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Antiviral Potential of Plants against Covid-19

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Abstract

The global outbreak of COVID-19, caused by the novel coronavirus SARS-CoV-2, has thrust the world into an unprecedented health crisis. In the quest for effective treatments and preventive measures, the antiviral potential of plants has emerged as a promising avenue of exploration. This study delves into the diverse array of plant-derived compounds and extracts that exhibit antiviral properties against SARS-CoV-2 and explores their potential contributions to managing and mitigating the COVID-19 pandemic. Plants have evolved an astonishing variety of secondary metabolites, including alkaloids, flavonoids, terpenoids, and polyphenols, many of which possess antiviral properties. These natural compounds have demonstrated the ability to inhibit viral replication, block viral entry, and modulate host immune responses. The antiviral potential of plants against COVID-19 represents a convergence of traditional wisdom and modern science. Nature's pharmacopeia, with its wealth of bioactive compounds and therapeutic knowledge, offers a multifaceted approach to managing and mitigating viral pandemics. As we navigate the complexities of the COVID-19 pandemic, harnessing the potential of plant-derived antivirals, while ensuring responsible sourcing and research rigor, holds promise for enhancing our arsenal of strategies against viral threats.

Keywords: COVID-19, pharmacopeia, traditional, pandemics, knowledge

Introduction

Viruses are the root cause of many different types of cancer as well as Type I diabetes, Alzheimer's disease, and hepatocellular carcinoma in humans. People have historically endured a tremendous deal of pain at the hands of viruses including polio, mumps, measles, dengue fever, SARS, MERS, AIDS, chikungunya fever, encephalitis, and influenza. The human papillomaviruses, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, human T-cell lymphotropic virus type 1, and Kaposi's sarcoma-associated herpesvirus are all viruses that may cause cancer in humans. The human enterovirus (HEV) has long been suspected of playing a role in the environmental initiation of T1D in humans. There is evidence that the human herpesviruses HHV-6A and HHV-7 are important causes of AD; nevertheless, co-infection of HSV with other viruses has also been observed. The 2019-nCoV virus was first identified in Wuhan, China at the end of December 2019, prompting the World Health Organization to declare a worldwide emergency and publish worldwide Health Regulations to address public health concerns. The pandemic nature of the illness makes it all the more important to find effective means of treatment and prevention without delay. Researchers have shown that 2019-nCov is caused by a member of the coronavirus family known as severe acute respiratory syndrome virus 2 (SARS-CoV-2). Fever, pneumonia, a dry cough, and difficulty breathing are only some of the complicated clinical signs associated with COVID-19. There have been 570,005,017 confirmed cases and

6,384,128 fatalities over the globe, according to the globe Health Organization as of 27 July 2022. Very few persons were diagnosed, and even fewer received therapy.

Recent years have seen widespread success from a vaccination campaign. However, SARS-CoV-2, the virus responsible for COVID-19, has posed a threat to public health ever since it emerged. Due to the recent COVID-19 epidemic, traditional medicines from all around the globe have come under scrutiny. There are a variety of diagnostic and therapeutic options for dealing with the condition. Researchers have also shown that SARS-CoV-2 may be transmitted to birds and animals. There are at least 21 different viral families that may infect humans. There are two families of enveloped viruses (Herpesviridae and Poxviridae) and three families of nonenveloped viruses (Adenoviridae, Papillomaviridae, and Polyomaviridae). The Hepadnaviridae family, which includes enclosed viruses, contains viruses with DNA that is only partly double-stranded (ds). Three families (Astroviridae, Caliciviridae, and Picornaviridae) are classified as nonenveloped single-stranded RNA viruses, whereas four families (Retroviridae, Coronaviridae, and Flaviviridae) are classified as enveloped single-stranded RNA viruses. All negative ssRNA families (Arenaviridae, Bunyaviridae, Filoviridae, Orthomyxoviridae, Paramyxoviridae, and Rhabdoviridae) are encased with helical nucleocapsids, whereas the nonenveloped families have icosahedral nucleocapsids. Hepatitis D is caused by a dsRNA virus (Reoviridae), although this viral family has not yet been classified. It has been suggested that the spike protein, nucleocapsid protein, membrane protein, envelope protein, and enzymatic proteins of SARSCoV-2, the virus responsible for COVID-19, may be used as therapeutic targets to prevent illness (Figure 1). Medicinal plants produce secondary metabolites as a kind of self-defense. Antibacterial, antifungal, and antiviral molecules are only a few examples of the many types of therapeutic molecules that have been identified, purified, described, and put to use in the treatment of illness.

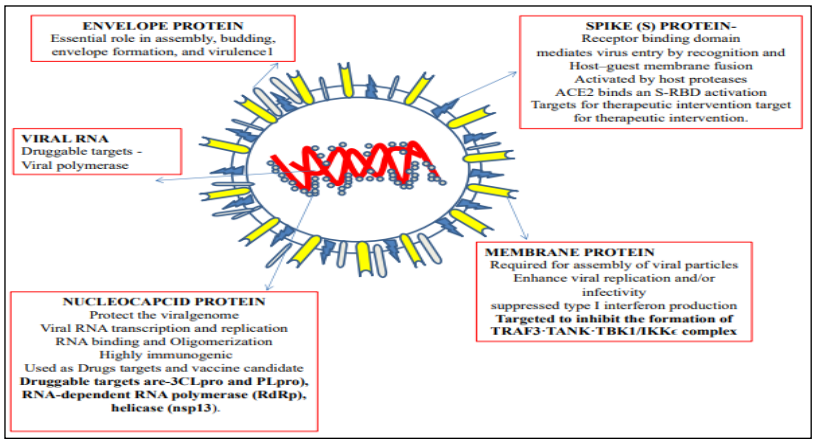

Figure 1: Structural features of a coronavirus

These secondary metabolites are key targets for the development of antiviral drugs, especially those for SARS-CoV-2. Flavonoids, a kind of secondary metabolite, have been shown to have antiviral characteristics. Table S1 details the antiviral properties of many medicinal herbs. Even while coronavirus infections may be treated with a variety of standard drugs, no comprehensive guidelines have been provided for doing so, nor have the mechanisms of virus activity been adequately described. To improve the availability of medicinal components with action against viruses, additional plants or herbs might be explored as treatments. Most earlier publications and research have ignored geographic context in favor of narrower focuses on single ethnobotanical substances like traditional Chinese or Indian medicine. Several cutting-edge computational methodologies have been adopted for screening and identifying natural compounds that may inhibit viral infection, and their use has increased during the

recent pandemic to find faster-acting and more potent vaccines and treatments, including drugs, for COVID-19. In order to aid in the identification of ethnomedicinal plants or herbs that may be useful as antivirals, including for the treatment of coronavirus, several large scientific databases have been constructed. Use the search phrases medicinal plants, herb OR herbal, (virus OR viral), and COVID-19/corona to locate all relevant articles published in databases such as PubMed, Scopus, Web of Science, and Google Scholar. We conducted a search of these databases and identified and incorporated relevant studies. Articles were selected based on a rigorous evaluation of their relevance, and are categorized according to the kind of study they provide (i.e., in silico, in vitro, or in vivo).

Therapeutic Targets for Coronaviruses

Since their discovery in the 1960s, researchers have been able to categorize human coronaviruses into four main groups: alpha, beta, gamma, and delta. Seven different coronaviruses have been identified as potentially harmful to humans; these include the alpha coronaviruses 229E and NL63, the beta coronavirus OC43, the beta coronavirus HKU1, the beta coronavirus responsible for Middle East Respiratory Syndrome (MERS-CoV), the beta coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), and SARS.

Genome sequencing and analysis at the molecular level have shown that SARS-CoV-2 shares over 80% of its genetic material with SARS-CoV-1 throughout regions 10b, 13, and 14.

Human ACE2 is used as an entrance receptor by SARS-CoV and SARS-CoV-2, and human proteases are used as entry activators by these viruses. Additionally, the viral strains vary somewhat in the most critical structural component, known as the spike protein (S). In comparison to other beta coronaviruses, SARS-CoV-2 may be more infectious due to its furin-like cleavage site, which facilitates priming of the S protein. Therefore, furin inhibitors may be a therapeutic focus for SARS-CoV.

However, with the help of cellular serine proteases, both viruses employ a spike receptor-binding domain for recognition and host cell infection.

There is currently no established therapy option for addressing COVID-19. Successful treatment of any illness requires the discovery of drug-targeting sites or cell-binding proteins. Therapeutics and treatment methods for this condition may benefit from recent discussions of the COVID-19 viral genome and putative cell-binding proteins (Figure 1).

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of the COVID-19 viral genome and putative cell-binding proteins (Figure 1).

Spike Protein

A dose-dependent blockade of the interaction between host ACE2 and viral S protein has been described using an anthraquinone glycoside identical to emodin that was previously identified encoded in the Polygonum and Rheum genera. By connecting with the receptor ACE-2 (the receptor of DPP-4), the spike protein enables viral entry via the viral S1 unit and the host enzyme cathepsin L. The spike protein is a Type-1 trimeric crown-like protein (Type I-TM protein). Spike is a tri-domain protein with an extracellular (EC) domain, transmembrane I segment, and intracellular (IC) domain. Three receptor-binding domains S1 are formed in the ectodomain, and the S2 subunit, a trimeric stalk that merges with the cell membrane, is formed at the C-terminus. It seems that SARS-CoV-2 entrance into cells requires attachment to its host cell receptor (ACE2). The spread of illness is mediated by viral RNA that has made its way into host cells. Moreover, spike proteins trigger the immune response of the host cell to viral invasion. Therefore, the constituents of spike proteins should be prioritized as drug development targets. Quercetin and kaempferol are only two examples of the many plant metabolites that have been employed to inhibit spike-mediated viral infection. Magdalena recently reported that piglets protected against a virus that causes diarrhea in pigs by giving them the coronavirus spike protein orally. For example, Magdalena said that giving the coronavirus spike protein orally to newborn pigs before they were exposed to the swine-epidemic diarrhea virus prevented infection.

Envelope Protein

The molecular weight of the smallest envelope protein is between 8.4 and 12 kDa. A hydrophobic domain and an electrically charged cytoplasmic tail make it up. Particularly important is its involvement in regulating intracellular protein activity, ion channel development, and morphogenesis during viral efflux and assembly. In addition, it has been called a virulence factor. The envelope protein is a membrane protein crucial for viral assembly, morphogenesis, and release from the host cell. Hexamethylene amiloride has been shown to be an ion channel linked with the E protein. E protein-mediated syntenin nuclear translocation activates p38 mitogen-activated protein kinase and promotes the production and release of proinflammatory cytokines like interleukin-1, which in turn causes oedema and other ARDS-specific symptoms. The E protein has just five known interactors on the host side so far: Three of these five molecules are syntenin, while the other two are the sodium/potassium (Na+/K+) ATPase-1 subunit, stomatin, and PALS1. As a membrane protein with viroporin-like performance attributes, the SARS-CoV-2 envelope I protein assists in viral reproduction and efflux, which may contribute to the etiology, severity, and breakdown of the epithelial barrier. The E protein of SARS-CoV-1, like other E proteins, has an extended C-terminal (ECT) region that contains a putative PDZ-domain binding motif (PBM).

Membrane Protein

Nucleocapsid protein stability, viral intracellular homeostasis, and the envelope shape maintained by Mand N-type proteins all rely on the membrane protein. The viral membrane protein has three domains: one at the C-terminus, one at the N-terminus, and one at the apex. Assembly of viruses requires many kinds of interactions, including M-M (host-virus), M-S (spike protein-Golgi complex contact), and M-N (nucleocapsid-RNA complex). The viral M protein serves a number of purposes during infection, including host cell stability and the induction of IFN-beta and the nuclear factor-kappa pathway. TBK1 degradation by the SARS-CoV-2 membrane protein through ubiquitin-mediated processes has recently been demonstrated to inhibit Type I interferon expression.

Similar envelope proteins can be found in both the Pangolin CoV MP798 isolate and the Bat CoV isolates. These two proteins are distinct from all others in the envelope because they lack a Gly or Cys residue at position 70 and have an Arg residue replaced by a Glu residue. When compared to membrane glycoproteins from other viruses, SARS-CoV is clearly distinguishable. However, the envelope peptides

are very similar. Mutations with significant effects on the envelope protein might significantly alter the structural features of the E-protein and, possibly, the molecular interactions between proteins. Possible relevance of membrane protein variation during viral adherence and uptake by cells, where it works in tandem with the spike protein. The way coronaviruses interact with host cells may thus be affected by changes in the E protein.

Nucleocapsid Protein

Members of the CoV family have a similarity in their nucleocapsid proteins, often known as N proteins. The protein has a C-terminal tail, a central linker (CL), a N-arm, and phosphorylation sites abundant in serine and arginine. CTD-driven dimerization relies on the NTD structure, which is required for efficient RNA binding. Furthermore, it has been revealed that the N protein controls viral RNA replication and transcription even in host cells. When bound to elongation factor EF1, however, it suppresses Mrna translation. It has been shown that the M protein, once synthesized in the cell, resides in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), where it acts as a platform for recruiting other viral structural proteins10. In order for virus-like particles (VLPs) to be generated when SARS-CoV-2-specific proteins are co-expressed in mammalian cells, at least M and N must be present. This result indicates that the M protein plays a crucial role in viral assembly. The M and N proteins of SARS-CoV and the mouse hepatitis virus (MHV) 14, another coronavirus, must link with the appropriate host cell types in order to generate viral particles. It has also been shown that the M protein of SARS-CoV-215 is linked to the genomic RNA that contains the MHV16 packing signal. These results on SARS-CoV-2 and similar viruses suggest that the M protein is crucial to the assembly of coronaviruses in many different ways.

Proteases

Enzymes are only one kind of protein that can be synthesized from the SERS-CoV genome. Large PP (PP1a and PP1b) proteins called NSPs are encoded by the 16 copies of the replica gene found in the CoV viral genome. Mopar or papain-like protease [Plpro]) processes cleaved N-terminal peptides, whereas 3C-like protease [3Clpro]) or the major protease [Mpro], a cysteine protease chymotrypsin, processes NSPs released from the C-termini of these PPs. The N-terminal PPs is cleaved by the papain-like protease Plpro, resulting in NSPs 1, 2, and 3 and replica substrates. The LXGG consensus sequence is essential for the cleavage process. Zinc and zinc conjugates are effective inhibitors of the proteases Plpro and Clpro. The viral envelope enzyme haemagglutinin esterase (HE) is specific to influenza and beta-coronaviruses. As receptor- and lectin-damaging enzymes, esterases allow for the reversible binding of O-acetylated sialic acids. The SF1 helicase family, of which NTPase/helicase is a member, plays a crucial role in the basic dogma of viral infection. It breaks down NTPs and uses them as substrates for Datp, ATP, and Dctp.

Endosomal Ph

Many medications and therapeutic compounds rely on Ph for their absorption, distribution, metabolism, and even excretion. In addition, many bacteria find an optimal Ph environment welcoming. The coronavirus life cycle functions best at a low Ph. Potentially beneficial molecules for controlling viral infection include those that block Ph-dependent endosomal proteases. The buildup of amiodarone is promoted by a low Ph, which causes changes to endosomes and blocks coronavirus infection.

Antiviral Potential of Plant Extracts/Metabolites for Treating Sars-Cov-2 Infection

Efforts to find natural antiviral compounds effective against a SARS-CoV-2 infection were ramped up when COVID-19 spread fast. Potential therapeutic compounds have been identified by a combination of in silico and in vitro/in vivo investigations on plants and repurposed medicines. The binding interactions between the ligand and the drug molecules need to be promoted for any noticeable impact to occur. Different cellular and animal models have been used to investigate the SARS-CoV-2 infection and evaluate therapeutic targets such the spike protein, envelope protein, membrane protein, nucleocapsid protein, and proteases. While in vitro research is useful for learning

about viral biology in lab conditions, it often fails to capture the full complexity of actual physiological systems. There are ethical concerns, high costs, and special BSL-3 animal facilities needed for in vivo research. In vitro models are based on the two- or three-dimensional (2D/3D) culture of immortalized cells or primary cells and tissues. In vitro investigations have been conducted recently on glycyrrhizin, chloroquine, hydroxychloroquine, and chloroquine. When given at 500 g Ml1, the rhizomes of the turmeric (Curcuma longa L.; Zingiberaceae.) plant, mustard (Brassica nigra W.D.J. Koch; Brassicaceae), and wall rocket (Diplotaxiserucoides subsp. Erucoides; Brassicaceae) were observed to significantly inhibit 3CLPro activity.

Essential oil extracted from garlic was suggested as a treatment option in a research paper. This essential oil's active component targeted the receptor with PDB ID 6LU7 (the major protease in SARS-CoV-2) and blocked ACE-2 protein function, both of which resulted in the loss of this viral receptor in the host cell (Figure 2). From a total of 18, only 17 were shown to block the binding of ACE-2 protein to viruses in a docking assay, making up 99.4% of all essential oils. Allicin, E/Z-ajoene, allin, Diallyl disulfide, Diallyl trisulfide, pyrogallol, protocatechuic acid, quercetin, and gallic acid from the Allium cepa L. bulb (Amaryllidaceae) have all been reported to exhibit significant antiviral and antibacterial activities. In addition, its antibacterial potential was reviewed by Singh et al.

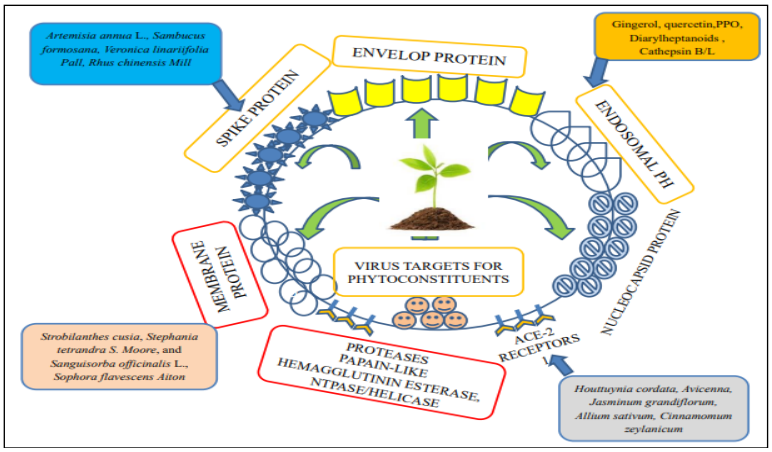

Figure 2: Plant- and herb-targeted envelope protein, spike protein, membrane protein, protease inhibitors, ACE-2 receptors, nuclear capsid protein, and endosomal-like parts of a virus.

The Piper Longum The presence of the essential oils -pinene, -pinene, limonene, myrcene, sabinene, camphene, -thujone, piperitone, caryophyllene, p-cymene, -terpinene, and piperamide has been linked to the fruit of the L. Piperaceae, also known as the Indian spice kali mirch. In addition to SARS-CoV-2, curcumin has been shown to prevent the spread of other viruses in a recent research. The curcuminoids curcumenone, bisacumol, bisacurone, curcumenol, curcumadiol, and demethoxycurcumin are particularly abundant in Curcuma longa L. (Zingiberaceae). Replication of SARS-CoV-2 in human cells is inhibited by curcumin, as has been previously documented for HIV, chikungunya, Zika, and herpes simplex virus (HSV).

Furthermore, curcumin has been shown to block SARS-CoV-2 from entering host cells. It has been shown that curcumin may stop the spread of chikungunya and Zika viruses, and this property of turmeric may be useful for the therapeutic inactivation of COVID-19.

There is antiviral potential in the flower buds of the Syzygiumaromaticum (L.) Merr. & L.M. Perry (Myrtaceae) plant, which have been reported to contain eugenol, acetyl eugenol, -caryophyllene, vanillin, eugenin, kaempferol, rhamnetin, and eugenitin.

According to a docking research, eugenol has weak binding energies with viral proteins. For example, its binding energies with the S protein (PDB ID 6VXX) and Mpro (PDB ID 6LU7) were 6.1 and 5.4 kcal/mol, respectively. Although the binding energies of nelfinavir with these proteins were 8.8 and 8.2 kcal/mol, respectively, the impact of this low binding energy was less dramatic.

There has been growing interest in the use of sage essential oils as phytomedicines, notably for their antiseptic and sanitizing properties. Salvia officinalis L. essential oil was shown to have a low IC50 (equivalent inhibitory concentration) against SARS-CoV in a patient at the Frankfurt University Hospital. Laurus nobilis L. essential oil contains 1,8-cineole, beta-ocimene, beta-pinene, and alpha-pinene, all of which have been shown to inhibit SARS-CoV and HSV-1 replication with an IC (50) value of 120 g/Ml. Research shows that essential oils do not have strong antiviral properties against viruses like SARS-CoV-2 [48]. Eucalyptus oil, eugenol, cinnamon oil, and neem oil are among essential oils that have been shown to reduce infection-related symptoms.

Several antiviral compounds have been isolated from the rhizome and stem of the Zingiberaceae plant, Zingiber officinale Roscoe. These compounds include 6-gingerol, 6-shogaol, 6-paradol, zingiberol, and gingerol. Computational methods have revealed the antiviral potential of Zingiber officinale Roscoe against viruses like SARS-CoV-2. According to docking experiments, 6-Sogaol binds to the S protein (PDB ID 6VXX) and the Mpro (PDB ID 6LU7) with binding energies of 5.5 and 5.8 kcal/mol, respectively, which are similar to the binding energies of nelfinavir for these proteins (8.8 and 8.2 kcal/mol). Eight compounds isolated from the rhizomes of Alpinia officinarum Hance, Zingiberaceae, and gingerol were shown to inhibit the protease (Plpro) of SARSCoV-2 in in vitro tests. The results of these investigations demonstrate the antiviral activity of phytoconstituents and their extracts against SARS-CoV-2, indicating that these chemicals represent effective new targets for treating SARS. Schizachyriumurceolatum Stapf Poaceae's antioxidant function provides further evidence that cinnamon's high immunostimulatory effect may be attributed to its ability to boost phagocytic activity.

Conclusion

The pursuit of effective treatments and preventive measures against the COVID-19 pandemic has led to an exciting exploration of the antiviral potential of plants. Plants have evolved a remarkable array of secondary metabolites, including alkaloids, flavonoids, terpenoids, and polyphenols, with demonstrated antiviral properties. This natural pharmacopeia serves as a valuable resource for the development of antiviral therapies. Traditional systems of medicine, deeply rooted in the use of plant-based remedies, provide a rich repository of knowledge in managing viral infections. Ancient healing practices, such as Traditional Chinese Medicine (TCM) and Ayurveda, offer insights that can complement modern scientific research. The antiviral potential of plants against COVID-19 represents a harmonious convergence of ancient wisdom and cutting-edge science. Nature's bounty, with its diverse bioactive compounds, offers multifaceted solutions to combat viral threats. As we continue to navigate the complexities of the COVID-19 pandemic and prepare for potential future viral challenges, the study of plant-derived antivirals holds promise for enhancing our toolkit of strategies in the fight against infectious diseases. Responsible research, rigorous testing, and ethical practices are imperative as we tap into the vast potential of nature to safeguard human health and well-being.

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