World Journal of Biology Pharmacy and Health Sciences

eISSN: 2582-5542

Cross Ref DOI: 10.30574/wjbphs

Journal homepage: https://wjbphs.com/

(Review Article)

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Natural phytoconstituents and herbal supplements: A potential therapeutic strategies against COVID infection

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World Journal of Biology Pharmacy and Health Sciences, 2023, 13(01), 028–038

Publication history: Received on 16 November 2022; revised on 30 December 2022; accepted on 01 January 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.13.1.0282

Abstract

The SARS-cov-2 virus was initially identified in Wuhan in November 2019, and later spread globally sparking the present pandemic. Since there are currently no specified cures for COVID-19, researchers have the chance to develop alternative drugs or vaccines, thus numerous synthetic bioactive molecules are now being explored in clinical studies. The broad therapeutic scope and negligible health consequences, traditional medicines have been utilized for a relatively long time in various clinical emergencies. Considering there weren't enough synthetic antiviral medications available, pharmaceutical and alternative therapies have been established using a number of plant constituents. 85% of the immune system is made up of good gut bacteria, which were enhanced by plant-based meals. People routinely utilize a wide variety of natural plants and herbs to cure several categories of disorders owing to the wide access of herbal and nutritional products globally. This article illustrates how earlier studies have demonstrated that several plants have immunomodulatory and antiviral properties, as well as role of their active constituents in order to build immunity against COVID-19. Despite the availability of FDA approved therapies and vaccinations for the management of COVID-19, the goal is to promote the usage of natural supplements as immunotherapies and vaccine adjuvants.

Keywords: Natural Phytoconstituents; Herbal supplements; COVID treatment; SARS-cov- 2; Post-COVID syndrome; Targets for SARS-cov-2

1. Introduction

Patients in Wuhan, Hubei, China, who had severe respiratory diseases were the first to be diagnosed with the unpredictable coronavirus epidemic in 2019. Globally, COVID-19 has resulted in 621,797,133 confirmed cases and 6,545,561 fatalities before until October 18th, 2022(Sohrabi et al. 2020). Researchers initially classified this epidemic as pneumonia of unknown origin but subsequently discovered that it is a member of the SARS family and exhibits fundamental features such bronchitis, pneumonia, runny nose, dyspnoea, myalgia, andfatigue(Yousef Alimohamadi et al. 2020)(Yuki, Fujiogi, and Koutsogiannaki 2020). When symptoms are severe, these can result in pulmonary failure and pulmonary collapse, which would need intensive care unit (ICU)-level treatment (Wang et al. 2020). Despite all of the vaccines and conventional medications like casirivimab, imdevimab, sotrovimab, molnupiravir, lopinavir, ritonavir, and chloroquin have been offered to slow the spread of infection, the disease instances are still rising globally (White et al. 2022). The consumption ofplant-based immunity enhancers as well as some nutraceuticals might give further care againstthe COVID since the cardiopulmonary collapse that predominates in COVID causes the immune system to become dysregulated (J and WM 2020).

Humans have relied on nature for cure and prevention of numerous ailments since the earliesttimes according to WHO data, 80% of public rely on herbal medicinal products for their basichealth (Khadka et al. 2021). Due to more availability and cost, natural medicinal herbs have evolved as a promising source for the development of novel medications. The

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widespread use of several functional dietary foods that can strengthen immunity by enhancing or inhibiting immunological response, leads to defend the body against pathogens, control allergies, and promote healing. Countless studies were conducted throughout the outbreak to explore effectiveness of phytonutrients and herbal remedies in combating COVID. According to the published studies, plants and phytochemicals may be able to treat the illness. As several research on natural bioactive compounds is presently being conducted, it is conceivable that herbal traditional remedies might contribute to a number of natural goods delivering therapy and protection from viral infection (Milliken 1998)(Wainwright et al. 2022). This articlepresented the comprehensive blueprint of how previously studies have shown that certain plants have immunomodulatory and antiviral attributes, as well as the involvement of their bioactive components in order to boost immunity against COVID-19.

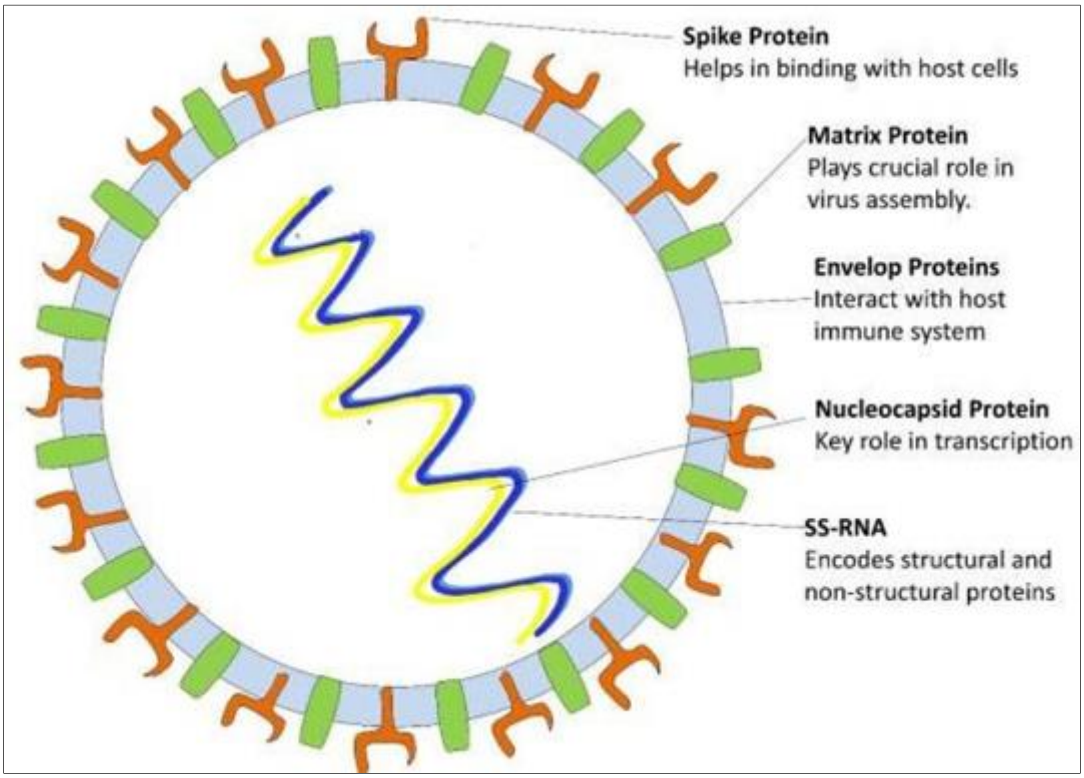

Figure 1 Morphology of COVID Virus

2. Brief Morphology and Pathogenesis

Coronaviruses are *coronaviridae* family virus, size ranges from 65-160 nm in diameterContains Single-stranded RNA ubiquitous in living animals and birds, especially drive intestinal disorders in animals and pulmonary complications in humans (Mahy 1987) (Andersenet al. 2020).The development and dissemination of viruses are facilitated by the Envelop protein, which encapsulates the RNA virus and facilitates in the infection's propagation. The trimeric spike proteins are embedded in a lipid double layer that forms the viral envelope engages with cell receptors to permit viral invasion. The transmembrane matrix proteins in thevirus's centre retain the ss-RNA-integrated nucleocapsid. When the virus is outside the host cell, the surface membrane, capsule, associated proteins, and nucleoproteins safeguard the DNA. (Sohrabi et al. 2020).

The ordinary spike protein present on the SARS-CoV2 is vital for the viruses to adhere to the host's cell surface receptor characterised by presence of specific receptor binding domain (RBD). Spike protease and host RBD interaction determines coronavirus pathogenicity and is essential for invasion. Each species of COVs having different RBD at specific site which is mostly located at C and N terminal of spike proten. Numerous proteases found on host cells, such as aminopeptidase, ACE2R, and dipeptidyl-peptidase 4, are known to serve as entrance points for pathogens. The spike protein's glutamine sequence builds a virus-host receptor complex by reacting with the lysin side - chain of human ACE2 receptors. (Chen et al. 2020)(Shirbhate et al. 2021). Once the membranes of the host cell and the virus have fused as a result of virus-host receptor complex, single-stranded genomic RNA is discharged in cytoplasm of host’s cells. The single-stranded RNA is then subjected via translation and replication processes to create the polyproteins pp1a and pp1ab, which further cleave into 15– 16 non-structural protein (nsp) fragments, and from which the negative sense copies of genomic and subgenomic RNAs are synthesized. Positive-sense genomic RNA and sub-genomic mRNAs are formed after the development of complementary copies. The abundance of structural and other proteins is synthesised using the subgenomic mRNAs as a template. (Doke, Bhagwat, and Lokhande 2020)(D. Kim 2007). Afterwards, viral genomic RNA and N protein together forms the nucleocapsid, which further integrated with endoplasmic reticulum (ER). In ER these viral genome undergoes series of processes to form M, S, E proteins which then localised to endoplasmic reticulum-golgi intermediate compartment (ERGIC)(Knoops et al. 2008).The membrane carrier process called as exocytosis then carries the smooth vesicles encased new viral DNA across the membrane of the infected cell. Nevertheless, the overabundance of viral RNA and other structural proteins inside the ER and ERGIC subsequently leads to cellular death ((Zhou, Chen, and Chen 2020).

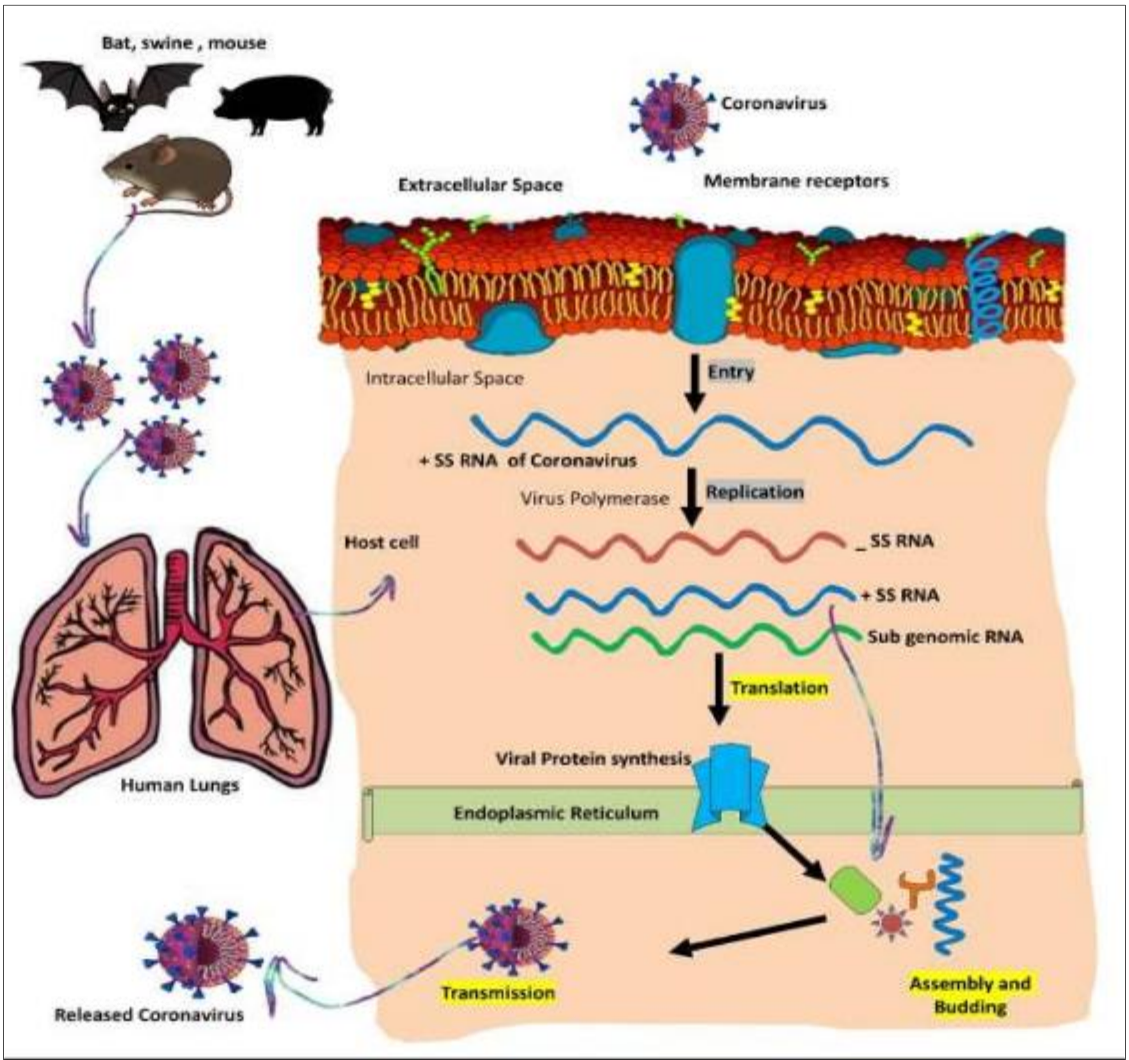

Figure 2 Pathogenesis of COVID Virus

COV's attaches to the host cell surface receptor ACE2R with the help of viral S proteins followed by viral RNA discharged into the cytoplasm, where it is translated and replicated to produce new genomic and sub-genomic viral material as well as other structural and nsp's. All the genetic materials along with nsp moved into ER and transported across the cell by mechanism of endocytosis. (Suresh et al. 2022).

3. Potential Therapeutic Targets for COVID-19 Treatment

3.1. Transmembrane serine protease 2 (TMPRSS2)

Proteases initiate and regulate numerous fundamental physiological processes through precise and timely processing of proteins and peptides. TMPRSS2 is a serine protease presents on cell surface of host to which COVID virus interact leads to induction of viral invasion and replication. TMPRSS2 is an essential enzyme that cleaves the hemagglutinin of many influenzas virus subtypes and the coronavirus protein S and thus facilitate introduction of COV's inside the host cell. Inhibition of TMPRSS2 expression or protease activity results in reduced prostate cancer growth and viral entry (Posadas-Sánchez et al. 2022)(Wettstein, Kirchhoff, and Münch 2022). As TMPRRS2 plays a major role in the entry of several respiratory viruses including COVID19. It would be a promising therapeutic target. Most herbs supplements which inhibit the activity of serin transmembrane including the natural products act as promising therapeutic interventions.

Cannabidiol (CBD) and cannabivarin (CVN) found in cannabis are key biactive compounds which reduces post-COVID symptoms, particularly those associated to nervous system. After a successful recovery from COVs infection, it has been noted that in some instances, both the ACE2 protein and the TMPRSS2 protein are still triggered as a result of remnant COVs proteins. The binding sites of receptor proteins are dealt with by CBD/CVN, which also inhibits the production of these proteins and leads to enforced displacement of COVID residues from the target proteins (Sarkar et al. 2021). The ashwagandha extracts contains withanone and withaferin-A bind to the TMPRSS2 catalytic site and block it, however they can simultaneously modify the allosteric region, suggesting that they have the capacity to inhibit TMPRSS2 and prohibit virus from entering host cells. (Kumar et al. 2022). As cepharanthine has potent antioxidizing, anti-inflammatory properties, it reacts well with TMPRSS2 and suppresses its expression. Additionally it displays cytotoxic actions that kills pathogens. (Jain D, Hossain R, Khan RA, Dey D, Toma TR, Islam MT, Janmeda P 2021).

3.2. Cathepsin L (CTSL)

Lysosomal cysteine protease CTSL has a spatial helix-like L domain and a sheet-like R domain that assembles collagen from procollagen and plays a role in cell proliferation, namely, proteolytic control by cyclins. In addition to that it also contributes in physiological processes such as cell-matrix degradation in the inflammatory process, apoptosis, antigen processing,immune responses (Hardiany 2013). Its primary purpose is to lyse antigenic proteins generated by endogenic pathogens. An association between CTSL and COVs has recently been described, indicating that exposure to COVs causes elevated levels of blood CTSL to breakdown the virus' S-protein and promote viral penetration into cells.(Zhao et al. 2021). As a result, plants and natural antioxidants having the power to block CTSL may provide a useful therapeutic target for the management of COVID sufferers. Natural herbs like Tectona grand, Hypecoum pendulum, Senna occidentalis, and Cinchona calisaya were computationally screened in a recent study to investigate its antiCOVID effects. It was discovered that all of these herbs contain bioactive constituents that have CTSL inhibitory potential and may be useful in preventing COVID.

3.3. Angiotensin-converting enzyme 2 Receptor (ACE2R)

The pathogenic genomes spread or enter the host cell as a result of the complex between the S-protein and its cellular target ACE2R, which sets off the Cov's incursion. Angiotensin I is basically converted by ACE and ACE2 into angiotensin II and the inactive fragments I to IX. The expression of ACE2R is highly expressed in the cardiovascular, intestinal mucosa, upper and lower respiratory tracts, as well as other organs. According to research, the ACE2R can bemore tightly bound by the COVs RBD (Oz and Lorke 2021)(Jackson et al. 2022). ARBs workby interfering with angiotensin II's ability to bind to receptor, whereas ACE inhibitors stop theconversion of angiotensin I to angiotensin II. However, selective ACE2 inhibitors prevent COVs from recognising human ACE2, which prevents the virus from entering the host cytoplasm (Shukla and Banerjee 2021).

In-silico studies have shown that several natural bioactive constituents might be helpful to halt the disease progression as they are mainly exerting effect by inhibiting S-protein-ACE2Rcomplex formation The plant extract Cinnamomum zeylanicum has a broad spectrum of pharmacological characteristics Cinnamomum zeylanicum has been linked to several benefits,including being anti-diabetic, antimicrobial, antioxidant, anti-inflammatory, and immunostimulant, Each of these features are crucial to improving human health. Cinnamomum zeylanicum inhibit viral transmission and multiplication by its modulating actions on ACE2R (T. et al. 2020). A list of phytonutrients exhibiting proven inhibitory effectover ACE2R provided in Table 1.

3.4. Main protease (Mpro/3CL-protease)

The primary SARS-CoV-2 protease, 3CLpro, majorly responsible of viral replication. 3CLpro acts on the coronavirus polyprotein at 11 polymorphic sites, as contrasted to PLpro, which only binds at three sites. As a significant target for SARS-CoV-2 drugs, 3CLpro plays significant role for viral replication as well as able to produce 11 of the 16 NSPs required for viral development. There have been reports that some medicinal herbs can prevent 3CLpro would provide better therapeutic cure against and promising drug candidate for COVID disease (Tahir ul Qamar et al. 2020) (Mody et al. 2021). Recent research based on a molecule's binding energy reveals that a number of natural compounds, notably resveratrol, puerarin, apigenin, crocetin, and epigallocatechin, were successfully slowing the course of the Cov's outbreak. (Pandey et al. 2021)

Table 1 Potential Therapeutic Targets for COVID-19 Treatment

Target Molecule	Descriptive Function	Natural Molecule Modulators	Ref
TMPRSS2	The spike protein and ACE-2 are broken down by TMPRSS2,which makes it easier for viruses to cause disease. Deprivation of TMPRSS2 prevents host cell viral entrance	Cannabidiol, Cannabivarin Withanone Withaferin-A Cepharanthine	(Sarkar et al.2021)(Kumar et al. 2022)(Jain D, Hossain R, Khan RA, Dey D, Toma TR, Islam MT,Janmeda P2021)
CTSL	The upregulation of CTSL, a pH-dependent lysosomal protease, increased viralinvasion in host. S-glycoprotein was effectively broken down by CTSL, which accelerated viral entrance via endosomes.	*Senna occidentalis,), Ziziphus rugosa, Tectona grandis, Silybum marianum,* 3α, 17α-cinchophylline *(Cinchona calisaya) Gallinamide*	(Vivek- Ananth et al.2020)
ACE2R	This are membrane proteins to which viral spike proteins binds and forms virus-host cell receptors complex which in turn facilitates virus penetrationinti host cell. It has been determined that the repression of the ACE2R-S protein complex is a prime target for antivirus drug candidates.	*Cinnamomum zeylanicum, Phaseolus Vulgaris, Curcuma Longa,* *Ocimum Gratissimum, Syzygium Aromaticum, Artemisia Absinthium, Inula Helenium*	(T. et al. 2020)(31)
Main protease	Crucial for viral replication and production of 11 of the 16 NSPs required for viral growth	*Cinnamomum zeylanicum,Turmeric,* *Quercetin wormwood, elecampane Baicalein*	(T. et al. 2020)(34)
Papain-like protease (PLpro)	Linked to proteolytic processing of nsps and crucial for CoV reproduction and transmission	*Mulberry Morus alba Phyllanthus emblica) Tribulus terrestris Paulownia tomentosa*	(Ranjan, Mohapatra, and Das 2020)(Song etal. 2014)(Cho et al. 2013)(D. W. Kim et al.2014)
RNA- Dependent RNA Polymerase	Essential for viral genome multiplication	*Carica Papaya Argemone mexicana Nigella sativa*	(Pandeya, Ganeshpurkar and Mishra2020,
PACE (paired basic amino acid cleaving enzyme)	It is a proprotein convertase that transforms dormant proteins into their functional version, also causes viral protein disruption.	Epigallocatechin, Ellagic Acid Limonin, Pedunculagin, Betunilic acid	(Vardhan andSahoo 2022)

3.5. Papain-like protease (PLpro)

The predominant nsp of COVs is papain-like protease (PLpro), indeed member of the cysteine protease family and offers an incredible prospect for the development of novel drug option against Cov's disease. Interferon-stimulated gene 15 (ISG15) is a ubiquitin-like modifier triggered in infections and implicated in host immune system responses. Interferon responsive factor 3 (IRF3) and ISG15 interact in response to COV exposure to begin the production of IFNs and nuclear factor kappa B (NF-B), strengthening host resistance versus viral diseases. ISG15 and IRF3 are nonetheless dysregulated by PLpro via cleavage of both, which weakens the host's defences. The viral polyproteins are broken down by PLpro at 3 specific locations, resulting in 3 nonstructural isoforms (nsp 1-3). The proliferation andtranscription of pathogens are promoted by these nsp. Successful knockdown of PLpro expression shields and promotes ISG15 and IFR3 functionality, suppresses viral life cycle, and strengthen the host immune system.(35). Medicinal plants have shown promising inhibitory potentials against SARS-CoV-2 PLpro are discussed in table 1.

3.6. Post-corona symptoms and immunity

The post-COVID condition does not now have a notion that is widely recognised., however it is understood that it is accompanied by persistent complications of the COVID-19-associated ailment that last longer than 12 weeks after the commencement of symptoms. Post-COVID or long-COVID syndrome was classified based on the severity and period of manifestations: Chronic COVID, which develops when symptoms worsen longer than 12 weeks and acute COVID, which happens when signs stay longer than 3 weeks but fewer than 12 weeks.. (Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS 2021)(Yong and Liu 2022)

Because SARS-CoV-2 significantly weakened most of the organs, it brought in ultrahigh rates of morbidity and mortality around the globe. Despite the fact that a substantial number of sufferers are surviving the acute stage of COVID-19, there is considerable reports suggesting that the long-term consequences of SARS-CoV-2 exposure can impair a person's quality of life and capability to work. Symptoms such as dyspnea, weariness, loss of taste and smell, cognitive decline, chest discomfort, and arthralgia are frequently present. By triggering the innate immune response, which results in the generation of inflammatory cytokines and a procoagulant state, and further damages cells. These symptoms began with the virus exposure and continues even after 4 weeks, may be fresh, reoccurring, or persistent. When suffering from an acute infection, people with post-COVID-19 conditions may have variable degrees of these manifestations (Pierce JD, Shen Q, Cintron SA 2022).

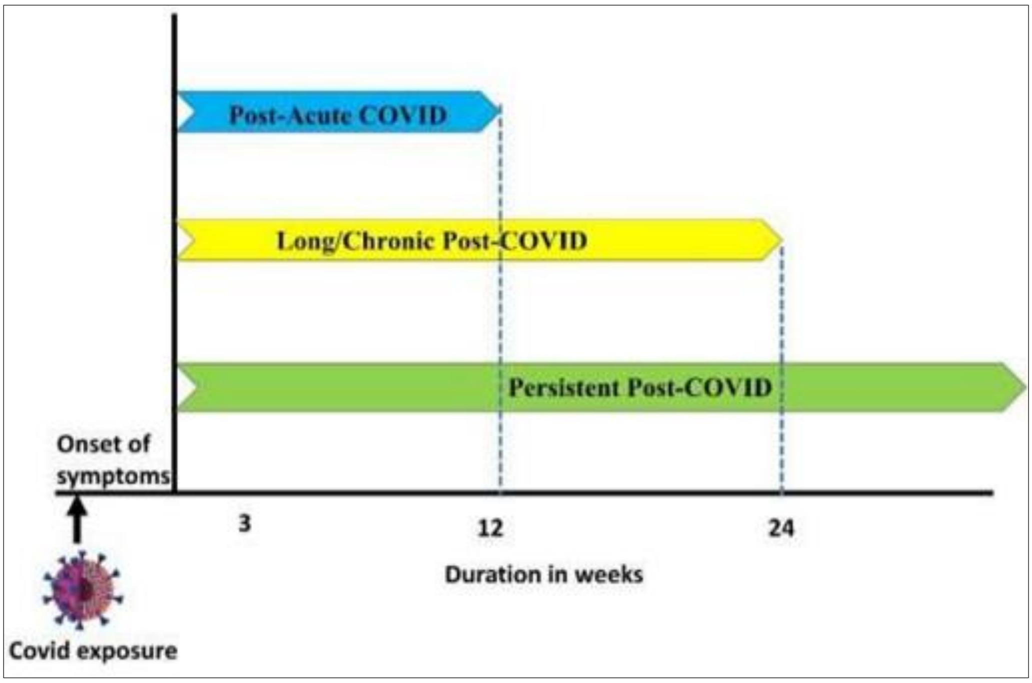

Figure 3 Classification of Post-COVID Syndrome

The new classification is required for post-COVID condition as in the recent studies' new concepts such long COVID, long haulers, and chronic COVID were revealed. A comprehensive categorization of post-COVID symptoms was suggested (Figure 3.), with post- acute COVID symptoms (those lasting from 5 to 12 weeks), long post-COVID symptoms (those lasting from 12 to 24 weeks), and persistent post-COVID symptoms (symptoms last for more than 24 weeks) (Giusto and Asplund 2022). The several natural products and nutraceuticals help to manage these post-COVID manifestations either by upregulating defence system of human i.e immunity or their antiviral activities. The details of the herbs mentioned in the table 2.

Table 2 Medicinal bioactive compounds with immunostimulant and anti-COVIDproperties

Medicinalherbs	**Immunostimulant actions**	**Ref**
Aloe Barbadensis	It is a remarkable source of an array of antioxidants, including as aloe-emodin, anthranol, barbaloin, isobarbaloin, and aloetic acid, which disrupt the viral lipidmembrane and impede subsequent multiplication. Aloin and aloe-emodin upregulates blood IgG levels and CD4 lymphocyte count.	(Tshibangu et al. 2020)(Vahedi et al. 2011)
Zingiber officinale	Pro-inflammatory cytokines were inhibited by ginger extract and its constituents, including gingerenone A, geraniol, and gingerol. Likewise, molecular screening evidence demonstrates that gingerol noticeably alters the functions of Mpro, spike protein, and ACE2R, resulting in their downregulation and the malfunction of viral replication.	(Malekmohammad and Rafieian-Kopaei 2021)(Wijaya et al. 2021)
Carica papaya	It improves the synthesis, use, and storage of energy while reinstating body 's defense functioning through its inhibitory up-shot on pro-inflammatory interceder and free radical scavenging activity. Lutein & β-Cryptoxanthin which modulates the activity of RdRp and spike protein.	(Kharaeva etal. 2022)(Saif R, Zafar MO, Raza MH, Zia S 2022)
Cinnamon zeylanicum	The presence of its active ingredients, such as tenufolin (TEN), eugenol, pavetannin (PAV), linalool, and alpha- caryophyllene, dalchini exhibits powerful antioxidant, antiviral, antibacterial, hypoglycemic, and immunomodulatory qualities. TEN & PAV posseses stronger affinity for Mpro/3CL-protease and determine its functions. Furthermore, it governs viralreplication via regulation of cytokines, inflammatory mediators.	(Lucas et al. 2021)(DSNB K et al. 2020)
Allium sativum	Modulate the activity of main protease (MPro) i.e., chymotrypsin-like protease (3CLpro) By altering the T-helper1/T-helper 2 ratio in favour of the T-helper 2 type, garlic oil established its anti-inflammatory milieu.	(Pandey et al. 2021)
Glycyrrhiza Glabra	Glycyrrhetinic acid, the primary constituent, has the ability to inhibit the production of proinflammatory mediators likeinterleukin and TNF even while triggering the discharge of WBCs and downregulating the activity of ACE2 to impedeviral ingress.	(Giri et al. 2021)
Ocimum sanctum	Tulsi is widely recognised for its antiviral, antifungal, antidiabetic, anti-inflammatory, and immunomodulatory properties Urosolic acid which is present in it inhibits Mpro's activity and stops it from interacting with other inciting factors, limiting protein replication and slowing theprogress of SARS.	(Srivastava et al. 2020)
Curcuma longa	It mostly includes polyphenols, bisdemethoxycurcumin, desmethoxycurcumin, and Those molecules enable turmericto display a variety of pharmacological properties, including anti-inflammatory, antioxidant, and neuroprotective effects.The main protease and RdRp-RNA are two essential replication-related enzymes that are suppressed by curcumin.	(Jini et al. 2022)(Rajagopal et al. 2020)
Caffea arabica	Anti-oxidant, anti-inflammatory, anti-bacterial, and anti-viral properties are present in caffeine. In addition, it prevents the virus from binding to the host cell, and directs 3CL protease blocks the virus from multiplying	(Elzupir 2022)
Azadirachta indica *Tinospora cordiofolia*	The neem and giloy does have anti- inflammatory,antipyretic, fungicidal and antiseptic activities. Limonoids from neem found to have stand out inhibitoryactivity against TMPRSS2 and ACE2R. Tinosporin and diterpenoid has potential role against different subgroups of retroviruses	(Chaudhary, Farswan, and Bahuguna 2021)

List of abbreviations

RBD: Receptor binding domain
ERGIC: endoplasmic reticulum-golgi intermediate compartment
ER: Endoplasmic Reticulum
ACE2R: Angiotensin-converting enzyme 2 Receptor
CTSL: Cathepsin L
TMPRSS2: Transmembrane serine protease 2
COV's: Coronavirus
CBD: Cannabidiol
CVN: Cannabivarin
nsp: non-structural protein
PLpro: Papain-like protease
ISG15: Interferon-stimulated gene 15
IRF3: Interferon responsive factor 3

4. Conclusions

People with inadequate immunity are more susceptible to the global outbreak known as COVID-19. Plant-based meals have an important role in boosting immunity by fostering goodmicrobiota in the body. Herbal remedies have been practiced since antiquity and encompass abroad spectrum of disorders. Because of their anti-viral characteristics, they have been regarded as potent clinical therapies against a wide range of viral illnesses. These Ayurvedic natural substances are explored for the management of COVID-19. These substances are largely including phytochemicals such as, polyphenols, tannins, saponins, alkaloids, flavonoids, and polysaccharides, proteins which have a wide range of functions against viral life cycle at different stages such as invasion, penetration, replication and release. Several vitamins rich plant-based product and good gut microbiota as a prebiotics and probiotics have been found toenhance immunity and thus offers prevention and cure against COVID. The current review speaksabout, the possible use of herbal remedies to treat COVID-19 and their proposed mechanismsagainst this devastating virus. Unfortunately, there is not enough studies to assess several plantgenera as anti-SARS-CoV-2 agents. Moreover, research has been underway to sort out their potential benefits, and we anticipate that transforming of these studies will be more detailed. Possible futures may show the significance of natural products in offering immunity against COVID-19 by fusing this research with advanced technologies.

Compliance with ethical standards

Acknowledgments

The authors are thankful to Indira College of Pharmacy, Tathwade, and Pune 411033 for allthe guidance and support.

Disclosure of conflict of interest

All authors declare that no conflict of interest.

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