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Review Article

# SCIENTIFIC EVALUATION OF *DHUMA YOGA* (AN AYURVEDIC FUMIGATION MEDICINE) AS PREVENTIVE AND CURATIVE ON SYMPTOMS OF COVID-19 DISEASE

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**ABSTRACT**

Covid-19, an infectious disease caused by a novel coronavirus SARS-CoV-2 spreads primarily through droplets of saliva or discharge from the nose when an infected person talks, coughs or sneezes where the viruses are active in the environment within the suspended micro droplets. Sanitization of environment to weaken/terminate the virus and halting the replication of virus inside the host along with symptomatic treatment is the primary approach to end the pandemic. In Ayurveda, *Dhupana* (medicated fumigation of vicinity) and *Dhumapana* (medicated smoking) therapies done by drugs of herbal/animal/mineral origin are a swift way to decontaminate the environment and Respiratory system. *Dhuma* (medicated fumes) is a unique drug delivery system acting directly on respiratory tissues which can deliver quick results in this Covid-19 pandemic by its local and systematic effects recommended by AYUSH ministry in the guidelines for Covid-19. We intend to put forward the scientific explanation of powerful Ayurvedic *Cannabis* based polyherbal *dhumapana* (medicated smoking) medication named *Dhuma Yoga* available in the market as an alternate remedy for Covid-19 whose four out of five herbal ingredients are in the list of WHO manual of traditional medicine. We emphasized on *Vijaya (Cannabis sativa* Linn.*)* as the centre of formulation because it is a *Rasayana* (rejuvenative) herb having *Vyavayi* (fast acting) and *Yogavahi* (synergetic) properties. Phytochemicals of all the herbal ingredients of *Dhuma Yoga* formulation are studied through in silico, In vitro and In vivo studies for Covid-19 with favourable outcomes.

**KEYWORDS:** *Dhumapana*, *Dhupana*, *Dhuma*, Herbal smokes, Fumigation, *Cannabis*.

## INTRODUCTION

The Covid-19 pandemic is causing damage to public health irrespective of developed and developing nations across the globe. This disease is caused by the virus classified as SARS (severe acute respiratory syndrome) due to its nature of inducing direct infection in respiration system with suffocation and breathing disorders, hence named SARS-CoV-2. As per WHO (World Health Organisation) modes of SARS-CoV-2 transmission is mainly by droplets and also airborne through aerosols (micro particles/droplets).[1] Researchers are striving to investigate anti-viral drugs, immunity modulators and vaccines for SARS-CoV-2 with not much efficacy and bringing backend side effects too like the steroid medications which cause immune suppression.[2]

Ayurveda, the science of life is an Indian medical science well established and practiced for several thousand years which is the oldest medicinal literature known to mankind and traditionally considered a part of *Adharvana Veda* (4th text of ancient Indian knowledge).[3] The exposure to droplets/ aerosols contaminated with novel corona viruses in environment is comparable to polluted air and land which may cause *Janapadodhwamsa* or *Maraka,* a broad term used for epidemic or pandemic in Ayurveda.[4] The word Virus is derived from Latin language which means poison.[5] The Covid-19 disease caused by SARS-CoV-2 can be compared to *Bhuta, Rakshasa, Graha*, etc, a kind of microbes elucidated in Ayurveda which may cause *Bhutabhishangaja Jwara* (fever caused by invisible organisms), a kind of *Agantu Jwara* (fever caused by external factors) negatively effecting *Pranavaha srotas* (the vessels carrying the vitals) related to Lungs, Heart and Brain.[6]

Respiratory disorders like *Swasa* (asthma, dyspnoea/breathing difficulty), *Kasa* (cough) developing in deadly diseases like in Covid-19 pandemic require quick relief and *Dhuma* (medicated fumes) is one such rapid drug delivery method in Ayurveda which gives various local and also systemic effects in *Vata* and *Kapha Dosha* origin diseases by swiftly entering the circulation through inhalation giving instant results mainly acting on *Urdhvajatrugata roga* (diseases/disorders of head

and neck) and respiratory system.[7] *Acharya Charaka* advised to perform fire ritual like *Yagna*, etc, a kind of *Dhuma* (medicated fumes) in *Janapadodhwamsa* (pandemic diseases).[8] *Dhuma* (medicated fumes) shows predominance of *Agni* (fire) and *Vayu* (air) of *Panca-mahabhuta* (five fundamental elements) having subtle, microscopic and all-pervading quality known as *Sukshma guna* which helps in enhanced bioavailability and quick spread of medicine into all the nooks and corners of the head and neck regions. On the basis of mode of administration there are two varieties of *Dhuma* (medicated fumes) one is internally given to a patient as a part of inhalation therapy called *Dhumapana* (medicated smoking/ inhalation therapy) and the other *Dhupana* (medicated fumigation of vicinity) which is fumigation of the environment commonly performed in ceremonies of holy places, during fire ritual like *Homa*, *Havana*, *Yajna* and in wards of Ayurvedic hospitals viz. *Sutikagara* (labour wards), *Kumaragara* (paediatric wards), *Vranitagara* (post-operative), etc, for benefits like *Rakshoghna* (ward off infectious microorganisms), *Krimi-hara* (anti-parasitic), *Balagraha-nasa* (attenuate microbes that specifically affect newborn and children), *Bhutagraha*-nasa (attenuate disease causing microbes) to sanitize the atmosphere from infectious bacteria, virus, fungi, etc harmful organisms. *Dhupana* (medicated fumigation of vicinity) is frequently used for sterilizing the pots in which medicines are to be prepared or stored.**[9]** It is also used for quick modulation of muscular and connective tissue function like in *Garbhasanga* (obstructed labour), *Aparasanga* (retained placenta), *Arsas* (piles) and also shows systemic effects in *Jwara* (fevers), *Visha* (poisoning), *Unmada* (psychosis), etc ailments. **[10]**

## MATERIALS AND METHODS

Ayurveda divides the universe into two broad categories: *Sthavara* means immobile beings which include plants, minerals and *Jangama* means mobile beings which include animal kingdom, micro-organisms, etc. For every disease that is caused by any *Jangama*, there exists a cure from *Sthavara*.[11] Likewise Virus like SARS-CoV-2 which is included in *Jangama* category can be cured by plant or mineral based medicines. Globally accepted potent herbal based (*Sthavara*) medicines are required to quickly address the damage/infection caused by the Covid-19 disease. Immune modulators, anti-inflammatory drugs and symptomatic treatment are the main focus in tackling the Covid-19 disease by AYUSH personnel.[12,13] So, apart from looking for a rapid drug delivery system like *Dhuma* (medicated fumes) we focused on certain attributes said in Ayurveda which are required for the quick stimulation of both body and mind for improving immune system and fitness of the body to help tackle the Covid-19 disease.

*Vyavayi guna* (fast diffusing quality) is a specific property of few herbs in Ayurveda which first spreads/ circulates quickly throughout the body to exert its action and them undergoes *Paka* (digestion).[14] *Sattva* (goodness) is the purest quality among the three primary attributes of mind which is said to be required for homeostasis in the neuronal impulses which triggers all the physiological functions in the body.[15] *Medhya* (intellect promoting) is also a unique quality among certain herbs to help maintain the neuronal health and psychological balance.[16] *Vajikarana-Rasayana* (aphrodisiac and rejuvenative) herbs are the best in improving and maintaining energy levels, stamina and immunity.[17] All these qualities are present in one single herb called Vijaya (Cannabis sativa Linn.)[18] and recent scientific researches done on the phytocannabinoids of Cannabis plant showed encouraging results in decreasing the pro-inflammatory cytokine storm and to an extent halting the replication of SARS-CoV-2 which will be explained below in brief. There are more than 200 formulations of *Vijaya* (*Cannabis sativa* Linn.) in Ayurveda that are mostly unexplored.[19]

We searched online journals for scientific research articles on Elsevier, PubMed, Research Gate, Science Direct, Medline, Google Scholar, Semantic Scholar, Ayush research portal, etc, for Ayurvedic herbs useful in Covid-19 disease; in parallel also explored classical *Vijaya* (*Cannabis sativa* Linn.*)* based *Dhumapana* or *Dhupana* formulations with respect to ailments Viz. *Swasa* (Asthma, Dyspnoea), *Kasa* (Cough) in the classical Ayurvedic texts listed in the first schedule of drugs and cosmetics act (1940) that are presently available in the AYUSH medical shops or online pharmaceutical markets having such combination of researched herbs on Covid-19.

## RESULTS

We found only one classical *Cannabis* based Ayurvedic *Dhumapana* formulation available in the market called *Dhuma Yoga* from a GMP certified Ayurvedic company Charaka Hanf Pvt. Ltd.[20] *Dhuma Yoga* is a polyherbal formulation taken from a classical book *Siddha yoga sangraha,* containing herbs Viz. *Vasa* (*Adhatoda vasica* Nees.), *Kala Dhatura* (*Datura metel* Linn.), *Vijaya* (*Cannabis sativa* Linn.), *Cavya* (*Piper retrofractum* Vahl.) and *Parasika yavani* (*Hyoscyamus niger* Linn.).[21] In silico, In vitro and In vivo research is available on the phytochemicals of these five herbal ingredients for symptomatically treating Covid-19 and also inhibiting the replication of SARS-CoV-2 with positive outcomes which will be

discussed below in brief. *Dhuma Yoga* is indicated for *Swasa* (Asthma, Dyspnoea/breathing difficulty) as per the classical Ayurvedic text.[21] The above herbal coarse powder is used as an inhalation therapy and can also be fumigated to sanitise the environment.

**Table1: Showing the herbal ingredients of *Dhuma Yoga* [22]**

| S.No. | Sanskrit name | Scientific name | Family | Part used |
|---|---|---|---|---|
| 1. | *Vijaya* | *Cannabis sativa* Linn. | Cannabinaceae | Leaf |
| 2. | *Kala Dhatura* | *Datura metel* Linn. | Solanaceae | Leaf |
| 3. | *Vasa* | *Adhatoda vasica* Nees. | Acanthaceae | Leaf |
| 4. | *Cavya* | *Piper retrofractum* Vahl. | Piperaceae | Root |
| 5. | *Parasika yavani* | *Hyoscyamus niger* Linn. | Solanaceae | Leaf |

**Table 2: Showing the Ayurvedic pharmacological properties of the above researched herbs [22]**

| S.No. | Herbs | ***Rasa* (taste)** | ***Guna* (qualities)** | ***Virya* (potency)** | ***Vipaka* (taste after digestion)** | ***Dosha* (fundamental bio-elements)** |
|---|---|---|---|---|---|---|
| 1. | *Vijaya* | *Tikta* (bitter), *Katu* (pungent) | *Laghu* (light), *Tikshna* (sharp) | *Ushna* (hot) | *Katu* (pungent) | Alleviates *Kapha-Vata* |
| 2. | *Kala Dhatura* | *Madhura* (sweet), *Tikta* (bitter), *Kashaya* (astringent) | *Guru* (heaviness), *Tikshna* (sharp) | *Ushna* (hot) | *Katu* (pungent) | Alleviates *Kapha-Vata* |
| 3. | *Vasa* | *Tikta* (bitter), *Kashaya* (astringent) | *Laghu* (light), *Ruksha* (dry) | *Sita* (cold) | *Katu* (pungent) | Alleviates *Kapha-pitta* |
| 4. | *Cavya* | *Katu* (pungent) | *Laghu* (light), *Ruksha* (dry), *Tikshna* (sharp) | *Ushna* (hot) | *Katu* (pungent) | Alleviates *Kapha-Vata* |
| 5. | *Parasika yavani* | *Tikta* (bitter), *Katu* (pungent) | *Laghu* (light), *Tikshna* (sharp) | *Ushna* (hot) | *Katu* (pungent) | Alleviates *Kapha-Vata* |

**Scientific research on phytocompounds in the herbs of *Dhuma Yoga* on SARS-CoV-2**

***Vijaya* (*Cannabis sativa* Linn.)**

Inhaling fumes of cannabis is being researched across the globe for its potential use in Asthma. The bronchodilator effect is because of the THC (delta-9 tetrahydrocannabinol) which activates prejunctional CB1 receptors to mediate the inhibition of cholinergic contractions in human bronchus.[23] Endo-cannabinoid Anandamide (AEA) has broncho-dilator effect whose levels are increased by phyto-cannabinoid CBD.[24] CBD inhibits FAAH which is responsible for breakdown of Anandamide (AEA).[25] Both THC & CBD are good antioxidants and prevent hydroperoxide-induced oxidative damage.[26,27] In a study aerosolized tetrahydro-cannabinol (THC) has been investigated for bronchodilator effect showed satisfactory results at a dose of 100µg of THC as measured by improvement in peak expiratory flow rate (PEFR), forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC).[28,29] Research is also done on CB1 receptors as target for bronchodilator therapy in β2-receceptor agonist resistant asthma.[30] An experimental study concluded oral administration of 10 mg of delta 9-THC induced significant bronchodilation.[31]

The endocannabinoid system is found in multiple systems within the human body, including the immune system. Its activation can lead to beneficial results such as decreased viral entry, decreased viral replication, and a decrease in pro-inflammatory cytokines such as IL-2, IL-4, IL-6, IL-12, TNF-α or TNF-γ. Moreover, endocannabinoid system activation can lead to an increase in anti-inflammatory cytokines, mainly represented by IL-10. Overall, the cannabinoid system can potentially reduce pulmonary inflammation, increase the immuno-modulatory effect, decrease PMN infiltration, reduce fibrosis, and decrease viral replication, as well as decrease the cytokine storm.[32] In an in vitro study Cannabis compounds Viz. CBD, CBG and THCV exhibited anti-inflammatory activity in COVID-19-related inflammation in lung epithelial cells and pro-inflammatory activity in macrophages.[33]

In an experimental study CBD (Cannabidiol) and its metabolite, 7-OH-CBD potently blocks SARS-CoV-2 replication in lung epithelial cells. CBD acts after 5 cellular infections, inhibiting viral gene expression and reversing many effects of SARS-CoV-2 on host gene transcription. CBD induces interferon expression and up-regulates its antiviral signaling pathway.[34] CBD might represent as a potential anti-inflammatory therapeutic approach against SARS-CoV2-induced inflammation.[35] In an animal experimental study the treatment of SEB-mediated ARDS mice with Delta-9 Tetrahydrocannabinol (THC) led to a 100% survival, decreased lung inflammation, and the suppression of cytokine storm. This was associated with immune cell apoptosis involving the mitochondrial pathway, as suggested by single-cell RNA sequencing. A transcriptomic analysis of immune cells from the lungs revealed an increase in mitochondrial respiratory chain enzymes following THC treatment. THC caused the downregulation of miR-185, which correlated with an increase in the pro-apoptotic gene targets. Interestingly, the gene expression datasets from the bronchoalveolar lavage fluid (BALF) of human Covid-19 patients showed some similarities between cytokine and apoptotic genes with SEB-induced ARDS. Collectively, this study suggests that the activation of cannabinoid receptors may serve as a therapeutic modality to treat ARDS associated with Covid-19.[36]

Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, is a peptide hormone secreted mainly by the stomach. Interestingly, ghrelin possesses promising antioxidant, anti-and inflammatory effects, making it an attractive agent to reduce the complications of the SARS-CoV-2. In addition, ghrelin exerts a wide range of immunomodulatory and anti-inflammatory effects and can mitigate the uncontrolled cytokine production responsible for acute lung injury by upregulating PPARγ and down-regulating NF-κB expression. Ghrelin has also been reported to enhance Nrf2 expression in inflammatory conditions which led to the suppression of oxidative stress. The current opinion summarizes the evidence for the possible pharmacological benefits of ghrelin in the therapeutic management of SARS-CoV-2 infection. Delta-9 Tetrahydrocannabinol (THC) compound of cannabis is responsible for the stimulation and release of ghrelin.[37]

High cannabidiol *Cannabis sativa* extracts are able to down-regulate the expression of the two key receptors for SARS-CoV2 in several models of human epithelia. Cannabidiol exerts a wide range of immunomodulatory and anti-inflammatory effects and it can mitigate the uncontrolled cytokine production responsible for acute lung injury. CBD being a PPARγ agonist, it can display a direct antiviral activity and PPARγ agonists are regulators of fibroblast/myofibroblast activation and can inhibit the development of pulmonary fibrosis, thus ameliorating lung function.[38]

### *Kala Dhatura* (*Datura metel* Linn.)

The main compounds of *Kala Dhatura (Datura metel* Linn.*)* are tropane alkaloids Viz. Scopolamine (Hyoscine), Hypocyamine (Daturine), Atropine which have anti-cholinergic and anti-muscarinic activity that exhibit strong bronchodilation, prophylactic anti-emetic and antispasmodic (relieving abdominal pain/ spasms) property.[39] *Datura* ameliorates asthma symptoms by promoting naive T-cell development and reducing activated T-cells. Asthma relief is attributed by blocking the action of the neurotransmitter acetylcholine (ACh) at synapses to cause depression of the receptive mechanism of the parasympathetic nerves in the bronchi.[40] Researches on *Datura* smoking are also conducted to know its pharmacological effects.[41-44]

It is a potential source of antioxidants which neutralise free radicals and is being researched for its potent anti-bacterial and anti-fungal action.[45,46,47] In a molecular docking study Scopolamine showed a favourable binding affinity of -8.7 kcal/mol towards Mpro of SARS-CoV-2. It forms hydrogen bonds with Phe294 and Thr304 apart from interacting with Asp295 and Val303 residues of Mpro (main protease).[48] In siloco studies of Hyoscyamine showed significant binding potential to spike glycoprotein of SARS-Cov-2 in the post-fusion, closed state, open state conformations with a binding affinity of -8.14, -6.0, -5.7 kcal/mol respectively with better interaction and stability. The binding energy of the docked complex of Hyoscyamine and spike glycoprotein is estimated to be -48. 25 kcal/mol suggests that Hyoscyamine can act as a potential lead molecule against the spike glycoprotein of SARS-CoV-2.[49]

### *Vasa* (*Adhatoda vasica* Nees.)

An in-silico docking of *Adhatoda vasica* constituents reveal higher negative binding affinity for C and O-glycosides for HIF-1α, IL-6, Janus kinase 1/3, TNF-α and TGF-β key players of hypoxia-inflammation. This study for the first time provides a molecular basis of action and effect of *Vasa* (Malabar nut) whole extract that is widely used in Ayurveda practice for diverse respiratory ailments.[50] These alkaloids inhibit antigen-induced mast cell degranulation and histamine secretion from target tissues. By its mucolytic property it reduces the viscosity of mucus and helps to expel the mucus out

through its expectorant action.[51,52,53] It is a proven anxiolytic (anti-anxiety), nootropic (improves cognition) and the herb *Adhatoda* as a whole (full-spectrum) has dual action which counteracts the overdose of anti-cholinergic compounds by its cholinesterase inhibiting activity.[54,55] It maintains cardiac and respiratory health by inhibition of oxidative stress and inflammatory factors.[56] Researchers claim smoking *Adhatoda Vasica* herb reduces tobacco withdrawal symptoms and hence is very useful in de-addiction of tobacco smoking.[57,58]

In an in-vitro experiment Vasicinone, a quinazoline alkaloid of *Vasa* (*Adhatoda vasica*) exhibited anti-proliferative activity in lung carcinoma cells.[59] *Adhatoda Vasica* extract attenuated inflammatory and hypoxic responses in preclinical mouse models. It reduces the levels of transforming growth factor-β1 (TGF-β1), IL-6, Hypoxia inducible factor-1 α (HIF-1α) and improves the overall survival rates of mice in the models of pulmonary fibrosis and sepsis and rescues the siRNA induced inflammation and associated blood coagulation phenotypes in mice. There was down regulation of hypoxia, inflammation, TGF-β1, and angiogenesis genes and up regulation of adaptive immunity-related genes in the lung transcriptome. *Adhatoda Vasica* (100µg/ml) treatment also reduced the viral load in Vero cells infected with SARS-CoV-2 by 63%.[60] Trans membrane protease serine type 2 (TMPRSS2) is responsible for the priming of the viral S-protein to enter into the human alveolar epithelial cells. An in vitro study revealed the inhibition of protease TMPRSS2 by bromhexine hydrochloride, one of the derivatives of alkaloid vasicinone of *Adhatoda vasica* plant.[61]

The quinazoline alkaloids Viz. Vasicoline, Anisotine of Adhatoda vasica has shown acceptable binding energy values in a docking study towards inhibition of SARS-CoV-2 protease and RdRp (RNA-dependent RNA polymerase) which are the essential enzymes for viral genome replication. Vasicoline and Anisotine displayed binding energies of -7.0, -7.8 kcal/mol with protease and -8.5, -9.2 kcal/mol with RdRp respectively.[62] Another molecular docking study revealed the primary alkaloid Vasicine of *Adhatoda vasica* with ACE-2 Receptor shown higher docking affinity score -7.1 K/cal and also showed good inhibitory constant 486.54 mM on 3CL protease..[63] An in silico experimentation with the alkaloid Anisotine of *Adhatoda vasica* interacted with both the catalytic residues (His41 and Cys145) of Mpro of SARS-CoV-2 and exhibited good binding affinity (-7.9 kcal/mol). Mpro-anisotine complex is was stable, conformationally less fluctuated. Even the number of intermolecular H-bonds and MM-GBSA analysis suggested that anisotine is a more potent Mpro inhibitor than the two previously recommended antiviral drugs (lopinavir and darunavir) and may evolve as a promising anti-Covid-19.[64] These results substantiate the potential of *Adhatoda Vasica* in management of Covid-19.

### *Cavya* (*Piper retrofractum* Vahl.)

Prime alkaloids of *Cavya* (*Piper retrofractum* Vahl.) Piperine, Guineesine collectively exhibits a potent bronchodilation and also regulates thermogenesis to maintain the energy balance in the body. These active alkaloid compounds help in enhancing the effect of other drugs by its synergetic action. Piperine alkaloid effectively treats Asthma by anti-histaminic activity, inhibiting eosinophil infiltration and airway hyper-responsiveness by suppressing T cell activity and Th2 cytokine production.[65,66] Guineesine alkaloid an anti-inflammatory agent is an Anandamide (AEA) reuptake inhibitor[67] and this fatty acid endo-cannabinoid ligand-AEA acts as a bronchodilator by inhibiting the release of the neurotransmitter acetylcholine (ACh) from the cholinergic nerve endings.[68,69] Research on the inhalation of vapour from black pepper, a member of piper family having similar API's to *Cavya* (Java long pepper) reduced cues to tobacco smoking.[70] In a study chabamide, a phytochemical in *Cavya* (Java long pepper) has anti-inflammatory effects via the activation of the Nrf2/heme-oxygenase-1 pathway.[71]

A computational study revealed piperine, an alkaloid present in *Cavya* (Java long pepper) showed high binding affinity of -7.0 kcal/mol with RNA-binding pocket of the nucleocapsid of SARS-CoV-2 which shows its potential anti-viral property.[72] Scutifoliamide-A, a phytochemical in *Cavya* (Java long pepper) has shown favourable binding potential to the spike glycoprotein in the post-fusion, closed state, open state conformations with the significant binding energies of -6.4, -5.4, -6.6 kcal/mol, respectively. Scutifoliamide-A showed highest binding energy (-6.9 kcal/mol) to replicase polyprotein 1 ab which is responsible for the transcription and replication of SARS-CoV-2 RNAs. The binding energies of the docked complex of replicase polyprotein 1 ab and Scutifoliamide-A was estimated to be -45. 97 kcal/mol. Scutifoliamide-A could be a therapeutic agent for Covid-19.[73]

## DISCUSSION

*Dhuma* (medicated fumes) shows its local therapeutic effects mostly in *Urdhvajatrugata roga* (diseases/disorders of head and neck), respiratory ailments and also has systemic effects like in *Jwara* (fever), *Sopha* (inflammation), *Visha* (poisoning), *Unmada* (psychosis), etc as per Ayurvedic

literature.[8,9,10] Nasal and oral are the routes of administration of *Dhumapana* (medicated smoking/ inhalation therapy). Nasal cavity is the pathway to brain said the great sage Charaka and other *Acharyas* (physicians) of Ayurveda,[74] also is the quickest route to the respiratory system. Through inhalation the medicated fumes will directly enter the lung tissue to show its effect. The olfactory region is one of the prominent sites from where the API's (active pharmaceutical ingredients) will be absorbed directly into the brain by olfactory and trigeminal nerve pathways. When the drug is administered it comes in contact with mucosa and it is directly transported into the brain bypassing the BBB, thereby achieving excellent bioavailability. Through the oral route of administration the GI-tract ailments can also be addressed. The mucous membranes in the oral and nasal cavity are thin and allow quick absorption into the blood stream. Avoidance of hepatic first pass metabolism is the main advantage.[75] Ayurveda has vast knowledge regarding the nasal route of drug administration long before than the contemporary modern researchers. Indications, contraindications, appropriate time, method of inhaling smoke have been specifically mentioned. Inhalation and exhalation are two main aspects of *Dhumapana*. Inhalation/ Puff drag is done by mouth or nostrils as per requirement and exhalation has to be breathed out/ exhaled only by mouth which is the correct way to smoke as per as Ayurveda. No smoke should come out of the nostrils or else eyes will be damaged.[76]

Major symptoms of COVID-19 are fever, cough, shortness of breath and severe inflammation. Other common symptoms are headache, loss of taste and smell, tiredness, aches, sore throat, chest pain, loss of appetite, nausea, diarrhoea, etc.[77,78] Excess mucus/phlegm secretions in throat, nostrils, sinus cavities, trachea, etc, may increase the severity of bacterial, viral or fungal infections developing in the body especially in the lungs like in Covid-19.[79] The cytokine storm caused by SARS-CoV-2 in the respiratory tissues may result in decreased oxygen intake by damaging the thin walls/ lining (endothelium) of air-sacs (alveoli) and capillaries (small blood vessels) causing thickening of inter-alveolar septa which disrupt the gas exchange mechanism in the lungs leading to loss of elasticity and may also lead to the collapse of alveoli.[80,81] Micro-vascular thrombosis (micro blood clots) or embolism resulting from the damaged walls/ lining within the pulmonary circulation and also hyper-coagulation and immune-thrombosis by deranged immunity is one of the reason Covid-19 patients are facing hypoxemia (decreased oxygen saturation in blood) which can also lead to multiple organ damage.[82,83,84]

All the five herbs of *Dhuma Yoga* have common properties Viz. *Kapha Dosha* alleviating, *Tikshna guna* (sharp attribute) and *Katu vipaka* (pungent taste after digestion) which can decrease the excess mucus/ phlegm and helps to recover from respiratory ailments like *Swasa* (asthma, dyspnoea/ breathing difficulties), *Kasa* (cough) by controlling the cytokine storm with their anti-inflammatory action as per contemporary research and classical Ayurvedic literature. These five herbs also exhibit anticoagulant or thrombolytic properties which in combination may have more pronounced effect. In an animal study cannabinoids viz. THC (tetrahydro-cannabinol) and CBN (cannabinol) showed anticoagulant activity in obese rat model.[85] An in vitro study on anticoagulant activity of chloroform and methanol extract of *Datura* showed significant results.[86] Another in vitro study revealed favourable anticoagulant and clot-lysis activity with aqueous extract of leaves of *Datura metel*.[87] Molecular docking studies on *Adhatoda vasica* methanol extract showed favourable thrombolytic activity (breakdown of blood clots).[88] An in vitro and in vivo studies on Piperlonguminine, a phytochemical present in *Cavya* (*Piper retrofractum*) exhibited significant anticoagulant activity.[89] In an animal study *Yavani* (*Trachyspermum ammi* Linn.) methanol extract significantly increased the prothrombin time which reveals its anti-thrombotic effect.[90] As per Ayurveda *Parasika yavani* (*Hyoscyamus niger* Linn.) has similar properties like *Yavani* (*Trachyspermum ammi* Linn.), So the anti-thrombotic effect can be correlated to Henbane (*Hyoscyamus niger* Linn.) too.

*Cannabis* is the sacred plant of Ayurveda and by mythology is believed to be originated from the Gods.[18] It is called *Vijaya* in Sanskrit which means victory from all ailments and imparts *Sukham* (health) and *Satvam* (highest level of consciousness/ goodness).[91] *Cannabis* has a unique relation to neuroendocrine signaling specifically related to Endocannabinoid System (ECS) which has been found to be pervasive in mammalian species. *Cannabis* plant produces phyto-cannabinoids which are similar to endo-cannabinoid molecules produced naturally in the body.[92] They are involved in various physiological functions such as immune modulation, stress response, respiratory health, appetite stimulation, reproduction, analgesia, sleep, thermoregulation, memory and learning, etc, by binding to cannabinoid receptors (CBRs) that are spread throughout the tissues to maintain homeostasis (equilibrium state of psychological and physiological activities).[93] In Ayurvedic texts *Vijaya*

(*Cannabis*) has been incorporated in many formulations related to respiratory system and GI-tract ailments. *Vijaya* herb (*Cannabis*) has a special property to act as a catalyst and enhance the bioavailability of the other medicinal drugs used along.[94] Selective strains of Cannabis of varied cannabinoid ratios can be used for different ailments. *Cannabis* has *Grahi* (Absorbent), *Dipana* (appetiser), *Pachana* (digestive) and *Ruchya* (improves taste) properties[18] which can quickly correct the metabolism of impaired digestion, the root cause leading to complications in most of the diseases (*Rogah Sarve api mandagnou*)[95] said by *Vagbhata*. *Ojas* (immunity) is the *Upadhatu*[96] (tissue derivatives) of *Sukra dhatu* (tissues and components of reproductive system present in both males and females)[97] which is circulated all over the body[98] along with *Rasa dhatu* (blood plasma). This may be the Ayurvedic explanation why plasma donation was once an off label recommendation for patients to recover fast from Covid-19 as the *Ojas*/ antibodies (immune components) are in circulation with blood plasma, but was discontinued from Covid-19 treatment guidelines as the antibodies in donor's plasma were not sufficient enough for patient recovery and also researchers hypothesized the risk of developing new variants of Virus. *Sukra* is the par excellence of well digested food said in *Charaka samhita* which is later converted to *Ojas* (immune system components).[99] Diminished *Sukra* may lead to various diseases and even death so, one should preserve the *Sukra dhatu* by indulging in wholesome food and lifestyle; hence potent *Vajikarana* (aphrodisiac) and *Sukra Stambhana*[100] (drugs prolonging ejaculation time) herbs like *Vijaya (Cannabis sativa* Linn.*)* can improve *Ojas* (immune system). *Vijaya (Cannabis sativa* Linn.*)* is a *Vata-Kapha* alleviating herb which according to *Acharya charaka* is an essential *Dosha karma* for curing *Swasa* (breathing difficulty/asthma)[101].

The cytokine storm is one of the major side effects of SARS-CoV-2 virus infection. Pro-inflammatory cytokines like interleukins, TNF-α and TNF-γ that are involved in the inflammation of alveoli and damage the lungs can be controlled by activating the endocannabinoid system through *Vijaya* (*Cannabis sativa* Linn.).[32] In vitro experiment with CBD (cannabidiol), a major phytocannabinoid was effective in stopping the replication of SARS-CoV-2 in lung epithelial cells.[35] CBD (cannabidiol) is a known anti-inflammatory and immune modulator molecule. CBD (cannabidiol) being an agonist at PPAR-γ receptor (peroxisome proliferator-activated receptor) reduced pulmonary inflammation and fibrosis in animal models of asthma. High CBD (cannabidiol) extracts have been reported to down regulate Angiotensin-converting enzyme 2 (ACE2) and Transmembrane Serine Protease 2 (TMPRSS2) receptors, viral gateways in oral, lung and intestinal epithelia constituting important routes of SARS-CoV2 invasion. In an animal study, CBD (cannabidiol) caused marked amelioration of the pulmonary function by acting at adenosine A2 receptor site and reducing of leukocyte migration into the lung, accompanied to a marked inhibition of both pro-inflammatory cytokines (TNF-α, IL-6) and chemokines (MCP-1 and MIP-2).[38] THC (delta-9 Tetrahydrocannabinol), the main phytocannabinoid in an animal study prevented mortality from ARDS (Acute Respiratory Distress Syndrome) by inducing apoptosis in immune cells responsible for increase in pro-inflammatory molecules, leading to the suppression of cytokine storm.[36] Ghrelin, a peptide hormone whose secretion is stimulated by THC (delta-9 Tetrahydrocannabinol) can decrease the uncontrolled cytokine production responsible for acute lung injury by up regulating PPARγ and down-regulating NF-κB expression. Ghrelin also enhance transcription factor Nrf2 expression in inflammatory conditions which can suppress oxidative stress.[37] This shows the preliminary antiviral property of the phytocannabinoids of *Cannabis* herb.

*Kala Dhatura (Datura metel* Linn.*)* is the best and potent among various species of *Datura* having *Jwaraghna* (antipyretic), *Krimi-hara* (anti-parasitic), Visha-hara (antitoxic), *Agnidipana* (appetiser) properties[102] and the *Arka* (distillate) of *Datura* is said to be *Ojo-vardhaka*[103] (Immune booster) too. Inhaling *Kala dhatura* (*Datura metel*) smoke is a famous age old traditional folk medicine[104,105] for quick relief in asthma attacks and all types of productive and non-productive cough (antitussive).[106] It dries up the excess mucus secretions in the body by its mucolytic action. It is used internally in *Jwara* (fevers) and *Vajikarana* (aphrodisiac) formulations as per traditional literature. *Datura* is also a *Sukra Stambhana*[107] herb (drugs prolonging ejaculation time) like *Vijaya (Cannabis sativa* Linn.*)* which explains its immune boosting property. *Datura* is a potent anti-inflammatory and Pain killer herb[108] which can control the cytokine storm of Covid-19 specific to respiratory system. Active alkaloids of *Datura* Viz. Scopolamine and Hyoscyamine act on the SARS-CoV-2 Mpro (main protease) and spike glycoprotein respectively, showing their anti-viral property.

*Vasa (Adhatoda vasica* Nees.), common name Malabar nut is a *Hridya* (cardiotonic), *Jwaraghna* (antipyretic), *Swarya* (voice promoting), antitussive and respiratory healer indicated in *Swasa* (asthma,

dyspnoea/ breathing difficulty), *Kasa* (cough) as per Vedic literature[109]. Leaves of *Adhatoda* are commonly smoked in asthma and bronchitis as per folk lore. [110] Major alkaloids of *Vasa (Adhatoda vasica* Nees.*),* Viz. Vasicine (peganine) and Vasicinone are very effective bronchodilators and have antihistamine activity. API's of *Vasa* (*Adhatoda vasica*) relaxes the tracheal smooth muscle to produce bronchodilator effect by anti-cholinergic action on the vagal innervations of the bronchii.[111] *Vasa Kashaya* (aqueous extract of *Adhatoda vasica*) in mouse (in vitro study) reduced the levels of transforming growth factor-β1 (TGF-β1), IL-6, Hypoxia inducible factor-1 α (HIF-1α) which are responsible for cytokine storm. [112] Vasicoline, Anisotine alkaloids inhibits main protease (Mpro) and RdRp (RNA-dependent RNA polymerase) of SARS-CoV-2 in molecular docking studies which shows their antiviral properties.

*Cavya (Piper retrofractum* Wahl*.)* commonly called Java long pepper is a stimulant herb which improves taste and appetite. It is indicated in *Krimi* (parasites), *Swasa* (Asthma, dyspnoea/ breathing difficulty), *Kasa* (cough), commonly prescribed for respiratory and GI-tract ailments in traditional medicine.[113] *Cavya* (*Piper retrofractum*) phytochemicals Viz. Piperine, Guineesine and chabamide exhibits potent anti-inflammatory activity. Piperine is proven to be a bioavailability enhancer to several compounds including Vasicine, an alkaloid in *Adhatoda vasica*.[114-118] In silico studies reveals Piperine binds to RNA-binding pocket of the nucleocapsid thereby inhibiting virus replication; Scutifoliamide-A, an alkaloid in *Cavya* (*Piper retrofractum*) showed favourable inhibition of spike glycoprotein and replicase polyprotein 1 ab of SARS-CoV-2 which reveals its antiviral action.

Smoking of *Parasika yavani* (*Hyoscyamus niger* Linn.) in folk medicine has been in wide practice to relieve respiratory ailments.[119] Active alkaloid compounds are similar to those found in *Kala Dhatura* Viz. Scopolamine and Hyoscyamine acts as bronchodilator besides improving digestive power along with helping in anorexia. It manages psychological disorders by modulating monoamine oxidase activity and possesses neuroprotective potential by scavenging hydroxyl radical.[120] *Parasika yavani* (Henbane) as per Ayurveda is having similar properties like *Yavani* herb (*Trachyspermum ammi* Linn.) having *Dipana* (appetiser), *Pachana* (digestive), *Hridya* (cardiotonic), *Anaha-prasama* (alleviating abdominal distension/ bloating), *Krimi-hara* (anti-parasitic) properties.[121] Henbanes's Tropane alkaloids Scopolamine, Hyoscyamine acts on Mpro (main protease), spike glycoprotein of SARS-CoV-2 respectively showing their anti-viral property.

*Dhupana* (medicated fumigation of vicinity) has been recommended by ministry of AYUSH as per the Guidelines for Ayurveda, Siddha and Unani Practitioners for Covid-19 pandemic.[122] The above researched herbs if used as *Dhupana* (medicated fumigation of vicinity) may weaken the Virus in the environment which probably can break the chain of transmission and if used as *Dhumapana* (medicated smoking/ inhalation therapy) can be helpful in decreasing the need of emergency artificial oxygen supply for the patient and also reduce the virus load inside the body. All the herbs of *Dhuma Yoga* are being scientifically studied for their beneficial aspects as prophylactic and curative to Covid-19 symptoms, resist the entry of virus into the host along with halting the replication of SARS-CoV-2 with preliminary significant outcomes. Also the Ayurvedic properties of these five herbs mentioned above reveal their benefits in handling the prime symptoms of Covid-19.

As per Ayurveda polyherbal combinations are effective than single herbs and a whole herb (full spectrum) if used as medicine will have an entourage effect with negligible side effects when compared to phytochemical extracts and isolates. So, we propose the combination of these herbs in the form of *Dhuma Yoga* formulation may act in synergy to amplify the benefits which in a blend of powerful quinazoline and tropane alkaloids along with highly potent cannabinoids infused with bio-enhancing molecules which have a potential to deliver quick results in Covid-19 by their bronchodilation, mucolytic, anti-inflammatory, antitussive, antipyretic, appetising, absorbent, anticoagulant, thrombolytic and immunomodulatory properties, which needs to be evaluated with proper clinical trials.

## CONCLUSION

*Dhuma* (Medicated fumes) has been validated by many traditional medical systems since ages and is also recommended in the Guidelines for Covid-19 by ministry of AYUSH. *Dhuma Yoga* is a very effective bronchodilator which has many additional therapeutic benefits as per the present review. Pre-clinical experimentations like in silico, in vitro and in vivo studies on phytochemicals of *Dhuma Yoga* herbs Viz. *Vijaya (Cannabis sativa* Linn.*), Kala Dhatura (Datura metel* Linn.*), Vasa (Adhatoda vasica* Nees.*), Cavya (Piper retrofractum* Wahl.*) and Parasika Yavani (Hyoscyamus niger* Linn.*)* showed encouraging results in alleviating major symptoms of Covid-19 disease and to an extent may stop the entry and also halt the replication of SARS-CoV-2. The medicine *Dhuma Yoga* can be used as an alternate remedy in the form of

*Dhumapana* (medicated smoking/ inhalation therapy) and *Dhupana* (medicated fumigation of vicinity) in decreasing the severity of Covid-19 disease which needs further scientific evaluation.

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