



Review Article

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NATURAL ANTIVIRALS FOR THE MANAGEMENT OF SARS-COVID-19: A REVIEW

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ABSTRACT

Unlike previous outbreaks like SARS and MERS, caused by corona family viruses, COVID-19 became a much worse worldwide pandemic. SARS CoV-2, another coronavirus, causes it. Finding effective therapeutics against this global health crisis became a significant challenge for researchers. However, Allopathic medicine is effective to some extent with severe side effects, which cause concern. In this process, some researchers focused on natural compounds like plant-synthesized secondary metabolites (PSMs) for the treatment of COVID-19. Because these natural compounds like PSMs had a history of tackling a wide range of viral pathogens successfully without significant side effects. Many medicinal plants from different families have antiviral activities. This review intends to systematically evaluate the natural metabolites that could be used against this new disease looking at their natural sources, mechanism of action, and previous pharmacological usages. So, it can be a good initiation for the greater goal of finding effective natural therapeutics for the treatment of Covid-19 without any severe side effects.

Keywords: Corona; Allium; Gallic acid; Withanone; Curcumin

INTRODUCTION

Corona virus disease 2019 (covid-19) is a new infectious disease caused by severe acute respiratory syndrome corona virus 2 (SARS - CoV - 2) which belongs to the corona virus family. The first case was identified in Wuhan, China in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic. Till now 115 million cases are reported worldwide and 2.55 million people died because of COVID-19. In India, till date, 11.1 million cases are reported, and 1.57 lakhs of people died with COVID-19.

Among all countries United States, Brazil, Mexico, India, UK have reported highest deaths. As the number of infections and deaths from Covid -19 continue to rise, researchers are working to identify suitable treatments and vaccines to curb the pandemic. Initially when COVID-19 started and proper information is unavailable regarding COVID-19, many treatment options are tried and tested to cure the disease.

In this process, as expected Allopathic medicine became first choice to majority of medical practitioners from all over the world to treat COVID-19. It has given satisfactory results for some extent but along with its obvious side effects. Later in some countries researchers are started experimenting with natural compounds to treat COVID-19 and avoid possible side effects¹.

Here in this article, we have discussed about various natural compounds from different parts of the world regarding their origin, mechanism of action, merits & demerits in controlling COVID-19. Apart from allopathic medicine certain natural compounds might be effective for the treatment of COVID-19 based on general concepts from previous experiments. Let us discuss about few of them.

Echinacea purpurea

It is most popular in Europe and North America. Its common name is purple coneflower. The preparation is made in the form of sprays, teas, tinctures, extracts. Many Native Americans use this for respiratory infections. It contains bioactive compounds like chicoric acid, alkyl amides and caffeic acid. Viruses with membranes are very sensitive to *E. Purpurea* extract. Since SARS - CoV-2 is an enveloped virus; it has promising result against COVID-19. Whether *Echinacea purpurea* is immunostimulatory (or) Immunosuppressor is still debatable. But it definitely had virucidal effect^{23,24}.

Curcumin

It is extract of turmeric plant. Turmeric plant belongs to Zingiberaceae (ginger) family and curcuma genus. Turmeric plant also known as *Curcuma longa*²⁵. *Curcuma longa* extracts contains curcuminoids like Curcumin, Demethoxy Curcumin and Bisdemethoxy Curcumin. Some studies showed that Curcumin had anti-inflammatory effect via inhibition of toll - like receptor (TLR - 4), Phosphatidyl inositol - 3 kinase (PI3K), nuclear factor - Kappa B (NF - K8). It decreases the production of IL - 6 and tumor necrosis factor (TNF - alpha), IL - 1beta etc. It helps in COVID-19. But another study showed that Curcumin causes hyper inflammatory state; so more detailed study is needed to clarify the effect of Curcumin²⁶.

Cinchona

Bark of cinchona trees produces quinine alkaloids which is effective against malaria. Nowadays quinine sulphate has become one of the most wanted drugs for COVID-19. A clinical trial proved that quinine in combination with Azithromycin decreases the SARS - CoV - 2 viral loads and have beneficial effects against COVID-19. Quinine inhibits the viral infection by interfering with virus replication, activating protein heat shock response,

inhibiting NF - KB. Quinine is also categorized as an immunomodulatory agent. When quinine increases the production of cytokine IFN - alpha, it functions as immunostimulatory. When it inhibits the release of TNF - alpha, it functions as immunosuppressant. These two different activities may have a beneficial effect on COVID-19²⁷⁻³⁰.

Xanthorrhizol

Java turmeric (or) *Curcuma xanthorrhiza* Roxb is an herbal plant that is widely used in Southeast Asian countries. This plant

belongs to the Zingiberaceae family and *curcuma* genus. It contains curcuminoids and Xanthorrhizol. Presence of Xanthorrhizol distinguishes this plant from *Curcuma longa*. Xanthorrhizol decreases inflammatory genes in adipose tissue. It inhibits CRP, a nonspecific marker of systemic inflammation in the liver. It inhibits interleukin (IL – 1 beta) gene expression in muscle. It decreases IL-6 level in serum. Taken together, Xanthorrhizol is an immunosuppressant that may be used as a treatment for COVID-19 because of its ability to inhibit proinflammatory cytokines. But it still requires more evaluation³¹⁻³⁴.

Table 1: Active metabolites inhibiting SARS COVID

Plant metabolite	Plant name	Mechanism of action
Emodin ²	<i>Darmera peltata</i>	Blocked the binding of s-protein ACE2
Escin ³	<i>Aesculus hippocastanum</i>	Decrease the levels of TNF-α, IL-6
Scutellarein ⁴	<i>Scutellaria baicalensis</i>	Inhibit the nsP13ATPase activity
Theaflavin-3 Gallate ⁵	<i>Camellia sinensis</i>	Inhibition of SARS-CoV 3C-like Protease Activity
Tannic acid ⁵	<i>Camellia sinensis</i>	Inhibition of SARS-CoV 3C-like Protease Activity
Limonene and Linalool ⁵	<i>Citrus sinensis</i>	Decrease replication through the involvement of TRP genes family
Tomentin ⁶	<i>Paulownia tomentosa</i>	Papain-like protease inhibition
Chalcones Xanthoangelol-E ⁷	<i>Angelica keiskei</i>	Inhibitory activity against Cysteine protease specifically using the cell-based 3C pro cis-cleavage assay
Diarylheptanoid ⁸ (hirsutenone)	<i>Alnus japonica</i>	Inhibits papain-like protease of SARS Coronavirus which controls replication of the SARS-CoV
Indigo, Singrin, Aloe emodin and hesperidin ⁹	<i>Isatis indigotica</i>	Inhibits the cleavage activity of the SARS coronavirus 3C-like protease
Amentoflavone, Bilobetin, Ginkgetin, Sciadopitysin ¹⁰	<i>Torreya nucifera</i>	Inhibits the SARS CoV 3CLpro
Acanthoside, Chilsanoside and phytosterols ¹¹	<i>Acanthopanax gracilistylus</i>	Reduce intracellular viral RNA levels with comparable reduction in viral Proteins and MHV-A59 production [11]
Torilin ¹¹	<i>Torilis japonica</i>	Reduce intracellular viral RNA levels with comparable reduction in viral proteins and MHV-A59 production
Lycorine ¹²	<i>Lycoris radiata</i>	Inhibits SARS-CoV [12]
Carvacrol and a-pinene ¹³	<i>Anthemis hyalina</i>	Decrease replication through the involvement of TRP genes family
Thymoquinone, ρ-simen, Karvakrol, t-anetol, 4-terpineol and Longifolene ¹³	<i>Nigella sativa</i>	Decrease replication through the involvement of TRP genes family
Quinone-methide triterpenes ¹⁴	<i>Tripterygium regelii</i>	SARS-CoV 3CLpro inhibitors
Physcion, Rhein ¹⁵	<i>Senna tora</i>	Inhibits the 3CL protease activity of SARS-CoV
Scabanol ¹⁵	<i>Gentiana scabra</i>	Inhibits the 3CL protease activity
Luteolin, Quercetin ¹⁵	<i>Taxillus chinensis</i>	Inhibits the 3CL protease activity of SARS-CoV
Procyanidin A2, Procyanidin B1 ¹⁶	<i>Cinnamomum verum</i>	Inhibits the internalization of TfR Indicating the interference of clathrin dependent endocytosis
Chrysophanol ¹⁷	<i>Rheum palmatum</i>	High level of anti SARS-CoV 3CL protease activity

Table 2: Active metabolites inhibiting SARS COVID-2

Plant metabolite	Plant name	Mechanism of action
Gallic acid ¹⁸	<i>Toona sinensis</i>	High binding affinity to RdRp tested by Molecular docking
Withanone ¹⁹	<i>Withania somnifera</i>	Bind and interact at catalytic site of TMRSS2
Curcumin ²⁰	<i>Curcuma longa</i>	Decrease the production of IL-6α and TNF-α Cytokines
Brazilein, Brazilin ²¹	<i>Caesalpinia sappan</i>	High binding affinities with SARS-CoV-2 protease, Spike glycoprotein-RBD and ACE2
Allyl disulfide, allyl trisulfide, allyl methyl trisulfide and diallyl tetra sulfide ²²	<i>Allium sativum</i>	Inhibition of the ACE2 and PDB6LU7 proteins

Many other foods and herbs all over the world are known to display immunomodulatory activities and antiviral effects against COVID-19.

- Angelica gigas*
- Astragalus membranaceus*
- Ganoderma lucidum*
- Panax ginseng*
- Scutellaria baicalensis*

All of the above exhibit immunomodulatory properties by stimulating cytokines, activating lymphocytes, increasing natural killer cell count and enhancing macrophage actions.

Eucalyptus essential oil - Improves innate cell mediated immune response.

Lawsonia alba - stimulates phagocytosis.

Saikosaponins

It represents a group of oleanane derivatives, usually as glucosides, that are found in a number of plant families. Saikosaponins isolated from medicinal plants such as *Bupleurum* spp., *Heteromorpha* spp. and *Scrophularia scorodonia* have been reported to possess various biological activities, specifically anti-hepatitis, anti-nephritis and anti-hematoma, anti-inflammation, immunomodulation and antibacterial effects³⁵.

NATURAL PRODUCTS INHIBITING SARS-COV

The envelope S protein of SARS-CoV is also essential for virus tropism and invasion into host cells, which is a potential target for the development therapeutics. Angiotensin-converting enzyme 2 (ACE2) is identified as a functional receptor for SARS-CoV, which facilitates S protein-mediated infection, indicating it is also a possible target.

Emodin

It is an anthraquinone. It is isolated from *Rheum officinale* Baill and *Reynoutria multiflora* (Thinb) Moldenke. Emodin blocks the binding of S protein to ACE2 and reduces the infectivity of SARS CoV because in SARS CoV ACE2 is identified as functional receptor for facilitation of S protein mediated infection²⁵.

Scutellarein

It is a flavone found in *Scutellaria lateriflora* L and other members of genus *Scutellaria*. The nonstructural protein 13 (nsp 13) of SARS CoV is a helicase which unwinds dsDNA using ATPase. *Scutellaria* inhibits this activity and this holds a promising potential for tackling SARS outbreaks. However more preclinical / clinical studies are needed to evaluate their anti-viral effect³⁶.

Tannic acid and Theaflavin-3-gallate

Tannic acid is a polyphenol found in *Caesalpinia spinosa*. Theaflavin -3- gallate is a theaflavin derivative found in black tea. Both have inhibitory effect against 3CLPro of SARS CoV, an enzyme responsible for proteolysis which is vital for coronavirus replication. 3CLPro stands for Chymotrypsin like protease⁵.

Escins

Escins are saponin mixtures found in *Aesculus turbinata* Blume. It shows anti-inflammatory and anti-viral activity against SARS CoV by decreasing the levels of TNF - alpha and IL-6. But severe cytotoxic effects of this limit its potential to be a prophylactic. Usually, a more efficient and safer drug can be designed based on the original natural compound which can exhibit wanted activity without much cytotoxicity³.

NATURAL PRODUCTS INHIBITING SARS-COV-2

Phytoestrogens (Daidzin, Genistein, Formononetin and Biochanin A) and Estrogen

HSPA5 (Heat Shock Protein A5) is also called BiP. It presents in host cell. Upon viral infection it translocates to the cell membranes where it is subjected to be recognized by the SARS CoV-2 spike. The phytoestrogens and estrogen have proximal binding affinities with HSPA5 and this interfere with SARS CoV-2 attachment to the host cells.

Withanone

It is derived from Ashwagandha leaves (*Withania somnifera* (L). TMPRSS2 (Transmembrane Protease Serine 2) is a host enzyme which facilitates viral particle entry into host cells. Withanone could bind and stably interact at the catalytic site of TMPRSS2 and then ramp down TMPRSS 2 function and this inhibits viral particle entry into host cells¹⁹.

Papain like protease (PLPro)

It is an essential coronavirus enzyme which cleaves the viral polyproteins a/b which are essential for its survival and replication. Lead compounds from Galangal and ginger bound with high affinity to PLPro and thus works against SARS CoV-2³⁷.

10 - Hydroxyusambarensine, Cryptoquindoline, 6-Oxoisoiguesterin

These are the compounds mainly derived from African plants. They inhibit 3CLPro enzyme (3 Chymotrypsin like protease). 3-CLPro enzyme cleaves coronavirus polyproteins and controls virus replication and thus these compounds work against SARS CoV-2³⁸.

Polyphenols

RNA dependent RNA polymerase (RdRp) is an essential viral replica that catalyzes the synthesis of complimentary RNA strands using the virus RNA template. And EI - Aziz *et al* investigated that eight natural polyphenols (quercetin, naringenin, caffeine, Oleuropein, ellagic acid, benzoic acid, resveratrol, gallic acid poly phenols) inhibits SARS CoV -2 RdRp by forming hydrogen bonds with the Nucleotide triphosphate (NTP) entry channel amino acids (ARG 555, LYS 545)³⁹.

Cepharanthine

It is an alkaloid tetrandrine isolated from *Stephania tetrandra* S. Moore. It has anti-inflammatory and antioxidant activities. Cepharanthine could bind to the interface active pockets of the SARS CoV -2 NSP12- NSP 8 and acts against SARS CoV-2⁴⁰.

CONCLUSION

Collectively using the immunomodulatory and antiviral herbs and foods could protect the body against COVID-19. However, these observations must be verified through scientific (or) clinical studies.

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