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Role of phytochemicals to combat infection

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Abstract
The viral or bacterial infection is constantly diffusing worldwide and the incidence of death is dramatically increasing, representing one of the greatest disasters in human history. Nowadays, no effective therapeutic approaches have been licensed, despite the rising interest of the scientific research in this specific field, and the daily growing number of publications, while the need to find novel strategies is urgent. Evidence in the literature reported the antimicrobial activity of bioactive compounds in nature.

Plant biosystems are easy to scale up and inexpensive, and they do not require refrigeration or a sophisticated medical infrastructure. Regarding the context, the implementation of plant-made biopharmaceuticals in the developing world is an unescapable event.

At the same time, it is fundamental to invest in technical platforms able to cut down the time to tailor the eventual vaccine candidate to be effective to the epidemic. Plant Molecular Farming and improved genetic vaccines capable of plant sequences with immune-modulating activity, represent two promising approaches for the rapid and affordable production of countermeasures against emerging and bioterrorism-related infections.

Keywords: Alkaloids, Flavonoids, ginger, turmeric, phenols, SARS-CoV2, polyphenols, antiviral, nutraceuticals

1. Introduction
During this unescapable situation, world is facing unhealthy circumstances impeding the normal lifestyle. It is very much necessary to develop drugs or vaccine for this current deadly infectious disease at the earliest, but unfortunately there are no FDA approved drugs available in the market and development of new therapeutic moieties and vaccine remains a costly and time-consuming affair with high failure chances too (Abd El-Aziz *et al*, 2020) [1]. Keeping that in mind it is very crucial to use alternate options to combat the current situation. Medicinal plants offer the most common treatment options since ancient times against various viral diseases because of their safer, cheaper and less toxicity profile (Khan *et al*., 2020) [10]. The National Health Commission of China suggested traditional Chinese medicine as an alternative defence treatment option (Mirzaie *et al*., 2020) [36]. From literature studies it was seen that phytoconstituents such as polysaccharides, triterpenes, phenolic acids, alkaloids, proanthocyanidins and anthraquinones etc., possessed anti-viral activity against rabies virus, HIV, Chandipura virus, Japanese Encephalitis Virus, Enterovirus, Influenza A/H1N1 and other influenza viruses, and SARS (Ganjhu *et al*., 2015; Pillaiyar *et al*., 2020; Khaerunnisa *et al*., 2020) [24, 42, 32]. Table 1 shows a list of different phytoconstituents which have shown anti-viral activity against different types of coronaviruses.

The practice of medicinal plants and their extracts as medicine is based on data from spiritual traditions, individual cultures, and experience of therapeutic preparations. Traditional therapeutic methods and the use of medicinal plants were the only way to maintain the health of the human population. It is becoming more and more clear that medicinal plants have a strong place in modern medicine. The use of medicinal plants along with professional medicine suggests that mankind is returning to old experience and knowledge (Devi *et al*., 2012; Mishra *et al*., 2015; Yashin *et al*., 2017) [19, 37, 57]. Research and implementation of natural medicines as well as traditional therapeutics are driven by the emergence of new diseases such as viral COVID-19. The chemical constituents found in medicinal plants are natural and are therefore considered the most rational to use. Plants have a large range of viral protein inhibitors that are usable in the treatment of viral-type diseases such as SARS. Overall, plants can produce chemical components that exhibit inhibitory effects on enzymes, proteins, and virus proliferation. Various plant and natural chemical compounds have been shown to be effective antivirals against SARS-CoV and similar viruses (Srivastava *et al*., 2020) [53]. A variety of secondary metabolites are bioactive components and some of them have displayed activity against the coronavirus. These include papain-like proteases, 3-chymotrypsin-like proteases, spike proteins, angiotensin-converting enzyme II receptor, RNA-dependent RNA polymerase or affect the life cycle of a coronavirus. Thus, this chapter focuses on summarizing medicinal plants and/or herbs showing antiviral properties, which may be useful in drug discovery programs (Singh *et al*., 2016; Rajagopal *et al*., 2020) [50, 44].

This review focuses on deciphering the potential of different secondary metabolites from medicinal plants as therapeutic options either as inhibitors of therapeutic targets of SARS-CoV-2 or as blockers of viral particles entry through host cell receptors. The use of medicinal plants containing specific phytomoieties could be seen in providing a safer and long-term solution for the population with lesser side effects

Various methods are available for the *in vivo* and *in vitro* screening of medicinal plant extracts. This review focuses on the use of plant-based components in medicinal chemistry. The analysis, process, and development of herbal ingredients have increased dramatically with innovation in laboratory techniques and instrumentation (Fitzgerald *et al*., 2020) [23].

Table 1: Possible antiviral drug candidates from natural products

Plant sources	Isolated molecules	Active against virus	References
Scutellaria baicalensis Georgi	Isoscutellarein	Influenza virus	(Nagai *et al*., 1992) [39]
Kaempferia parviflora Wall. ex Baker	5,7-Dimethoxyflavone, Tetramethylluteonin, Tri methyl apigenin, 5-Hydroxy-7-methoxyflavone,	Avian influenza virus (H5N1)	(Sornpet *et al*., 2017) [52]
Curcuma longa L.	Curcumin(diferuloylmethane)	H5N1	Sornpet *et al*., 2017 [52]
Houttuynia cordata Thunb.	Quercetin 3-rhamnoside	Influenza virus	Choi *et al*., 2009 [18]
Tripterygium regelii Sprague &Takeda	Celastrol, Pristimerin, Tingenone, Iguesterin	SARS-CoV	Ryu *et al*., 2010 [47]
Ecklonia cava	Dieckol, Eckol, Triphloretol A, Dioxinodehydroeckol, 2-Phloroeckol, 7-Phloroeckol, Phlorofucofuroeckol A, Fucodiphloroethol G	SARS-CoV	Park *et al*., 2013 [40]
Ginkgo biloba L.,	Ginkgetin	Influenza virus	Miki *et al*., 2007 [35]

Innumerable plant chemical constituents that are being studied for the various viral treatment are as following:

Flavonoids are polyphenolic complexes present in plants and perform various biological functions. Various flavonoids have an effective role against viral infections, especially at the molecular level, to inhibit the growth of the virus. Flavonoids interfere with viral replication and translation and thus prevent virus entry into the cell by blocking cellular receptors (Aucoin *et al*., 2020; Agarwal *et al*., 2020) [13, 2]. Epicatechins and EGCG belong to the class of flavan-3-ols. It is widely present in tea. Epicatechins showed significant inhibition of IL-6 and IL-8 induced by phytohemagglutinin (PHA) and lipopolysaccharide (LPS). Epicatechins exert a potent reverse transcriptase inhibitory activity *in vivo* (Chang *et al*., 1994; Chan *et al*., 1999) [17, 16].

It was described that EGCG exhibits effects on IL-6, TNF-α, and IL-8 levels in phorbol 12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-stimulated human mast cells (HMC-1). In contrast, EGCG suppresses the secretion of IL-6, IL-1β and TNF-α in fluoride and marine aspiration-induced lung injury in rat models through regulation of the Nrf2/Keap1 and JAK/STAT pathways, respectively (Chan *et al*. 1999; Srivastava *et al*., 2020) [16, 53]. EGCG exerted a remarkable inhibition of reverse transcriptase enzymatic activity in murine leukemia virus (Chang *et al*., 1994) [17].

Rutin is one of the common flavonols widely distributed in citrus fruits and buckwheat. It is the glycoside form of quercetin. Rutin treatment suggestively inhibited the secretion of IL-6, IL-1β, IL-8 and TNF-α in PMACI-stimulated HMC-1 cells. Rutin treatment reduced the secretion of IL-6, IL-1β and TNF-α in LPS-induced acute lung injury in ICR mice by targeting oxidative stress and inhibition of the MAPK-NF-B pathway in *in vivo* studies (Ahmed *et al*. al., 2015) [7]

Luteolin is one of the most common flavones, widely distributed in fruits and vegetables such as cabbage, carrots, broccoli, celery, parsley and apple skins. The compound had antiviral activity against SARSCoV in Vero cultured cells with an EC50 of 10.6 µM. Luteolin was reported to interfere with the spike, core protease and nucleocapsid protein of SARS-CoV-2 to prevent viral infection (Huang *et al*., 2019; Ansari *et al*., 2020) [31, 10].

The potential role of flavonoids in the management of SARS-CoV-2 conditions is not limited to the examples above. There are many other flavonoids of different subclasses in various stages of research that have shown activities in *in vitro* and *in vivo* models, such as flavan-3-ols such as catechins and theaflavins; flavanones such as liquiritigenin, eriodictyol, taxifolin and pinocembrin; flavonols such as myricetin, castisine, galangin and kaempferol; flavones such as fisetin, apigenin, chrysin, wogonin and velutin; Isoflavones such as formononetin.

2. Alkaloids

Alkaloids are naturally occurring organic compounds that contain basic nitrogen atoms. Alkaloids were found to have an important role in the inhibition of viral replication as it blocks the function of viral DNA polymerase (Rajagopal *et al*., 2020) [44]. As these plant secondary metabolites have DNA intercalating properties, they may be effective candidates against viral infections and lead to the development of drug molecules. Resoquin, a synthetic derivative of quinine (alkaloid), an anti-malarial drug has been found to be an effective therapeutic agent against COVID-19. Isoquinoline was effective against the spike protein and nucleocapsid protein of SARS-CoV-OC43 in human lung cells, suggesting that it may serve as a drug candidate against SARS-CoV-2. Some alkaloids that have DNA intercalating activity are sanguinerein, quinine, cinchonain, hartamine, chelidonine, coptisine, berberine, palmetin, tetradine, etc., and can be used for the development of drug molecules (Ahmed *et al*., 2015) [7]; Agarwal *et al*., 2020) [2].

3. Phenolics

Phenolics are naturally occurring plant polyphenolic compounds that contain one or more hydroxyl groups attached to an aromatic hydrocarbon group. They have chemical properties where the hydroxyl group dissociates under different physical conditions (Chibi 2020). Phenolic compounds carrying five or more hydroxyl groups along with a methoxyl group have antiviral properties (Dillard and German 2000; Rajagopal *et al*., 2020) [20, 44]. Plants such as Euphorbia spindens and Bombax malabaricium were tested for anti-HSV and anti-RSV respectively and were as effective as ribavirin (antiviral) synthetic drugs. Phenol helps in inhibiting the fusion of virus in the host cell by binding with the viral proteins present in the viral envelope. Since most polyphenols are polar molecules and hence cannot be taken up by host cells and thus may prove to be good candidates against infection (Singh *et al*., 2016; Srivastava *et al*., 2020) [50, 53].

4. Essential Oils

Essential oils are volatile concentrated hydrophobic liquids extracted from plants. Essential oils are widely used in phytomedicine and aromatherapy, and also in pharmaceuticals. They have various biological functions like antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, anticancer etc. Several reports describe the effective antiviral activity of essential oils on influenza virus, simplex virus, etc. A mixture of essential oil and oleoresin from medicinal plants was also tested for coronavirus, bronchitis virus, etc. The essential oil readily interacts with the phospholipid bilayer of the cell membrane and this disrupts the viral envelope, thus initiating their activity prior to host cell attachment. Various essential oils have been shown to be effective against a variety of viruses, including isoborneol, a monoterpene with antiviral effects against HSV1. Essential oils thus constitute a major group of phytochemicals that need to be thoroughly investigated to discover new effective treatments against virus severity (Rejching *et al*., 2009; Yashin *et al*., 2017) [45, 57].

5. Saponins

Saponins are non-ionic detergents that have antifungal, cytotoxic, antibacterial and antiviral properties. Saponins are used in the development of steroidal drugs and thus are used in modern medicine (Srivastava *et al*., 2020) [53]. Saponin exerts antiviral activity because it can interact with viral envelope and capsid proteins resulting in the disintegration of viral particles, as well as it can interact with host cell membranes inhibiting viral particle attachment to host cells Thus prevents fusion by coating the surface of the cell which reduces the spread of infection. Some studies found that Quillaja saponaria extract containing the triterpenoid saponin had very strong activity in both human and animal vaccines. Some studies demonstrated the antiviral activity of saponins on other viruses such as simplex virus, hepatitis B virus and cytomegalovirus. Thus, this approach to saponins requires the attention of scientists to be investigated in detail for the development of an effective therapeutic candidate against viral infections (Dillard and German 2000; Aucoin *et al*., 2020) [20, 13].

6. Tannins

Tannins are naturally occurring compounds found in plants, seeds, bark, wood and fruits etc. and have various biological properties and medical uses. Viral infection leads to overproduction of free radicals and thus oxidative stress triggers the production of reactive oxygen and nitrogen molecules and tannins extracted from plants are very effective against oxidative stress (Gupta *et al*., 2013; Singh *et al*., 2016) [29, 50]. Several studies confirmed the antioxidant effect as a potential treatment against various viral infections. The antiviral activity of tannins against various viruses such as enterovirus, calicivirus, rotavirus, simplex virus, and coronavirus, etc. has been well established. Tannins such as pedunculgin, tercatenase and punicalin can bind effectively with SARS-CoV-2 by interfering with the viral binding site and destroying protease enzymes such as His41 and Cys145 and more recently by molecular docking methods (Srivastava *et al*., 2020) [53].

7. Anthraquinones

Anthraquinones are naturally occurring aromatic compounds that have a wide range of medicinal applications such as constipation, arthritis, multiple sclerosis, cancer and others and exhibit low toxicity with high activity. At present molecular docking studies have shown the effect of anthraquinones against SARS-CoV-2. Using docking studies, derivatives such as emodin, aloin A and B, rubiadin, aloe-emodin, pseudohypericin, danacanthal and cryosphanic, etc., were found to be inhibitors of SARS-CoV-2 to Mpro. But detailed *in vivo* and *in vitro* studies are needed to develop promising drug candidates against COVID19. Emodins extracted from Rheum officinale and Polygonum multiflorum were also able to block S-protein binding with the ACE-2 receptor in the SARS coronavirus. Anthraquinone derivatives such as hypericin are effective against various other viruses such as vaccinia virus and parainfluenza virus. Various computational tools showed the data of phytoconstituents from different medicinal plants against different therapeutic targets of COVID-19 and thus could be effective against this viral disease.

8. Potential activity of various spices and herbs

Various medicinal plants/herbs are known as immunity boosters, such as Allium sativum (garlic), Tinospora cordifolia (Giloy), Ocimum basilicum (Tulsi) and so on (Devi *et al*., 2012) [19]. Various spices like clove, cinnamon, black pepper and turmeric are known for their antiviral properties as well as immunity boosters. Neem leaves contain various compounds such as zinc, quercetin, vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin C, vitamin E, etc., which can enhance immunity (Dillard and German 2000) [20].

Turmeric (Curcuma longa L.) rhizomes contain several secondary metabolites that include curcuminoids, sesquiterpenes, steroids and polyphenols as major bioactive substances (Gupta *et al*., 2013; Mishra *et al*., 2015) [29, 37]. Several studies have shown that curcumin has some pharmacological properties such as anti-inflammatory, anti-angiogenic and anti-neoplastic, without toxicity. Curcumin's role in targeting various cellular pathways, further inhibiting growth, and replication of the virus makes it an ideal candidate as an anti-viral drug. Based on their molecular docking study, reported that curcumin binds to and inhibits target receptors, including the SARS-CoV-2 protease, the spike glycoprotein RBD, and PD-ACE2, which are involved in virus infection (Ali and Banerjee 2016) [9].

Ginger is a rich source of bioactive compounds such as alkaloids and steroids, which have medicinal effects. The main aromatic agent of the rhizome is zingiberole, which has analogs such as shogaols, paradol and zingerone. In addition to the main bioactive compounds, Ginger also contains other sub-compounds such as 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol and 14-shogaol. They have been reported to exhibit antiemetic, antipyretic, analgesic, antiarthritic and anti-inflammatory activities (Aboubakr *et al*., 2016; Adhikari *et al*., 2020) [2, 3]. Antiviral activity of lyophilized juice extracted from Zingiber officinale has been studied on hepatitis C virus (Admas 2020) [4].

Cinnamon (Cinnamomum cassia) is used for a number of conditions such as; Flatulence, amenorrhea, diarrhoea, toothache, fever, leukorrhea, common cold and headache (Fatima *et al*., 2016) [22]. It has also been reported that throat infections can be avoided with regular use of cinnamon. Numerous scientific studies have shown the antimicrobial, antiviral, antifungal, antioxidant, antihypertensive, antidiabetic, antitumor, gastroprotective and immunomodulatory effects of cinnamon (Hajimonferdnejad *et al*., 2018; Goldstein and Shumka 2019; Moshvarmiyev *et al*., 2020) [30, 28, 38].

Ocimum Basilicum L. (OB) is a popular medicinal herb of the Labiatae family also known as Sweet Basil. Ocimum basilicum has been reported to contain several interesting compounds, such as monoterpenoids (cineole, fenchone, geraniol, linalool), sesquiterpenoids (caryophyllene and farnesol), triterpenoids (ursolic acid), and flavonoids (apigenin) (Pattanayak *et al*., 2009) [41]. Three phytochemical compounds of basil, namely, visenin, soriantin 4'-O-glucoside 2 ”-O-hydroxy-benzoate, and ursolic acid showed inhibition of the main protease of SARS-CoV-2 in molecular docking studies. OB extracts and selected purified components also showed a broad spectrum of anti-DNA and RNA virus activities (Ghoke *et al*., 2018) [27].

Allium sativum L (garlic) has a wide range of pharmacological effects with low toxicity such as anthelmintic, anti-inflammatory, antioxidant, antifungal, and so on. Allicin (dily-dithiosulfinate), which is produced from alliin by the garlic enzyme allinase, is known to have broad-based antifungal and antiviral activities (Mehrbod *et al*., 2009) [34]. The decreasing order of compounds with antiviral activity in garlic was azoene, allicin, allyl methyl thiosulfate and methyl allyl thiosulfate. Antiviral activity of garlic extract has been studied in cell culture against influenza virus A/H1N1 and found to inhibit virus (Gebreohens 2013; Rajagopal *et al*., 2020) [26, 44].

Neem (Azadirachta indica) exhibits insecticidal, antimicrobial, larvicidal, antimalarial, antibacterial, antiviral and spermicidal effects. Various terpenoids isolated from the bark of this herb include nimbin, nimbidin, nimbolide, limonoids, β-sitosterol, 6-deacetylnimbine, nimbione, margosin, quercetin, and so on (Saha *et al*., 2010) [49]. A compound hyperoside from neem leaf extract showed potential as a universal drug against influenza strains due to its free radical scavenging property. Natural bioactive compounds extracted from Tulsi and Neem, namely Methyl Eugenol, Oleanolic Acid and Ursolic Acid act as inhibitors against SARS-CoV-2. These bioactive compounds act as effective inhibitors of SARS-CoV-2 by binding to spike glycoprotein, RNA polymerase, and/or its protease, resulting in both prevention of viral attachment and replication (Garba *et al*., 2019) [25].

Tinospora cordifolia (Giloy) has been extensively used for commercial purposes and used as an effective medicine for the treatment of many diseases like jaundice, urinary disorders, skin diseases, diabetes, anemia, inflammation, allergic conditions, etc. goes. Tinocordicide, one of the phytochemicals of Giloy, showed inhibition of the main protease of SARS-CoV-2 in a molecular docking study (Sagar and Kumar 2020) [48]. The berberine, isocolumbin, magnoflorin, and tinocordicide compounds isolated from giloy showed high binding efficacy against all four major SARS-CoV-2 target surface glycoproteins (6VSB), receptor-binding domain (6M0J), RNA-dependent RNA polymerase (6M71), and appeared. Key protease (6Y84) involved in virus attachment and replication (Sonkamble and Kamble 2015; Prithish and Gopinath 2018) [51, 43].

9. Future Perspectives and Conclusions

Considering the high cost and time-consuming drug discovery process, therapeutic repositioning of existing drugs was explored as treatment option in COVID-19, however several molecules have been retracted as therapeutics either due to no positive outcomes or the severe side effects. These effects call for exploring the alternate treatment options which are therapeutically effective as well as safe. Keeping this in mind, phytopharmaceuticals derived from medicinal plants could be explored as important resources in the development of COVID-19 treatment, as their role in the past for treatment of viral diseases like HIV, MERS-CoV, and influenza has been well reported. To avoid the next catastrophic loss of life from viral outbreaks such as Ebola, Zika, avian flu, MERS or a biological warfare (BW) attack whose epidemiology is linked to a sudden and unexpected infectious explosion, It is essential to rely on small reserves ready when the next outbreak begins. In the current pandemic scenario, taking precautions and boosting immunity is one of the best options to avoid viral infections. Despite rapid advances in modern systems, there is no effective and safe treatment available to date for the management of viral infections. Therefore, there is a need to evaluate the exploration of dietary supplementation for their beneficial role in the management of the acute condition. At the same time, it is fundamental to invest in technology platforms that are able to cut down on the time taken to prepare the final vaccine candidate to be effective for the pandemic. In other words, when there is an outbreak, vaccines will be ready for field-testing and mass manufacturing in just a few weeks/months. Plant-derived therapeutics have been produced for major diseases occurring in these countries through either time-consuming transgenic approaches or accelerated transient expression systems using viral vectors. With regard to context, the implementation of plant-made biopharmaceuticals in developing countries is an inevitable phenomenon. This will require new biotechnological tools for protein expression, such as new strong promoters, silencing suppressors or efficient viral expression vectors.

Problems encountered when using bioactive secondary metabolites such as their solubility, stability and bioavailability need to be addressed for using these metabolites as medicine. Furthermore, the application of artificial intelligence tools such as molecular docking studies, toxicity analysis and pharmacological studies will provide important information about the potency of the above secondary metabolites. However, mutations occurring in the targets should be taken into account. Extensive studies and investments are calling for new drug development strategies using herbal extracts today and tomorrow, to save the lives of sapiens on our planet from pandemics like COVID-19.

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