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Plant-Derived Metabolites as Potent Inhibitor and Treatment for COVID-19

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ABSTRACT

Pandemic disease, COVID-19, caused by the SARS-CoV-2 virus, which is potentially fatal for vulnerable individuals, generated global panic. Medicinal phytochemicals have a lengthy history of being used to treat a wide range of pathogens and diseases. The utilization of natural plant products will be the subject of this review, based on the results of previous researches in preventing the infection of COVID-19. In this review, all data sources including Google Scholar, Scopus, PubMed, and Science Direct were searched for publications with no particular time restriction to get a holistic and comprehensive view of the research. It was seen that plants natural products like Polyphenols, Alkaloids, Flavonoids, Coumarins and essential oils were able to inhibit main targets in the virus life cycle such as main protease (Mpro), SARS CoV 2 helicase Nsp13 and Angiotensin Converting Enzyme (ACE2). It has been established that natural plant derivatives can be utilized for treating and prevent SARS-CoV-2 and other coronaviruses by inhibiting several prominent viral portions. However, it is imperative to emphasize on standardization and control the quality of medicinal plants-based products in future studies and there should be further properly investigations of these products in order to clinical usage against COVID-19 infection.

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Abbreviations; ATPase: Adenosine 5'-TriPhosphatase, IFA: Immune Fluorescent Assay, CPE: Cytopathic Effect, ACE2: Angiotensin−Converting Enzyme, IC50: Median Inhibitory Concentration, Mpro or 3-Chymotrypsin-like protease (Mpro/3CLpro), PLpro: Papain-like proteases, SARS CoV 2: Severe Acute Respiratory Syndrome Coronavirus 2, COVID 19: 2019 Coronavirus Disease.

Introduction

The world is currently struggling with a public health issue in the manner of rising coronavirus outbreak, causing contagious and multi-organ COVID-19 infection. It was originated toward the last week of December 2019, in Wuhan, Hubei Province, central China, harboring nearly 11 million people and quickly spread to all countries, provoking devastating health, psychological and socioeconomic consequences around the world (1, 2).

Removing the source of infections is the underlying purpose for preventing and controlling the infectious disease thereby protecting the very sensitive population. COVID-19 is a diverse family of viruses that are susceptible to heat and ultraviolet (UV) radiation. This virus can be preserved at -80°C for many years since being inactivated at 56°C for half an hour. COVID-19 can also be successfully inactivated by 75 percent ethanol, chlorine-containing disinfectants, and peracetic acid (3). Totally, taking personal protective measures such as avoiding contact with patients, regular handwashing and using disinfectant solutions is necessary to avoid of COVID-19 infection (4).

Mainly there are two strategies to combat against this virus: first the already biotechnological products and repurposing existing drugs through computational tools and novel algorithms including cheminformatics, molecular resemblance quantitative-structure activity relation (QSAR), network pharmacology, docking and de novo computational pharmacogenomics design and etc. that are highly studied and approved and they may be most reliable and useful. Second, utilizing natural anti-parasitic, anti-microbial, and anti-inflammatory medicines derived from plants, animals, and microbes (5, 6). It has been concluded after studies that herbal medicines have efficiency in fighting against COVID-19 with activities in blocking the essential proteins for the life cycle of this virus (7).

Worldwide scientist collaborative efforts to producing antiviral drugs and vaccines leaded to identification of small molecules as potential SARS- COVID–19 inhibitors and vaccines that have started to be applied recently (8). In this case vaccines included BNT162 developed by Pfizer Inc. (New York, USA) and BioNTech (Mainz, Germany), (AZD1222, created by the Oxford/AstraZeneca, and mRNA-1273, Moderna (Cambridge, USA) manufacturing vaccine, (Sputnik V, Gam-COVID-Vac, manufactured by Gamaleya National Research Center of Epidemiology and Microbiology in Moscow) and (ZyCoV-D was created by the Indian pharmaceutical company Zydus Cadila.) have been proposed. Moreover, rbACE2, recombinant proteins created by Kafrelsheikh University, and Rh-ACE2 APN01 (human angiotensin-converting enzyme-2 soluble recombinant form) by Austrian Apeiron Biologics, and Rhu-pGSN (recombinant human form of plasma gelosin) created by BioAegis Therapeutics have been developed (5, 9, 10). Unfortunately, due to vaccine manufacturing and distribution capacities limitations and constant mutations of virus also put its effectiveness at serious risk (11). Apart from the vaccine, the Remdesivir has been certified by the US FDA (Food and Drug Administration) for human use in approved COVID-19 cases as an emergency treatment (8).

In addition, approved drugs like Hydroxychloroquine (FDA-approved malaria drug) and chloroquine (The virus's adhesion to the cell membrane can be inhibited by altering the pH of the cell membrane at its surface), Dexamethasone with anti-inflammatory effect, lopinavir and ritonavir combined (anti-HIV), camostat mesylate (inhibiting viral entry), ivermectin and nafamostat have been repurposed as potential drug against COVID-19 affected pandemic (12-15). Also Favipiravir, amodiaquine, 20-fluoro-20-deoxycytidine and ribavirin are known as antiviral drugs (3, 16). Since these drugs have not shown conclusive benefits, so single and custom made anti-viral agents for severe cases are needed.

On the other hand, there are therapeutic plants with secondary metabolites which may be utilized against coronavirus. As a result, the current review's purpose is to locate and collect medicinally reported plants and their natural compounds with antiviral activity to inspire the researchers working on inhibitory activity of plant extracts against SARS-CoV-2.

Methods

In this review, all data sources including Google Scholar, Scopus, PubMed, and Science Direct were searched for publications with no particular time restriction to get a holistic and comprehensive view of the research through molecular docking and dynamics investigations. Following terms and keywords were used in searching of publications: anti-corona plants secondary metabolites, herbal medicine, medicinal plants, anti-oxidant properties of plants, anti-

inflammatory activity of plants, Viral mechanism of covid-19, plant natural products, herbal therapy, anti-corona drugs and vaccines.

Results

In this review, at first, titles were searched regarding to the terms and key words, then abstracts of papers were reviewed and suitable papers selected according to this paper's topic and at last 63 papers were included in this review paper.

Coronavirus and its Viral Mechanism

Coronaviruses (crown based on their shape) are single-stranded, encapsulated large RNA viruses that can infect humans and a large number of animals and belong to the Coronaviridae family and Nidovirales order. These viruses have four subfamilies: alpha-, beta-, gamma-, and delta-subtypes. Each one originated from different sources, Alpha and beta coronaviruses were firstly found in bats, whereas pigs and birds were found to have gamma and delta viruses (3, 17).

The viral polymerase, RNA synthesis materials, and two big nonstructural polyproteins (ORF1a-ORF1b) that do not modulate host response, are encoded by the bulk of the RNA in these viruses. Four proteins with structural properties encodes by the rest of the RNA including:

Spike (S, constructs homo-trimers which budding from the virus's surface and facilitate its attachment to the infected cells by attracting ACE2, which is distributed throughout the lower respiratory tract cells that are directly implicated in the infectious process. In human cells angiotensin converting enzyme (ACE2) is its receptor with two subdivisions named S1 and S2, with S1 being the receptor-binding domain (RBD) (18) has a significant impact on the attachment mechanism by playing a key function in the attachment mechanism of Spike protein to ACE2. After the attachment between them, the virus enters the cell and starts the replication process (19)),

Envelope (E, plays an important part in the phase of virus's growth and genesis)

Membrane (M, specified the envelope's shape of the virus),

Nucleocapsid (N, related to the interaction with the genome of the virus),

and the helper proteins (20).

Because of these viruses' proclivity to create continual transcription mistakes and RNA-Dependent RNA Polymerase protein (RdRP) leaps, these viruses have exceptionally high recombination rates (4).

SARS-CoV-2 viruses belonged to the β-coronavirus family with 60-100 nm diameter, has a shape in oval/round-form contains spike glycoproteins. The RNA chain's nucleotide sequence (30,000 nucleotides) of this virus is virtually equal to the observed nucleotide sequence of SARS-CoV (1).

After that membrane fusion is started by interacting between spike glycoproteins of virus and ACE2, and releasing the virus's genome, encapsulation and polyadenylation modify genomic RNA, which encodes numerous structural and nonstructural genes (21). ORF1a and ORF1b are two genomic RNAs that are translated into two overlapping polyproteins (pp1a and pp1 ab) with the main protease named as Mpro/3CLpro, as well as papain-like proteases (PLpro), which are converted into virus nonstructural proteins that play a critical part in a range of actions during a virus's life cycle (4). The viral nucleocapsid is joined in the cytoplasm by R protein and genomic RNA, and after that spreads into the lumen of endoplasmic reticulum. Through exocytosis, the infected cell subsequently emits viral particles. The virus can then infect kidney and liver cells, T lymphocytes, intestines and the tract of lower respiratory, causing the above-mentioned symptoms and indicators. In view of this, it was found that the CDT lymphocytes of three patients infected with SARS-CoV were less than 200 cells/mm (22).

Main protease domain (Mpro), with its important function in enzymatic activity has been categorized as a protected target. It is a 306 amino acid protein with two catalytic dyads and three domains (H41 and C145) (C-terminal domain-III, N-terminal domain-II, and N-terminal Domain-I) and plays a key role in replicas protein post-translational processing (23).

The replicase-transcriptase complex of SARS-CoV-2 contains PLpro. It is structurally separated into palm, thumb and ubiquitin-like fingers and primarily shows its effects by reduction the signals of inflammation in the infected cells via detecting the Leu-X-Gly-Gly tetrapeptide motif on viral protein (24). As a result, these components are a critical target for SARS-CoV-2 antiviral medication development due to their important functions (24). Figure 1 shows the infection cycle of COVID-19 virus in infected cells, its replication and possible medications against it (25).

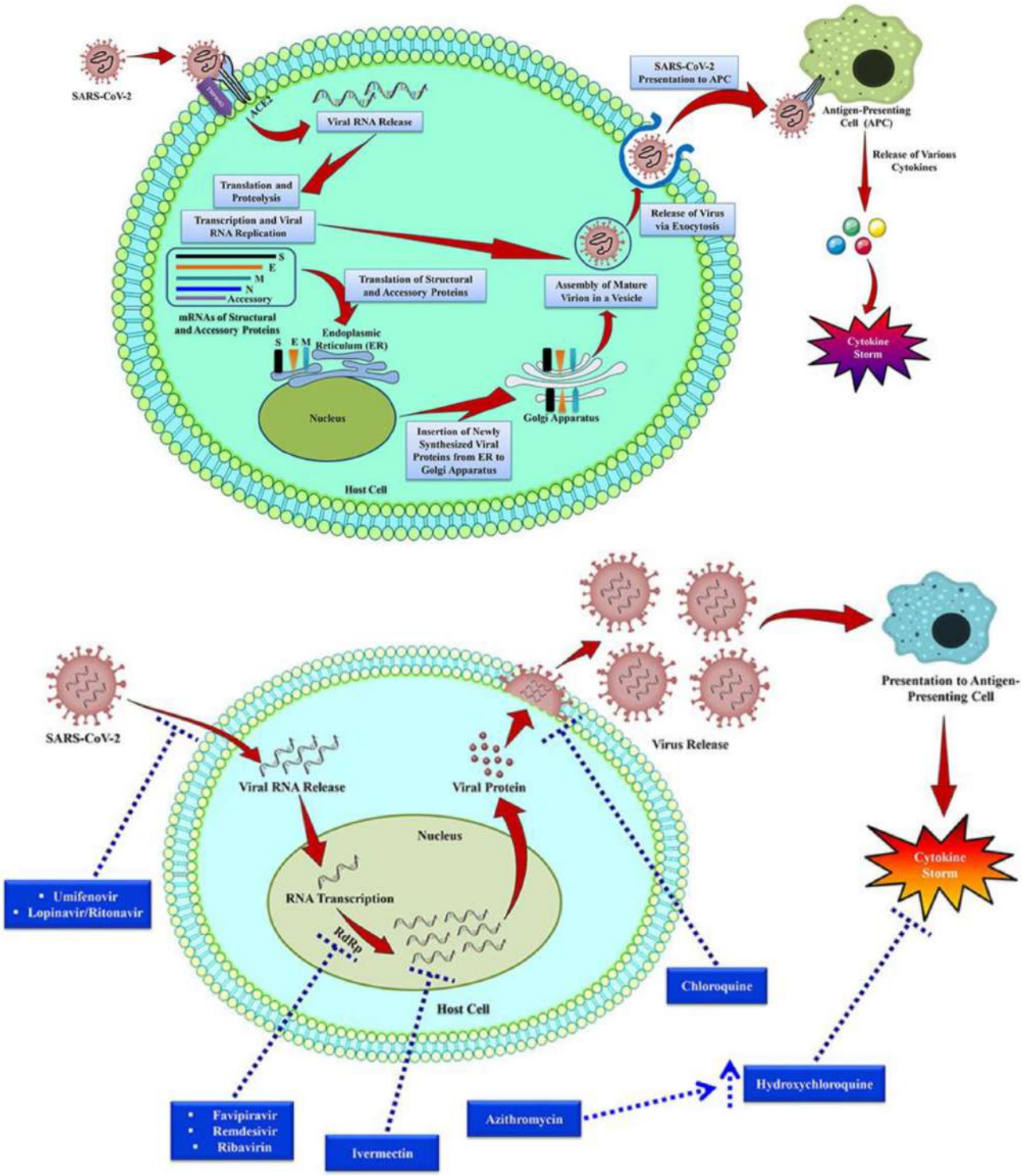


Figure 1 a. The infection cycle of COVID-19 virus in infected cells, b. Its replication and possible medications against it.

Possibly phytochemical inhibitors against major protease of COVID-19

SARS- CoV-2's main protease (Mpro) has become a target for the development of potential treatment options since its critical involvement in the virus replication process and its transcription. Kumar et al. (2020) discovered 19 possible inhibitors and

six drugs (Withaferin A, Nelfinavir, Rhein, Withanolide D, Enoxacin, and Aloe-emodin) as possible COVID-19 main protease inhibitors, implying that repurposing of these components against major protease of COVID-19 might help control Coronavirus spread (4).

Verma et al., (2020) examined the docking of molecules and dynamics of phyto-compounds from three plants with therapeutic properties, *Andrographis paniculata*, E*urycoma harmandiana*, and *Sophora flavescen*, against SARS-COV2. PLpro and 3CLpro showed that SARS CoV-2 can be treated with canthin-6-one 9-O-beta-glucopyranoside molecule. This process conducted through effectively interaction with the Mpro and PLpro, inhibiting the virus's replication and transcription activities, and finally halt the virus's multiplication (20).

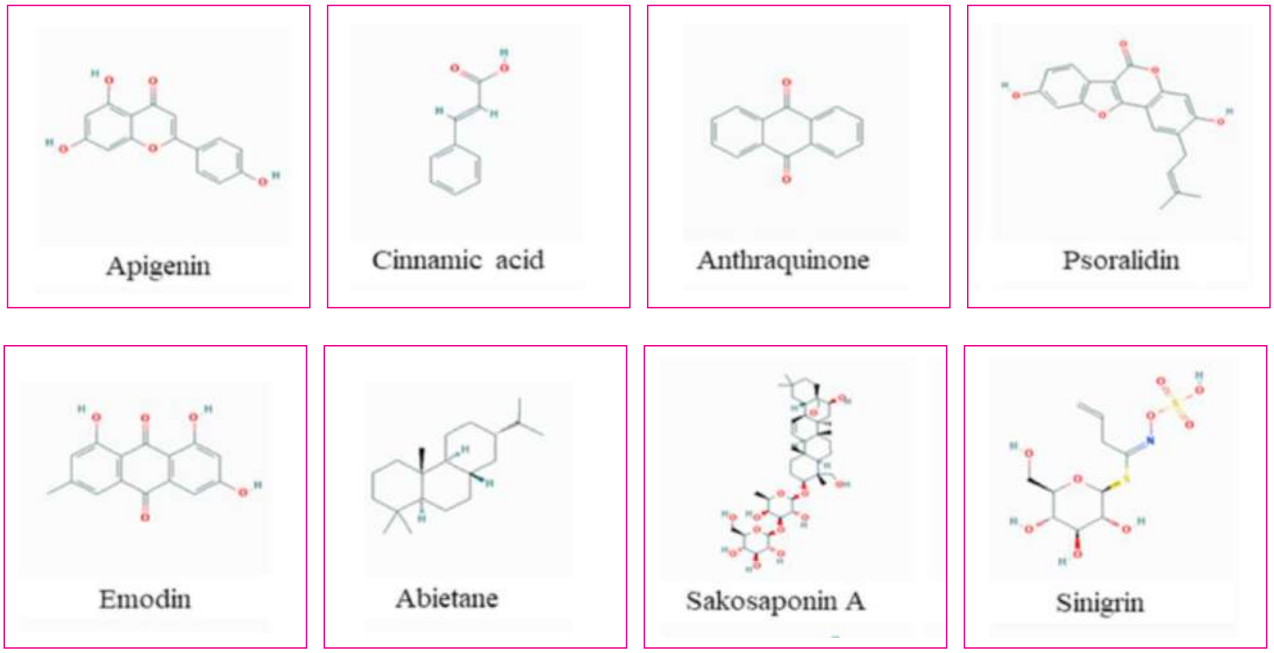
Chikhale et al., (2021) evaluated the potency of sixty-six tested *Phyllanthus emblica* ((Euphorbiaceae) a high-quality source of vitamin C) compounds via molecular docking and dynamics investigations which performed on three considered protein targets, including, Mpro, receptor binding domain of perfusion spike protein, and NSP15 endoribonuclease. According to the findings, the most effective compounds were quercetin, chlorogenic acid, and myricetin against protein targets of COVID-19. The major protease complex of Quercitrin-SARS-CoV-2 had a larger binding energy (Gbind = -36.27) than the major protease complex of Remdesivir-COVID19 virus (Gbind = -27.59), indicating that it could be a more constant complex. Myricetin-COVID-19 RBD complex Gbind's energy (-17.41) is higher than that of the Remdesivir-COVID-19 RBD (Gbind = -0.91), indicating the Remdesivir's poor affinity for the SARS-CoV-2 RBD. Additionally, chlorogenic acid binds to the target NSP15 endoribonuclease with a low binding energy (Gbind = -0.42). *Phyllanthus emblica*, which modulates the immunological response, the inflammatory cascade, as well as the cytokine storm via several signaling channels, can be used to treat and control COVID-19 (26).

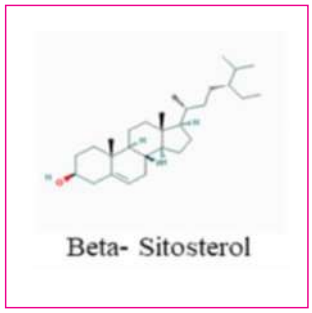
It is suggested that 3-galloylcatechin, proanthocyanidin B1, and luteolin 7-galactoside in Terminalia catappa (almond), *Vitis vinifera* (grape), and Verbena officinalis (common verbena), among 65 compounds from a section of the ZINC database subset (AfroDb Natural Products) may serve as therapeutic leads in the combat against the coronavirus pandemic. These multi-target activity compounds outperformed previously reported repurposed pharmaceuticals in binding to specific receptors and enzymes targets, as well as showing antiviral capabilities. (21).

Furthermore, the antioxidants quercetin, kaempferol, and aloe-emodin found in *Dendrophthoe petandra* and *Cassia alata* proved to operate as anti-COVID-19 against its Mpro and 3CLpro main proteases (27).

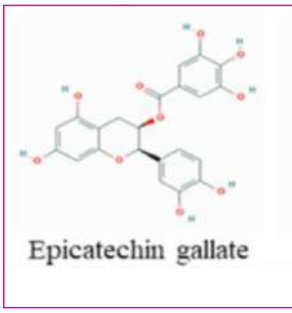
According to blind docking studies of eight compounds comprising Chloroquine, Nitazoxanide, Cetirizine, Quinine, Doxycycline, Indinavir, Mizolastine and Lymecycline, on the virus's primary protease (Mpro), Lymecycline and Mizolastine with binding free energies ranging between -8.87 and -8.71 kcal/mol, proposed as potential SARS-CoV-2 inhibitors, allowing for the formation of protein ligand complexes in a spontaneous and energy-efficient manner (28).

Figure 2 shows some plants derived phytochemicals proposed against coronavirus (29).

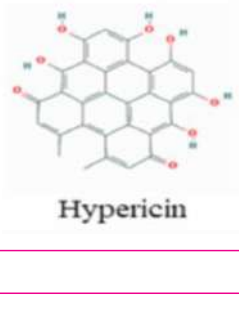



Beta- Sitosterol


Hesperetin

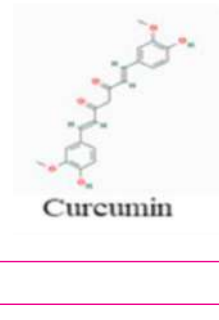

Epicatechin gallate

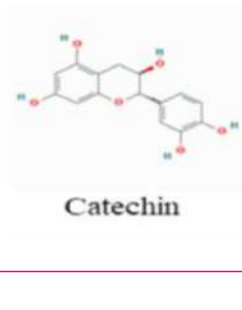

Sinigrin

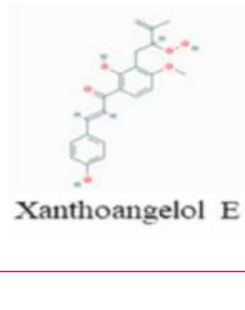

Hypericin

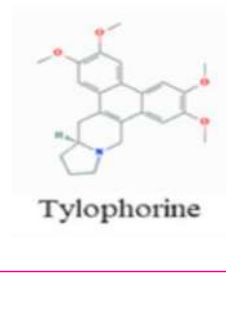

Theaflavin

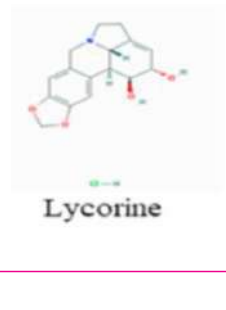

Tryptanthrin


Curcumin

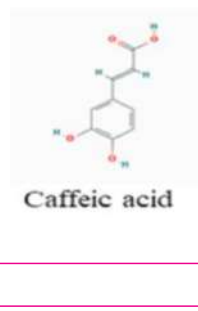

Catechin

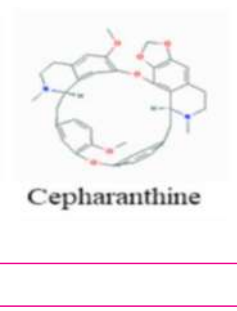

Xanthoangelol E


Tylophorine

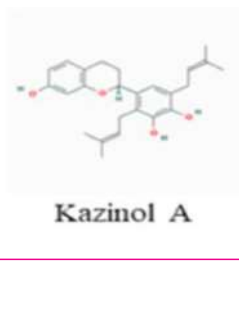

Lycorine

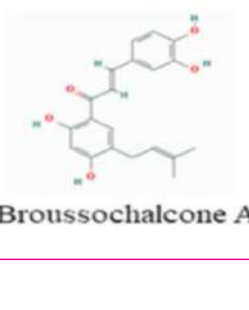

Tetrandrine


Caffeic acid

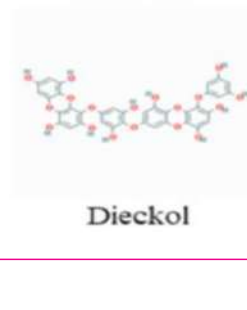

Cepharanthine


Silvestrol


Kazinol A


Broussochalcone A


Bavachinin


Dieckol

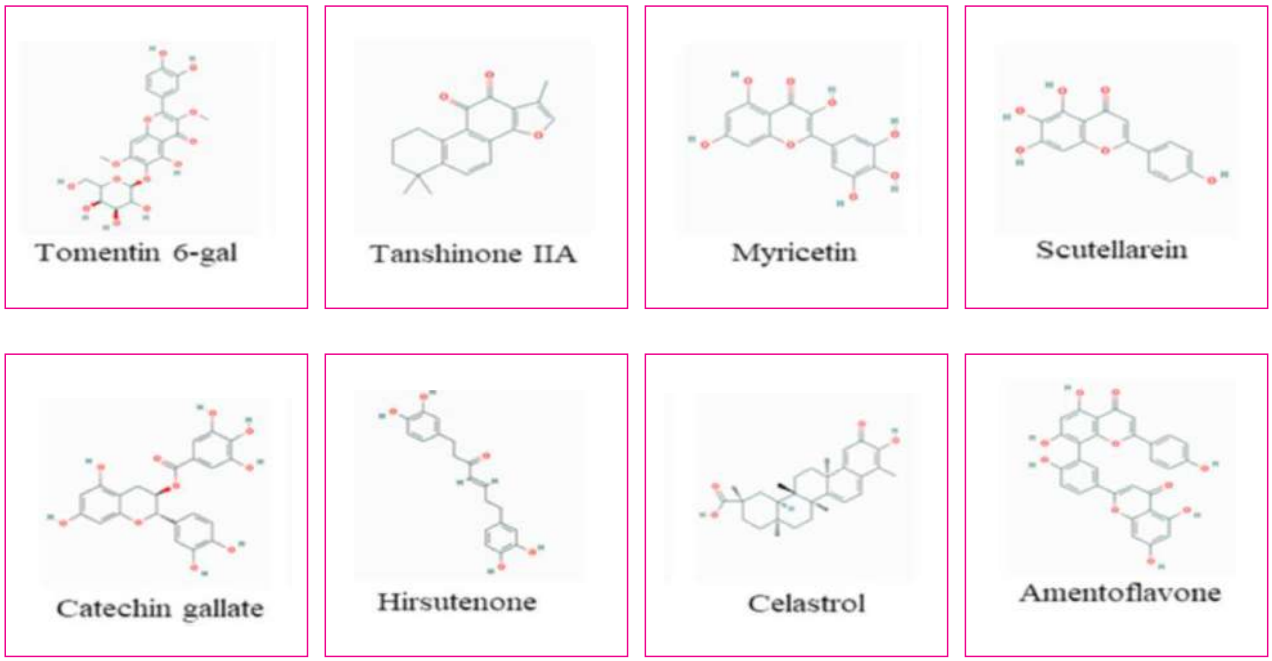


Figure 2. Some phytochemical compounds against corona virus (29).

Potential phytochemical with inhibitory role on helicase Nsp13 of COVID-19

Nsp13 (COVID-19 helicase) is a viable target for developing medicinal against COVID-19. It is an ATPase as well as a helicase and may hydrolyze a variety of NTPs, including ATP in an ATP-dependent way for RNA helices unwinding (30).

In a study using docking and dynamics molecules simulations, the top identified compounds with possible inhibition role against SARS-CoV-2 helicase Nsp13, comprising (+)-Epiexcelsin, Picrasidine M, Isorhoeadine, Euphorbetin, and Picrasidine N, were proposed for experimental studies against this virus using a phytochemical library of over 14,000 natural products from medicinal plants of India (31).

Potential phytochemical inhibitors of the SARSCoV2 Spike protein's HR1 domain

ARS-viral CoV-2's fusogenic process is mostly dependent on the interaction of the spike protein's heptad repeat 1 and 2 (HR1 and HR2) domains. After binding, some changes occur in the spike protein conformation and the virus fuses and enters the host cell (32, 33). Based on Molecular Docking, among phytochemicals evaluated upon to the HR1 domain in the COVID-19's spike protein, it was observed that Isopomiferin, SilybinC, SilydianinB, Silydianin and Lycopene because of their high binding affinity and excellent binding stability can be chosen as substances with possible inhibitory properties HR1 domain-specific protein (34).

Inhibitors of Spike Receptor-Binding Domain Attachment to the Receptor of Human ACE2

Júnior MLP and Júnior LAR (2021) by virtual screening of sixteen different flavonoids present in the peppermint (*Mentha piperita*) leaf investigated possible inhibitors in attachment of spike receptor-binding domain (RBD) of COVID-19 to the receptor of human ACE2. They proposed Luteolin 7-O-neohesperidoside as peppermint flavonoid with a higher binding affinity regarding the RBD/ACE2 complex (about -9.18 Kcal/mol). Mentha *piperita* is a perennial herb and medicinal plant native to Europe widely used for treating stomach pains, headaches, and inammation of muscles.

Sakuranetin, as a flavonoid in this plant was the one with the lowest affinity (about -6.38 Kcal/mol) to RBD/ACE2 complex. Moreover, Fisetin, Quercetin, and Kamferol molecules with good binding affinities could couple to RBD/ACE2 complex indicated effective roles of flavonoids. This class of small molecules found in fruits, vegetables, flowers, honey, teas, and wines (35, 36) has a good antimicrobial, antioxidant, anti-inflammatory, and antiviral functions (37) against COVID-19 infection (38). Ngwa and colleagues (2020), showed the ability

of caflanone used computer simulations of caflanone, Hesperetin, and Myricetin flavonoids in inhibiting for the RBD/ACE2 attachment of the SARS-CoV-2 virus from mother to fetus in pregnancy (39).

Moreover, Pandey et al., showed effective treatments of ten flavonoids in inhibiting the RBD/ACE2 interaction conducted molecular docking and dynamics simulations (40).

Natural Molecules zfrom Plants and their potential inhibitory properties against Coronavirus

Active phytochemicals and their derivatives have been identified medicinal properties to treat many diseases due to their antioxidant properties, scavenging abilities, and ability to inhibit DNA and RNA synthesis in some circumstances, and prevention of virus entry or reproduction. These phytochemicals with a wide variety include the terpenoids, flavonoids, limonoids, organosulfur compounds, coumarins, lignans sulphides, polyphenolics, polyines, furyl compounds, chlorophyllins, thiophenes, alkaloids, saponins, proteins and peptides (4).

In Figure 3, Natural products' potential anti-SARS-CoV-2 effects are summarized (41).

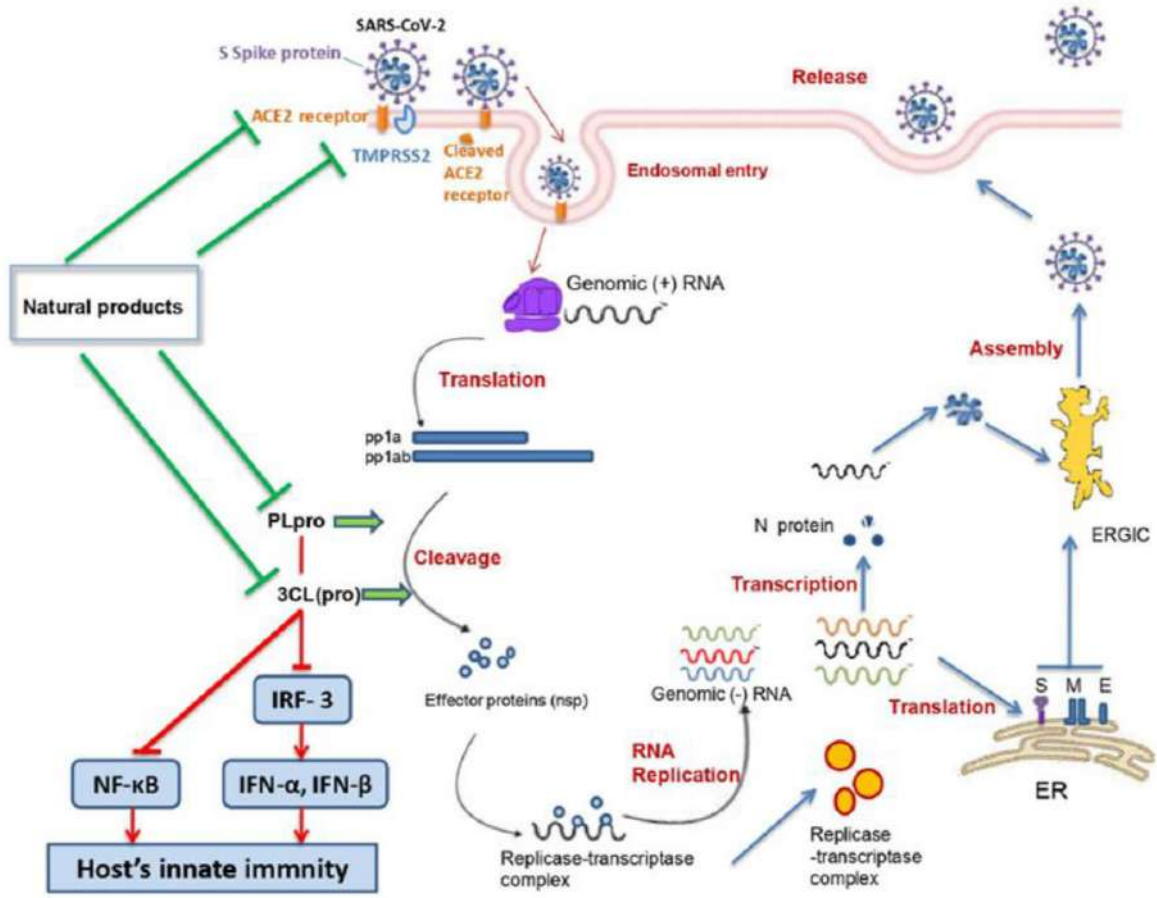


Figure 3. Summary of natural products possible activity against SARS-CoV 2 actions.

Conclusion

COVID-19, caused by new SARS coronavirus 2 (SARS-CoV-2) strain, is a serious global public health issue. Because of inherent complexity of this virus, it is difficult to identify effective remedies to combat this disease. Natural products as a rich source of therapeutic compounds can be utilized to prevent or treat several diseases. It demonstrated that several prominent viral portions can be inhibited by different natural products of medicinal plants. This review demonstrates that some natural medicinal products with high IC50 values can be considered anti-COVID-19 agents, as well as having the ability to inhibit some specific proteins, such as Mpro, PLpro, cellular receptor ACE2, and RdRp. Hence, these molecules with therapeutic potential derived from plants will enable the development of novel natural solutions for COVID-19 treatment.

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