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HERBAL MEDICINES IN MANAGEMENT AND PREVENTION OF CORONAVIRUS DISEASE 2019 (COVID-19)

Ritav Brahmbhatt

Vardhman Raw House, Opp. Shankeshwar App, New Kosad Road, Amroli, Surat - 394107, Gujarat, India.

Keywords:

Traditional Herbal Medicine, COVID-19, AntiCOV-19, Structural levels, RNA synthesis, *Tribulus terrestris*, *Withania somnifera*, *Curcuma longa*, *Ocimum sanctum*, *Phyllanthus emblica*

Correspondence to Author:

Ritav Brahmbhatt

Vardhman Raw House, Opp. Shankeshwar App, New Kosad Road, Amroli, Surat - 394107, Gujarat, India.

E-mail: ritavbrahmbhatt@gmail.com

ABSTRACT: Traditional herbal medicines are widely accepted in the world. Certain countries and WHO have research investment in traditional herbal medicines. Coronavirus disease 2019 (COVID-19) came as a major health care challenge for humans in 2019. 480 deaths have been recorded till 18th of April 2020 in India. No pharmaceutical products have yet been shown to be safe and effective for the treatment of COVID-19. Major 3 types of targets of Coronavirus were identified by researches, which are as follow-1) Inhibit coronavirus at a structural level, 2) Inhibit Coronavirus RNA synthesis and replication and 3) inhibit virulence factor of Coronavirus. Certain herbal medicines like *Tribulus terrestris*, *Withania somnifera*, *Curcuma longa*, *Ocimum sanctum*, and *Phyllanthus emblica* have potent anti-viral (Anti-COV-19) properties against novel Coronavirus, which is indicating new sunrise in the direction of herbal medicine.

INTRODUCTION: Traditional herbal medicines are getting significant attention in global health debates. India, The United States of America (USA), China, Nigeria, and the World Health Organization (WHO) have all made substantial research investments in traditional herbal medicines¹. Herbal medicine finds itself in a race to develop new medicines, with fewer or no adverse effects, for therapeutic and preventive application in illnesses². As per the Ministry of Health and Family Welfare, Government of India, there are 11, 906 Active Cases of COVID-19. 480 deaths have been reported, 1991 patients were discharged till 18th April 2020³.

But still, no pharmaceutical products have yet been shown to be safe and effective for the treatment of Coronavirus (COV-19). However, a number of medicines have been suggested as potential investigational therapies, many of which are now being or will soon be studied in clinical trials, including the SOLIDARITY trial co-sponsored by WHO and participating countries⁴.

MATERIALS AND METHODS:

Bibliographical Databases: Google Scholar, PubMed, Preprint, ChemRxiv.

Search Terms: Herbal medicine, COVID-19, *in-vitro*, *in-vivo*, preclinical, clinical trials.

Search Strategies:

- Phytoconstituents and its effectiveness against COV-19.
- Herbal medicine and its binding sites to COV-19.

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Selection Criteria:

Inclusion: Phytomedicine and its binding capacity with COV-19 (Primary virtual examination). *In-vitro* and *in-vivo* studies associated with COV-19

Exclusion:

- ❖ Clinical trials (due to lack of research)
- ❖ Unknown source of Herbal Medicine

- ❖ The number of studies screened more than 500
- ❖ The number of studies included: 25

Major 3 Types of Targets of COV-19:⁵

1. Inhibit Coronavirus at a structural level.
2. Inhibit Coronavirus RNA synthesis and replication.
3. Inhibit the virulence factor of Coronavirus.

1.1 Major Targets of COV-19:**TABLE 1: ENLIST THE MAJOR TARGETS OF COVID-19**

S. no.	Major Targets of COV-19 ⁵		
#	Inhibit SARS-CoV-2 RNA Synthesis and Replication	Inhibit SARS-CoV-2 at Structural Level	Inhibit Virulence Factor of SARS-CoV-2
1	Papain-like protease (PLpro) ⁵	Spike Protein ⁵	Nsp1 ⁵
2	3C-like main protease (3CLpro) ⁵	E protein Or N protein ⁵	Nsp3c ⁵
3	RNA-dependent RNA polymerase (RdRp) ⁵	-	ORF7 ⁵
4	Helicase ⁵	-	-

1.2 Effective Herbal Plants against COVID-19:

Certain natural products from Indian natural medicines bind to the active sites of COV-19 proteases, hence are likely to hinder viral replication⁶.

1.2.1 *Tribulus terrestris*: *Tribulus terrestris* fruits are well known for their usage in pharmaceutical preparations and food supplements. The methanol extract of *T. terrestris* fruits showed potent inhibition against the papain-like protease (PLpro), an essential proteolytic enzyme for protection to pathogenic viruses and bacteria. Major bioactive compounds, aresix cinnamic amides, and ferulic acid were showing inhibition of Papain-like protease (PLpro), which is the major protein target of COV-19.(7)

1.2.2 *Withania somnifera*: *Withania somnifera* contains a variety of phytoconstituents like Withanolide A & B, Withaferin A, Withanone, Withanosides⁸. *W. somnifera* glycoprotein (WSG) isolated from *W. somnifera* root tubers revealed (protease inhibitor) antimicrobial activity against few bacterial and phytopathogenic virus⁹. *W. somnifera* would be an effective agent in the management of COV-19 through modulation of host Th-1/Th-2 immunity. *W. somnifera* may be beneficial in inducing anti-viral immunity (owing to increased IFN-gamma responses) and optimum anti-inflammatory activities (down-regulation of IL-1, IL-6, TNF-alpha and other inflammatory mediators), which are the key targets relevant to

COVID-19¹⁰. As per the recent molecular docking studies, Withanolide D, Withaferin A, as most appropriate inhibitors against 3C-like main protease (3CLpro), which can be further explored to test against Coronavirus (COV-19) in pre-clinical and clinical settings¹¹. Withanolide-B, Withanone, and Withaferin - A, major phytochemicals of *W. somnifera* have predicted binding energy lower than the pharmacological inhibitor, N3. The binding of these phytochemicals with the main protease may slow down the cleavage of pseudo-particles (PPs) to releases non-structural proteins (NSPs) and decrease the process of viral replication and transcription¹².

1.2.3 *Curcuma longa*: *Curcuma longa* contains demethoxy Curcumin, Curcumin, Diacetyl Curcumin¹³, as a major phytoconstituents, which are the most potent compounds that may act as potential inhibitors of COV-19 Main Protein (Mpro)¹⁴. Curcumin strongly binds to 3CL-protease of COV-19 in comparison to the antimalarial drugs and promote important structural changes in this viral protease, inducing folding of the enzyme¹⁵.

Diacetyl Curcumin present in *C. longa* has been found as more effective on COV-19 (Mpro) than Nelfinavir¹⁶. Docking studies suggesting that the binding energy of Curcumin (-38.84 kcal/mol) had greater than hydroxychloroquine (HCQ) (-35.87 kcal/mol) in the case of S1 receptor binding domain¹⁷. As, Curcumin and HCQ interact with the C-

terminal of S1 domain with different binding energies¹⁸. Therefore, Curcumin could be used as combination therapy along with hydroxyl-chloroquine for disrupting the stability of SARS-CoV2 receptor proteins.

1.2.4 *Ocimum sanctum*: *Ocimum sanctum* extract can be included as a preventive measure against COVID-19 due to its potential to inhibit replication of COV-19 supported with its immune-modulatory feature and ACE II blocking properties. *O. sanctum* containing Tulsinol (A, B, C, D, E, F, G) and dihydrodieuginol-B inhibit COV-19 Main Protease and Papain-like Protease⁹. *O. sanctum* is being used in the management of pain, diarrhea, cough and fever, which are the common symptoms of

COV-19²⁰. *O. sanctum* boosts the immunity of the body and helps to defend the threatening virus and bacteria²¹.

1.2.5 *Phyllanthus emblica*: *Phyllanthus emblica* also have immunomodulatory properties and may have the potential to bolster the health and immunity of the community in the fight against COV-19 infection¹⁰. Phyllaemblicin-B and phyllaemblinol from *P. emblica* showed a high binding affinity to helicase protein, which is one of the major targets of COV-19. Phyllaemblicin G7 from *P. emblica* exhibited a high binding affinity to the Spike Protein of COVID-19⁵. The antioxidative and anti-inflammatory properties of *P. emblica* are the key to its therapeutic effect²².

TABLE 2: HERBAL MEDICINES AND ITS EFFECTIVE TARGETS AGAINST COV-19

S. no.	Herbal Medicines	Effective Targets of COV-19	References
1	<i>T. terrestris</i>	Papain-like protease (PLpro)	(7)
2	<i>W. somnifera</i>	3C-like Main protease (3CLpro)	(11)
3	<i>C. longa</i>	3C-like Main protease (3CLpro)	(15)
4	<i>O. sanctum</i>	Main Protease and Papain-like Protease.	(19)
5	<i>P. emblica</i>	Helicase protein and Spike Protein	(5)

CONCLUSION: Novel evidence based approach of herbal medicine plays preventive role in the COVID-19 pandemic. Naturally occurring plants are source of wide variety of phytoconstituents. *Tribulus terrestris*, *Withania somnifera*, *Curcuma longa*, *Ocimum sanctum*, *Phyllanthus emblica* are primarily observed as effective against COVID-19. Moreover, *in-vitro* and *in-vivo* studies require to identify the efficacy of herbal medicine.

However, Combination therapies of allopath and herbal medicines lead towards the best treatment options. Still, many unknown herbals medicines are waiting for their identification and purification and pharmaceutical evaluation. There is a major research gap between the primary effectiveness of herbal medicine and its clinical trials. Further, research can be carried out on the basis of *in-vitro* and *in-vivo* studies, along with preclinical and clinical reports.

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CONFLICTS OF INTEREST: Nil

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