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A review on the correlation of traditional plants used for antiviral therapy as a possible treatment for Covid-19

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Review Article

A review on the correlation of traditional plants used for antiviral therapy as a possible treatment for Covid-19

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Abstract

The viral infection related to SARS and COVID-19 has led to a challenge among healthcare providers to search for efficient antiviral medicines. World Health Organization (WHO) has declared the current epidemic as a global disaster for people safety. That is why the research on drugs is considered as the current emergency in several clinical laboratories. The vaccines for the disease are still being tested in clinical trials to check for their efficacy. It could take a while before a safe and effective vaccine is made available for use to the global population that could specifically act against these viruses. But other methods for their treatment and prevention, including the use of medicinal plants, is available. Thus, it is important to develop a treatment regimen using medicinal plants and their phyto-constituents as a potential alternate substitute till an effective vaccine is developed to suppress the transmission of the virus. Based on current research information available, this review summarises the medicinal plants with antiviral activity for the prevention of SARS and COVID-19.

Key words: Viral infection, SARS, COVID-19, treatment, medicinal plants

Introduction

Viral infections, both new and persistent viruses, are a growing health issue worldwide. A global disease caused by viral infections, both severe acute respiratory syndrome (SARS) and coronavirus disease 2019 (COVID-19), has led to an emerging urgent need for novel and more efficient antiviral medicines. COVID-19 is a clinical condition synonymous with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the symptom involving a complex type of respiratory condition, varying from one to the other. While SARS-CoV-2 belongs to a similar genus of beta-coronavirus similar to the coronaviruses responsible for severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), this new virus appears to be related to milder infections.[1]

The most successful approaches to fight virus infection, particularly for COVID-19, are being investigated and developed, among which Remdesivir has been recommended for the therapeutic management of the patients. Currently, multiple clinical trials examining remdesivir for the treatment of COVID-19 are in progress or under development. Early in the pandemic, owing to the obvious positive outcomes of the first few patients, a combination of antiviral medication and corticosteroids was introduced as normal therapy in some countries.[2] The greatest challenge faced in virus therapy is their rapid drug-resistance tolerance and growth as well as the advent of modern hybrid viruses. Given the advances made in the development of immunization and medications, there is a lack in preventive vaccinations and successful antiviral therapies. Identification of novel antiviral drugs is important and natural medicinal products are an outstanding source of these findings.[3]

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Natural therapies have been gaining growing acceptance in the field of medical research over the last few years. The concept of herbal medicines is common in general population due to ease of access, cost-effectiveness, lack of side effects and high tolerance.[4] Consumption of herbal remedies is increasingly growing worldwide as an effective therapy for a variety of illnesses.[5] Many scientific studies conducted on medicinal plants reveal evidence of their beneficial applications for the prevention of viral diseases and infections.[6] The exact mechanism by which these plants act is not known. However, certain studies revealed that phytochemicals have superimposed response pathways and their antiviral activity may include the inhibition of DNA or RNA formation and viral replication.[7] Within this review, we summarise the recorded antiviral effects of many natural products and herbal medicines and the correlation of this to further treat SARS and COVID-19.

Medicinal plants used in South India for the management of COVID-19

1. Ginger

Ginger (Zingiber officinale, Family: Zingiberaceae) is the most commonly consumed herbal supplement worldwide. Though often used for culinary reasons, patients also use it as medicine for several conditions.[8] Ginger has demonstrated tremendous antimicrobial activity and efficacy in combating many viral, bacterial and fungal diseases.[9] Oleoresin from ginger's rhizomes includes multiple bioactive ingredients such as 6-gingerol, the main pungent element known to perform a variety of extraordinary pharmacological activities. Gingerols are the main constituents of fresh ginger, while Shogaol is more common in dry ginger.[10]

It has been tested in the plaque reduction study for antirhinoviral activity. Isolation of sesquiterpenes was done, among which beta-sesquiphellandrene was very effective in inhibiting rhinovirus.[11] Ginger is an important ingredient in conventional Chinese medications known to have antiviral efficacy against the human respiratory syncytial virus (HRSV).[12]

2. Licorice or Liquorice

Licorice (Glycyrrhiza glabra, Family: Fabaceae) is another popular herb that has been for centuries used in traditional Chinese medicine.[13] Phytochemical studies have shown that flavonoids and pentacyclic triterpene saponin, including isoliquiritigin, glabridin, glycyrrhizic acid and glycyrrhizin are the main chemical components of the licorice root.[14]

Glycyrrhizin was shown to be an active antiviral agent against SARS-CoV. It blocked adsorption and penetration of the virus.[15] The alkaline extract from the roots of licorice showed good anti-HIV efficacy than the extract from aqueous solvents. Licorice root flavonoids, especially liquiritinapioside, isoliquiritinapioside, lucurzide and isoliquiritin exhibited greater anti-HSV activity than other polyphenol and flavonoid compounds.[16] Animal studies conducted on Glycyrrhiza species reported reduced death rate and viral activity of pneumonia virus and herpes virus. In vitro studies were also conducted on the HIV virus, SARS-CoV, respiratory syncytial virus (RSV) and results were very promising.[17]

3. Garlic

Garlic (Allium sativum, Family: Amaryllidaceae) is considered an essential herb. Recent researches have established garlic's functional behaviour on cardiovascular disease and cancer. In fact, garlic has been shown to have immunomodulation, anti-inflammatory, antimicrobial, antioxidant, and antiviral effects.[18] Allicin (allyl 2-propenethiosulfinate or diallylthiosulfinate) is the most bioactive compound found in the garlic aqueous extract or the homogeneous raw garlic.[19]

One research suggested a possible path to combating the emerging pandemic SARS-CoV-2 with the use of basic garlic oil. The phytoconstituents in the essential garlic oil inhibit the angiotensin-2 (ACE2) converting enzyme, resulting in the virus missing the host receptor and targeting the SARS-CoV-2 central protease, PDB6LU7. The data on docking stimulation showed that 17 of the 18 basic garlic oil compounds had the capacity to inhibit the interaction between ACE2 and SARS-CoV-2.20 The in vitro antiviral study of the garlic extract was conducted against herpes simplex virus and influenza B virus. The virus infectivity titer was found to be reduced

upon incubation of the garlic extract with both the viruses.[21]

4. Ashwagandha

Withania somnifera (Family: Solanaceae), locally known as "Ashwagandha" is an Indian primary medicinal source for Ayurvedic and indigenous medicines and has been used for the treatment of various types of human diseases.[22] It includes alkaloids, steroidal lactones and flavonoids, including somniferine, withanine, withananine, pseudotropine, anaferine, choline, isopelletierine, withanolide, withanosine, withanonequercetine.[23]

The root f the plant has been documented against viruses such as herpes simplex, hepatitis, H1N1 influenza, HIV, coxsackie virus, their infections and replications for its effective antiviral function. Ashwagandha's antiviral function, adaptogenic and immunomodulatory ability was recorded. The findings of the simulation of in silico docking and the review of molecular dynamics suggested that certain phytoconstituents such as withanoside, dihydrowithaferin, withanolide and ashwagandanolide have the promise to inhibit the main viral proteins of SARS-CoV-2.[24]

The Ashwagandha plant has been tested as an antiviral agent against virus replication of infectious bursal disease. The hydroalcoholic extract of Withania somnifera roots showed virus inhibition in its highest nontoxic concentration, 25 μg/ml.[25]

5. Pepper

Piper nigrum (Family: Piperaceae) is the most prominent species of this genus. Owing to its pungent element, piperine, it is regarded as the "father of spices". It has beneficial health and disease-preventing properties such as antiviral, immunomodulatory, anti-inflammatory, antipyretic and bioavailability enhancement.[26] Phytochemical work done on its fruits indicated the existence of volatile oils and alkaloids including piperine, piperidine and piperidine analogs.[27]

It was found that the natural drug piperine has a better affinity to bind towards spike glycoprotein and its cellular response ACE2 compared to hydroxychloroquine. Thus inhibiting the interaction of spike glycoprotein of SARS-CoV-2 and its cellular receptor ACE2.[28] The results from the molecular docking study on the chemical constituents of black pepper performed to find the interaction with Covid-19, demonstrated better arrangement at the dynamic site.[29]

Piperamides isolated from the fruits were tested for their antiviral properties against viruses showing upper respiratory tract infection and their multiplication in vascular smooth muscle cells.[26]

6. Gooseberry or Amla

Emblica officinalis (Family: Euphorbeaceae) is widely found in ayurvedic medicines. Emblica officinalis is also called by the name Phyllanthusemblica or Indian gooseberry. It is a rich source of vitamin C along with other citrus fruits.[30] Pentagalloyl glucose (PGG), in amla, can inhibit Influenza A virus replication.[31] It greatly decreased the aggregation of nucleoprotein by the plasma membrane at the late stage of the replication process. PGG greatly reduced the budding virus and the production of progeny from contaminated cells.[32] It is also claimed to increase the white blood cells count and strengthen immunity.[33]

7. Tulsi

Ocimum sanctum (Family: Labiatae) is a medicinal herb used in indigenous system of medicine. The aqueous extract of the leaves contain chemical constituents like eugenol, carvacrol, urosolic acid, rosmarinic acid, linalool, α & β-caryophyllene, eugenic acid, geraneol, ocimene and β-elemene.[34]

The leaves extract contain useful secondary metabolites that were found to have antiviral activity against various viruses.[35] The extracts from the plant and its essential oil were found to possess inhibitory effect against the multiplication of viruses such as infectious pancreatic necrosis virus (IPNV), polio virus type-3, hepatitis B virus, white spot syndrome virus (WSSV), coxsackie virus B1 (CVB1), adenoviruses (ADV), herpes viruses (HSV) and enterovirus 71(EV71).[36]

The phytoconstituents found in tulsi, i.e., oleanolic acid, rosmarinic acid, methyl eugenol and ursolic acid have been used to test their activity against

SARS-CoV-2 protein targets. Tulsi compounds may be successful inhibitors of SARS-CoV-2 by binding to the spike glycoprotein, RNA polymerase and/or its protease, either in their pure form or as an extract.[37]

8. Guduchi

Tinospora cordifolia (Family: Menispermaceae) is the most widely used herbal supplement worldwide. It is recognized by various names such as giloy, guluchi, guduchi and amrutharasakinda.[38,39] Major constituents like cardiac glycosides, alkaloids, flavonoids, saponins, lignans, steroids, terpenoids, tannins are present in it.[40,41] The plant is also used in traditional ayurvedic medicine and has many clinical properties.[42,43] Guduchi has demonstrated tremendous immunomodulatory due to the presence of berberine and syringin.[44] It has been found that the plant extract has anti-HIV potential and inhibited HIV reverse transcriptase activity.[45]

Nanoparticles formulation of the plant witnessed potential antiviral action against the chikungunya virus. These showed increased phagocytosis and intracellular killing property which was responsible for reported antiviral activity.[46] The study was conducted on purified compounds from the plant, among which cordifolioside A and syringin were found to show significant immunomodulatory activity.[47]

9. Clove

Syzygium aromaticum (Family: Myrtaceae) is one of the most popular ancient spices. Cloves has the abundance of the following types of phytochemicals: monoterpenes, sesquiterpenes, phenolic compounds and hydrocarbons. The most important phytochemical in clove oil contains eugenol, eugenyl acetate and β-caryophyllene.[48]

The aqueous clove extract was studied as a counterpart to human norovirus, as an antiviral agent against feline calicivirus (FCV). The inactivation of FCV was found to be dose-dependent when the host cells were handled with clove extracts at concentrations equivalent to or below the mean non-toxic concentrations.[49] Eugenol, essential oil from clove was tested for antiviral activity against two strain of human syncytial viruses, which showed inhibition in the replication of these viruses. Surface application of the eugenol slowed down the progression of herpes virus-induced keratitis.[50]

10. Neem

Azadirachta indica (Family: Meliaceae) generally referred to as "Indian Lilac", is part of the Meliaceae family. It has been used by several civilizations for its pharmacological activities. Several compounds of medicinal value were shown to be present in the plant.[51] The neem tree contains chemical constituents like isoprenoids, tannins, polysaccharides, flavonoids, fatty acid, amino acids, dihydrochalcone, coumarins, aliphatic compounds, etc.[52] The different parts of the plant/tree has been reported to possess several pharmacological benefits including antiviral activities.[53]

Neem has shown its proven efficacy against coxsackie B group of viruses. Evidence suggested that certain compounds in the plant were found to be active against the virus as virucidal agent at sub-toxic concentrations during the early stage of replication.[54] Aqueous extract from the neem plant bark serves as a powerful inhibitor for entry into natural target cells against herpes simplex virus-1 infection. Neem bark extract (NBE) treated target cells also inhibited the development of HSV-1 glycoprotein-mediated cell–cell fusion.[55]

The polysaccharides obtained from the leaf of the plant and its sulphate derivatives demonstrated that compounds acted during the initial stage of viral replication and were powerful in inhibiting the multiplication of polio virus.[56]

Medicinal plants with antiviral activity against Covid-19

Research gap

Recent times have led to an increasing need for treatment of COVID-19. In most viral infections, e.g., SARS-CoV, hepatitis B, dengue, etc., there is no specific treatment. Presently, the therapeutic treatment used for COVID-19 is the same that has been used for older viruses like MERS, SARS and HIV. However, this treatment is not specific for the novel coronavirus since they are broad-spectrum. Newer antiviral drugs are still under clinical trials, for which safety and effectiveness are not confirmed. The pharmaceutical companies are under pressure to develop a safe and effective vaccine and have also considered focusing on natural product drug discovery.

Conclusion and future prospects

The medicinal plants studied in the review have been used for centuries by indigenous people either in combination to bring a synergistic effect or individually. The evidence provided in this review altogether reinforces the idea that herbs have promising potential against infection caused by various viruses. The potential future implications will be to further analyse the precise mechanism process against the new strain of viruses and to establish a drug delivery system that actually works over an extended time at the target location.

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