Indian Journal of Traditional Knowledge
Vol 19(Suppl), December 2020, pp S 11-S 24

Identification of therapeutic targets for controlling COVID-19 pandemic by traditional system of Ayurvedic medicines: A systematic review

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Received 29 June 2020, revised 18 September 2020

COVID-19 is a severe respiratory disorder caused by the SARS COV-2 virus that involves limited innate immunity. Numerous publications have suggested that plants/minerals used in the traditional system of *Ayurveda*, has revealed much about the biology of COVID-19. One theory is that combination of anti viral, anti inflammatory, agents activating immune cells, herbs and metals may be helpful for severe acute respiratory syndrome coronavirus infection. Anti-viral drugs used for COVID-19 are those which block RNA synthesis and virus invasion, and bind to receptor proteins on the surface of cells, cell cycle protein, and physiological and pathological processes inhibitor. Anti-inflammatory drugs used for COVID-19 are those which controls transcription of DNA, cytokine production, break down the basement membrane, regulate outer mitochondrial membrane permeability, controlling the host cell life, stimulates activated B-cell and T-cell proliferation, virus dissemination, a slowdown of cell metabolism or secretion of cytokines. Drugs which is having role in the innate immunity, inhibits ROS, enhances cell lifespan, activates macrophages, physiological effects on cells activates the Lung resident immune cells. The focus of this review is to elucidate the *Ayurvedic* pharmacological properties with their therapeutic targets.

Keywords: Ayurveda system of Medicine, Anti-inflammatory, Anti-viral, Immune cells, SARS-CoV-2, Therapeutic target
IPC Code: Int. Cl.[20]: A61P 29/00; A61P 37/02

According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. Recently, the world is suffering from an epidemic of cases with unexplained low respiratory infection caused due to novel coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused coronavirus disease 2019 (COVID-19). It began in Wuhan, China, in December 2019 and subsequently spread worldwide. The first case of the COVID-19 pandemic in India was reported on 30th January 2020. WHO declared the outbreak as a Public Health Emergency of International Concern and again on 11th March 2020, declared as Pandemic, with more than 57 million reported casesin over 188 countries resulting in more than 357688 deaths across the globe[1]. The infection rate of COVID-19 in India is significantly low (1.7) in comparison to the worst affected countries. As of May 30 2020, the Ministry of Health and Family Welfare has confirmed a total of 168791 cases, 82369 recoveries (including 1 migration) and 4971 deaths in the country[2].

WHO clinical management guidelines clearly state that there is no current evidence to recommend any specific treatment for COVID-19 positive patients[3]. The guidance regarding the role of supportive care based on the severity of illness, ranging from

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Abbreviations

SARS-CoV: Severe acute respiratory syndrome coronavirus; **COVID-19:** coronavirus disease 2019; **SARS-CoV-2:** SARS coronavirus-2; **Nsps:** Nonstructural proteins; **PLpro:** Papain-like proteinase; **RdRp:** RNA-dependent RNA polymerase; **3CLpro:** 3CL protease inhibitor; ***IL-1β* :**Interleukin-1 family; **BCL2:** B-cell lymphoma 2; **Bfl-1/A1:** human homolog of the murine **A1**, **EGR-1:** Early growth response protein 1; **TYK:** Non-receptor tyrosine-protein kinase; **COX:** Cyclooxygenase; **TNF:** Tumor necrosis factor; CYP7A1: Cholesterol 7 alpha-hydroxylase; JAK: Janus kinase; **MMP:** Matrix metalloprotease; **NF-κB:** Nuclear factor-kappa B; **STAT:** Signal transducer and activator of transcription; **ACE2:** Angiotensin-converting enzyme-2; **RNA:** Ribose nucleic acid; **C3 or C5:** Complement component 3 & 5; **p38MAPK:** P38 mitogen-activated protein kinases; **AhR:** Aryl hydrocarbon receptor; **Th1:** Type 1 T helper; **SOD:** Superoxide dismutase; **CAT:** catalase; **GPX:** Glutathione peroxidase; **LPS:** Lipopolysaccharides; **MPO:** Myeloperoxidase; **AS_2O_3:** Arsenic trioxide , **ROS:** Reactive oxygen species.

symptomatic treatment for the mild disease to evidence-based management for acute respiratory distress syndrome (ARDS) and early recognition and treatment of bacterial infections and sepsis in critically ill patients has been emphasized. Although no system of medicine has any evidence-based treatment for COVID-19 so far, clinical interventions are being done worldwide.

At present, the drug repurposing strategy[4] is being tried across the globe on investigational drugs that are outside the scope of the COVID-19. A similar strategy is required to be implemented by the traditional systems of medicine, including the Ayurveda system of medicine which is practiced in India more than 5000 years ago. The main objective of the Ayurveda system of medicine is to achieve optimal health and well-being through a comprehensive approach that addresses mind, body, behavior, and environment. It is based on two aspects of treatment i.e., to maintain the wellness of a healthy person and to treat a patient inflicted with a disease[5]. Thus, in the present context, for providing preventive, supportive and rehabilitative care to COVID-19 patients, the Ayurveda system of medicine may be an absolute answer. In China too, from where the disease originated and spread across the globe, the evidence of the role played by Traditional Chinese Medicine (TCM) cannot be overlooked[6]. In India, many of the states are using Ayurvedic intervention in their treatment protocol as a standalone treatment and encouraging results are coming[7]. Although high quality scientific evidence are lacking, some immunomodulator Ayurvedic herbs are being evaluated by multicentric clinical on asymptomatic cases of COVID-19 disease. Ministry of AYUSH, Government of India has also invited research proposals for clinical trials on AYUSH interventions for COVID -19 disease and very soon such trials will begin.

The preclinical report suggests the anti-viral, anti-inflammatory, activation of immune cells and antitoxic therapeutic targets may be beneficial in viral infections[8]. Based on targets, anti-coronavirus therapies may be divided into four categories: (i) anti-viral therapies, (ii) immune system boosting therapies, (iii) anti-inflammatory therapies and (iv) therapies with antitoxic effects. The anti-viral therapies, itself include preventing the synthesis of viral RNA through acting on the genetic material of the virus, inhibiting virus replication through acting on critical enzymes of the virus, and blocking the virus binding to human cell receptors or inhibiting the virus's self-assembly process through acting on some structural proteins[9]. The therapies acting on the human immune system or human cells[10] cause activation of immune cells. Anti-inflammatory therapeutic targets control transcription of DNA, cytokine production, break down the basement membrane, regulate outer mitochondrial membrane permeability, controlling the host cell life, stimulates activated B-cell and T-cell proliferation, virus dissemination, a slowdown of cell metabolism or secretion of cytokines[11]. Due to the over-exuberant of the inflammatory response, one could inhibit inflammation by different pathways and thereby may inhibit the viral infection of cells. One more therapy known as neutralizing antibodies therapy, which could prevent the attachment of the virus to its receptors on targeted cells by reversing toxic modes induced by virus toxins[12] may also be applied. Many scientific studies have revealed that the herbs or metals/minerals used in Ayurvedic system of medicine either alone or in combination, have anti-viral, anti-inflammatory, anti-toxic and immune boosting potential[13]. In this article, an attempt has been made to compile all possible target-based roles of different herbs and mineral used in *Ayurveda*. These herbs may be useful in prophylaxis, disease state and during the convalescence period, based on their use in traditional practices for similar clinical conditions. Pathophysiology of SARS-COV-2 infection, over load on the immune system, progression of the disease, therapeutic targets and treatment protocol are also highlighted.

Methodology

The literature available in *Ayurveda* fundamental textbooks, technical reports, and online scientific databases such as Pubmed, Science Direct, Scopus, Lancet, and Springer for the most recent information regarding the Pandemic were searched. The search words used were 'SARS-CoV-2', 'COVID-19', 'causes', 'types', 'pathogenesis', 'associated risks', 'diagnosis', 'targets', 'treatments. For scientific evidence regarding *Ayurveda* drugs prescribed during epidemics, we searched Google scholar search engines. For this search, we focused on *Ayurveda* herbs, nano *Bhasmas* to understand their role in therapeutic targets for antiviral therapy', 'therapeutic targets for anti-inflammatory', 'therapeutic targets for activation of immune cells'. This search was commenced during January 2020 to June 2020. Searches were limited to the English language. Biased reviews, unpublished records without results were

excluded. Plant names were validated by "The Plant List" (www.theplantlist.org).

Coronavirus disease 2019 (COVID-19)

Structure of Coronavirus

The Coronavirus are large, roughly spherical, particles with bulbous surface projections[14]. The envelope of the virus consists of a lipid bilayer in which the membrane (M), envelope (E) and spike (S) structural proteins are attached. The S protein mediates the receptor binding and membrane fusion between the virus and the host cell. The E and M protein forms the viral envelope and maintains its structure. The envelope contains nucleocapsid that is bound to the positive-sense single-stranded RNA genome. The lipid bilayer envelope, membrane proteins and nucleocapsid protect the virus when it is outside the host cell.

Mechanism of invasion

The life cycle of the virus with the host consists of attachment, penetration, biosynthesis, maturation, and release Virus binds to host receptors (attachment) and enters into the host cells (penetration). Viral RNA enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released.

The spike for SARS-CoV-2 bound to ACE2 undergoes protease cleavage at S1/S2 cleavage site[15] which is also subjected to cleavage by other proteases TMPRSS2[24,25]. In the host cells, the virus likely to destroy ACE2 present in the lung epithelial cells, dendritic cells and macrophages. T cell responses are initiated by antigen presentation via dendrites and macrophages. SARS-CoV-2 virus also binds to dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein (DC-SIGNR, L-SIGN) in addition to ACE2. It increases the concentration of pro-inflammatory cytokines including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemo attractant protein 1 (MCP1), macrophage inflammatory protein (MIP) 1α and tumor necrosis factor (TNF)-α. Exhaustion of T cells occurs due to higher expression of CD4+, CD8+, CD69, CD38, and CD44. Exhaustion of T cells leads to the progression of the disease.

Targeted therapy

COVID-19 is a multiorgan disease and thus requires multiorgan therapy[16]. Phyto-constituents present in herbs and nano-metals used in the *Ayurveda* system; work on a multi-targeted action principle[17]. The potential of combination therapy is very efficacious because of its low plasma protein binding[18]. A combination of several herbs and or nano-metals in particular ratio, gives a better therapeutic effect, through their *Amapachana* (balancing of *Dosha*, a kindling of *dhatu*, maintenance of homeostasis), targeting various antiviral, anti-inflammatory, immune target mediators. Photographs of different plants used antiviral activities, anti-inflammatory activities, immune cells potentiating activity, and nano minerals for COVID-19 are shown in Figure 1. The anti viral, anti inflammatory and immune cells activation properties of *Ayurvedic* herbs during SARS-CoV-2 infection are provided in Figure 2, 3 and 4. The action and molecular targets of herbs & metals for their possible anti-viral, anti-inflammatory and immune cells activation activity in COVID-19 are presented in Table 1, 2, 3 and 4.

Discussion

Targeted therapy is supposed to be most parallel to the *Ayurvedic* treatment approach to Infection. It is clearly said that the mechanism of action of *Ayurveda* drugs depends upon the homeostasis of *dosha dhatu* & *malas* is called as healthy status & disbalance is manifested into disease state wherein *Agni* & external factors play a keyrole[19] *Vata, Pitta* & *Kapha* are present in every cell of the body. The various organs of the body are the aggregates of *paramanus*, the biological cell of an organism, of particular nature. The cell/*paramanu* is responsible for the pysical and psychological life activities of that particular organism. Since *Vata, Pitta, Kapha*, are responsible for all activities it is logical & scientific to infer that three *dhatus* reside in a cell/*paramanu*. Therefore, biological cell serves as a site for the three *dosas*.

This concept is unique to Ayurveda. However, a parallel exists in modern science in the form of targeted therapy where target emphasis is giving on structural proteins abnormality, mRNA genome code abnormality, transcription of DNA abnormality that may constitute a novel dimension to COVID-19 treatment. In the pathogenesis of any disease, may it be *Nija or Agantuja, asatmeyaindriyarthasam yoga, pargyaparadha* and *parinama,* play a role of catalyst in disease pathogenesis[20]. These are epigenetic factors responsible for structural protein abnormality, genome code regulation, transcription of DNA abnormality susceptibility to disease[21]. Disturbance

Fig. 1 — Photographs of different plants used for anti viral potential, anti inflammatory potential, activate immune cells potential, Nano minerals in COVID-19

in epigenetic factors that interfere with viral replication and infection, thus may contribute to COVID-19 susceptibility[22].

The exact pathogenesis of COVID-19 is not known in most cases. In Ayurveda, the concept of *Aam* plays a significant role in the vitiation of *Dosha* (bio-humours) and disturbances in all the seven *dhatus*[23]. Weakened *Dhatus* and *Dhatu Agnis* are responsible for the pathophysiology of *Agnimandya* (hypo functioning of bio-fire) which in turn results in the formation of *Aam*. The statement "*rogasarveapimandagnau* (रोगासर्वेअपिमन्दाग्नौ)" is only to stress the importance of agni in any disease process. *Ayurveda* suggests that when the *Dhatus* are weakened, patients are vulnerable to infective disease[24]. In the present context of COVID-19, *Aam* may be considered as bio-toxins, in form of an abnormal protein, genetic code, genetic material, and inflammatory mediators, etc., released during the progression of the disease[25]. The treatment approach for the infectious disease includes balancing of *Dosha*, kindling of *dhatvagni* by *Aampachana* (eliminating toxins)[26]. In COVID-19, the events that follow after infection, impairs the functioning of *Kayagni* (digestive secretions and enzymes). The first *dhatu*, the *Rasa* (Chyle) is not properly formed and instead *anna rasa* retained in the *amashaya* (stomach & small intenstine) mixed up with *Vatadi dosha*. For *Dhatu samyata* (equilibrium of body tissues), restoration of *Kayagni* by *Deepana pachana* drugs; supportive drugs which helps in formation and nourishment of proper subsequent *dhatus (rasa→*

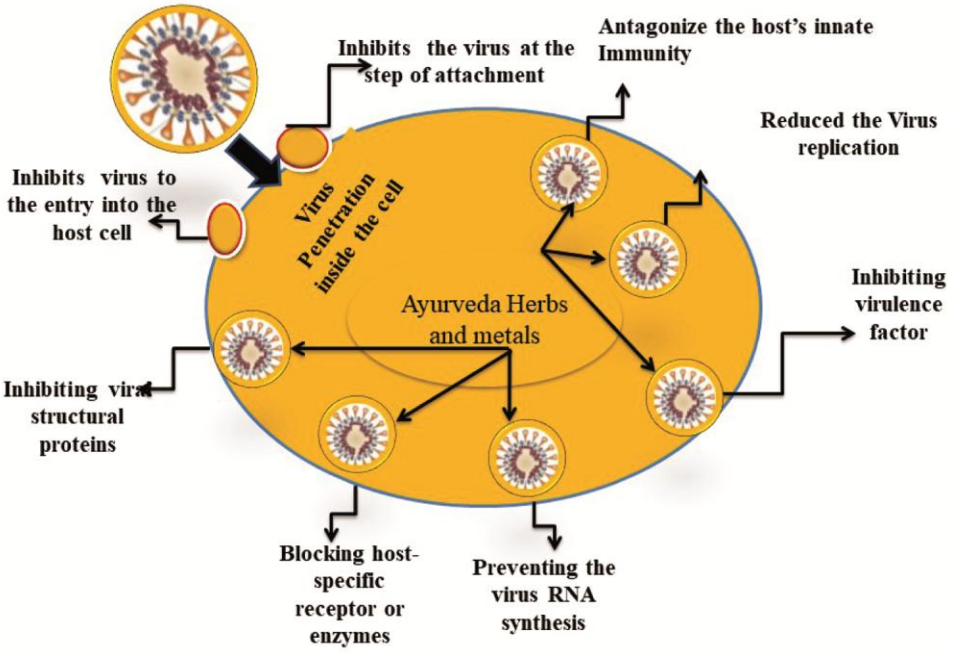

Fig. 2 — Proposed Ayurveda herbs anti-viral responses

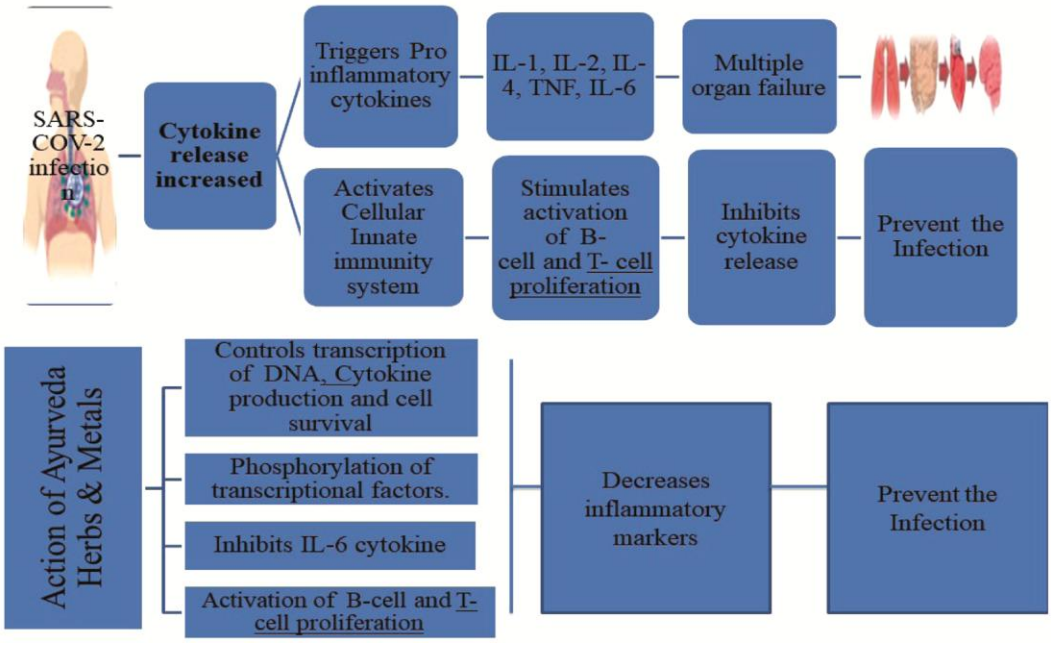

Fig. 3 — Proposed Ayurveda herbs anti-inflammatory responses

rakta→ *mamsa*→ *meda*→ *asthi*→ *majja*→ *shukra); Rasayana* drugs (rejuvenation therapy) for maintaining the essence of life i.e., *ojus* is required. *Deepana-pachana* drugsstimulate *agni*, present in each and every cell of an organ, thus, helpful in bringing *sama* stage to *nirama* stage[27]. After *Ama doshapachana*, the vitiated *doshas* present in *sakha* (extremities) are brought to the *Kostha* (alimentary tract) and are removed from the body. According to *Ayurveda*, like any other disease, treatment principle for COVID-19 includes *Samprapti vighatana* (breaking the pathogenesis) through *Nidana parivarjana* (avoiding the factors responsible for the cause of the disease), *Prakriti vighata* (correcting the damaged or weaker tissue of the body to normal), *Prakriti sthapana* (correcting the respective site of

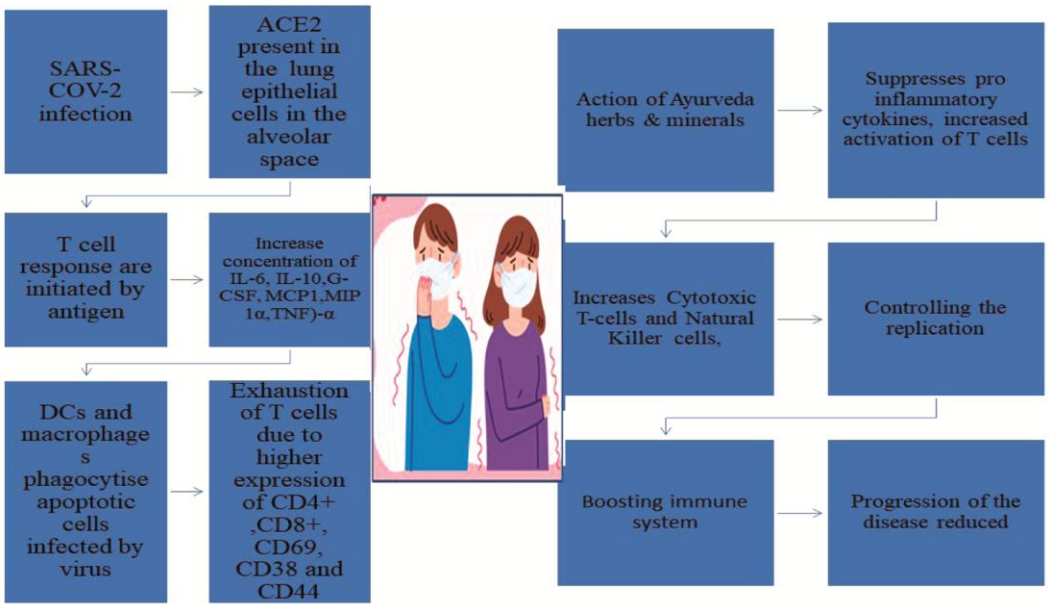

Fig. 4 — Proposed Ayurveda herbs Activating immune cells responses

Dosha–dushya conglomeration), *Dosapratyanika chikistha* (*Dosha* specific treatment), *Dhatusamya hikitsa* (equilibrium of body tissues)[28].

Total 72 herbs and *bhasmas* with 55 therapeutic major molecular targets have been presented in Table 1-4. After systematic search from different databases, 16 herbs have been identified which block the coronavirus from entering into the host cells through two major targets (e.g., spike proteins, hesperidin); prevents the virus RNA synthesis and replication by five major targets (e.g., NSPs, PLpro, RdRp, 3CLpro, Helicase); inhibits viral structural proteins by one major targets (e.g., E protein or N protein); inhibits virulence factor by three major targets (e.g., NSP1, NSP3c, Orf7a); blocks host-specific receptor or enzymes by two major targets (e.g., ACE2 protein, TMPRSS2); are described in Table 1.

Thirty herbs that could inhibit inflammation by different pathways and thereby inhibit viral infection of cells are described in Table 2. Identified molecular therapeutic targets that control transcription of DNA, cytokine production and cell survival include three major targets e.g., NF-KB, TNF, IL-1β. MMP-9 is another target that breaks down the basement membrane surrounding blood vessels as well as Parenchymal extracellular matrix. Similarly, toxic metabolites are produced by one major target (e.g., CYP7A1); regulation of outer mitochondrial membrane permeability controlling the host cell life by two major targets (e.g., BCL2, Bfl-1/A1); having direct role in T cell differentiation by one major targets (e.g., JNK); activation of B-cell and T-cell proliferation by six major targets (e.g., IL-1, IL-4, IL-6, IL-8, IL-12 IL-13); virus dissemination by one major targets (e.g., CASPASE-3); reduces demyelination in the CNS by one major targets (e.g., EGR-1); phosphorylation of transcriptional factors by one major targets (e.g., STAT1); have a role in a variety of immune activation responses by one major targets (e.g., Akt); inhibition of IL-6 cytokine expressed by alveoli cells in the lungs by one major target (e.g., JAK2) and reduction in endosomal entry by one major target (e.g., TYK) have been discussed in Table 2.

Seventeen herbs that could affect 18 major molecular therapeutic targets which inhibit C3 or C5; increase Cytotoxic T-cells (CTLs) and Natural Killer (NK) cells; inhibit p38MAPK, STAT3, AhR, Th1, PAG, 5ht3, Nk1, IL-1β, and PLA_2; increase SOD, CAT, GPX, LPS, H_2O_2, MPO, and may be useful to activate the immune cells are presented in Table 3.

Nine *bhasmas* have been identified and described in Table 4 that are supposed to work like nano metal particles based on their morphology. It helps in pharmacokinetics of the herbal drugs, optimize the immune response during vaccination, adjuvant to arrange antibodies *in vivo* and design vaccines against viral, bacterial and parasitic infections. Major five identified molecular targets which inhibits RIG-I,

Table 1 — Molecular targets of different plants used for anti-viral potential in COVID-19

S. No	Botanical name & family	Ayurveda name	Chemical constituent	Molecular target	Possible effect on COVID-19	Ref.
1.	*Ocimum basilicum* L., Lamiaceae	*Van Tulsi*	Ursolic acid	↓Spike protein	Inhibition of viral entry & attachment	[29]
2.	*Glycyrrhiza* species., Fabaceae	*Mulethi*	Flavanoids, Licoflavonol	↓Spike protein	Inhibition of viral entry & attachment	[30]
3.	*Garcinia* species, Clusiaceae	*Vrikshmla*	Mangostin	↓Spike protein	Inhibition of viral entry & attachment	[31]
4.	*Swertia chirayita*, Gentianaceae	*Chirayita*	Kouitchenside d, A-glucosyl hesperidin, kouitchenside H, Triptexanthoside d, & deacetylcentapicrin, 1,7-dihydroxy-3-methoxyxanthone, Andrographolide derivatives, Xanthones, Phyllaemblicin g7	↓Spike protein, ↓Nsp13 (helicase), ↓3Clpro, ↓Rdrp, ↓Nsp3c, ↓Orf7a, ↓Ace2 protein, ↓TMPRSS2	Inhibition of viral entry & attachment; Reduction of viral replication; Inhibition of virulence factor; Blocking of host specific receptor or enzymes	[31]
5.	*Phyllanthus emblica* L., *Phyllanthaceae*	*Amalaki*	Phyllaemblicin g7	↓Spike protein	Inhibition of viral entry & attachment	[31]
6.	*Vitis vinifera* L., Vitaceae	*Draksha*	Piceatannol	↓Spike protein	Inhibition of viral entry & attachment	[31]
7.	*Citrus* species, Rutaceae	*Nimbu/ Matulunga/ Jambira*	Neohesperidin and hesperidin	↓Hesperidin, ↓Rdrp	Blocking viral entry; Reducing vital enzymes of Replication/ transcription complex	[32]
8.	*Cyperus rotundus* L. Cyperacae	*Musta*	Sugetriol-3,9-diacetate,14-hydroxycyperotundone	↓PLpro protein	Correction of virus replication; Antagonize the host's innate Immunity	[33]
9.	*Andrographis paniculata* (Burm.f.) Nees	*Kalmegha*	14-deoxy-11,12-didehydroandrographolide	↓3Clpro	Prevents viral RNA synthesis & replication	[31]
				↓Rdrp	Reducing vital enzyme of Replication/transcription complex	[31]
10.	*Xylocarpa* species, Fabaceae	*Jambu*	Betulonal	↓Rdrp	Reducing vital enzyme of Replication/transcription complex	[31]
11.	*Diffusa* species, Nyctaginaceae	*Punarnava*	2b,30b-dihydroxy-3,4-seco-friedelolactone-27-Lactone	↓Rdrp	Reducing vital enzyme of Replication/transcription complex	[31]
12.	*Vitex negundo* L., Verbenaceae	*Nirgundi*	Vitexin	↓Nsp1	Inhibits virulence factor	[31]
13.	*Phyllanthus emblica* L. Phyllanthaceae	*Amalaki*	Phyllaemblicin G7	↓Ace2 protein	Blocks host specific receptor or enzymes	[31]
			Phyllaemblicin b Phyllaemblinol	↓Nsp13 (helicase)	Reducing replication	[31]
14.	*C. Aurantium*, Rutaceae	*Jambira*	Neohesperidin and hesperidin	↓Ace2 protein	Blocks host specific receptor or enzymes	[31]

enhancing IL-8 production, inhibiting NF-κB signaling, blocks E protein-associated ion channel, modulating the glutathione redox system.

The action of majority of the ingredients described in Table 1-4 like *Swertia* species, *Vitis vinifera* L., *Commiphora mukul* (Hook. ex Stocks), *Curcuma longa* L., *Aloe vera* (L.) Burm.f., *Garcinia* species etc. are mostly inhibiting the virus at the step of attachment and entry into the host cell, reduced the replication, inhibiting virulence factor and blocking

Table 2 — Molecular targets of different plants used for anti-inflammatory potential in COVID-19

S. no	Botanical name & family	Ayurvda name	Chemical constituent	Molecular target	Supportive therapy effect on COVID-19	Ref.
1.	*Commiphora mukul* (Hook. ex Stocks)., Burseraceae	*Guggulu*	Guggulsterone	↓NF-κB, ↓MMP-9, ↓BCL2-A1, ↓Bfl-1/A1	Controls transcription of DNA, cytokine production and cell survival; Inhibition of cell invasion through suppression of MMP-9; Regulates NF-kappaB-dependent genes	[34]
2.	*Brassica genus* Brassicaceae	*Sarsapa*	Allylisothiocyanate	↓NF-κB	Regulates glycerophospholipid metabolism	[35]
3.	*Foeniculum vulgare* var. *capillaceum* Burnat, Apiaceae	*Saunf*	Anethole	↓NF-κB, ↓JNKs pathway	Blocks the inflammatory processes induced by LPS; Regulating pro-inflammatory cytokine production, transcription factors.	[36], [37]
4.	*Coriandrum sativum* L., Apiaceae	*Dhanyaka*	Anethole	↓NF-κB	Activats host defence through innate immunity	[38]
				↓JNKs pathway	Antioxidant, Anti-Inflammatory, And Erk Signalling Inhibitory Properties	[39]
5.	*Gmelina arborea* Roxb. Lamiaceae	*Gambhari*	Apiosylskimmin, luteolin, quercetin	↓NF-Kb	Blocks phosphorylation of ERK & JNK; Blocks translocation of NF-κB	[40]
				↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13	Increase the secretion of IL-8 by human primary dendritic cells.	[41]
6.	*Citrus limon* L. Osbeck, Rutaceae	*Nimbu*	Citral, Citronyllyl acetate, Hesperidin Hesperetin	↓NF-κB	Reducing inflammatory targets including NF-κB, iNOS and COX-2,	[42]
7.	*Curcuma longa* L., Zingiberaceae	*Haridra*	Curcumin, Demethoxy curcumin, Bisdemethoxy curcumin, Curcumin (diferuloylmethane),	↓NF-κB ↓JNKs, ↓EGR-1, ↓Akt, ↓JAK2, ↓TYK2	Through NF-κB pathways affected on HBV infections, Decreases phosphorylation of JNK, ERK1/2 and p38 and COX-2 expression thereby nuclear factor κB (NF-κB) activation Enhances immunity through T cell stimulation	[43], [44], [45], [46], [47]
8.	*Boswellia serrata* Roxb. ex Colebr., *Burseraceae*	*Sallaki*	B-boswellic acid	↓NF-κB	Inhibiting HSV-1 through modulation of NF-κB & p38 MAPK pathway.	[48]
9.	*Boerhavia diffusa* L., Nyctaginaceae.	*Punarnava*	Boeravine, hypoxanthin-9-larabinofuranoside	↓NF-κB	Inhibiting ACE and xanthine oxidase	[49]
10.	*Citrullus colocynthis* (L.) Schrad., Cucurbitaceae	*Indravaruni*	Caffeic acid Derivatives, Cucurbitacins	↓NF-κB	Improves lipid profile, antioxidant capacity & inflammation by altering gene expression	[50]
11.	*Glycyrrhiza glabra* L., Fabaceae	*Yastimadhu*	Glycyrrhetic acid, isoliquiritigenin, liquiritigenin	↓NF-κB	Hepatoprotection against chronic liver inflammation through attenuating NF-κB activation	[51]
				↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13	Regulating the expression of inflammatory cytokines and CXCL-2 by blocking the IL-17/STAT3 pathway	[52]
12.	*Withania somnifera* (L.) Dunal, Solanaceae	*Aswagandha*	Withaferin a, Withanolide	↓NF-κB	Inhibits cell adhesion through inhibition of ICAM-1 and VCAM-1 expression; Blocks Akt; Down-regulates NF-kappaB activity.	[53]
13.	*Semecarpus anacardium* L.f., Anacardiaceae	*Bhallataka*	Anacardic acids	↓NF-κB	Suppressed LPS activated nitric oxide production in mouse macrophage cell line	[54]

(*Contd*.)

Table 2 — Molecular targets of different plants used for anti-inflammatory potential in COVID-19 (*Contd*.)

S. no	Botanical name & family	Ayurvda name	Chemical constituent	Molecular target	Supportive therapy effect on COVID-19	Ref.
14.	*Aloe vera* (L.) Burm.f., Asphodelaceae	*Kumari*	Anthraquinone, loe-emodin (1,8-dihydroxy-3-(hydroxymethyl)-anthraquinone)	↓MMP-9, ↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13, ↓Caspase-3 pathway	Suppression of the mRNA, Regulate inflammasome-mediated responses, Modulation of cAMP-dependent protein kinase, protein kinase C	[55], [56]
15.	*Zingiber officinale* Roscoe., Zingiberaceae	*Shunthi*	10-gingirol	↓MMP-9	Suppression via MMP9 expression.	[57]
			Zingerone	↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13	Protects lungs from severe damage due to inflammation.	[58]
16.	*Coriandrum sativum* L., Apiaceae	*Dhanyak*	Anethole	↓JNKs pathway	Antioxidant, Anti-Inflammatory, And Erk Signalling Inhibitory Properties	[39]
17.	*Vitis vinifera* L., Vitaceae	*Draksha*	Resveratro, Oxalic acid	↓JNKs pathway	Regulation of cellular ROS through superoxide radical; Decreases intracellular glutathione levels.	[59]
				↓NF-κB	Reduces airway inflammation by inhibition of Syk/NF-κB pathway	[60]
			Resveratrol, Oxalic acid, anthocyanins, flavan-3-ols, flavonols, stilbenes and organic acids, proanthocyanidins	↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13, ↓EGR-1	Inhibits inflammatory cytokines, IgE, nitrites in blood/serum and bronchoalveolar fluid	[61], [62]
18.	*Nigella sativa* L., Ranunculaceae	*Kalaunji*	Oil	↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13	Anti-inflammatory effects by reducing IL-4 and NO production, restoring the antioxidant status, Reducing lipid peroxidation	[63]
19.	*Phyllanthus amarus* Schumach. & Thonn. Phyllanthaceae	*Bhuiamalaki*	Polyphenol compounds	↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13	Reduces proinflammatory cytokines MIP-2, TNF-α, IL-6, and IL-1β in lung tissue	[64]
20.	*Cinnamomum zeylanicum* Blume Lauraceae	*Dalchini*	Type-A procyanidin polyphenols	↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13	Stabilizes mast cell and inhibits allergic markers i.e., histamine, IL-4, and β-HEX in IgE-mediated manner.	[65]
21.	*Citrus limon* (L.), Rutaceae	*Nimbu*	2'-hydroxyflavonone (2HF)	NF-κB, iNOS, COX-2	Reducing inflammatory targets including NF-κB, iNOS and COX-2	[42]
22.	*Citrullus species*, Cucurbitaceae	*Indravaruni*	Phytol	↓Akt	Inhibits the growth of human T-cell	[50]
23.	*Piper longum* L., *Piperaceae*	*Pippali*	Piperlongumine	↓Akt	Activation may have a priming effect which can predispose lung tissue to pulmonary fibrosis.	[66]
				↓JAK2	Regulating the Frequency of Th17 and Regulatory T Cells	[66]
			Aryl Hydrocarbon	↓IL-1, IL-4, IL-6, IL-8, IL-12 IL-13	Regulation of T cells; increases T helper (Th) 1 and Th17 cells	[67]

host specific receptor or enzymes. Other drugs such as *Brassica* genus, *Andrographis paniculata* (Burm.f.) Nees, *Phyllanthus emblica* L. *Foeniculum vulgare* var. *capillaceum* Burnat, *Gmelina arborea* Roxb., *Cyperus rotundus* L. etc. facilitate it to perform its action by preventing the virus RNA synthesis and replication, blocking the phosphorylation of ERK and JNK and the translocation of NF-κB in macrophages. Few ingredients such as *Tinospora cordifolia* (Willd.) Miers, *Phyllanthus emblica* L., *Vitis vinifera L*, *Withania somnifera* (L.) etc. act like cumulative beneficiary effect by activating the immune cells. Few help the main drug such as *Swarna bhasma*, *Zingiber officinale* Roscoe to release at the requisite

Table 3 — Molecular targets of different plants used for activate immune cells potential in COVID-19

S.no	Botanical name & family	Ayurveda name	Chemical constituents	Molecular target	Supportive therapy effect on COVID-19	Ref.
1.	*Tinospora cordifolia* (Willd.) Miers, Menispermaceae	*Guduchi*	Syringin (TC-4) and 20ordial (TC-7)	↓C3-convertase	Enhances phagocytic activity; Increases in nitric oxide and ROS generation	[68]
2.	*Phyllanthus emblica* L.	*Amalaki*	Ascorbic acid, Tocopherol Malanodialdehyde, Embelicanin a & b, Punigluconin	↑NK, ↓p38MAPK	Potent activity against influenza A virus	[69]
3.	*Piper nigrum* L., Piperaceae	*Maricha*	Piperine	↓STAT3 pathway	Blocks p-STAT3/p65 and Bcl-2 activation.	[70]
4.	*Piper longum* L., Piperaceae	*Pippali*	Piperine	↓STAT3 pathway	Blocks p-STAT3/p65 and Bcl-2 activation.	[70]
5.	*Glycyrrhiza glabra L.*, Fabaceae	*Yastimadhu*	Glycyrrhizin	↓AhR	Potential toxicity-alleviating agent	[51]
6.	*Aloe vera (L.) Burm.f.*, Asphodelaceae	*Kumari*	Anthraquinone glycosides	↓Th1, ↓PAG	Regulats Th1 and Th2 cytokines.	[71]
7.	*Zingiber officinale* Roscoe., Zingiberaceae	*Shunthi*	Gingerols, Shogaols	↓5ht3, ↓IL-1β	Possess a high binding affinity to sites	[58]
8.	*Boerhavia diffusa* L, Nyctaginaceae	*Punarnava*	Alkaloid *Boerhavia diffusa* L.	↓PLA_2	Antioxidant activity.	[72]
9.	*Momordica charantia* L, Cucurbitaceae	*Karela*	Alkaloids	↑ SOD	Markers of oxidative stress which may be used as biomarkers of the aging process.	[61]
10.	*Luffa cylindrica* (L.) M.Roem., Cucurbitaceae	*Ghiatori/Dha margava*				
11.	*Syzygium cumini* (L.), Myrtaceae	*Lavanga*				
12.	*Hordeum vulgare* L., Skeels, Poaceae	*Yava*				
13.	*Gossypium herbaceum* L, Malvaceae	*Karpasa*				
14.	*Withania somnifera* (L.) Dunal, Solanaceae	*Aswagandha*	Isopelletierine, Anaferine, Withanolides, Withaferins	↑ SOD, ↑ CAT, ↑GPX	Antioxidant activity	[53]
15.	*Nigella sativa* L., Ranunculaceae	*Kalunji*	Nigellidine	↑LPS	Reduces severity of lung damage	[73]
16.	*Vitis vinifera* L., Vitaceae	*Draksha*	Resveratrol, -e-viniferin	↑ MPO	Protective against pulmonary fibrosis.	[61]
			Alkaloids	↑ SOD	Markers of oxidative stress which may be used as biomarkers of the aging process.	[61]

site. Few ingredients such as *Glycyrrhiza glabra* L., *Swarna bhasma* etc act like adjuvant, and some others like *bhasmas* enhance the bioavailability of the drugs. Some drugs help while correcting the underlying pathogenesis, like *Zingiber officinale* Roscoe., *Piper longum L.* increasing *agni*, correcting the *doshas* and also acting as bioavailability enhancers etc.

So, Ayurveda formulations can be developed by identifying the major targets either alone or by various permutation and combination that may fulfill the treatment for COVID-19. Their combination probably has little more advantage as it is the sum total of synergism, attenuation, antagonistic related to correction of status of *dosha, dushya, agni* and *srotovikriti* and finally attaining the *Dhatusamyata* (homostasis). Their combined action offers anti-viral, anti-inflammatory and immune cells activation activities usually aimed at the pathogenic picture of the disease COVID-19.

Table 4 — Molecular targets of different Nano minerals used for anti viral/anti inflammatory/ activate immune cells potential in COVID-19

S. No	Nano metal	Ayurveda name	Molecular target	Supportive therapy effect on COVID-19	Ref.
1.	Nano Gold particles	*Swarna bhasma*	BAL-macrophage	Blocks viral entry process, viral replication, viral self-assembly process, attachment and penetration into the cells; Used as an antigen carrier and adjuvant to arrange antibodies *in vivo* studies.	[74], [75], [76] [77]
2.	Nano silver	*Rajata bhasma*	Enhancing IL-8 production	Mobilizes antibacterial responses	[77]
3.	Nano Tin	*Vanga bhasma*	Not known	Stops viral entry of HSV-1	[78]
4.	*Nano arsenic*	*Purified & processed Manahshila*	Modulating the glutathione redox system	Inhibits RNA replication	[61], [79]
5.	Nano copper	*Tamra bhasma*	Not Known	Inhibited the entry of virus	[80]
6.	Nano Iron	*Lauha bhasma*	Not known	Inhibited the viral replication	[81]
7.	Nano zinc	*Yasada bhasma*	↓E protein, N protein, Membrane protein, Nucleocapsid protein (N)	Inhibiting virus structural proteins; Intracellular homeostasis; RNA binding; Inhibits viral replication	[82], [77]
8.	Nano mica	*Abhraka bhasma*	Not known	Disrupting the morphological and physiological activity of the cells.	[83]
9.	Nano Calcium	*Mukta/Mukta shukti bhasma/ Pravala bhasma*	Not known	Protective	[84]

Conclusion

Although no system of medicine has any evidence-based treatment for COVID-19 so far, clinical interventions are being done worldwide based on drug repurposing strategy. This review reveals that there are ample evidences available, both in classical and contemporary science that shows the role of plant and mineral-based agents used in Ayurvedic medicine in suppressing multiple pathways involved in the genesis of COVID-19 through anti-viral, anti-inflammatory and immune cells activating molecular targets. Extensive research is needed on Ayurvedic formulations containing these therapeutic targets for establishment of their role in the treatment of COVID-19.

Glossary

Definition of Standard Ayurveda terms:

Agni Represents the digestive power and metabolic rate of the body tissues.

Agnimandya Represents the improper functioning of digestive power and metabolic rate of the body tissues resulting in low digestive power.

Aam Biotoxin released associated with food or other physiological entities to mean incomplete transformation or metabolism causing a harmful effect on health.

Dhatu One of the body tissues. Ayurveda describes 7 *dhatus*

Dhatu agni The metabolic rate of the body tissues.

Dosha Regulatory functional factors of the body. There are 3 doshas: V*ata*, *pitta*, and *kapha*. The three doshas are often called *Tridoshas*.

Kapha The dosha representing structure.

Pitta The dosha representing transformation.

Deepana drugs Therapeutic action of the drug which kindles the *agni* but cannot digest the *Aam*. Process by which the metabolic fire is enhanced

Pachana drugs Drugs by which the undigested food, *dosha*, *Aam* are digested.

Acknowledgments

None

Author Contributions

MKD-Concept Designing, Technical Inputs, Original Draft, Review & Editing; **NJ-**Technical inputs, Review & Editing; **YBT-**Technical inputs.

Conflicts of Interest

There is no conflict of interest among the authors.

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