



Review Article

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SCOPING ANTIVIRAL AND IMMUNO-MODULATORY ACTIVITY OF SPECIFIC AYURVEDA BOTANICALS IN THE WAKE OF COVID-19 PANDEMIC

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ABSTRACT:

COVID-19 is an ongoing pandemic characterized by a rapid spread and high virulence across the world. None of the conventional antimicrobial and chemotherapeutic agents including vaccines have been identified to be disease-specific for this illness. The swiftly changing and resistant nature of the virus augments an imperative need to explore novel pharmacotherapeutic agents, such as those involving herbal medicine. Ayurvedic pharmacopoeia offers wide range of botanicals, polyherbal and herbomineral formulations proven to be effective against viral

diseases. This manuscript is an outcome of extensive literature search with Ayurveda background to identify few such botanicals that are adopted effectively in Indian community to curb the features of COVID 19. All of them possess anti-viral, immunomodulatory or both the activities established through in vitro and in vivo models. Further, compound formulations of Ayurveda comprising these medicinal plants that could be adapted at various stages of COVID-19 are discussed here. Considering future perspectives, real time clinical documentation conjoined with reverse pharmacology studies in the laboratory setup are the current need. In view of the global burden of the disease and the corresponding health expenditure vis-a-vis the community, there is an imperative need to consider using these suggested plants which are easily available, cost effective and adaptable into multiple dosage forms to suit different age groups and patients with underlying comorbidities. Considering the gravity of the disease and its massive impact on the society, we exhort upon policy makers to propagate their cultivation, preservation and promotion as medicament and usage as home remedies. Thus it aids in self-reliance within communities to fight against COVID-19.

Keywords: Ayurveda, Antiviral, Botanicals, COVID-19, Immunomodulatory, Sannipataja Jwara

Running title: Introducing few Ayurvedic botanicals helpful in COVID 19

INTRODUCTION:

Corona virus disease 2019 (COVID-19) is an acute infectious illness caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2).^[1]The condition is declared as Pandemic² with its unique manifestations resulting in multiple health hazards and multitude deaths all over the world. The disease manifestations typically range from no symptoms (asymptomatic) to severe pneumonia and death.^[3]When present, symptoms include fever, cough, fatigue, shortness of breath and loss of smell.^[4, 5, 6]Complications may include pneumonia and acute respiratory distress syndrome.^[7]There have been reports on atypical manifestations including that of skin and gastro intestinal system. The present management strategies as followed by states and governments have

encountered challenges. This has resulted in over 3, 71,166 deaths and more than 60, 57,853 positive cases so far and statistics can go on.^[8]The current suggestion for prophylactic and management measures such as hydroxychloroquine do not have requisite evidence base to be translated into policy decision for application at population level. The prophylactic and therapeutic efficacy of traditional and complementary medicines like Ayurveda remains largely unexplored in the efforts to combat COVID-19. The aim of Ayurveda is preservation of health and treatment of specific ailments through diet, lifestyle modifications along with social codes and conduct. Ayurveda employs three principles viz., knowledge of etiology (hetujnana), knowledge of symptomatology (lingajnana) and knowledge of therapeutics (oushadhajnana) for the maintenance of equipoise of tridosha (bio humours- Vata, Pitta and Kapha), dhatu (tissues) and mala (metabolic waste) thus contributing for the state of health. Wide ranges of herbal, herbo mineral and mineral drugs are employed in Ayurveda materia medica and therapeutics for this purpose. In the current context of pandemic a lot is spoken on hygiene, social distancing and food to prevent viral impact on health. This manuscript is an attempt to identify few Ayurvedic botanicals utilized in Jwara, Kasa, Shwasaroga, Krimi and Pratishtyaya chikitsa with corroborated anti-viral and immuno - modulatory activities as main or adjuvant therapy for community self-reliance in the wake of COVID-19 pandemic. The selected medicinal plants are Guduchi (*Tinosporacordifolia* (Willd.) Miers), Amalaki (*Phyllanthusemblica* L.), Haritaki (*Terminaliachebula* Retz.), Bhunimba (*Andrographispaniculata*(Burm.f.) Nees), Punarnava (*Boerhaviadiffusa* L.), Haridra (*Curcuma longa* L.), Pippali (*Piper longum* L.), Shunti (*Zingiberofficinale* Roscoe), Yashtimadhu (*Glycyrrhizaglabra*L.), Tamalaki (*Phyllanthusniruri* L.), Ashwagandha (*Withaniasomnifera* (L.) Dunal) and Datura (*Daturastramonium* L.). Evidences in support gathered are updates on pharmacological properties, major bioactive compounds, preclinical studies and possible mode of action of the selected herbs of Ayurvedic pharmacopoeia.

Scientific validation of antiviral and immunomodulatory activities of selected Ayurvedic botanicals.

Guduchi (*Tinospora cordifolia* (Willd.) Miers), Menispermaceae):

Tinospora cordifolia is a fast growing climbing shrub with multi faceted medicinal use and easy availability.^[9]Stem of *Tinospora cordifolia* are strengthening (Balya) ,tissue rejuvenating (Rasayana) and alleviating Tridosha,and used for treating fevers, diabetes, dyspepsia, liver diseases, rheumatological complaints and recommended as immune booster. It is known for its antistress, anti-leprotic and anti-malarial activities. ^[10, 11]It is used in the form of fresh juice, decoction, powder and *Satwa* (starch extract of stem). Important chemical constituents include alkaloids (Berberine, Tinosporineetc), diterpenoid lactones, glycosides (Syringin, Cordifolioside A, Cordifolioside B etc), steroids, sesquiterpenoid, phenolics, etc. The alcoholic and aqueous extract haveimmunomodulatory activity. ^[12]Aqueous and ethanol extracts of the stems, significantly increased totalleucocytescounts and antibody production in vivo. The aqueous extract increased phagocytosisin vitro. Syringin, Cordiol, Cordioside, CordifoliosidesA&B are attributed with anticompliment and immunomodulatory activities.^[13] Otherimmunomodulatory active components are 11-hydroxymustakone, N-methyl-2-pyrrolidone,N-formylannonain,cordifolioside A, magnoflorine and tinocordiside. ^[14,15]It is a rich source of Zinc and Copper having antioxidant property and protects cells from the damaging effects of oxygen radicals generated during immune activation. ^[16] It increases the blood profile and has lead scavenging, ^[17], anti-infective andantipyreticactivities. Hepatitis B and E surface antigens get inactivated by the extract ^[18] besides being hepato protective. ^[19]

Amalaki (*Phyllanthus emblica* L.Euphorbiaceae): is a small deciduous tree commonly known as Amla, holds a high esteem in indigenous medicine. Together with fruits of Terminaliachebula and Terminaliabellicica, it constitutes Triphala. Amla fruits are used for the treatment of haemorrhage, diarrhoea, anaemia, jaundice and dyspepsia. Amalaki, the best tissue rejuvenating herb, ^[20] and anti-aging, is prescribed in daily diet. ^[21]Amalaki fruit enhances the immune-defence ^[22] and has hypolipidemic ^[23] and hepatoprotective activity. ^[24]Tannins like emblicanin A , emblicanin B, punigluconin and pedunculagin exhibit antioxidant action and preserve erythrocytes against oxidative stress induced by asbestos, generator of superoxide radical. Recently fruits demonstrated antiviral activity, by inhibiting reverse transcriptase in the replication of retroviruses like HIV-1. ^[25] Pentagalloyl glucose in the fruit inhibits Influenza A virus replication by prevention of virus adsorption and suppression of virus release.

Haritaki (*Terminalia chebula* Retz., Combretaceae): is a large deciduous tree bearing fruits (chebulicmyrobalan) used in fever, loss of appetite, indigestion, hemorrhoids, vomiting, cough, hiccup, asthma, anemia, jaundice, enlargement of liver and many abdominal diseases. Bioactive compounds in *haritaki* are gallic acid, ellagic acid, tannic acid, ethyl gallate, chebulic acid, chebulagic acid, corilagin, mannitol, ascorbic acid (vitamin C), tannin, polyphenols, saponins, flavonoids and alkaloids.^[26] *Chebulahas proven* anti-inflammatory properties that could be attributed to chebulagic or gallic acid via NF- α B and p38 mitogen-activated protein kinase pathways. ^[27, 28] Aqueous extracts exhibit most prominent anti HBV activity by inhibiting HBV viron DNA levels in extracellular medium and inhibited secretion of HBsAg surface antigen in dose dependent manner. ^[29] Chebulagic acid (CHLA) and punicalagin (PUG) are effective in abrogating infections of human cytomegalovirus (HCMV), hepatitis C virus (HCV), dengue virus (DENV), measles virus (MV), and respiratory syncytial virus (RSV), at μ M concentrations and in dose-dependent manners without significant cytotoxicity. It also inhibits viral attachment, penetration, and spread, to different degrees for each virus. Specifically, the tannins block all the steps of infection for HCMV, HCV, and MV, but had little effect on the post-fusion spread of DENV and RSV. ^[30] Ethanol extract of fruit showed significant antioxidant activity and anti-diabetic activity.^[31] Further *T. Chebula* increases humoral antibody titer and is useful in delayed type of hypersensitivity in mice. ^[32] Gallic acid and three galloy glucoses inhibit immunodeficiency virus type 1 (HIV-1) integrase. ^[33] It also shows retroviral reverse transcriptase inhibitor activity. ^[34] It protects epithelial cells against influenza A virus, supporting its traditional use for aiding in recovery from acute respiratory infections.^[35] *T. chebula* has demonstrated therapeutic activity against Herpes Simplex Virus (HSV) both in vitro and in vivo tests. ^[36] Acetone extract of *T.chebula* showed activity against swine influenza A virus.^[37] Further *T. chebulais* also known for its antibacterial, antioxidant, adaptogenic, cardioprotective and cytoprotective activities. ^[38] It was found to be very safe on toxicity evaluation.

Bhunimba (*Andrographis paniculata* (Burm.f.)Nees, Acanthaceae): Erect annual or biennial bitter tasting herb indicated in indigenous medicine for liver disease, worm manifestation, skin diseases and fever. Major class of phyto constituents include Lactones like andrographolides, flavones, diterpene glucosides etc. Andrographolides

from AP enhance immunity through production of white blood cells (scavengers of bacteria and other foreign matter), release of interferon, and activity of the lymph system. Interferon is a protein (called a cytokine) made by cells in response to viruses. It is even more effective when combined with immune stimulators, such as the herb Echinacea, and with zinc and vitamin C. Noteworthy antiviral activity are against viruses, such as dengue virus serotype 1 (DENV-1),^[39] human papilloma virus type 16 (HPV16),^[40] herpes simplex virus type 1 (HSV-1),^[41] influenza A virus,^[42] and HIV.^[43] The aqueous aerial part extract have antiviral activity to reduce the percentage of HIV antigen-positive H9 cells. Methanol extract possesses significant inhibition activity against DENV-1 in vitro assay.^[39]

Punarnava (*Boerhavia diffusa* L.) Nyctaginaceae: Punarnava is a perennial herb traditionally used to treat Pandu, Hrdroga (cardiac disorders), Kasa (cough), Urakshata and Garavisha (chronic toxic conditions). It has diuretic,^[44] anti-bacterial,^[45] hepatoprotective,^[46] anti-convulsant,^[47,48] cardiogenic,^[49] immunosuppressant, anti-inflammatory,^[50] anti-diabetic,^[51] and anticancerous activity.^[52] Root extracts possess broad spectrum and very high antiviral activity.^[53] The extract prevented in vitro cytotoxicity in human NK cells and also inhibited NO generation in mouse macrophage cells along with production of IL-2 and TNF- α (MIC ~ 10 μ g/mL) in human PBMCs. The immune suppressive properties are possibly because of alkaloid/lignin.^[54] Eupalitin-3-O- β -D-galactopyranoside isolated from the ethanolic extract more effectively decreased the production of IL-2 and TNF- α in human PBMCs and repressed NF- κ B and AP-1, thereby depressing activation and proliferation of T cells.^[55] Further, the roots have been the source of two documented immunostimulants, syringaresinol mono- β -D-glucoside (eleutheroside E1 and acanthoside B) and punarnavine.

Haridra (*Curcuma longa* L.) Zingiberaceae: Rhizome of Haridra (*C. Longa*) is popularly known as the 'Golden spice' and is widely cultivated in India. Turmeric powder is a regular ingredient in Indian cuisine for enhancing the colour and flavour of most dishes and also a favourite home remedy. Traditionally, used to treat obesity, skin diseases, allergy, asthma, cough, diabetes, liver disorders and toxic manifestations. *C. longais* rich sources of polyphenolic curcuminoids, i.e., curcumin, demethoxycurcumin, and bisdemethoxy curcumin. Also sesquiterpenes. Curcumin has broad spectrum antimicrobial activity including antibacterial, antiviral, antifungal, antimalarial, antioxidant,

and wound healing etc. [56] Because of its extended antimicrobial activity and safety property even at high doses (12g/day, it is extensively used in designing other antimicrobial drugs through its derivatives.[57,58] Curcumin has anti-influenza activity against influenzaviruses PR8, H1N1, and H6N1. In H1N1 and also H6N1 subtypes, the inhibition of haemagglutinin interaction, time of drug addition experiments reflected the direct effect of curcumin on infectivity of viral particles. Viruses show no resistance to curcumin proving its potential for inhibition of influenza.[59] In vitro study of curcumin and its derivatives, namely, gallium-curcumin and Cu-curcumin, exhibited remarkable antiviral activity against herpes simplex virus type 1 (HSV-1) in cell culture with IC50 values of 33.0 microg/mL, 13.9 microg/mL, and 23.1 microg/mL, respectively. Curcumin considerably decreased the immediate early (IE) gene expression and infectivity of HSV-1 in cell culture assays. Curcumin has an effect on recruitment of RNA polymerase II to IE gene promoters through mediation of viral trans activator protein P16, by a p300/CBP histone acetyl transferase effect. [60] In vitro replication of HSV-2 is decreased by curcumin with ED50 value of 0.32 mg/mL. [60] In vivo study on mouse model with intravaginal HSV-2 challenge showed significant protection against HSV-2 infection. Curcumin exhibited the antiviral activity against coxsackie virus by reduction of viral RNA expression, protein synthesis, and virus titer. In addition, it was found to have a protective effect on cells against virus induced apoptosis and cytopathic activity. The inhibition of coxsackie virus replication is through dysregulation of the ubiquitin-proteasome system (UPS). [61] Antiviral effect of aqueous extract of curcuma longa rhizome against HBV in HepG 2.2.15 cells is through repression of HBsAg secretion from liver cells without any cytotoxic effect. It also suppresses the HBV particles production and the rate of mRNA production of HBV on infected cells. The Curcuma longa extracts suppressed HBV replication by increasing the ratio of p53 protein through enhancing the stability of the protein as well as trans activating the transcription of p53 gene. It was understood that the extract has suppressed HBV enhancer I and X promoter leading to repression of HBx gene transcription by affecting p53. [62] In vitro investigation of the antiviral activity of curcumin Huh7 replicon cells expressing the hepatitis C virus (HCV) indicated it be a potent anti HCV compound. Results showed the decrease in HCV gene expression and replication through suppressing the Akt/SREBP-1 pathway. In addition, the mixture of

curcumin and IFN γ induced profound inhibitory activity on HCV replication and demonstrates curcumin can be possibly used as a complementary therapy for HCV. [63] Curcumin showed the inhibitory activity against the expression of E6 and E7 genes of HPV-16 and HPV-18 as two main highly oncogenic human papilloma viruses. [64] Curcumin down regulates the AP-1 binding activity in HeLa cells with decreasing effect on the transcription of HPV-18. [65] Thus proving its utility in management of highly oncogenic HPV infections. Curcumin on Neuro2a cell line infected with JEV showed reduction in production of infectious viral particles through inhibition of ubiquitin-proteasome system. [66] Curcumin was reported to have antiallergic properties with inhibitory effect on histamine release from mast cells. [67] Curcumin modulates the inflammatory response and release of cytokines by suppressing nuclear factor kappa-B (NF- κ B) activation, through inhibition of phosphorylation and degradation of NF- κ B inhibitor alpha (I- κ B α) and blockade of phosphorylation of I- κ B α kinase (IKK α). [68] Curcuminoids possess potential radical molecules that prevent free radical formation. Curcumin is shown to be eight times more powerful than vitamin E in preventing lipid peroxidation and that curcuminoids are potent in neutralizing free radical molecules. [69] It has been suggested that curcumin has role in reducing oxidative stress by down regulation of nitric oxide (NO) formation, scavenging or neutralizing free radicals, and by breaking the oxidative chain reaction caused by free radicals. [70]

Pippali and Maricha (*Piper longum L.* and *Piper nigrum L.*, Piperaceae): Piper longum fruit together with fruit of Piper nigrum and tuber of Zingiber officinale, constitutes the Ayurvedic formulation Trikatu. Pippali fruits are effective in improving digestion and used to relieve cough and asthma. Bio active compounds of these family include Phenolics, flavonoids, alkaloids, amides and steroids, lignans, neolignans, terpenes, chalcones and many other compounds. [71] Piperine, pipene, piperamide and piperamine are the major one. Piper longum (pippalirasayana) was found to activate macrophage migration index and phagocytic index, indicating immune stimulatory activity [72] Piperinic acid exhibits immunomodulation through suppression of proinflammatory cytokines [73] Piperine enhances the bioavailability and bioefficacy of structurally and therapeutically diverse drugs including antimicrobial and nutritional substances, possibly by altered membrane lipid dynamics and conformational change of enzymes in the intestine. [74] Petroleum ether and ethyl acetate extracts of P. longum exerts

antimicrobial effects against various microorganisms, [75] anti-viral and anti-cancer activity in HeLa cells. [76] Acute and chronic toxicity (for 90 days) studies do not show any mortality or morbidity in a dose of 3 to 5 g/kg in experimental animals. [77] *Pipernigrum* also decreases lipid peroxidation *in vivo*. The antioxidant activity may be attributed to flavonoids and phenolic contents. [78] Piperine seems to be analgesic via opioid pathway [79] also useful in arthritis due to its anti-inflammatory and anti-arthritic activities. [76] Protective efficacy of piperine and rifampicin (1 mg/kg) combination against *Mycobacterium tuberculosis* was reported due to immuno-modulatory activity. [80]

Shunthi (*Zingiber officinale* Roscoe, Zingiberaceae): Ginger is the most commonly used dietary condiment also well known for its medicinal value. Rhizome of Shunthi are pungent in taste, hot in potency and having Vata-kapha-passifying effect. Fresh or dried rhizome are used in many Ayurveda formulations to treat loss of appetite, indigestion, jaundice, diarrhoea, haemorrhoids, asthma, colicky pain and urticaria. Essential oils, phenolic compounds, flavonoids, carbohydrates, proteins, alkaloids, glycosides, saponins, steroids, terpenoids and tannin as the major phytochemical groups. [81] Ginger is widely used for its Antimicrobial, Anthelmintic, Larvicidal, Anti-diabetic, Nephroprotective, Anticancer, Analgesic, Anti-inflammatory, Immunomodulatory and antioxidant activities [82] besides being anti-viral. Fresh ginger dose dependently inhibits human respiratory syncytial virus-induced plaque formation in both HEP-2 and A549 cell lines ($P < 0.0001$) by blocking viral attachment and internalization. In higher concentration it stimulates mucosal cells to secrete IFN- β that possibly counteracts viral infection. [83] Ethanol-soluble extracts of rhizome promote the secretion of IL-1 and IL-6 in a time- and dose-dependent manner. [84] Ginger essential oil recovered the humoral immune response in immunosuppressed mice. [85] Ginger is considered to be a very safe drug. [86]

Yastimadhu (*Glycyrrhiza glabra* L., Fabaceae): It is a perennial climbing shrub with woody, stoloniferous root stock of sweet taste. Fine powder of dried root is used internally for therapeutic purpose. Active ingredients are glycyrrhizine, flavonones, [87] isoflavones, glycyrrhetic acid, [88] six phenolic compounds. [89] 12-methyl isoflavones [90] found in Indian sample contribute to the antiviral activity at a lower concentration. Glycyrrhizin is antiviral and inhibits the virus cell binding. In study

antiviral activities of ribavirin, 6-azauridine, pyraziofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of SARS (severe acute respiratory syndrome) virus, namely FFM-1 and FFM-2 showed that glycyrrhizin was most effective in controlling viral replication and hence it could be used as a prophylactic measure. Glycyrrhizin is also used in treatment of patients suffering from HIV-1 and chronic hepatitis C virus. [90,91,92] Glycyrrhizin is said to be effective against varicella - zoster virus and human immunodeficiency virus in vitro. Glycyrrhizin found to be effective therapeutically and prophylactically against chronic active viral hepatitis B. [93] Glycyrrhizin was tested against some RNA (Chandipura, Measles, Polio vaccine type 1,2 and 3, Polio wild type 1,2 and 3) and DNA (Herpes type 1 and 2) viruses. It inhibited plaque formation for HSV-1 and HSV-2 at a concentration of 0.606 mM. [94,95] Glycyrrhizin is known for its endogenous interferon induction *in vivo*. [96] Polysaccharide fractions stimulate macrophages and hence elevate and assist immune stimulation. [97] N-acetylmuramoyl peptide is glycyrrhizin analogue with potential in vitro immune-stimulating properties, [98] also effective against the influenza virus through stopping the viral replication. Glycyrrhetic acid is inhibitory on replication of some RNA and DNA viruses in vitro. Glycyrrhizic acid is an immunomodulator that inhibits virus growth and inactivates virus particles.

Bhumyamalaki (*Phyllanthus niruri* L., Euphorbiaceae): Bhumyamalaki is well known for its wide range of therapeutic uses. Methanolic extract of *P. niruri* exhibited immunomodulatory activity and anti HIV activity. The active component of *P. niruri* is niruriside, which has antiviral activity that extends to Human Immuno Deficiency Virus by inhibiting the reverse transcriptase enzyme. [99] Active constituents of *P. niruri* are lignans (Phyllanthin Hypophyllanthin Niranthin Nirtetralin Phyltetralin Hinokinine etc), tannins, coumarins, triterpenes, etc. Aqueous extracts of *P. niruri* possess antiviral potential and especially to hepatitis B carriers. [100] Anti-HBsAg and anti-HBeAg activities of niranthin and nirtetralin (extracts from *P. niruri*) and the compounds suppressed HBsAg and HBeAg expression effectively at a non-cytotoxic concentration of 50mM. [101] Clinical studies on hepatitis B patients showed that 50– 60 per cent of patients who were administered *P. niruri* extract experienced HBsAg seroconversion proving the inhibitory effect on viral genetic replication. [102,103] *P. niruri* inhibits the hepatitis B virus and it is extensively used to treat jaundice and hepatitis B virus. [104] The

extracts of five different traditional herbs (with *P. niruri* being one of them) for at least half a year resulted in significant rise in CD4 count in HIV patients. [105] *Phyllanthus* extracts co administered with DENV-2 inoculum showed effective anti Dengue activity by affecting the viral attachment and entry. [106]

Ashwagandha (*Withania somnifera* (L.) Dunal, Solanaceae): is a short perennial shrub, roots are widely used for its range of therapeutic activities and used for immunomodulation, combating infectious agents, anti-cancer, anti-epileptic, cardio-respiratory endurance enhancer, anti-ageing, anti-oxidant, hypoglycemic, hypocholesterolemic and is an effective adaptogen [107] Alkaloids, Steroidal lactones, Steroids, Salts, Flavonoids and Nitrogen containing compounds are the major class of phytoconstituents. Consistent with the folkloric use of *W. Somnifera* against infections, methanolic leaf extract are effective against Gram-positive clinical isolates of methicillin-resistant *Staphylococcus aureus* and *Enterococcus* spp. [108] Plant extracts synergized the anti-bacterial effect of Tibrim (rifampicin and isoniazid) against *Salmonella typhimurium* and *E. Coli*. [109] The root extracts exhibit anti-inflammatory and mucorestorative activity by resolving necrosis, edema, neutrophil infiltration in trinitrobenzyl-sulfonic acid (TNBS) -induced inflammatory bowel disease. Extract of *W. somnifera* has been shown to significantly increase the Cell Mediated Immunity (CMI) in normal mice. Root extract enhances the level of interferon gamma (IFN- γ), interleukin-2 (IL-2) and granulocyte macrophage colony stimulating factor (GM-CSF) in mice, suggestive of an immune potentiating and myeloprotective effect. Ashwagandha enhances nitric oxide synthetase activity of the macrophages, which in turn increases the microbial killing power of these immune cells. [110] Withaferin A has significant hepatoprotective effect in CCl₄ -induced hepatotoxicity in rats at a dose of 10 mg kg b.wt. [111] Ashwagandha is proposed as an effective agent in the management of COVID-19 through modulation of host Thelper cell-1/Thelper cell -2 immunity. It may be beneficial in inducing anti-viral immunity (owing to increased IFN- γ responses) and optimum anti-inflammatory activities (downregulation of IL-1, IL-6, TNF- α and other inflammatory mediators) which are the key targets relevant to COVID-19. [112]

Dhattura(*Daturastramonium*L)is an aggressively growing invasive weed traditionally used for treatment of ulcers, wounds, inflammation, sciatica, bruises and swellings, rheumatism, gout, asthma bronchitis and toothache. [113] Major phytochemical constituents include alkaloids, lectin, tannins, cardiac glycosides, flavonoids, carbohydrates, amino acids and phenolic compounds. [114]Thealkaloids are responsible for both the medicinal and hallucinogenic properties,they are toxic in higher amounts, and careless use can result in hospitalization and deaths. Considering this, the plant has been grouped under Schedule E-1 of Drugs and Cosmetics Act-1940. [115]Important bio active compounds Atropine, hyoscyamine and scopolamine are competitive antagonists of muscarinic cholinergic receptors and are central nervous system depressants.Atropine in the plant inhibits the growth of enveloped viruses independent of the nucleic acid content of the virus. The test viruses included Herpes simplex virus, influenza virus, newcastle disease virus, *Sindbis*, *Vaccinia*, adenovirus, Japanese encephalitis virus. [116]Atropine blocks the glycosylation of viral proteins of *Herpesvirus* and hence the production of new infectious virus particles. Virions formed in the presence of atropine said to be non-infectious. [117]

DISCUSSION:

Viral diseases have been in existence since immemorial. Human body has overcome or found a way to outgrow these through developing immunity or with medicines and vaccines. The current understanding in the medical community is that one may have to coexist with COVID-19 till the point a specific vaccine or medicine is invented. None of the existing antivirals and chemotherapeutic agents are considered to be specific for the infection. Hence there is greater emphasis now on improving immunity through natural methods of diet, lifestyle and regimen involving immense utility in the science of Ayurveda. There are innumerable formulations in vogue predominantly polyherbal outnumbering those containing animal products, metals or minerals. The mode of action of these drugs are understood based on five inherent principles such as Rasa (taste), guna (attribute/quality), virya(potency), vipaka(biotransformation) and prabhava(principle responsible for specific activity).This is identical with modern pharmacology that any activity of a drug is due to the presence of specific chemical constituents or secondary metabolites possessing the pharmacological effect. This paper explores Ayurveda botanicals which are common in formulations used to treat

fever, cough and respiratory diseases that have also shown some promising antiviral and immunomodulatory potential based on the pharmacokinetics of their bioactive compounds.

Major phytoconstituents in the above mentioned drugs with proven antiviral activities are phenolic compounds, flavonoids, isoflavonoids, triterpenoids glycosides, punigluconin and pedunculagin, chebulagic acid, punicalagin, andrographolides, curcumin, gallium-curcumin and Cu-curcumin, glycyrrhizine, lectin, niruriside, lignans, niranthin and nirtetralin. The possible mechanisms of action explored are by inactivating surface antigen, inhibiting the reverse transcriptase activity, reducing viral infectivity, inhibiting viral binding by plaque formation or via protein and inhibiting viral replication (Table 1).

Table 1: Specific antiviral activity of selected Ayurveda botanicals and their mechanism of action

SN	Selected Herb	Specific Antiviral activity	Mechanism of Action
1.	<i>Tinosporacordifolia</i>	Hepatitis B and E HIV	surface antigens inactivation Interference with the gp120/CD4 interaction and inhibition of viral Reverse Transcriptase.
2.	<i>Phyllanthusemblica</i>	HIV-1 Influenza A virus	inhibit reverse transcriptase in the replication of retrovirus by prevention of virus adsorption and suppression of virus release
3.	<i>Terminaliachebula</i>	anti HepatitisBVirus(HBV) activity human cytomegalovirus (HCMV),	Inhibit HBV viron DNA levels in extracellular medium and inhibit secretion of HBsAg

		<p>hepatitis C virus (HCV), dengue virus (DENV), measles virus (MV), and respiratory syncytial virus (RSV)</p> <p>HIV-1</p> <p>human cytomegalovirus</p> <p>swine influenza A virus</p>	<p>surface antigen</p> <p>Inhibition of the enzyme HIV 1 Integraseinhibitorand reverse transcriptase inhibitor activity</p> <p>inhibiting the replication of human cytomagalovirus in vitro</p>
4.	<i>Andrographispaniculata</i>	<p>Denguevirusserotype 1 (DENV-1), human papilloma virus type 16 (HPV16),herpes simplex virus type 1 (HSV-1),influenzaAvirus,and HIV</p>	<p>Reduce the percentage of HIV antigen-positive H9 cells.</p> <p>SuppressesHPV16 transcription activity, leading to the reduction of E6 oncoprotein andrestoredp</p>
5	<i>Curcuma longa</i>	<p>InfluenzavirusesPR8,H1N1,andH6N1</p> <p>Herpes simplex virus type 1 (HSV-1)</p> <p>HSV-2</p>	<p>Reduces the viral replication</p> <p>Reduces viral infectivity</p> <p>Decrease the immediate early (IE) gene expression and infectivity</p>
6.	<i>Boerhaviadiffusa</i>	Broad spectrum antiviral activity	

7.	Zingiberofficinale	human respiratory syncytial virus	Inhibits the virus induced plaque formation on respiratory mucosa by blocking viral attachment and internalization
8.	Glyzyrrhizaglabra	SARS (severe acute respiratory syndrome) virus, i.e., FFM-1 and FFM-2 HIV-1 Hepatitis C virus Hepatitis B virus varicella - zoster virus HSV-1 and HSV-2	does not allow the virus cell binding and control viral replication Inhibits viral plaque formation
9.	Phyllanthusniruri	HIV Hepatitis B DENV-2 inoculum	inhibiting the reverse transcriptase enzyme reduces the viral antigen load by inhibiting the hepatitis B viral genetic replication and DNA polymerase reaction probably attacking the viral attachment and entry.
10	Daturastramonium	Herpes simplex virus, Influenza virus, Newcastle disease virus, Sindbis, Vaccinia, adenovirus, Japanese encephalitis virus	inhibits the growth of enveloped viruses blocks the glycosylation of viral proteins

The pandemic called COVID-19 is an illness caused due to novel corona virus 2, presents with mild to severe respiratory features including fever, influenza, sore throat, cough, respiratory distress, pneumonia and in severe cases multi organ dysfunction and death. The nature and trajectory of the disease equates to epidemics or pandemics described in Ayurveda as Janapadodhwamsakara vyadhi. [118] Further, understanding of the disease based on ayurvedicdosha analysis yields that in an evolutory phase it appears to be Goodhalingavyadhi(with no or very mild nonspecific features). During the progress especially in vulnerable and weak persons it can manifest as vatakapalbanahaena pitta sannipatajwaralakshana^[119] and in terminal stages it can even progress to vatolbana pitta Madhya kaphaheenasannipatajwaralakshana. [120]

Thus the plan of management should be involving triphasic approach viz nidanaparivarjana (avoidance of contact with causative factor), doshapratyaneeka (to alleviate the symptomatology based on dosha) and vyadhipratyaneekachikitsa(to curb the specific and complicating features of the illness). Nidanaparivarjana further involves all the methods to contain the spread of disease from one person to another like all forms of close contact, sharing and using contaminated objects etc. [121] Doshapratyaneekachikitsa involves amapachana (removing metabolic waste) by drinking warm water, medicated hot infusions, steam inhalations, nasal drops, gargling, and cough relieving preparations. Vyadhipratyaneekachikitsa is required for full blown manifestations of the illness. This comprise of jwarahara, shvasahara, kasahara and parshvashulaharachikitsa. Treatment of any illness would be incomplete without management of convalescence (apunarbhava and rasayanachikitsa).Ayush department have already come up with the action plans for the stage wise management of the illness. The above enlisted drugs are mentioned in the published and unpublished Ayurveda protocols for Covid 19. [122]

The medicines useful in doshapratyaneekachikitsa are agnideepana (stimulates digestion), amapachana and doshashaman (alleviating tridosha) which can be employed in people with history of travel, suspected to have an exposure or quarantined and also those presenting with non specific features like mild GI disturbances or mild influenza like features.

Simple remedies for these people could be internal administration of

1. Repeated intake of hot infusions made from Shunti, Maricha and Guduchi.
2. Licking of powder of Yashtimadhu, Pippali and Hareetaki
3. Milk with Haridra and Pippali/ Shunthi
4. Gargling with water boiled with Triphala, Yashtimadhu, haridra and salt
5. Steam inhalation with Tulsi leaves followed by instillation by Anutaila
6. Diet should be warm and easily digestible soft carbohydrate rich food with vegetable soup, meat soups garnished with garlic, cumin seeds, curry leaves, shallots, cinnamom and coriander.
7. Fumigation with Turmeric, mustard, Pippali, Aparajitadhuma^[123]

The herbs used in these preparations would restore Agni (digestion) thereby reducing viral replication, arresting disease progress and restoring vitality. Easily available, compound formulations containing these herbs are Vilwadigutika, ^[124] Balajeerakadikashaya, ^[124] Vyoshadivatakam, ^[125] Sitopaladichoorna^[124] and Chitrakahareetakirasayana. ^[124]

Asymptomatic Covid positive and those individuals with mild features such as influenza, fever, sore throat and cough requires Vyadhipratyaneekachikitsa as sthanasamshraya (localization) of the dosha is seen at respiratory system. Fever predominant presentation should be managed with formulations containing drugs like Guduchi, Triphala, Trikatu, Haridra, Vasa, Dashamoola, Punarnava. Some such formulations include Dashamoolakaduthrayamkashaya, ^[124] Amruthotharamkashaya, ^[124] Amritadikashaya, ^[126] Indukantakashaya, ^[124] TribhuvanakeerthiRasa, ^[124] sanjeevanivati, ^[124] MahalakshmvilasaRasa, ^[124] Chukkumthippalyadigutika, ^[124] Lavangadivati, ^[124] Khadiradivati, ^[124] Abrakabhasma, ^[124] Rasasindoora. ^[124]

Patients in convalescence would require medications to improve immunity and restore vitality. Guduchi, Punarnava, Ashwagandha, Haritaki, Amalaki and Tamalaki as single drug or in compound formulations can be utilised for a period of thirty to forty five days. Chitrakahareetaki,^[124] AgastyaHareetaki,^[124] Chyavanaprasha,^[124] Indukantaghrita,^[124] Vidaryadighrita,^[124] Swarnamalinivasanta Rasa,^[124] Swasakasachintamani rasa, ^[127] Kumarakalyana rasa,^[124] Purnachandrodaya Rasa^[128] and Rajamriganka Rasa^[124] can be utilized. Most of the above mentioned

herbomineral formulation contains gold. Gold is a well-known free radical scavenger possessing immune enhancing activity. It has high compatibility with the blood.

Darunagaradi kashaya,^[129] Makaradhwaja,^[124] Abhragarbhapotali rasa ^[130] and Hemagarbhapotali rasa ^[131] can also be used as rescue medications along with emergency care in severe cases and people with comorbidities, such as cardiac disease, respiratory disease, and diabetes. ^[132]

Out of the above enlisted drugs punarnava, bhunimbha, dhatura and bhuyamalaki are predominantly showing antiviral effect, Ashwagandha, Pippali and Maricha are immunomodulatory whereas Haridra, Yashtimadhu, Haritaki and Guduchi exhibit both activities. In the perspective of Ayurveda pharmacology, the above mentioned drugs exhibit antiviral activity by virtue of their tikta, katu rasa, ushnaveerya, jwaraghna, shothahara, krimihara and vishahara property. Immunomodulatory activity can be attributed to ushnaveerya, madhuravipaka, snigdha, rasayana, jeevaniya, balya and brihmaneya property. The above mentioned drugs contain most of these Properties prompting their use at various stages of disease in different dosage forms.

CONCLUSION:

COVID-19 is a pandemic for which the quest for disease specific drug or vaccine is ongoing. Current protocols of management focus on system specific presentations. However with a constant increase in the number of cases and the potential possibility of health system across states in the country getting overwhelmed, it is amply clear that the logical approach to protect the unaffected population should be aimed at boosting the immunity. This is where the potential of traditional disciplines like Ayurveda needs to be harnessed. This paper aims to contribute to that effect by showcasing few Ayurveda botanicals that are potentially effective in combating COVID aided by their probable mode of action. The value of these herbs are further enhanced by the fact that they adhere to the benchmark requisites of medicinal herbs postulated by Ayurveda (Bahukalpam bahugunam sampannam योग्यमौषधम्). In addition, afore said medicinal plants have already been validated for their broad spectrum antiviral and immunomodulatory activities. In lieu of the above, the active promotion of cultivation, preservation and usage of these herbs at the population level for achieving community self reliance towards protection against COVID-19 could be considered by the State.

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