV-2 takes place by its actions on the ACE2 receptor, main protease (Mpro, a 3C-like protease) and RdRp(RNA-dependent RNA polymerase [29].

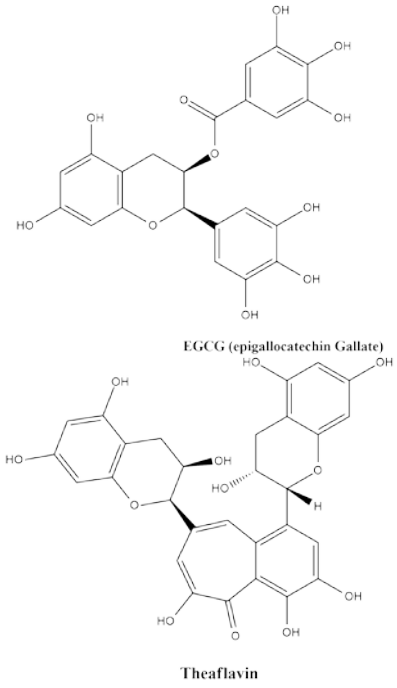


Fig. 8: a. Epigallocatechin gallate, b. Theaflavin

vii) *Panax ginseng* (Ginseng)

Ginseng belong to the *Panax ginseng family* Araliaceae. It is a Chinese herb which is used for treating respiratory diseases and also help to

boost immunity. 20(S)-ginsenoside Rg3, is the active ingredient of *Panax ginseng*. It blocks RBD-ACE2 interaction by directly inhibiting the RBD of the SARS-COV-2 spike glycoprotein [30] It acts by increasing the macrophage function i.e. CD14 and MHC class II and can be effective in the prevention of COVID-19 [31]. A recent study found that SARS-COV-2 binds to angiotensin-conversion enzyme 2 receptor (ACE2). The ACE2 were expressed in the cell membranes of the heart and lungs. The receptor binding domain (RBD) of the SARS-COV-2 spike glycoprotein, which binds to each other with ACE2 and inhibit the function of the ACE2. This further block SARS-COV-2 virus infection [32].

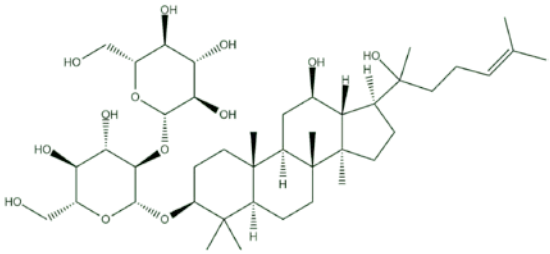
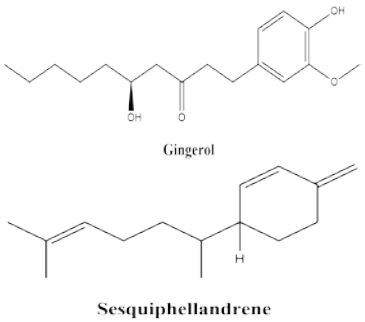


Fig. 9: 20(S)-ginsenoside Rg3

viii) *Zingiber officinale* (Sunthi)

Sunthi or, commonly known as ginger is a rhizome that belongs to *Zingiber officinale*, family Zingiberaceae. Various ginger compounds, like 8-gingerol, 10-gingerol, and 6-gingerol, have the ability to inhibit PLpro via molecular docking [33]. It was found that 6-gingerol exhibited a higher binding affinity with the main protease. Sesquiphellandrene, a ginger-derived terpene, bind to S protein and further interfere with the S protein-ACE2 interaction [34]. Ginger extracts also stimulates the secretion of interferon (IFN)-α and IFN-β from infected epithelial cells.(35)These have shown to inhibit the viral replication the respiratory tract. Studies show that the aqueous and alcoholic extracts have reduced the number of eosinophils and neutrophils in mouse models with overall decrease in goblet cell hyperplasia [36].



Gingerol

Sesquiphellandrene

Fig. 10: a. Gingerol, b. Sesquiphellandrene

ix) *Withaniasomnifera* (Ashwagandha)

It consists of the roots of plant *Withaniasomnifera*, belonging to the family Solanaceae. Ashwagandha is used as an immunomodulatory, antiviral, and anti-inflammatory. They act by reducing the inflammation and oxidative stress in the Covid patients. The actives present in the root are withaferin A, withanolide A, withanolide D, sitoindosides, 12-deoxywithastramonolide, and withanoside V [37]. The *in silico* study exhibited that it acts on SARS-CoV2 by inhibiting RNA polymerase. By inhibiting COX-2 and suppressing prostaglandins, it exhibits an antipyretic effect [38]. The primary viral protease (Mpro) was found to interact strongly with Withanoside V and Somniferine [39]. It could be a viable candidate for treatment and a safe alternative for hydroxychloroquine. These findings support the immunomodulatory activity of W. somnifera extract, which has well-known immunomodulatory action in traditional medicine [38].

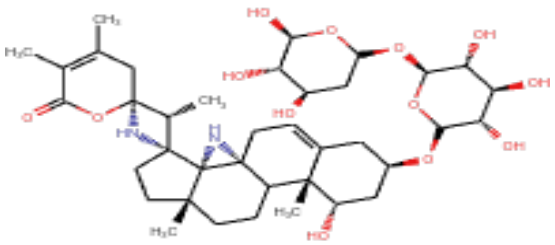


Fig. 11: Withanoside V

x) *Allium sativum* (Garlic)

Garlic can reduce the effects of proinflammatory cytokines and heal immunological disorders. The sulphur-containing components like thiosulfinates (allicin), S-allyl cysteine sulfoxide (alliin), ajoenes (E- and Z-ajoene), vinyldithiins (2-vinyl-(4H)-1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), and diallyl (di and tri) sulfide are present [40].

Allicin, which is a major active present in garlic, functions by inhibiting various thiol enzymes. Other components, such as ajone's, have demonstrated their effectiveness in viral infections through leukocyte prevention mechanism. Studies based on molecular docking have shown that the active allin has a better and higher anti-viral potential against the SARS-coV virus, efficient enough to reduce the symptoms with lesser side effects [41].

The immune parameters like leptin, leptin receptor, adenosine monophosphate-activated protein kinase, and peroxisome proliferator-activated receptor-gamma have also been associated with *Allium sativum*. And thus, it is used for as a preventative approach in Covid-19 to improve immune processes. *In vivo* studies have been done with garlic oil extract which have shown enhancement in the immunity and reduced inflammation in the rodent model [42].

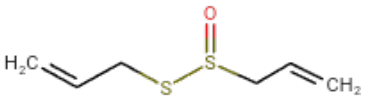


Fig. 12: Allicin

xi) *Andrographis paniculata* (Kalmegh)

The aerial parts and roots of *Andrographis paniculata* belonging to the Acanthaceae family have been used traditionally for different medicinal purposes. The plant contains many diterpenoids, lactones, and flavonoids. The active showcase anti-viral, immunomodulatory and anti-inflammatory action. Andrographis is commonly used as an anti-HIV and in COVID-19 as it shows protease inhibitory action. *A. paniculata* phytochemicals acts on five potential drug targets: the spike (S) glycoprotein, 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), and RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 and human angiotensin-converting enzyme 2 (hACE2) [43].

The mechanism of protease inhibition was studied using molecular docking and the toxicity profile was also surveyed [44]. Andrographolide isolated from the plant, was analysed by *in silico* computational docking tools. It showed that it can bind to RBD of the S-glycoprotein site of the SARS-coV virus [45].

Thus, displaying greater binding affinity than the synthetic drugs for the protease region (Mpro) and thereby better inhibition action. It also inhibits the production of infectious virions as a potential inhibitor of the main protease of SARS-COV-2 based on the *in silico* studies [46].

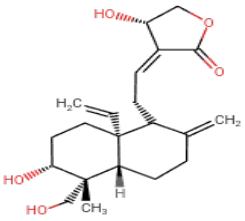


Fig. 13: Andrographaloid

xii) *Azadirachta indica* (Neem)

The leaves of *Azadirachta indica* belonging to the family Meliaceae has been utilized since ages for the number of medicinal advantages. It is well-known for its antimicrobial properties and has been used for fever in COVID-19 [47]. In specific to SARS-CoV-2, the molecular docking research has demonstrated that neem-derived compounds such as nimbolin, nimocin, and cycloartenol can bind to the SARS-CoV-2 envelope (E), membrane (M), glycoproteins, and thus have an inhibitory role against the virus [48].

xiii) *Ocimum sanctum* (Tulsi)

Leaves of *Ocimum sanctum* belonging to the family Lamiaceae are used as medicinal aromatic herb. The leaves have the ability to increase the levels of IFN-γ, IL-4 and T-helper cells and natural killer cells [50]. Thereby having immunomodulatory and anti-viral actions. Studies have shown that *O. sativum* has anti-inflammatory, antioxidant, anti-cancer, hepatoprotective, radioprotective, anxiolytic, adaptogenic, metabolic etc. [51, 52].

The phytoconstituents hinder the binding of virus by inhibiting the Papain-like-protease and SARS CoV19 Main Protease. Thus, preventing the binding to ACE2 host receptors. The hydroalcoholic extract shows inhibition against the multiplication of intracellular virus. The constituents like vicenin, isorientin 4′-O-glucoside 2″-O-p-hydroxybenzoagte, and ursolic acid have shown properties against Covid. Isorientin′ 4 -O-glucoside ″2 -O-p-hydroxybenzoagte and ursolic acid showed significant binding affinity for SARS-CoV-2 Mpro [53]. Ursolic acid, a major constituent of Tulsi, is a pentacyclic triterpenoid, reported to have anti-viral, anti-inflammatory, anti-microbial and anti-malarial activities [54, 55].

The neem extract has an activity to inhibit the PL-pro. The primary ingredient of neem, desacetylgedunin (DCG), demonstrated the greatest binding affinity for PL-pro. *Azadirachta indica* exhibited positive antiviral evidence specific to the severe acute respiratory syndrome coronavirus 2 based on preliminary *in silico* data [49].

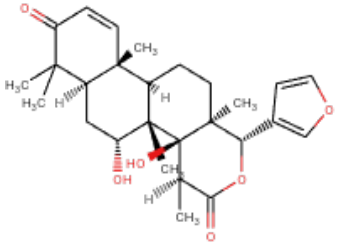
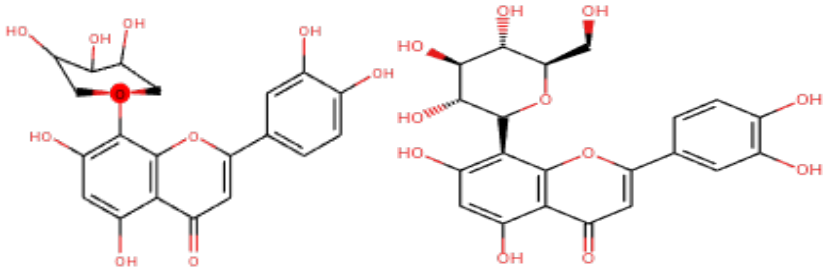


Fig. 14: Deacetylgedunin



Orientin **Vicenin**

Fig. 15: a. Orientin, b. Vicenin

xiv) *Curcuma longa* (Turmeric)

It consists of tuberous rhizomes and dried powdered roots of turmeric belonging to the ginger family Zingiberaceae. Turmeric shows immunomodulatory and anti-viral action against the virus. The *in vivo* studies show the aqueous extract of the drug has potential immunomodulatory action [56].

Curcumin acts by inhibition of 3CL (3 Chymotrypsin) like protease in viralcells, thus preventing replication in the host and also inhibit pro-inflammatory mediators like IL-6, IL-1 TNF , bradykinin, cyclooxygenase (COX), caspase 3 (Cas 3), and NF-kB. Different studies have also reported anti-inflammatory action when given in combination orused alone [57].

Curcumin activates the production of natural killer cells and cytokine production along with T-cell proliferation in mouse macrophage cells towards response of mitogen. The key element is cyclocurcumin which, when compared to remdesivir and hydroxychloroquine it is more active as well as binds to the active site of SARS CoV-2 primary protease better than the two. It is a potential inhibitory agent that blocks the host viral interaction (ACE2) at an entry site in humans and as an attenuator by modulating the proinflammatory effects of Angiotensin II-AT1 receptor-signaling pathways, reducing respiratory distress [58].

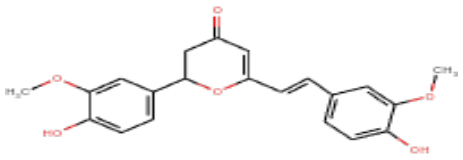


Fig. 16: Cyclocurcumin

xv) *Phyllanthus emblica* (Indian gooseberry)

Phyllanthus emblica, (Indian gooseberry) is an ephemeral tree belonging to the Euphorbiaceae family. It mainly consists of flavonoids astragalin, kaempferol, quercetin, quercetin-3-O-glucoside, quercetin, tannins [59]. The main function is having immunomodulatory action against COVID-19. Constituents like phyllaemblicin-B and phyllaemblinol have good binding to helicase protein and phyllaemblicin G7 which also binds to the spike protein and inhibits the same. It has been reported to increase splenocytes proliferation and the alcoholic extracts have reduced the levels of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokine [60]. The studies have reported anti-viral action towards HSV-1 and inhibition of the gene expression, thereby preventing the virus growth and

proliferation. They inhibit the enzymatic activity of COVID-19 Mpro, which is a key enzyme of coronaviruses and has a pivotal role in mediating viral replication and transcription, making it an activity drug target for SARS-CoV-2 [61].

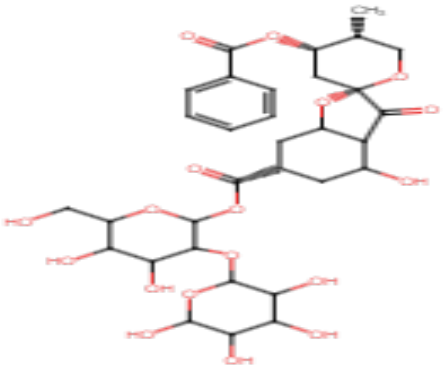


Fig. 17: Phyllaemblicin-B

xvi) *Linum usitatissimum* (Flax seed)

Linum usitatissimum (Flax seed) belonging to family Linaceae which is called super food contains main chemical constituents they are α-linolenic acid, lignans, and dietary fiber [62]. It shows immunomodulatory action along with anti-viral activity by acting on the mRNA and inhibiting the murine macrophages for respective actions. It has been used as vaccine adjuvant [63] and the phenolic constituents have shown a reduction in cell-mediated immunity. Whole flaxseed contains Omega-3 fatty acid which is an inhibitor of PEG-2 and NFk-B, which lead to an inflammatory response. By activating MAPK and GPR 120 it reduces inflammation. Also, Omega-3 fatty acid inhibits cytokine storm which may lead to lung injury and Acute respiratory distress syndrome (ARDS) [62, 64].

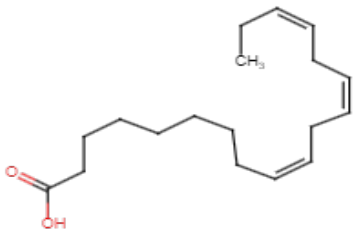


Fig. 18: α-linolenic acid

xvii) *Cinnamomum verum* (Chinese cinnamon)

Cinnamomum zeylanicum called as (Chinese Cinnamon) is obtained from dried bark belonging to family Lauraceae. The bark acts as an immunomodulator which inhibits CD18/11a expression of leukocytes and enhances the phagocytosis of leukocytes [65]. It strongly binds to human Angiotensin-converting enzyme 2 (h ACE2). It is beneficial in conditions like asthma, shortness of breath, cough, and especially chronic cold infections. Another species *C. zeylanicum* bark oil shows anti-viral activity against H1N1 and HSV1 viruses [66]. Trans-cinnamaldehyde (TCA) and p-cymene are active compounds that reduce the IL-8 secretion in lipopolysaccharides (LPS)-stimulated THP-1 monocytes. COVID-19 is a viral disease with hyperinflammation and excessive reactive oxygen species (ROS) production, which play a critical role in cytokine release in inflammation diseases. Inhalation of cinnamaldehyde helps to improve respiratory functions and inflammatory conditions in lipopolysaccharide-induced airway inflammation. The polyphenols like Type-A Procyanidin polyphenols (TAPP) from *Cinnamomum zeylanicum* shows anti-asthmatic and anti-inflammatory effects [67].

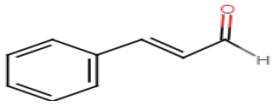


Fig. 19: Trans-cinnamaldehyde (TCA)

xviii) *Glycyrrhiza glabra* (Liquorice)

Glycyrrhizinic acid is a triterpenoid saponin obtained from the root and rhizome extracts of Liquorice (*Glycyrrhiza glabra*) belonging to family Fabaceae. It is used to treat respiratory tract infection, such as dry cough and hoarseness, currently also used for covid 19. It is believed to enhance the immune system against viral infection and for the protection of plasma membrane from viral load. GLR inhibits viral replication and penetration and absorption of the virus into cells [52]. SARS-CoV-2 infection also leads to immune dysregulation characterized by lymphopenia, altered neutrophil response, strong pro-inflammatory response, and elevated levels of reactive oxygen species (ROS) generation. The chronic SARS-CoV-2 infection leads to hyperactivation of T cells and T cell-dependent cytokine release causing immunopathology and poor prognosis [68].

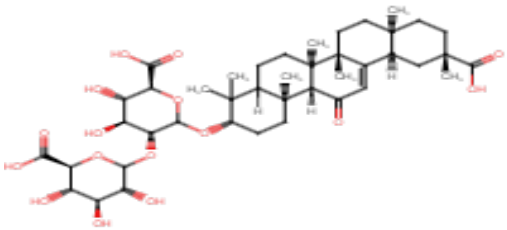


Fig. 20: Glycyrrhizinic acid

xix) *Piper nigrum* L. (Black pepper)

The isolated extract from *Piper nigrum* belongs to the family Fabaceae. Piperine, an alkaloid present in black pepper, inhibits the packaging of RNA in the nucleocapsid and inhibits viral proliferation. The consumption of black pepper may also help to combat SARS-CoV-2 directly through possible antiviral effects besides its immunomodulatory functions [69]. Itexhibits anti-inflammatory effects in RAW 264.7 cells and inhibits IL-1β, IL-6, and TNF-α. It has shown enhancing in the activation of Nrf2/HO-1 signaling, which has anti-allergic and anti-asthmatic activities [70]. The ADME studies further support the anti-SARS-CoV-2 potential of the dimeric piper amides from Piper species, primarily against the main protease (Mpro) of SARS-CoV-2, but also considerably against SARS-CoV-2 RdRp and the human ACE2. Pipercyclobutanamide B it inhibits SARS-CoV-2 forms a complex with Mpro which is a main enzyme of coronaviruses and has an important role in mediating viral replication and transcription, making it an main drug target for SARS-CoV-2 [71].

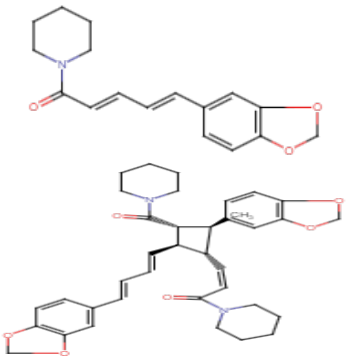


Fig. 21a: Piperine 21b: Pipercyclobutanamide

Antiviral therapy proved by *in silico* modelling

Fenugreek

Trigoneoside, derived from *Trigonella foenum-graecum* (Fenugreek), demonstrated the highest binding affinity and most stable interaction with the amino acid residues found in the active sites of COVID-19 proteins. It contains a variety of phytochemicals ranging from vitamins and essential volatile oils like Trigonelline, to flavonoids like kaempferol and luteolin. Trigoneoside IB shows a high affinity for selected COVID-19 proteins, whereas remdesivir and deoxynojirimycin have a high affinity for 1SSK and 6ACD proteins, and octanoic acid has the lowest affinity for selected SARS-CoV-2 proteins [72]. Further research suggests that these compounds could be used to treat SARS-CoV-2 by acting on proteases. *In silico* studies have shown that trigoneoside has a potential binding affinity of-7.6 and-8.5 kcal/mol for SARS-CoV nucleocapsid protein and SARS-CoV spike glycoprotein respectively [73].

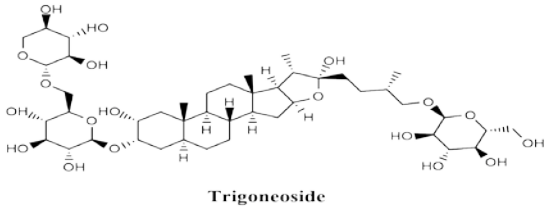
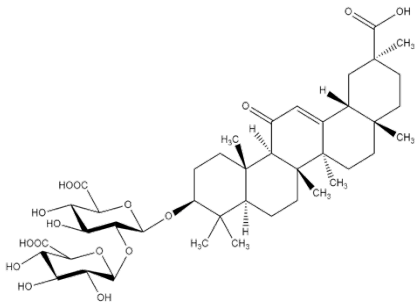


Fig. 22: Trigoneoside



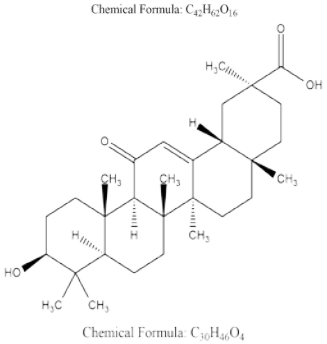


Fig. 23: a. Glyccyrhizin, b. Glycyrrhetinic acid

Liquorice

Liquorice extract and glycyrrhizin have shown an effect against coronavirus by binding with ACE2 and inhibiting its absorption and penetration. Glycyrrhizin fights CoV-19 by directly inhibiting the expression of type 2 transmembrane serine protease (TMPRSS2) which is important for entry of virus and mineralocorticoid receptor (MR) activation [74]. Glycyrrhizic acid has broad spectrum anti-corona virus by disrupting the interaction of the receptor binding domain of SARS-COV 2 and ACE2 [75]. According to *in silico* docking studies, glycyrrhizin and glycyrrhetinic acid may directly interact with viral internalization and replication enzymes such as spike protein, angiotensin-converting enzyme 2 (ACE2), the host transmembrane serine protease 2, and 3-chymotrypsin-like cysteine protease. *In silico* docking studies suggested a direct interaction of the virus for internalization and replication with ACE2, but not spike protein and its RBD, and 3CLPro. The auto docking studies have identified that the S protein having several glycyrrhizic acid binding pockets show close to open interaction with the ACE 2. Thereby having anti-viral activity against the virus-cell [76].

Glycyrrhizin suppresses coughing properties which is the main symptom of COVID-19 infection [77]. The main active component present in liquorice is glycyrrhizin. It has high antiviral activity, it blocks SARS cov-2 and inhibits viral replication by inhibiting main protease Mpro. In recent years, it has shown that liquorice extract may be a strong main protease inhibitor of SARS-CoV2 and glycyrrhizin has higher binding affinity than other liquorice constituents [78]. In the future, a search for compounds of therapeutic interest against SARS will be given by confirming the growth of SARS CV in human cells [79].

CONCLUSION

Herbal therapy with its unique advantages and lower side effects and toxicity issues proves to be an effective therapy for COVID-19 patients. With the vast availability of herbs and its unique phytoconstituents, they play an important role as therapeutic system for infectious and toxic conditions like Covid 19. Herbal agents like *Ocimum sanctum, Curcuma longa, Withaniasomnifera*, *Glycyrrhiza glabra, Andrographis paniculata, Zingiber officinale* etc. contain varied phytoconstituents which act by different mechanisms thus demonstration therapeutic efficacy in COVID-19. Further detailed research in herbs and herbal phytoconstituents could be intensely prospective for determining novel therapeutic actives against SARS-COV-2.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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