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Prevention of Viral Effect and Enhancement of Immune System with the help of Herbal Plants and Himalayan Crude Drugs in SAR-COV-2 Patient: A Review

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Abstract

After December 2019, Severe Acute Respiratory Syndrome (SAR-COV-2) become a life-threatening issue to the entire human society when it started to spread exponentially all over the world from Wuhan city of China. The virus directly hits the upper and lower respiratory tract of human airways and causes severe damage to the human lung, leading to multiorgan failure, hypoxemia, and dyspnea. Similarly, studies revealed that SAR-COV-2 severely hit the younger and aged population in which the immune system is seriously compromised. The cell of the immune system such as T-cells, B-cells, NK cells, etc. helps to fight against such viral antigen and resist critical viral damage. Therefore, enhancement of the immune system could also be an effective approach to prevent viral infection and even aid in the reduction of the death count. Nowadays, dietary, and herbal remedies are being integrated into the mainstream of the healthcare systems because of their multi-ingredient character, and some of them are known to render efficacy comparable to that of synthetic drug substances. Several studies have also revealed the immune enhancement, the immunomodulatory and antiviral activity of these herbal products in SAR-COV-2 patients. This study was carried out by using Google Scholar, Web of Science, PubMed, Science direct to search the literature related to the use of the herbal product and their actively isolated compound to fight against SAR-COV-2. The study has highlighted the role of several active phytoconstituents present in Himalayan crude drugs that helps to reduce the viral titer in the respiratory system as well as aid in immune enhancement.

Key Words: Severe Acute Respiratory Syndrome (SAR-COV-2), Immune enhancement, Human respiratory system, Herbal medicine, and Himalayan crude Drugs, Phytoconstituents

1. Introduction

After the first diagnosis of coronavirus patient in Wuhan China in December 2019, Severe Respiratory Syndrome Coronavirus 2 (SAR-COV-2) has spread exponentially all over the world and became a life-threatening issue to entire human society. Though the disease was expected to spread from the bat at the beginning, the intermediate host for the disease is still unclear. WHO declared the disease a pandemic on 11th March 2020. The clinical sign and symptoms of the patient suffering from SAR-COV-2 range from asymptomatic cases to severe acute respiratory distress syndrome, multi-organ failure (MOF), hypoxemia, dyspnea, severe pneumonia, etc. (Infusino et al., 2020). SAR-COV-2 is a single-stranded positive-sense RNA virus that shares a genomic sequence similarity of 96% with bat coronavirus and 79.6% sequence identity to SAR-COV. Upon entry into the human cells through Angiotensin Converting Enzyme (ACE2), and less likely by TMPRSS2, SAR-COV-2 takeover the protein synthesis pathway of human cells, start synthesizing viral protein, and assemble the protein for subsequent viral replication (Chen et al.). This virus directly hits the upper and lower respiratory tract of human airways and causes severe damage to the human lung. Damage to the alveolar cell causes inefficient exchange of oxygen and carbon dioxide between blood and lungs leading towards the shortage of oxygen in human blood. This is the main reason behind hypoxemia, dyspnea, MOF as well as death in SAR-COV-2 patients (Chilvers et al., 2001).

Currently, many nations are showing their best effort for the implementation of appropriate preventive and control measures. Neither vaccines nor direct anti-viral drugs are well established still now for the treatment of SAR-COV-2 in humans and animals (Wang et al., 2020). Though few attempts have been made by different American Pharmaceutical and biotechnological companies like Pfizer (Pfizer vaccine), Oxford University (AstraZeneca), their efficacy cannot last for long, shows multiple side effects, and patient even after vaccination also caught by coronavirus disease (Hunter et al., 2021, (Chagla et al., 2021). Similarly, in the late 2020s, after the recognition of mutant type SAR-COV-2 virus in the UK, the development of pharmaceutical remedies for treating COVID19 is becoming more challenging (Wise et al., 2020). Therefore, until the discovery of effective drugs and vaccines against coronavirus, complementary and alternative therapeutic approach with the use of herbal product, Himalayan crude drug, dietary remedies etc. should be encouraged for the prevention and control of disease. Traditional herbal remedies help to enhance the person's immunity, keep in check the symptoms of COVID19, and sometimes even showed curative effects as well. Government of Pakistan have urged their citizen to use garlic, turmeric, ginger, cinnamon, black pepper, and honey as home remedies. On the other hand, Bangladesh news suggested the public consume warm water with ginger and clove extracts, black cumin seeds, honey and fruit with vitamin C, etc. (Azam et al., 2020). Various primary and secondary metabolic products from plants are well known for different pharmacological actions. Phenol, flavonoid, saponin, terpenoids, glycosides, tannins, polysaccharides, alkaloids, etc. are some secondary metabolites that can be used effectively in the prevention and cure of various bodily ailment. Based on these, the pandemic world due to COVID-19 is even encouraged towards the use of herbal and dietary products. This review provides a brief overview of the use of the traditional herbal product and Himalayan crude drugs to fight against SAR-COV-2. The review is more focused on highlighting the mechanism of action of some isolated active chemical constituents against SAR-COV-2 from Himalayan crude drugs.

2. Methods

Data related to medicinal plants, their active constituents, mechanism of action were obtained using different search engines including Web of Science, PubMed, Google Scholar, and Science direct. The reference article includes only those that were published in English-language journals and meet required quality standards concerning the information. During the study, only those medicinal plants which are being commonly used as local and traditional medicine for the treatment of various ailments were selected. Different keywords which were used for data search include, 'herbal and dietary remedies', 'COVID-19', 'immunomodulatory action', 'anti-viral activity, and 'active phytoconstituents'. The data were organized and analyzed using Microsoft Excel (2010) software and then summarized into tables and figures.

Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-COV-2): *Structure and Genomic*: Coronaviruses have four genera: alpha(α), beta(β), gamma (γ), and delta (δ) of which SAR-COV-2 belong to the β-coronavirus family. This novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-COV-2) is the cause of Coronavirus disease 2019 (COVID-2019) and declared as a pandemic by World Health Organization (WHO) on March 11, 2020 (Astuti et al., 2020). SAR-COV-2 are enveloped, single-stranded RNA viruses whose surface is covered by protein spikes. The genome sequence identity of SAR-COV-2 is 79% identical with SAR-COV, 50% identical with MERS-COV, and genome organization is shared with other beta coronaviruses as well (Lu et al., 2020). Open reading frames (ORFs) having positive viral RNA genome organization in SAR-COV-2 code for structural and non-structural proteins. The structural protein is a spike (S), nucleocapsid (N), membrane (M), and envelop (E) proteins. The S1 subunit of S protein facilitates the attachment of the SAR-COV-2 virus with the host cell through Angiotensin Converting Enzyme (ACE2) receptor. The amino acid sequence of the S1 subunit involved in the viral attachment is glutamine, asparagine, leucine, phenylalanine, and serine. The S2 subunit promotes membrane fusion (Satarker et al., 2020). On the other hand, the viral genome of SAR-COV-2 is encapsulated by the N protein. The main role of N protein in SAR-COV-2 is to enhance the efficiency of viral RNA transcription and is even essential for viral replication. The nucleocapsid protein of human coronavirus is produced at a high level in the infected cell and is critically important for virion assembly (Savastano et al., 2020). Followingly, the M glycoprotein is the most abundant structural protein of SAR-COV-2. M protein binds to all other structural proteins and this binding helps in the stabilization of N proteins and promotes completion of viral assembly by stabilizing the N-protein RNA complex, inside the internal virion. Even the host cell entry of virus with the aid of S protein is mediated by the M protein (Bianchi et al., 2020 & Thomas et al., 2020).

Meanwhile, upon the viral entry into the host cell, the virus translates its replicase gene (ORF1) which is further divided into ORF1a and ORF1ab. At the end of ORF1a, a ribosome frame-shifting sequence consisting of two large polyprotein precursors of different lengths, pp1a and pp1ab are present. Polyprotein pp1a consists of non-structural proteins (Nsp) 1 -11, and polyprotein pp1ab comprises the complete translated coding region Nsp 1-16 (Ziebuhr et al., 2000 & Lee et al., 1991).

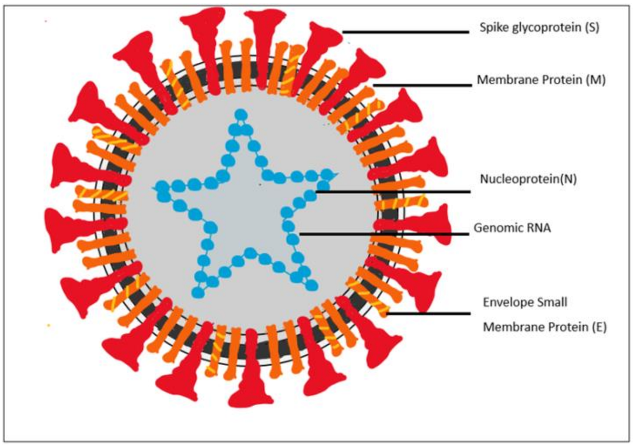

Figure 1. Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-COV-2). (Astuti et al., 2020)
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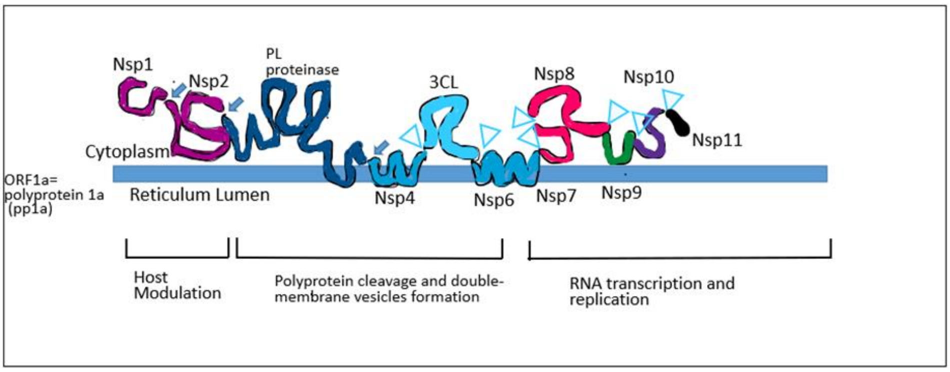


Figure 2: SAR-COV-2 polyproteins ORF1a. (Roe et al., 2021)

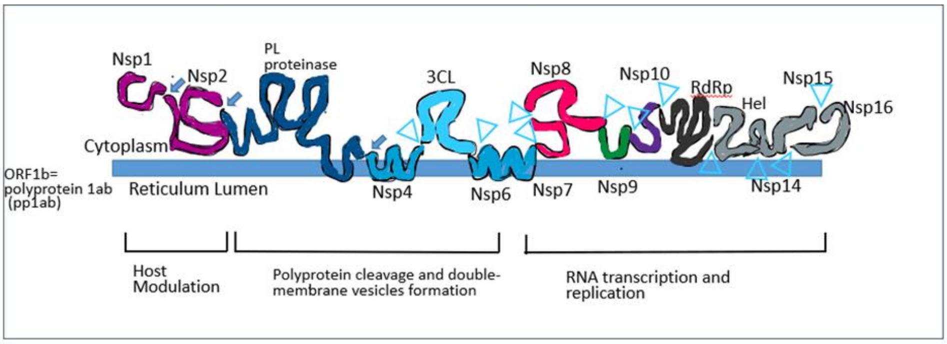


Figure 3: SAR-COV-2 polyproteins ORF1b (Roe et al., 2021)

The complete set of 16 Nsp of pp1ab is mainly divided into three categories. Nsp1 and Nsp2 are categorized for Host modulatory function. Nsp3 to Nsp6 are categorized for their polyprotein cleavage and double-membrane vesicle formation role. Lastly, Nsp7 to Nsp16 are categorized for their RNA transcription and replication function. papain-like proteinase (Nsp3), 3C-like proteinase (Nsp5), and helicase(Nsp13) play a major role in viral transcription and replication as these proteins help in the cleavage of the viral polyprotein (Roe et al., 2021).

Figure 2 shows that the Open reading Frame (ORF1a) in SAR-COV-2 is proteolytically cleaved into 11 putative non-structural proteins (Nsps). Nsp1 and Nsp2 are Hosts modulating genomic components, while Nsp3 to Nsp6 are polyprotein cleavage and double-membrane vesicles forming components. Similarly, Nsp7 to Nsp11 are RNA transcription and replication components. And Figure 3 shows that the Open reading Frame (ORF1b) in SAR-COV-2 is proteolytically cleaved into 16 putative non-structural proteins (Nsps). Nsp1 and Nsp2 are Hosts modulating genomic components, while Nsp3 to Nsp6 are polyprotein cleavage and double-membrane vesicles forming components. Similarly, Nsp7 to Nsp16 are RNA transcription and replication components.

Animal host and spillover: In December 2019, SAR-COV-2 was firstly recognized in Wuhan city, China. Those patients were found to be exposed to live animals such as poultry, bats, snakes, frogs, rabbits, marmots, hedgehogs, etc. during their work in the Huanan seafood wholesale market suggesting these as possible zoonotic spillover (Malik et al., 2020, Tiwari et al., 2020). SAR-COV-2 firstly reported to be originated from bats but still different animal species such as snake, pangolin, and turtle were suggested as potential intermediate hosts, however, the pangolin is even highly suggested among them. The exponential mutation rates of RNA viruses ease them to get adapted to a wide range of hosts. Though a bat is taken as the natural host of the SAR-COV-2 virus, the intermediate host is still unclear, and to interrupt the transmission chain, it is of utmost importance to identify the potential intermediate host. Few studies demonstrate Pangolin as an intermediate host while recently SAR-COV-2 infection is reported in cats, dogs, minks, tigers lions, mice, non-human primates, and tree shrews (Zhao et al., 2020 & Oreshkova et al., 2020).

Receptor and Pathogenesis: Among four structural proteins in the SAR-COV-2 structure, the attachment and entry inside the host cell are mediated by Spike protein (S). The cellular furin-like proteases such as transmembrane protease serine 2 (TMPRESS 2), furin, and cathepsins cleave the S protein into two distinct polypeptides S1 and S2 which is also known as S protein priming (Hoffmann et al., 2020). S1 is known to attach to the cellular receptor ACE2 and S2 leads to the fusion of viral and cellular membrane (Robson et al., 2020). Upon receptor binding, spike protein triggers the fusion of viral and cellular membranes through proteolytic cleavage (Glowacka et al., 2011). Polyprotein pp1a and polyprotein pp1ab are proteolytically processed by virus-encoded proteases which aid in the achievement of mature and functionally active replication machinery of the virus (Ziebuhr, Snijder, et al., 2000). Followingly, the modulation of host cell factors and preparation of cells for viral RNA synthesis could be achieved through the proteolytically processed polyprotein. Meanwhile, C-terminal translation products of pp1ab largely catalyze and or regulate the processes of RNA replication and transcription which is mediated by the virus RNA-dependent RNA polymerases, RdRp (Nsp12) (Fehr et al., 2015, (De Wilde et al., 2017). On the other hand, Nsp3, 4, and 6 mediate the configuration of replication complexes which help in the formation of membrane structures such as double-membrane vesicles and convoluted membrane vesicles. The active replication complex even promotes the continuous and discontinuous synthesis of negative-sense

RNA templates which subsequently ease the formation of genomic copies and a nested set of subgenomic RNA (Sawicki et al., 2007). Replication of genomic and subgenomic RNA on double-membraned vesicles leads to the formation of structural protein of SAR-COV-2 such as S protein, E protein, M protein is glycosylated before localizing to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) and are assembled into virions (Vennema et al., 1990, Krijnse-Locker et al., 1994 & Haan et al., 2005). The N protein which encapsidates the newly made RNA will be localized within the cytoplasm. As the completion of RNA synthesis, genomic RNA and N protein move to the ERGIC and assimilate into budding virions (Siu et al., 2008). Followingly, S protein which is expressed on the cell surface triggers cell-cell fusion between infected and nearby uninfected cells. Consequently, massive, multinucleated cell complexes called syncytia are often formed which facilitate the spread of the virus. This is how the pathogenesis of SAR-COV-2 is often expressed (Gallagher et al., 1992).

Effect of SAR-COV-2 in human Respiratory system: The respiratory system which consists of a network of organs easing in breathing includes mainly airways, lungs, and blood vessels. These parts work in coordination actually to move oxygen throughout the body and clean out waste gases like carbon dioxide (Sharma et al., 2006). On the other hand, the respiratory system is classified roughly as the upper and lower respiratory tract. The upper respiratory tract includes the nose, pharynx, and larynx while the lower respiratory tract includes the trachea, bronchial tree, and lungs. Both tracts are open to the outside and are lined with mucous membranes (Krause et al., 2017). SAR-COV-2, Severe acute respiratory syndrome by its name directly hit the respiratory system of the human body. The effect of SAR-COV-2 on the human respiratory system is well known and highly concerned fact in this pandemic era. The major target of this virus is in the epithelial cell of the respiratory system which finally leads to acute respiratory distress syndrome (ARDS). In most cases, the disease occurs as fever and without any respiratory symptoms at the beginning. However, as the disease progress, various degree of pulmonary abnormalities later appear in all patients due to severe damage in the lung tissue and alveoli (Gu et al., 2007). In the respiratory tract, epithelial stem cells are divided into epithelial cells in the distal airway and pulmonary alveolar epithelial cells. Two types of differentiated epithelial cells made the pulmonary alveolar epithelial cells: alveolar type 1 (AT1) cells, which mediate gas exchange, and alveolar type 2 (AT2) cells which secret surfactant. On the other hand, basal cells in the proximal airways give rise to multiple cell types such as secretory club cells and ciliated cells (Zacharias et al., 2018 & Nabhan et al., 2018). Other different cells present in the airway are bronchioalveolar stem cells, club cell-like stem cells, and p63+ basal cells, etc. Infection in this alveolar and distal epithelial cell leads to a defect in lung regeneration capacity and the hit in a ciliated and secretory epithelial cell leads to the death in the lungs cell due to the scarcity of mucus (Basil et al., 2020, (Wang et al., 2020). Though studies demonstrate that ACE2 and TMPRSS2 are present in nasal and bronchial epithelium cells by immunohistochemistry, gene expression of ACE2 and TMPRSS2 have been reported to occur largely in alveolar epithelial type II cells. Therefore, the lungs are the central part of SAR-COV-2 pathogenesis as compare to the upper respiratory tract (Wu et al., 2020 & Lin et al., 2020).

Role of Human Immune System to Fight against SAR-COV-2: The immune system of our body is developed in such a way that it protects us against diseases, harmful substances, germs, and cell changes. The key player white blood cells travel throughout the body through the blood vessel. The cell of the immune system can be classified as lymphocytes (which contain T-cells, B-cells, and NK cells), neutrophils, and monocytes/macrophages (Notarangelo et al., 2004). For examining invading microbes, the interchange of cells and fluids between blood and lymphatic vessels persist in which the lymphatic system as well in the immune response plays a significant role. Specialized compartments present in the lymph nodes encounter antigens and when such antigens are present in the bloodstream, they are transported to tissues throughout the body. But the immune cells gather and serve to dispose of such antigen and contribute to the prevention of the body from various diseases and ailments (Chowdhury et al., 2020). The three major types of immunity are innate immunity with rapid response, adaptive immunity with slow response, and passive immunity.

As the SAR-COV-2 virus gain access inside the target cell, the whole virus or its surface epitopes is recognized which causes innate or adaptive immunity to respond. Toll-like receptors 3, 7, and 8 firstly recognize the virus inducing the higher production of Interferon (INF) (Le Bon et al., 2002 & Thiel et al., 2008). With the invasion of the host cell by SAR-COV-2, the early response against the N protein is shown by the B cell, while antibodies against S protein could be detected after 4-8 days from the appearance of initial symptoms. The study demonstrated that SAR-COV-2 specific IgA, IgG, and IgM antibodies were detected after the onset of symptoms at different time points in infected patients. IgG level was revealed to persist for a longer period while IgM level is assumed to decline after 3 months (Li et al., 2008). On the other hand, Memory T cells are also a part of the immune system which are generated and designed to fight against re-infection. $CD4^+$ memory T cells ease in restimulation of B cells and other immune cells by cytokine production while $CD8^+$ cytotoxic memory T cells destroy the infected cell during subsequent infection (Stockinger et al., 2006). Meanwhile, $CD4^+$ helper T cells (Th) have two subtypes: Type 1 helper T cells (Th1) and Type 2 helper T cells (Th2). The pro-inflammatory cytokines may stimulate the Th1 cell response while specific generations of related cytokines like IL-4 and IL-10 divert the response towards the Th2 response (Velazquez-Salinas et al., 2019). Other parts of immunity system which are involved to fight against SAR-COV-2 are dendritic cell, phagocytes, NK cells, macrophages, Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes, etc. (Chowdhury et al., 2020). Therefore, above all, it is necessary to boost our immune system and strengthen it to make it able to fight against SAR-COV-2 by preventing its entry into the host cell or minimizing invasion or destruction of host cell after its entry inside the cell.

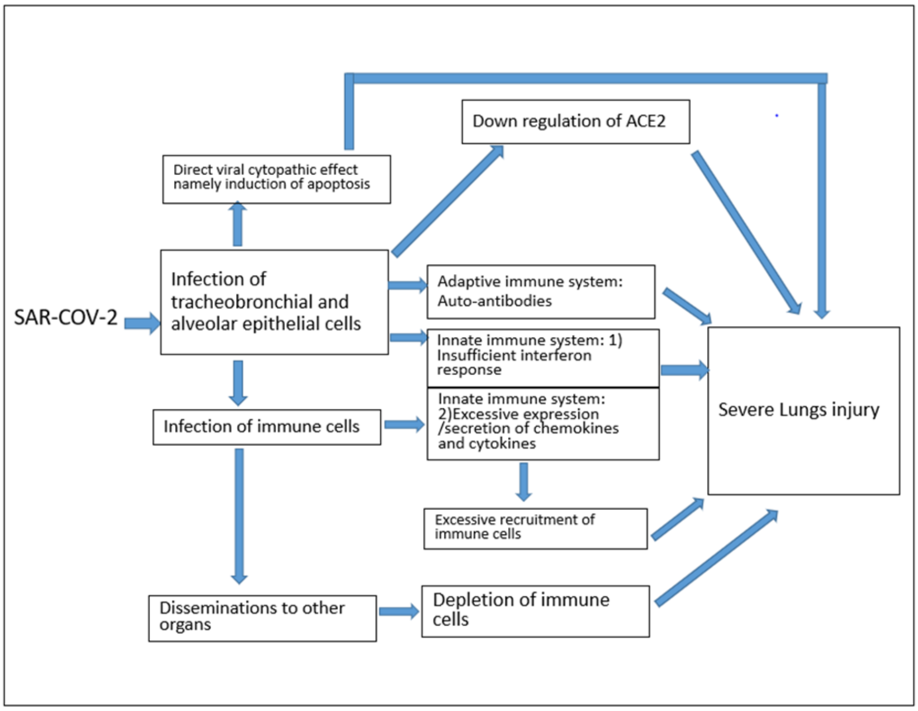


Figure 4: Flow chart showing the effect of SAR-COV-2 in the human respiratory system and human immune system. (Gu et al., 2007, Chowdhury et al., 2020).

Dietary and Herbal medicine: Recently dietary and herbal medicine is gaining widespread popularity all over the world and moving to get integrated into the mainstream of the healthcare systems (Bent et al., 2008). The major reason for the increasing interest in herbal therapy is low cost, wide acceptance of public for being included in natural product which claims itself as low toxic, flexibility in its accessibility, preparation, and use (Builders et al., 2019). Medicine from herbal products usually contains a variety of pharmacologically active compounds and this multi-component character of herbal medicines can render efficacy sometimes comparable to that of synthetic drug substances (Mosihuzzaman et al., 2012). Plants and herbs produce various chemicals for their metabolic activities and to protect themselves from various diseases and predators. Primary metabolites produced by them are carbohydrates, fats, amino acids, vitamins, hormones, etc. are utilized by plants for growth, development, stress adaptation, defense. On the other hand, herbal and medicinal plants even produce many secondary metabolites which can be utilized for therapeutic efficacy to treat various sort of ailments. The major class of secondary metabolites which could be utilized to treat disease and ailments are alkaloids, phenolics, flavonoids, terpenoids, and glycosides (Izhaki et al., 2002). Use of herbal medicine is taken for a wide range of marked advantages, such as energy and memory improvement, treatment of a specific condition such as glucose-lowering effect, antibacterial, anticancer, anticonvulsant, anti-inflammatory, antifungal, antiviral, and for various other diseases and ailments (Tyagi et al., 2003). Recently, SAR-COV-2 hit the global world destructively but medicine and vaccine for the treatment of viruses are not well defined and still in the phase of development. In this pandemic world, dietary and herbal remedies are nowadays being taken as appropriate options to boost the immune system as well as to fight against the effect of SAR-COV-2 in the human respiratory system (Panyod et al., 2020).

Dietary and Herbal Remedy for Immune Modulatory activity against SAR-COV-2: Several studies demonstrated the efficacy of herbal medicine as immunomodulatory and antiviral activities for influenza virus as well as SAR-COV-2. Food and herbs aid as a dietary or complementary therapy to stave off septicemia and reinforce immunity such as antiviral agents for masks, as disinfectants to curb aerosol transmission, or as sanitizing agents to disinfect surfaces (Panyod, Ho et al., 2020). Studies demonstrated that various natural compounds can be utilized to suppress viral-mediated cytokine production, tissue destruction as well as production of excessive inflammatory infiltrates. Of them, phenolics, polysaccharides, quinones, alkaloids, and terpenoids are shown as promising immunomodulatory phytochemicals (Wang et al., 2008 & Albulescu et al., 2020).

Phenolics: A study by Traboulsi et al. 2015, demonstrated that liquiritigenin (ILG), a phenolic compound retards the pronouncement of inflammatory cytokines which was induced after the infection of a cell with influenza virus. The study even demonstrates that the anti-inflammatory activity of ILG is dependent more on the stimulation of the peroxisome proliferator-activated receptor-gamma pathway (Traboulsi et al., 2015). In another study by Zu et al., 2012, it was demonstrated that theaflavins fractions derived from black tea has been found to exhibit a potent inhibitory effect against the influenza virus in vitro. The study revealed that among the various mechanisms for the inhibition against influenza virus, decrement in the expression level of the inflammatory cytokine Intraluekin-6 by theaflavin fraction is a potent cause (Zu et al., 2012). Similarly, quercetin, kaempferol, and some other derivatives obtain from bee pollen aid to fight against COVID-19 as an immune enhancer (Rzepecka-Stojko et al., 2015).

Polysaccharides: Several natural foods are being explored to obtain polysaccharides which help in immune-boosting and immune modulation as well as in reducing the damage caused by SAR-COV-2. The use of food rich in polysaccharides is a possible option to upsurge immunity and reduce the risk accompanied by SAR-COV-2 contamination. Still, the use of polysaccharides as a therapeutic strategy is not yet well established but application as dietary and food supplements is a rational possibility (Wang et al., 2020). peng et al. 2019, performed a study about the immunostimulatory activity of water-soluble polysaccharides which are derived from *Citrus medica L.var. sarcodactyis* and the study demonstrated that the active polysaccharide component isolated from the plant extract showed immune-enhancing ability (Peng et al., 2019). The immune system of our body is known to be stimulated through a bond between functional groups and molecular groups on the cell surface. The initiation of the signaling pathway is from the moment polysaccharides bind to the membrane receptors in the defense cells. This causes the cycle of biochemical reaction to getting activated regulating gene expression in the ribosomes initiating protein production (Barbosa et al., 2020). Similarly, polysaccharides even modulate the activity of gene expression. Some polysaccharides aid in the assembly and expression of messenger RNA during nitric oxide production and pro-inflammatory cytokines (Barbosa et al., 2020). In a study conducted by Shen et al. 2017, wheat obtained polysaccharides show that they can promote cytokine expression through the MAP38 p38 signaling pathway which is negotiated by Toll-like receptor 4 (Shen et al., 2017). In another study by Li et al. 2020, a fungus Ganoderma lucidum was studied for immune-modulatory function and the structure-activity relationship was studied with two characterized fractions i.e., GLP-1 and GLP-2 of Ganoderma lucidum polysaccharides. Among two fractions GLP-1 was proved to be potent with better immune response and promotion of production of Immunoglobulin A (Li et al., 2020).

Alkaloids: Another group of secondary metabolites which shows antiviral potential against coronaviruses is the alkaloids. In a study by Dong et al. 2019, the antiviral property of Stephania tetrandra was studied and from the study, it was revealed that benzylisoquinoline alkaloids tetrandrine, fangchinoline, and cepharanthine are proved to be potent antiviral agents for the prevention and treatment of human coronavirus infection as well as showed beneficial immunomodulation (Dong et al., 2019). In another study by Abdulrahman et al. 2020, *Nigella sativa* L was studied to explore the potency of this plant for hitting SAR-COV-2 targets and from the insilico study, it was demonstrated that few compounds like nigelledine, hederagenin, thymohydroquinone, and thymoquinone had high to moderate affinity with SAR-COV-2 enzymes and proteins. Coupling of SAR-COV-2 to host cell receptors and duplication is dramatically inhibited by these compounds (Koshak et al., 2020).

Terpenoids: The Terpenoid group of compounds are also known as an immune booster and enhances protection from viral replication and lowers levels of lung viral titers. In a study conducted by Yoo et al. 2012, Ginsenosides, triterpenic saponins, and other active compounds with different pharmacological effects were studied. From the study, it was demonstrated that red ginseng extracts containing a terpenoid group of compounds significantly enhanced protection, lessen the level of viral load in the lungs (Yoo et al., 2012). Similarly in another study by Goswami et al. 2018, methanolic extract of *Boswellia serrata* was examined to explore the antiviral activity. From the study, B-boswellic acid (BA), a pentacyclic terpenoid potently inhibits wild-type and a clinically isolated type of Herpes Simplex Virus. From the study, the mechanism of inhibition is significant downregulation of NF-kB and p38 MAP kinase which are directly related to the immune response of the human system (Goswami et al., 2018). Few other studies have also displayed the modulation of the NF-Kb pathway of virus due to plant extract. Pterodontic acid, a type of sesquiterpene compound isolated from *Laggera periodontal* was also exemplified to have a broad-spectrum effect against different types of influenza viruses like a human (H1N1) and avian (H9N2) influenza virus. The major mechanism for such inhibition is the reduction of the inflammatory response by retarding activation of the NF-Kb pathway (Guan et al., 2017).

Dietary and herbal remedies for prevention and cure of SAR-COV-2 patients by acting in the viral enzymatic system: In the recent COVID-19 pandemic, still, the scientific world is struggling to find specific drugs and vaccines to overcome the threat to the global population. When such actual allopathic remedies are still under development, the promotion of the application of crude herbal remedies to fight against COVID-19 is of utmost importance. Meanwhile, many studies have even reported that foods and herbs could be used as complementary and dietary therapy to prevent infection, strengthen immunity and some of them still have strong antiviral properties as well (Panyod, Ho et al., 2020). Two viral proteases of SAR-COV-2, a chymotrypsin-like protease ($3CL^{pro}$) and papain-like protease (PL^{pro}) are attractive drug targets for the development of herbal remedies as an antiviral agent.

***Chymotrypsin-like protease ($3CL^{pro}$) and papain-like protease (PL^{pro}) Phenolics*:** In a study by Jo-young et al. 2016, polyphenols obtained from *Broussonetia papyrifera* were evaluated to determine the inhibitory activity against 3CLpro. Phenolic compounds like broussochalone B, broussochaloneA, 4-hydroxyisolonchocarpin, papyriflavonol A, kazinol J, etc. were isolated for the study. The study revealed that all extract is potent against 3CLpro and PLpro, though activity against PLpro was found more potent. Among the isolated compounds, 3' -(3-methyl but-2-enyl)-3',4,7-trihydroxyflavane was found to be more potent with an IC50 value of 3.7 µM (Park et al., 2017). In another study (Jo et al., 2020)., three flavonoids were studied for their inhibitory activity against 3CLpro by using the tryptophan-based fluorescence method, and from the study, it was determined that three flavonoids Herbacetin, rhoifolin, and pectolinarin are effective to block the enzymatic activity of SAR-COV-2 3CLpro Meanwhile, Ananta et al. 2020, have performed a study to determine phytochemicals as potent inhibitors against 3CLpro and PLpro. The study determined that out of 32 phytochemicals used in the study, amentoflavone and gallocatechin gallate exhibit the best binding affinity to 3CLpro and PLpro (Swargiary et al., 2020). The study performed by Nguyen et al. 2012, demonstrated that quercetin, epigallocatechin gallate, and gallocatechin gallate resemble good inhibition towards 3CLpro with IC50 values of 73, 73, and 47 µM respectively (Nguyen et al., 2012).

***Terpenes*:** Gideon et al. 2020, performed a study to determine potential terpenoids and alkaloids from the African medicinal plants which inhibit 3CLpro. The study revealed that it 6-oxoisoiguesterin and 22-hydroxyhopan-3-one group of terpenoid binds to the receptor tie-up locus and the catalytic duo of SAR-COV-2 $3CL^{pro}$ inhibiting the enzyme activity (Gideon et al., 2020). Meanwhile, in another study by Ji-Young et al. 2012, the experiment was performed to determine the inhibitory activity of Tanshinones, a diterpenoid compound derived from Salvia miltiorrhiza, and the study, determined tanshinones as good inhibitors of both 3CLpro and PLpro. Additionally, the inhibitory activity was found selective since the compound showed no inhibitory activity against other proteases (Park et al., 2012). Following, Wen et al. 2007, experimented to investigate the SAR-COV-2 inhibitory activity of specific plant terpenoids and liquids. The experiment revealed that betulinic acid and savinin, abietane-type diterpenoids are competitive inhibitors of SAR-COV-2 3CL with K_i values of 8.2 mM and 9.1 mM (Wen et al., 2007).

Hydroxanthracene derivatives: Luo et al. 2009, experimented with the extract of *Rheum palmatum* L. to determine the 3CLpro inhibitory activity of the plant sample and from the study, it was revealed that emodin, an anthracene derivative have 3CLpro inhibitory activity along with activity against S protein and ACE2 receptor protein (Luo et al., 2009).

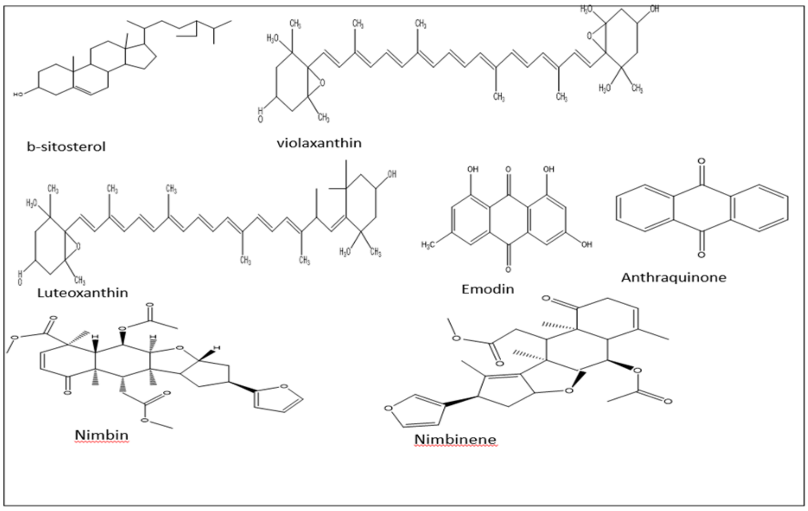
Table 1: List of Himalayan Crude drugs with their possible mechanism of action against SAR-COV-2

Herbs	Parts used	Active phytoconstituent	Mode of action	References
Lentinula edodes	Mycelium	α-glucan and β-glucan	α-glucan and β-glucan derived from this mushroom help inactivation of natural killer (NK) and T cells	(Dietologica et al., 2020)
Asparagus racemosus	Root	asparoside-C, asparoside-D and asparoside-F	An in-silico study showed that active constituents asparoside-C, asparoside-D, and asparoside-F showed potent inhibition against spike receptor-binding domain and NSP15 Endoribonuclease	(Chikhale et al., 2020)
Acorus calamus	Usually root		Help in the treatment of atopic dermatitis unusually seen in SAR-COV-2 patients	(Das et al., 2020)
***Aloe vera* L.**	Leaves	Aloin, aloe-emodin, acemannan	Aloin, aloe-emodin, acemannan interact with the viral enzyme and help in the breakdown of viral envelop protein	(Mpiana et al., 2020)
Azadirachta indica	Leaves and bark	Nimbin, nimbinene, nimbolide, nimbolinin, nimbandiol	Nimbin, nimbinene, Nimbolide, Nimbolinin, Nimbandiol from Azadirachta indica inhibits SAR-COV-2 main protease	(Umar et al., 2021)
Bauhinia variegata	Roots, bark, buds	Flavonoids, beta-sitosterol, lupeol	Flavonoids, beta-sitosterol, lupeol can be used as an immunomodulator and immune stimulant	(Mahalwar et al., 2021)
Camellia sinensis	Leaves	3-Isotheaflavin-3 gallate	3-Isotheaflavin-3 gallate inhibits Chymotrypin-like 3CLpro, viral protein	(Boozari et al., 2020)
Canavalia ensiformis	Seed		Binds to the glycosylated membrane proteins and prevent target cell recognition and viral entry	(Greig et al., 1977)
Cannabis sativa	Leaves, seed, bark		Use in the modulation of expression of host ACE2 receptor protein and downregulate serine protease TMPRSS2	(Wang et al., 2020)
Cassia fistula	Fruit	Procyanidin B2	Procyanidin B2 isolated from this plant extract is identified as a protease inhibitor of SAR-COV-2	(Ravi et al., 2020)
Cordyceps Sinensis	Whole animal and fungal part		Alcoholic extract enhance immunity and shows immunomodulatory effect by inducing IFN-c and regulating T lymphocyte.	(Le et al., 2020)
Ganoderma lucidum	Mycelium		Enhance the immune system by upsurging the level of virus-specific antibodies and their neutralizing activities	(Panyod et al., 2020)
Houttunia cordata	Whole Plant		Increase the proportion of CD4+ and CD8+ T-cells. Increase the secretion of IL-2 and IL-10. Inhibitory effect in RNA-dependent RNA polymerase (RdRp) and SAR-COV 3C-like protease(3CLpro)	(Lau et al., 2008)
Justicia adhatoda	Leaves, flower buds	Vasicolinone and anisotine	Vasicolinone and anisotine from this plant helps in the inhibition of SAR-COV-2 by binding in the RNA dependent RNA polymerase	(Gowrishankar et al., 2021)
Momordica charantia	Fruit		Helps to minimize binding of spike protein to ACE2 receptor as well as improve immunity	(Desai et al., 2020)

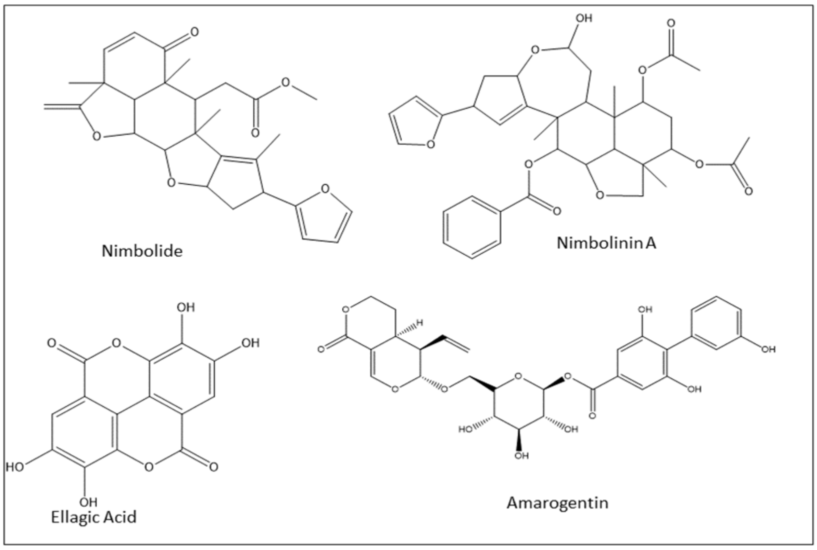
Table 2. List of Himalayan Crude drugs with their possible mechanism of action against SAR-COV-2

Herbs	Parts used	Active phytoconstituent	Mode of action	References
Ocimum sanctum	Leaves, small branches	Apigenin and Ursolic acid	Apigenin and Ursolic acid from this plant are known to improve respiratory parameter, enhance the level of Helper T cell and Natural Killer (NK) cells	(Srivastava et al., 2020)
Oroxylum indicum	Root, bark, and fruit	Oroxindin and scutellarein	Oroxindin and scutellarein help in SAR-COV-2 viral inhibition by acting in the Main protease (Mpro)	(Shah et al., 2021)
Phyllanthus Emblica	fruit	Ellagic acid	Ellagic acid stimulates the immune function and some other constituents are known for their inhibition of Spike receptor binding domain	(Arokiyaraj et al., 2020)
Picrorhiza scrophuulariiflora	Rhizome	Scrocaffeside A	Scrocaffeside A obtained from this plant significantly enhance the activity of peritoneal macrophages and natural killer cell boosting innate immunity	(Dongre et al.)
***Polygonum multiflorum* Thunb**	Root tubers and vines	Emodin and anthraquinone	Emodin and anthraquinone compounds derived from these plants significantly block the S protein and ACE2 interaction	(Ho et al., 2007)
Rauvolfia serpentina	Roots	Reserpine	Reserpine from Rauvolfia serpentina help in the inhibition of $3CL^{pro}$	(Krishna et al., 2020)
***Rheum officinale* Baill**	Root tubers	Emodin and anthraquinone	Emodin and anthraquinone compounds derived from these plants significantly block the S protein and ACE2 interaction	(Ho, Wu et al., 2007)
Rheum palmatum	Root, stem		Beneficially neutralize the binding of spike protein to the host ACE2 receptor. Subside the release of inflammatory mediators reducing lung injury.	(Hu et al., 2021)
Shilajit	Rock	Fulvic acid, humic acid, hippuric acid, and benzopyrones	Fulvic acid, humic acid, hippuric acid, and benzopyrones have immune-boosting as well as antiviral activity	(Saharan et al., 2021)
Swertia chirayata	Whole plant	Amarogentin	Amarogentin from this plant binds with the SAR-COV-2 spike glycoprotein and ACE2	(Maurya et al., 2020)
Terminalia chebula* and *Terminalia bellerica	Fruit		Highly use in strengthening immunity and improving cough in combination with *Phyllanthus emlica* as *Triphala churna*.	(Shankar et al., 2021)
Tinospora cordifolia	stem		Inhibition of SAR-COV-2 main protease as well as play role in immune enhancement	(Shree et al., 2020), (Kumar et al., 2020)
Urtica *dioica*	Rhizome, root, and leaves	B-sitosterol, luteoxanthin, and violaxanthin	B-sitosterol, luteoxanthin, and violaxanthin act as antiviral agent by binding to ACE2 receptor inhibitor	(Upreti et al., 2021)

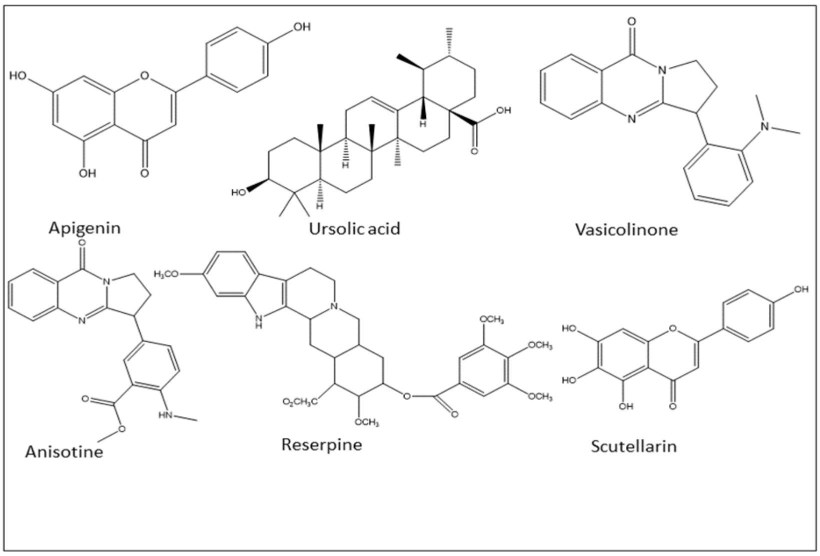
a.


b-sitosterol
violaxanthin
Luteoxanthin
Emodin
Anthraquinone
Nimbin
Nimbinene

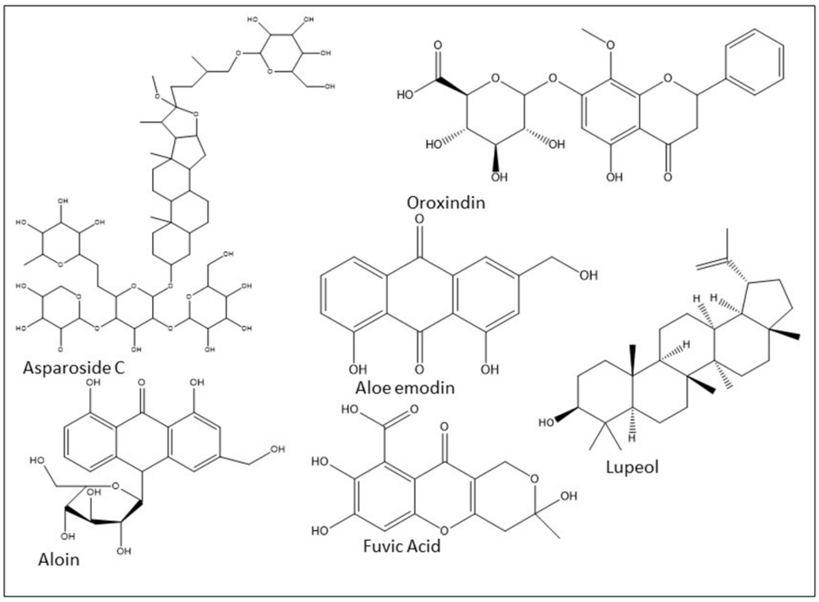
b.


Nimbolide
Nimbolinin A
Ellagic Acid
Amarogentin

c.


Apigenin
Ursolic acid
Vasicolinone
Anisotine
Reserpine
Scutellarin

d.



e.

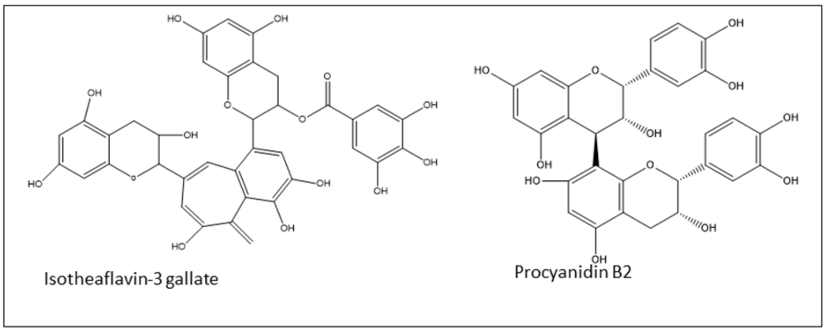


Figure 5. a. b. c. d. e. Chemical structures of active phytoconstituent against SAR-COV-2

Conclusion

A big population of indigenous and ethnic groups in different parts of the world is using Herbal medicine and Himalayan crude drug for the treatment of various bodily ailments and diseases. The use of these natural phytoconstituents is either for prevention and cure of disease or it plays the role of the enhancement of the human immune system to fight against such ailments. During the current situation of the SAR-COV-2 pandemic, herbal medicine could be consumed either as a diet or supplement to subside septicemia and upsurge immune power or it is applied as a supportive therapy along with known anti-COVID drugs to reduce viral titers in the upper and lower respiratory tract. Many active secondary metabolites present in these medicinal plants could be isolated and utilized against COVID-19 in various ways such as an inhibitor of the binding of spike protein to host cell ACE2 receptor, an inhibitor of virus PLpro, or 3CLpro, and many others. Similarly, SAR-COV-2 is proved to be deadly especially for the younger and older population whose immunity is compromised seriously. In such a population, Himalayan crude drug and herbal medicine could be utilized as an immune booster. In this regard, this review could be a mediator between modern allopathic therapy and traditional crude drug consumption which shows a strong impact on the capacity for the prevention and treatment of COVID-19.

Acknowledgments

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Conflict of Interest

The author declares no conflict of interest.

Author Contribution

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