Indian Traditional Ayurvedic Treatment Regime For Novel Coronavirus, COVID-19

Acharya Balkrishna

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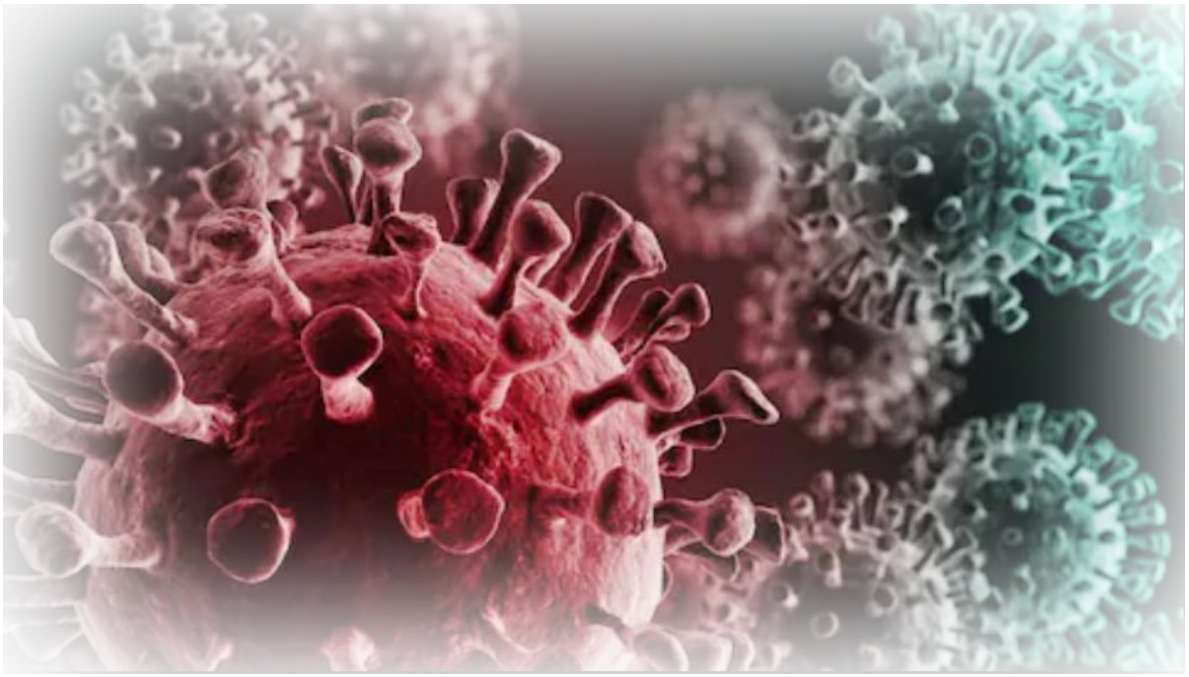

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Novel Corona Virus, COVID-19

The new coronavirus, COVID-19 has sent the world into a medical crisis, one which if not contained or prevented might take serious tolls on economy of India and world alike. There are more than 870000 confirmed COVID-19 cases cross the world; and more than 43000 lives have succumbed to it worldwide. According to Ministry of Health, Govt. of India, tallies of active COVID-19 cases have crossed 1400, with a death toll of 30 in India as of April 01, 2020. Inspite of paramount efferts by government of India, rapid spreding of COVID-19 infection calls for an eminent need for realizing treatment and intervention options to stop the crisis from spiralling out of control.

COVID-19 infection is known to affect individuals with weak immunity more severely. Therefore, enhancing immunity is definitely one of the ways the doctors across the globe have been using for treating COVID-19 cases. In fact, high doses of vitamin C, known to boost immunity, have been administered to the COVID-19 patients in China and elsewhere in the world with promising results. Recently on March 26, 2020, Indian Council of Medical Research (ICMR), Govt of India, has approved the use of hydroxyl-chloroquinone for prophylactic treatment of COVID-19 infection. Chinese traditional medicines have been used in combination with allopathic treatments for symptomatic alleviation in COVID-19 cases. Ayurveda, one of the world renowned forms of Indian traditional medicine, mentions several immunity boosting therapeutics. This presented regime propose to bring Ayurvedic natural medicines in the fore-front in healing COVID-19 ailments, concurrent with ICMR prescribed allopathic treatments.

- **To combat COVID-19 virus with Ayurveda, we have screened close to 1000 phytochemicals from more than 100 medicinal plants, *in-sillico*. We looked for their binding affinities to COVID-19 essential proteins and host protein interactions. We have discovered that natural phytochemicals in Ashwagandha, Giloy and Tulsi indeed have potentials to combat COVID-19 and its pathogenicity.**

- **Our data, for the first time, show that natural phytochemicals could well be the viable options for controlling COVID-19 entry into host cells, and Ashwagandha may be the first choice of herbs in these directions to curb the COVID-19 infectivity.**
  This work is currently under Peer-Review for publication in Virology Journal, in Springer-Nature, and available at their pre-print server [2]. (https://www.researchsquare.com/article/rs-17806/v1).

Scientific Rationale of *Pure Ashwagandha* (*Withania somnifera*) *Extracts*

Withania somnifera (WS) or Ashwagandha is a well-known medicinal plant used in traditional medicines for more than 3,000 years. This plant extract and its bioactive compounds are used in the prevention and treatment of many diseases, such as arthritis, impotence, amnesia, anxiety, cancer, neurodegenerative and cardiovascular diseases, and others.

Pharmacological Perspective

Immunomodulatory Activities: Immunomodulatory potential of Ashwagandha was tested in experimental azoxymethane induced colon cancer in mice. Animals were treated with 400 mg/kg of *W. somnifera* extract once a week for four weeks orally. *W. somnifera* significantly altered the level of leucocytes, lymphocytes, neutrophils, immune complexes and immunoglobulins (Ig) A, G and M [3]. Furthermore, the root extract of WS (*W. somnifera*) was also tested for immunomodulatory effects in three myelosuppression models in mice: cyclophosphamide, azathioprine, or prednisolone. Significant increases in hemoglobin concentration, red blood cell count, white blood cell count, platelet count, and body weight were observed in WS-treated mice in comparison to untreated control mice. The effect of WS was also studied on the functions of mouse macrophages obtained from mice treated with the carcinogen ochratoxin A (OTA) and it significantly decreased the chemotactic activity of the macrophages, and associated Interleukin-1 (IL1) and tumor necrosis factor alpha (TNF-α) production[4]. Immunomodulatory effect of *W. somnifera* was also assessed in IgE-mediated anaphylaxis as reduction of ovalbumin-induced paw edema, in animals treated with WS at doses of 150 and 300 mg/kg, and the results were compared with the standard drug disodium chromoglycate. Cyclophosphamide-induced immunosuppression was counteracted by treatment with WS, revealing significant increase in hemagglutinating antibody responses and hemolytic antibody responses towards sheep red blood cells [5].

Pulmonary Hypertension (PH): The effect of *W. somnifera* root powder on monocrotaline (MCT)-induced PH in rats has been studied. Preventive treatment with 50 and 100 mg/kg *W. somnifera* significantly reduced the RVP and all markers of RVH in MCT-challenged rats. There was an improvement in inflammation, oxidative stress and endothelial dysfunction, and attenuation of proliferative marker and apoptotic resistance in lungs [6].

Chronic Obstructive Pulmonary Disease: Ashwagandha has been given to patients with COPD due to its rejuvenating and strengthening effects. It has shown to reduce tiredness, frequency of breathing troubles and cough attacks [7].

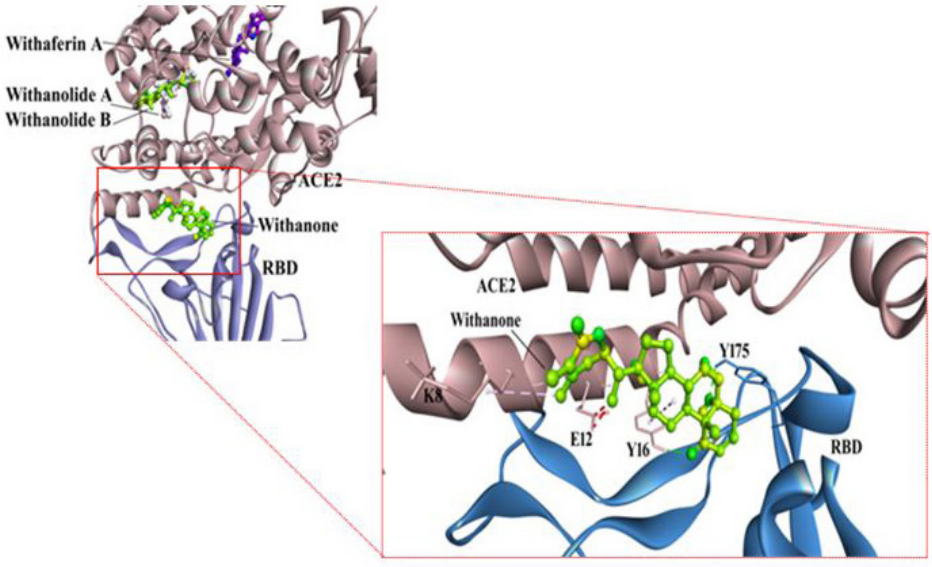
Pulmonary Fibrosis: The potential of Ashwagandha bioactive metabolite, Withaferin A to target pulmonary fibrosis (PF) has been tested in EMT and fibrotic events induced by TGF-β1 in alveolar epithelial cells and human fetal lung fibroblasts. Treatment with Withaferin A reduced the progression of PF by modulating the EMT related cell markers

both *in vivo* and *in vitro*. Withaferin A ameliorated the expression of inflammatory cytokines as well as attenuated the expression of pro-fibrotic proteins. Expression of angiogenic factors were also inhibited by Withaferin A. Collectively, Withaferin A could probably prove as an efficient and potential therapeutic against PF [8].

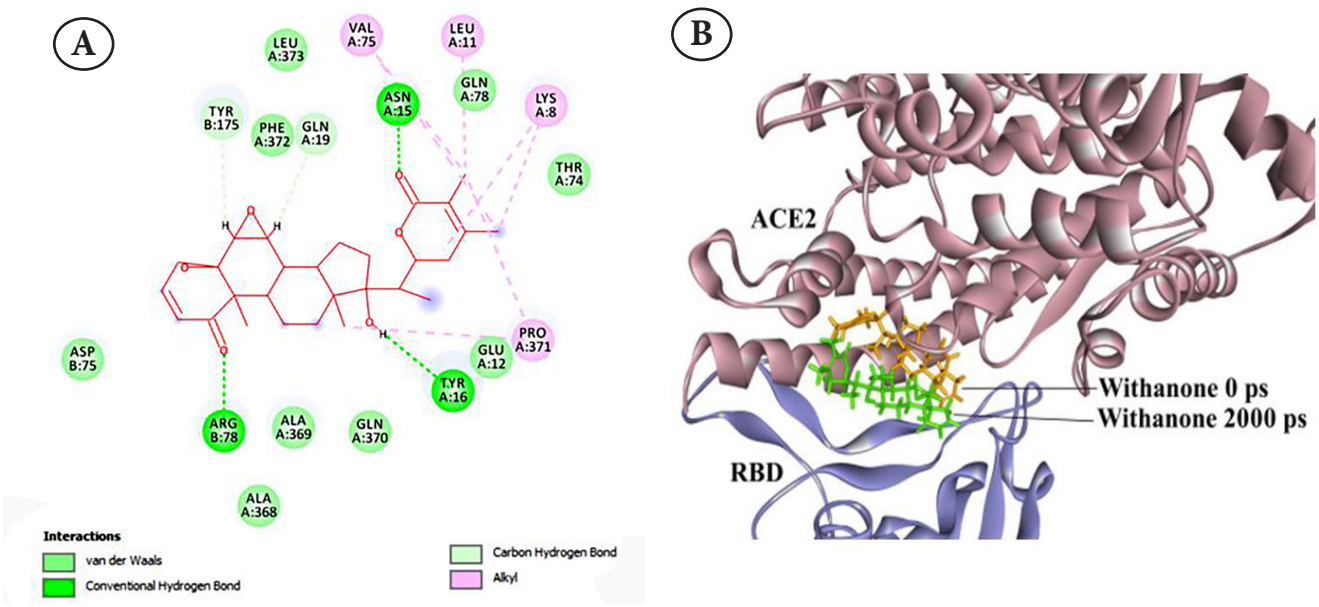
Toxicological Studies: Toxicological aspects of WS was evaluated to check whether it induced any negative impact over human body. The liver, spleen, lungs, kidneys, thymus, adrenals, and stomach were examined histo-pathologically and were all found to be normal after the treatment with estimated dose of 200 mg/kg/day for four weeks, in rats [65], suggesting a rather safe profile of Ashwagandha extracts.

Ashwagandha Might be Potent against COVID-19

Newly emerged COVID-19 has been shown to engage the host cell ACE2 through its spike protein receptor binding domain (RBD). We have shown that natural phytochemical from *Withania somnifera*, have distinct effects on viral RBD and host ACE2 receptor complex. It was found that *W. somnifera* compound, Withanone, docked very well in the binding interface of AEC2-RBD complex, and was found to move slightly towards the interface centre on simulation. Withanone significantly decreased electrostatic component of binding free energies of ACE2-RBD complex. Two salt bridges were also identified at the interface; incorporation of Withanone destabilized these salt bridges and decreased their occupancies. We postulate, such an interruption of electrostatic interactions between the RBD and ACE2 would block or weaken COVID-19 entry and its subsequent infectivity. It show that natural phytochemicals could well be the viable options for controlling COVID-19 entry into host cells, and *W. somnifera* may be the first choice of herbs in these directions to curb the COVID-19 infectivity. This work is under peer-review in Virology Journal, in Springer-Nature, and available at their preprint server [2].



Binding poses of withanolides (from *W. somnifera*) in ACE2-RBD complex. Withanone interactions at the interface of ACE2-RBD complex has been zoomed into. Withanone is well established in the pocket by two H-bonds - Y16 of ACE2, and Y175 (aa491) of RBD, in addition to alkyl interactions.



(**A).** Comparison of Withanone positions before and after MD simulation in ACE2-RBD complex. RMSD of all atoms is 5.08 Å. **(B).** Withanone' interactions within ACE2-RBD complex as seen in the final trajectory.

❖ **On similar way, we have found that a phytochemical Tinocordiside from Giloy (*Tinospora cardifolia*), also binds in the ACE2-RBD complex with substantial binding affinities. Our research on these *in-sillico* experiments is at the advanced stage, and being communicated for research publication.**

Scientific Rationale of *Pure Giloy (Tinospora cordifolia) Extracts*

Tinospora cordifolia has been used as an excellent immuno stimulant and serves as an excellent remedy against various microbial infections [9, 10]. This plant contains several important phytochemicals like; berberine, choline, columbin, chasmanthin, jatrorhizine, palmarin, palmatine, tinocordifolioside, tinosporon, tinosporic acid, tinosporin, tinosporol, tinosporaside, tembeterine, tinosporic acid, tinosporal, tinosporon, etc [11, 12, 13, 14]. Giloy is extensively used for the treatment in several etiologies like diabetes , dyspepsia, jaundice, rheumatoid arthritis, pyrexia, inflammations, gout, cardiac debility, excess mucus, urinary disorders, asthma, splenopathy and etc [9, 12, 15].

Pharmacological Perspectives

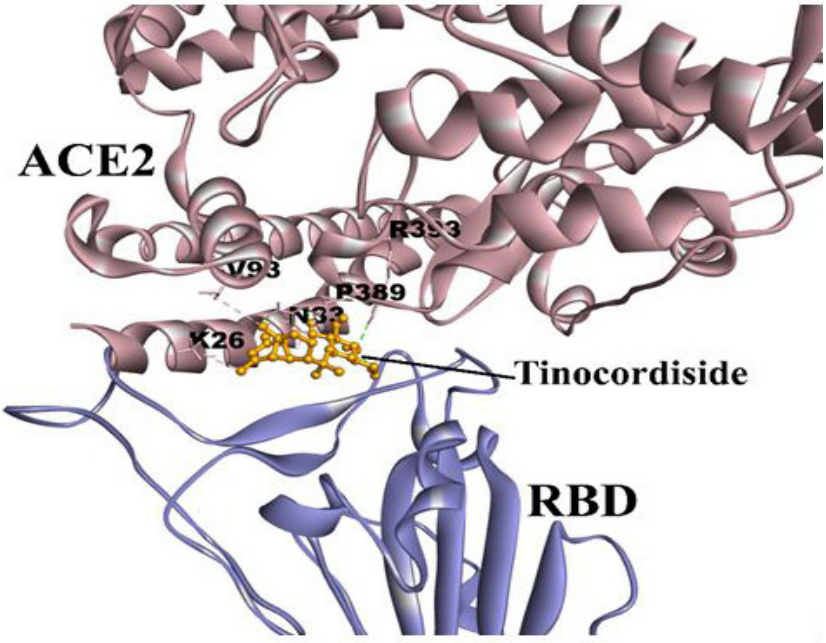
Clinical evaluation against tuberculosis: Rasayana drugs prepared from Guduchi (*Tinospora cordifolia*), Ashwagandha (*Withania somnifera*) Yastimadhu (*Glycyrrhiza glabra*) were found to be effective in mangement of tuberculosis with anti-Koch's treatment[16].

Immuno-modulatory activity: The isolated polysaccharide G1-4A from *T.cordifolia* was evaluated for immunomodulatory effects on *mycobacterium tuberculosis* (MTB) infected murine macrophage cell line RAW 264.7 and in aerosol mouse models. G1-4A treatment modulated the levels of pro-inflammatory cytokines (TNF-α, IL-β, IL-6, IL-12, IFN-γ) in cells infected with all the strains. Similarly, the treatment of G1-4A up-regulated the expression of TNF-α, INF-γ and nitric oxide in the lungs of MTB infected BALB/c mice. The results demonstrated that Giloy compound G1-4A modulate the host immune responses and improve the therapeutic efficacy to control tuberculosis [17].

Giloy Might be Potent against COVID-19

The major phytocomponents reported in Giloy (*Tinospora cordifolia)* are tinosporine, tinocordiside, diterpenoid furano lactone, tinosporaside, cordifolide, cordifol, syringin, clerodane furano diterpene, tinosporidine, columbin, heptacosanol, b-sitosterol and tinosporide. Cordifolioside A and syringin have been reported to possess immunomodulatory activity. Tinosporin, diterpenoid has been claimed specially for the treatment of the targeted viruses including (retroviruses) (HIV-1, HIV-2) all subgroups, HTLV, Herpes simplex Virus (HSV) and another viral disease.

We have tested all of the reported phytochemicals of Giloy in our *in-sillico* models. We have found that one of the Giloy compound, Tinocodiside, docks very well within the ACE2-RBD complex, akin to Withanone. The simulated state of Tinocordiside also showed favourable binding poses within ACE2-RBD interface with several interreacting sites.



We suggest that Tinocordiside rich extracts of Giloy would be one more viable options for controlling COVID-19 entry into host cells and general immunomodulatory nature of Giloy would enhance innate immunity against COVID-19 infections.

In addition, Tulsi (*Ocimum sanctum*) was also mined for its rich phytochemicals. We have discovered that Scutellarein, a natural flavone found in Tulsi, found to dock well in to the enzyme cavity of RDRP enzyme of coronavirus. RDRP, RNA Dependent RNA Polymerase, is the central enzyme needed by coronavirus for its multiplication and growth. Therefore, inhibition of RDRP provide an attractive means of controlling COVID-19 spread and its pathogenicity.

Scientific Rationale of *Pure Tulsi (Ocimum sanctum) Extracts*

In Ayurveda, tulsi is known as "Mother Medicine of Nature" and "The Queen of Herbs," for its medicinal and spiritual properties. Tulsi has been adopted into spiritual rituals and lifestyle practices that provide a vast array of health benefits that are just beginning to be confirmed by modern science [18].

The medicinal properties of Tulsi have been studied in hundreds of scientific studies including *in vitro*, animal and human experiments. These studies reveal that Tulsi has a unique combination of actions that include: Antimicrobial (including antibacterial, antiviral, antifungal, antiprotozoal, antimalarial, anthelmintic), anti-diarrheal, anti-oxidant, anti-inflammatory, hepato-protective, neuro-protective, cardio-protective, anti-diabetic, analgesic, anti-pyretic, anti-allergic, immunomodulatory, anti-asthmatic, anti-tussive, adaptogenic, anti-stress activities [19-20].

Pharmacological Perspective

Anti-asthmatic Activity: The anti-asthmatic activity of a ethanol extract of Tulsi leaves, and the oils of *O. sanctum* has been shown to be effective against histamine induced pre-convulsive dyspnea in guinea pigs. The activity was dose-dependent and validated the anti-asthmatic activity of Tulsi against histamine induced bronchospasm [21].

Broncho-dilatory Activity: Bronchodilator activity of *O. sanctum* in mild and moderate asthma patients has been evaluated. Capsules of *O. sanctum* (200 mg, twice daily) were administered in 41 patients. Drug was administered for a period of one week with a washout period of one week between the two drug schedules. FEV1 and PEFR were recorded in these patients to assess the bronchodilator activity before the drug administration, on 4^{th} and on 7^{th} day of administration of *O. sanctum* and the parameters obtained were compared with that of the standard drug, Salbutamol. *O. sanctum* produced significant improvement in both FEV1 and PEFR values and resolved symptoms of asthma. Results suggested that Tulsi (*O. sanctum)* possesses significant bronchodilator activity in mild and moderate bronchial asthma [22].

Immunomodulatory Activity: In the humoral immune responses, *O. sanctum* diminished

levels of IgG1 and elevated levels of IgG2a point towards the establishment of a protective immune response. The results were in line with the earlier studies on immunomodulatory potential of *O. sanctum* on the Swiss albino mice immunized with the sheep red blood cells, and subsequently treated with the various doses of the OS extract for 2 weeks. This treatment brought about a significant rise in the antibody titer as compared to the aqueous extract at a same dose. Many other studies have also supported the immunomodulatory activity of *O. sanctum,* like immunostimulation in cattle suffering from the subclinical mastitis as well as increased IL-2 gene expression and heightened IL-2 production in male Wistar rats [22].

Pulmonary Disorders: Beneficial Effect of *O. sanctum* (Linn) against monocrotaline-induced pulmonary hypertension in rats has been assessed. OS (200 mg/kg) treatment ameliorated increased lung weight to body weight ratio, right ventricular hypertrophy, increased RVSP, and RVoTD/AoD ratio. Moreover, OS treatment decreases Nox-1 expression and increases expression of Bcl2/Bax ratio caused by MCT. The present study demonstrates that OS has therapeutic ability against MCT-induced PH in rat which are attributed to its antioxidant effect [23, 24].

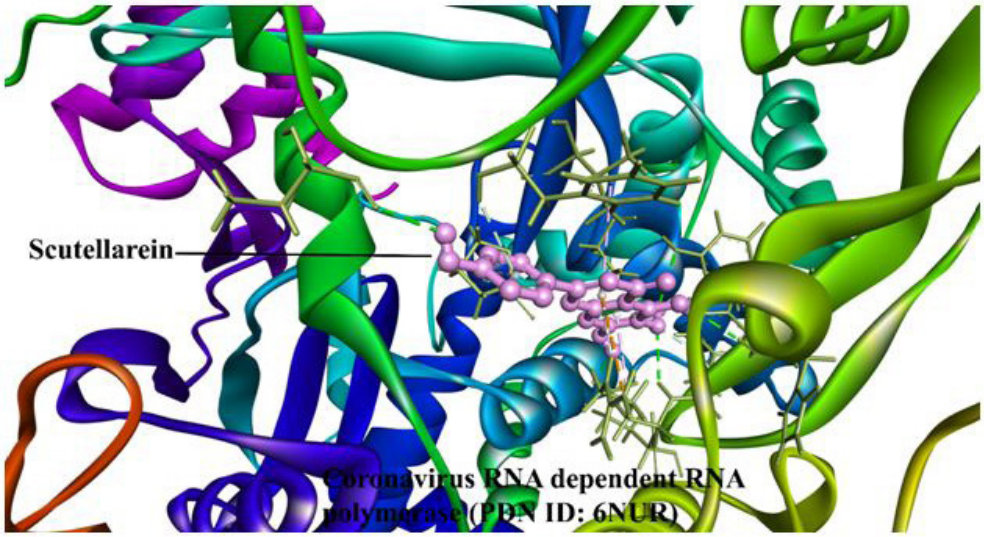
Tulsi Might be Potent against COVID-19

Tulsi extracts are rich source of Flavones and flavonoids. Flavones constitute a major class in the flavonoid family based on a 2-phenyl-1-benzopyran-4-one backbone. Natural flavones include apigenin, baicalein, chrysin, luteolin, scutellarein, tangeritin, wogonin and 6-hydroxyflavone. Scutellarein is one such flavone that is found in Tulsi (*Ocimum sanctum*) (83). The antiviral activity of flavones is known since the 1990s, when it was showed that the simultaneous application of apigenin with acyclovir resulted in an enhanced antiviral effect on herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in cell culture [25].

Naturally-occurring phytochemicals are regarded as a great source of potential medications against various ailments. Studies have demonstrated that selected naturally-occurring flavonoids exhibit anti-viral activities. There are evidences that the myricetin and scutellarein are strong chemical inhibitors of SARS-CoV helicase and this effect is mediated through inhibition of ATPase activity [26].

RNA-dependent RNA polymerase (RDRP), also called RNA replicase, catalyzes the replication of RNA from an RNA template and are essential proteins encoded in the genomes of all RNA-containing viruses with no DNA stage. These are essential for the survival of viruses. Hence, RNA-dependent RNA polymerase (RDRP) recently emerged as a promising target, because of its key role in viral replication and its high conservation among viral strains. We also targeted RDRP of SARS-CoV in our *in-silico* study using Tulsi (*Ocimum sactum*) ingredients. Our

study shows that a few phytocompounds present in Tulsi may hit the catalytic cleft of the RDRP (Figure below). Scutellarein is one of them; binds RDRP with a docking score of -8.3 kcal/mol, and it may perturb Motif B, which is used by the coronavirus for its polymerization.



We postulate that Tulsi phytochemicals may inhibit the coronavirus replication and could control its growth and spread. This is a different dimension of Ayurvedic medicines to curb COVID-19.

Taken together, Ashwagandha, Giloy and Tulsi would work well in tandem, as effective Prophylactics; and would also strengthen the innate immunity to fight off COVID-19 infections.

COVID-19 coronavirus causes lower respiratory tract infection in humans. The most common symptoms are dry cough, shortness of breath, coughing up sputum and presence of thick mucus in the lungs which lead to reduced ventilation and subsequent pneumonia. The symptomatic ayurvedic treatment for these aetiologies are also been recommended in the present treatment regime.

In addition, as per traditional ayurvedic practice of *Nasya* therapy, Anu taila, as nasal drops is also recommended to help in mucus discharge and other COVID-19 related disease symptoms.

❖ **More than 5000 years ago, Maharishi Charak has described the medicinal impotence of Anu Taila, in healing nasal congestions [27]. Maharishi Charak has advised the use of Anu Taila in ENT related ailments.**

अणु तैल

स्निधस्विङ्गस्य पिचुना नावनैस्त्रिभि:। त्र्यहात्त्र्यहाच्च सप्ताहमेतत्कर्म समाचरेत्।

निवातोष्णसमाचारी हिताशी नियतेन्द्रियः। तैलमेतत्त्रिदोषघ्नमिन्द्रियाणां बलप्रदम्॥

प्रयुञ्जानो यथाकालं यथोत्कानश्नुते गुणान्। (चरक संहिता सूत्रस्थान 05: 63-70)

Classical and Scientific Rationale for *Anu Taila Nasal Drops*

Anu Taila consist of several important medicinal plants like; Jīvantī (*Leptadenia reticulata*), Jala (*Pavonia odorata*), Devdāru (*Cedrus deodara*), Nāgarmothā (*Cyperus scariosus*), Dālacīnī (*Cinnamomum verum*), Sevya (*Chrysopogon zizanioides*), Anantmūla (*Hemidesmus indicus*), Śweta candana (*Santalum album*), Dāruharidrā (*Berberis aristata*), Muleṭhī (*Glycyrrhiza glabra*), Plawa (*Cyperus platyphyllus*), Agarū (*Aquilaria agallocha*), Śatāvarī (*Asparagus racemosus*), Bela (*Aegle marmelos*), Utpala (*Nymphaeanouchali*), Bṛhatī (*Solanum indicum*), Kaṇṭakārī (*Solanum surattense*), Surbhi (*Pluchea lanceolata*), Śālaparṇī (*Desmodium gangeticum*), Pṛśniparṇī (*Uraria picta*), Viḍañga (*Embelia ribes*), Tejpatra (*Cinnamomum tamala*), Truṭi (*Elettaria cardamomum*), Reṇukā (*Vitex agnus-castus*), Kamala keṣara (*Nelumbo nucifera*), Ajadugdha (Goat milk), and Tila Taila (*Sesamum indicum*).

Doses: 5 to 10 drops for Nasya, as Nasal Drops.

Classically Described Therapeutic Uses

Dryness of skin, Palita (Graying of hair), Ūrdhvajatrugata Roga (Disorders of body parts above clavicle), Skandha Śuṣkatā (Emaciation of shoulder), Grīvā śuṣkata (Wasting in cervical region), Vakṣa śuṣkatā (Emaciation of chest muscles), Tridoṣa janya vikāra. Cures diseases in head, shoulders and all sensory organs.

Scientific Reasoning for *Anu Taila*

COVID-19 causes viraemia after entering the body and the main clinical manifestations are fever, pharyngalgia, fatigue, diarrhoea and other non-specific symptoms. Based on the clinical symptoms observed in the COVID-19 patients, the preventive medication should be aimed in reducing the inflammation of the respiratory tract through anti-inflammatory activity, and

reduction of hypercoagulable state.

In the traditional Ayurveda *Anu taila* is used for Nyasa processes (nasal drops) involving reduction of nasal passage inflammation, sinusitis and that of respiratory tract. These poly-herbal components of *Anu Taila* have been described to have anti-inflammatory potential through amelioration of pro-inflammatory cytokines such as IL-1β, TNF-α, IFN-γ, IP-10, MCP-1, IL-4, and IL-8. Plants extracts obtained from Anu Taila component plants have been found to have direct effects on the respiratory tract, for example: *Aegle marmelos* [28, 29, 30], *Asparagus recemosus* [31, 32, 33], *Aquilaria agallocha* [34], *Cedrus deodara* [35], *Cinnamomum verum* [36], *Coleus vettiveroides* [37], *Cyperus esculentus* [38], *Cyperus rotundus* [39], *Desmodium gangeticum* [40], *Elettaria cardamomum* [41], *Embelia ribes* [42], *Glycyrrhiza Glabra* [43], *Nelumbo nucifera* [44], *Ocimum sanctum* [45], and *Pogostemon cablin* [46]. While most of the studies have been performed on lung epithelial cells, it closely represents the cellular composition of the nasal passage. Hence, *Anu taila* can be used as a potential poly-herbal medicine for COVID-19 related ailments.

- **For systemic symptomatic treatment of COVID-19, poly-herbo-mineral formulation, Tablet Swasari Ras has been generated for providing relief in lung congestion and to reduce mucus accumulation in the lungs. We have several thousand patient's clinical data in Patanjali Electronic Medical Record (PEMR) system.**

- **We have also validated Swasari Ras in our pre-clinical models of lung diseases. Treatment of Swasari Ras reduced excessive mucus production and airway remodelling; decreased pro-inflammatory cytokines in the inflamed lungs; and kept healthy oxidation state of the lungs.**

- **This work has been recently published in Biomedicine and Pharmacotherapy, an Elsevier publication [47] [https://doi.org/10.21203/rs.3.rs-17806/v1].**

Scientific Rationale of Tablet *Swasari Ras*

Tablet Swasari Ras is a poly herbo-mineral formulation; its constituents are mentioned in classical ancient Ayurveda, for the treatment of disorders related to respiratory tract such as, cough, bronchitis, asthma, rhinitis and excessive mucous formation. This formulation has been used in clinical settings at several chikitsalaya across India, on several thousand patients as per Patanjali Electronic Medical Records (PEMR). Scientists at Patanjali Research Institute have also validated Swasari Ras in the preclinical studies [47]. Swasari Ras consists of Mulethi, Lavanga, Dalchini, Karkatashringi, Rudanti, Ardraka, Maricha, Pippali and Akarkara. Swasari Ras contains several bioactive plant metabolites that are responsible for producing anti-inflammatory activity in respiratory diseases and alleviates the vitiated Tridosa (Vata-Kapha

and Pitta). Swasari Ras also contains calcium mineral components such as, Kapardak bhasma, Abhraka bhasma, Godanti bhasma and Mukta shukti bhasma. These mineral components are free from any metallic sources, and have been traditionally known for efficacy in the treatment of cough, asthma, inflammation and other lung disorders.

Tablet Swasari Ras is an unique combination of various plant parts, namely, it consists of fruit of *Glycyrrhiza glabra* (Liquorice/Mulethi), buds of *Syzygium aromaticum* (Cloves/ Lavanga), bark of *Cinnamomum zeylanicum* (Cinnamon/Dalchini), galls of *Pistacia integerrima* (Zebrawood/ Karkatashringi), fruit of *Cressa cretica* (Salt Cresse/Rudanti), rhizome of *Zingiber officinale* (Ardraka/Ginger), fruit of *Piper nigrum* (Maricha/Black pepper), fruit of *Piper longum* ( ) Long pepper/Pippali), root of *Anacyclus pyrethrum* ((Spanish chamomile/Akarkara).

Glycyrrhiza glabra (Mulethi), decreases the mucus production in lungs [48], interferes with replication and/or cytopathogenic effect induced by many respiratory viruses [49] such as SARS coronavirus [50], respiratory syncytial virus (RSV) [51], HIV [52] involving clustering of fusion-activated proteins and fluidization of the plasma membrane and viral envelope. (Glycyrrhizin exerts anti oxidative response against H5N1 Influenza A virus [53] and inhibits virus replication and pro-inflammatory gene Expression [54, 55]. Further, it inhibits the expression of Th2 cytokines, IL-4 and IL-5 levels and eosinophilia by decreasing the IgE-stimulating cytokines, airway hyper responsiveness [56] the incidence of which is increasing globally. The existing therapy is inadequate and has many adverse effects. It needs a better therapeutic molecule preferably of natural origin, which has negligible or no adverse effects. In view of this, we evaluated Glycyrrhizin (GRZ, bacterial Lipo-Poly Saccharide (LPS) induced TNF-α and IL-1β levels in lungs [57] asthma and chronic obstructive pulmonary disease (COPD and oxidative stress in lungs [58]. It contains glycyrrhizin as major bioactive ingredient, along with glycyrrhetinic acid, flavonoids, isoflavonoids, and chalcones as active compounds. Its roots have been traditionally used for cough, colds, asthma, and COPD [59]

The barks of *Cinnamomum zeylanicum* (Dalchini) is one of the oldest herbal medicine possessing an array of pharmacological metabolites including trans-cinnamaldehyde, eugenol, and linalool, which represent 82.5% of the total composition [60]. It exerts anti-inflammatory [61] analgesic, anti-pyretic, immunomodulatory, anti-complementary [62] properties. Cinnamon has anti-oxidant [60] properties [63] and suppresses IL-1β, IL-6 and TNF-α in LPS-activated macrophages in MAPK dependent pathway [64] and bleomycin-induced idiopathic pulmonary fibrosis [65] but its effect on IPF is unknown. The present study is to investigate the anti-fibrotic effect and action mechanism of cinnamaldehyde on IPF. Materials and methods: IPF was induced by intratracheal bleomycin in mice. Submicron emulsion of cinnamaldehyde was given by intraperitoneal injection once every day for 7 or 21 continuous days after bleomycin administration. Lung histological and injury indexes were analyzed. The protein expressions of inflammation and oxidative stress as well as EMT markers alpha-smooth muscle actin (α-SMA). Type-A procyanidine polyphenols of Cinnamon improves lung function, decreases inflammatory cell infiltration in lung tissue and goblet cell hyperplasia

and mucus hyper secretion [66]. Further, cinnamon bark oil is a potent fungi-toxicant against respiratory tract mycoses [67].

Traditionally, essential oil of *Pistacia integerrima* (Karkatashringi) is used for the treatment of various respiratory diseases like chronic bronchitis, and other ailments for the respiratory tract. It abolishes the Broncho provocative response and bronchoconstriction [68, 69] by inhibiting Phosphodiesterase-1 and regulating smooth muscle cell activity [70]. In lungs it exerts anti-inflammatory properties by reducing the levels of TNF-α, IL-4, and IL-5, IL-1β and IL-6 and inhibits acute lung injury [71] alongside intranasal challenge. Lung tissues were stained with Hematoxyline and Eosin (H & E) [72]. Ethyl gallate present in galls attenuates acute lung injury through Nrf2 signaling [73] few therapeutic have emerged for ALI/ARDS. Thus, in the present study we evaluated the therapeutic potential of ethyl gallate (EG and inhibits cell adhesion molecules by blocking AP-1 transcription factor [74].

Cressa cretica (Rudanti), has been used for cough and other respiratory problems [75]. It exhibits Bronchodilatory and mast cell stabilising activity [76] and antitussive activity [77]. Its aerial parts contain noctacosanol-1, β-sitosterol, 6-hydroxy-3,4-dimethyl coumarin, 6-methoxy-7,8-methylene dioxy coumarin, β-sitosterolglucoside, quercetin, kaempferol and rutin modulated antioxidant parameters [78]. Rhizome of *Zingiber officinale* (Ardraka) has been used in the treatment of cold and bronchitis [59]. It has antiviral activity against respiratory syncytial virus [79], n-gingerol present in ginger prevents Th2-mediated immune responses and airway inflammation and 6-gingerol was sufficient to suppress eosinophilia[80] and inhibit the production of TNF-α, IL-1β, and IL-12 [81].

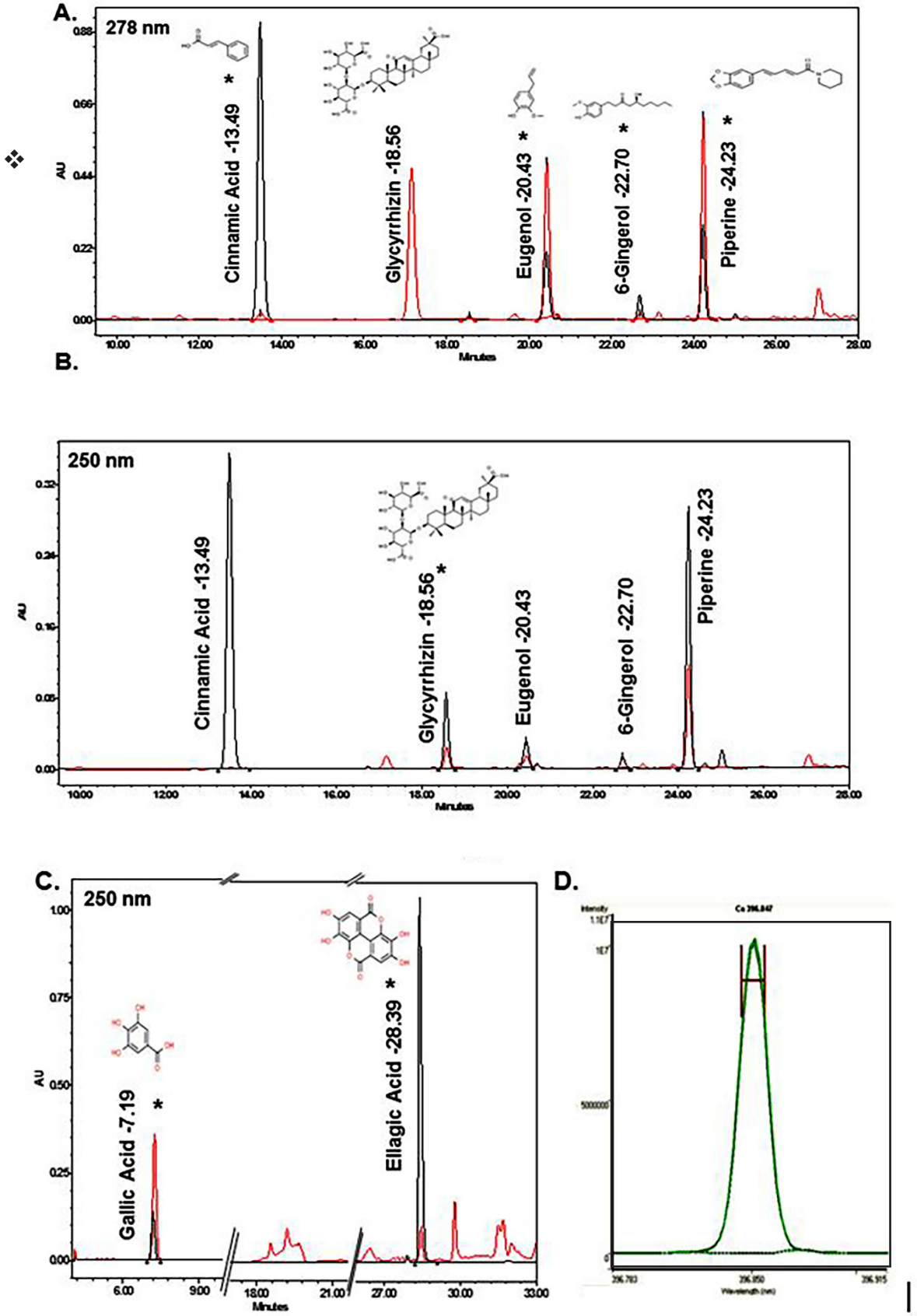
Piper nigrum (Maricha) and *Piper longum* () (Pippali) are used for treating various bronchial diseases, tuberculosis, due to its anti-oxidant, anti-inflammatory, anti-bacterial, [82, 83, 84]. Piperine is a major component of *Piper nigrum* and *P. longum*. *P. longum* is a rich source of alkaloids and amides; pipericide, piperine, piperlonguminine, piplartine, and aristolactams [83, 85]. *P. Nigrum* inhibits allergic Inflammation by Inhibiting Th2/Th17 responses and mast cell activation and regulated the balance of cytokines production from Th1, Th2, Th17 and Treg cells, and inhibited GATA3, IL-4, IL-6, IL-1β, RORγt, IL-17A, TNF-α expression and increased the secretions of IL-10, INF-γ [86]. Piperine also reduced histologic damage and myeloperoxidase (MPO) activity in the pancreas [87]. *Piper longum* exhibited endothelial barrier protective effects and leukocytes migration in vivo, supressed IL-6 and TNF- α levels by acting upon NF-*k*B and ERK1/2 pathways [88]. Fruits of *P. longum* inhibited the release of Th-2-mediated cytokines, eosinophil infiltration in lungs [89].

Syzygium aromaticum (Lavanga) has anti-inflammatory [90] properties and it inhibits eosinophilia, cytokine levels in a NF-*κ*B pathway dependent manner [91] in lungs. Further, it has free radical scavenging [92] and antioxidant properties [93]. It is efficacious against herpes simplex virus type 1 (HSV-1) [94] and influenza A virus [95]. Eugenol is a phenylpropanoid phenolic compound constituting 45–90% of its essential oil of *Syzygium aromaticum* [90].

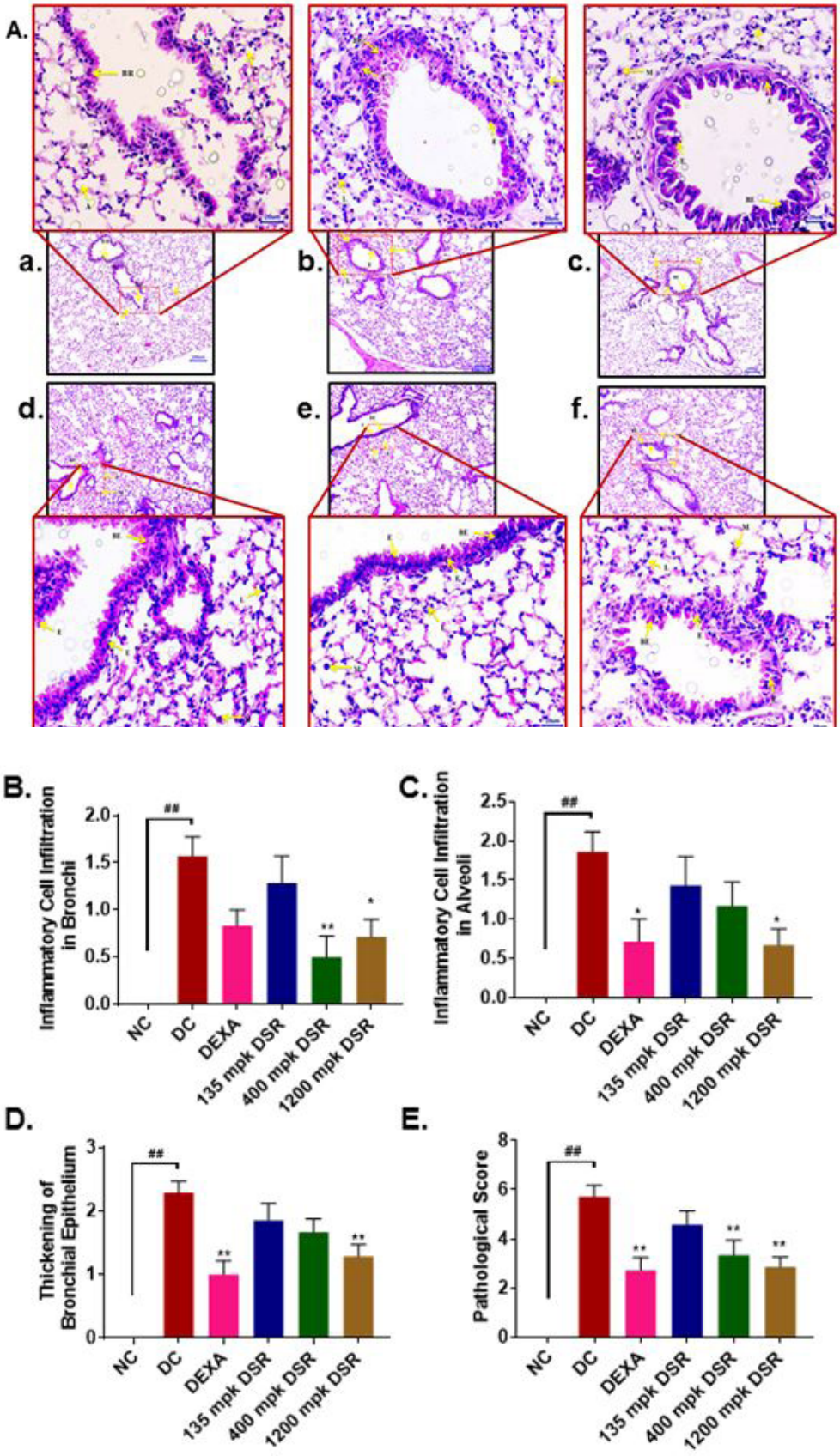
The roots of *Anacyclus pyrethrum* . (Akarkara) exerts immune modulatory and immune stimulating properties [96] along with anti-inflammatory and antioxidant properties [97]. It is a rich source of N-isobutyldienediynamide and polysaccharides [98] along with aponins, sesamin, inulin, gum and traces of essential oil [99, 100].

Swasari Ras contains Abhraka bhasma, Mukta shukti bhasma, Kapardak bhasma, and Godanti bhasma. These Bhasma are unique incinerated ayurvedic minerals preparation, treated with herbal juice or decoction [101, 102] and rich in Calcium. Abhraka bhasma is a calcined mica ash that has anti-inflammatory properties and provides relief from chronic and incessant cough and respiratory illnesses [103]. Prepared from Pearl oyster, Mukta shukti bhasma has been traditionally used for its anti-inflammatory properties [104] and lung diseases [105]. Kapardak bhasma is prepared from shell of sea animal *Cypraea moneta* [106] and has reported anti asthmatic properties [107]. Godanti bhasma is combination of calcium rich gypsum and aloe vera juice. It has anti-inflammatory function [108] and antipyretic activity [109].

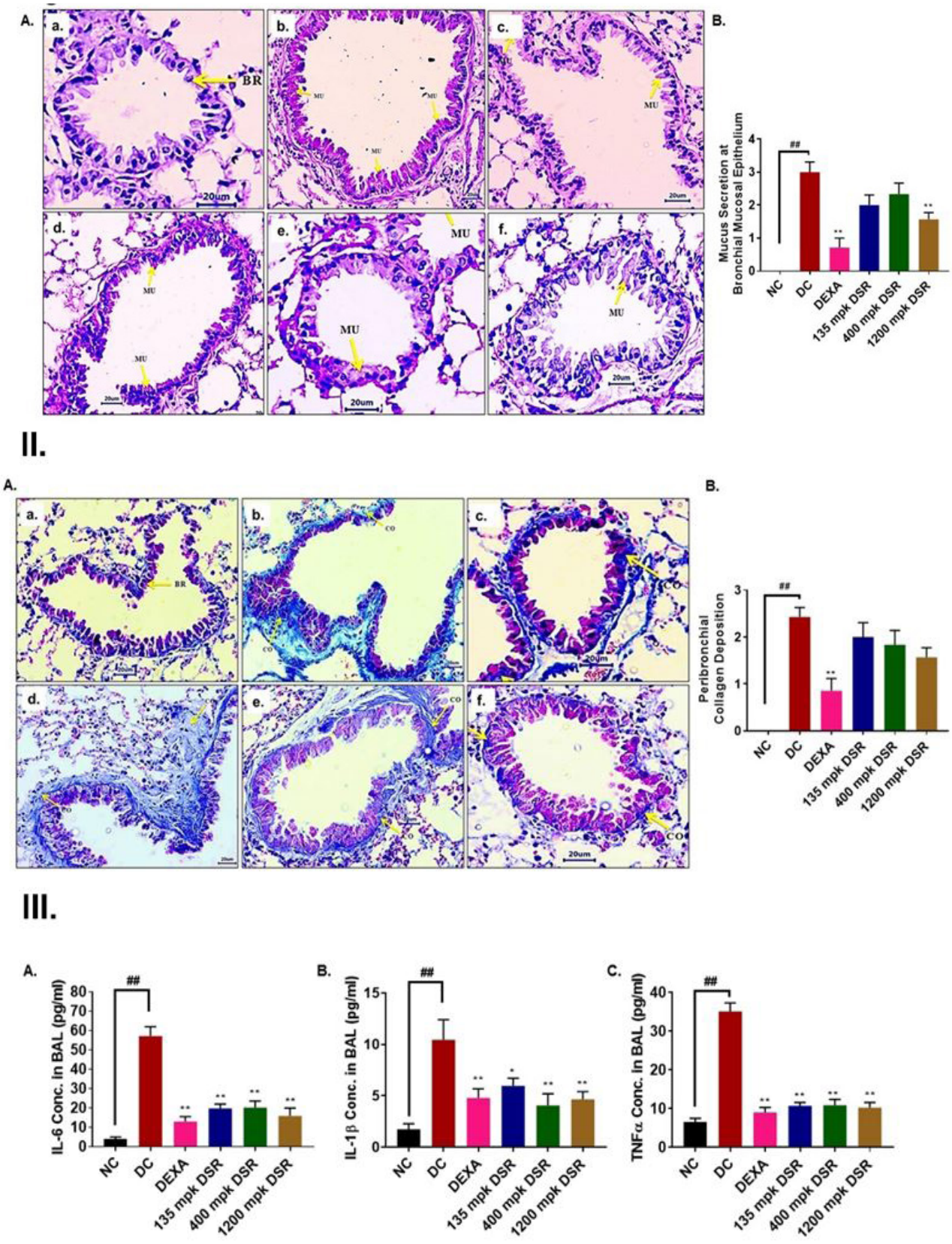
Presence of these poly-herbs and bhasma combination in Tablet Swasari Ras with proven lung protective properties would serve as superior formulation for symptomatic treatment of respiratory illnesses observed in COVID-19 patients.



Phyto chemical profiling of Swasari Ras (DSR) using HPLC **(A-C)** identified the presence of various bio active secondary metabolites with proven biological activity namely, Cinnamic acid, Eugenol, 6-Gingerol, Piperine, Glycyrrhizin, Gallic acid and Ellagic acid. Further, ICP-OES analysis **(D)** identified the presence of calcium mineral in DSR.



Swasari Ras (DSR) decreases the lung airway inflammation and asthma related histo-pathological changes. Ovalbumin allergen induced pathological features **(B)** are reduced upon oral Swasari Ras treatment in a dose dependent manner **(D-F)**, similar to Dexamethasone, DEXA**(C)**. Oral intake of DSR reduced, inflammatory cell infiltration in bronchi, alveoli and supressed the bronchial epithelial thickening. Over all, DSR reduced total inflammatory pathological scores in lungs.



Oral Swasari Ras (DSR) administration decreased the cardinal features of lung inflammation. **(I)** Allergen induced mucus hyper secretion by bronchial epithelial cells was decreased by DSR in a dose dependent manner. **(II)** Allergen induced Peri bronchial collagen deposition was reduced by Swasari Ras treatment. **(III)** Pro inflammatory cytokine secretion in bronchial lavage was attenuated by Swasari Ras oral treatment. These responses were comparable to standard drug Dexamethasone, DEXA.

Treatment Regime

The proposed treatment regime is designed to add efficacy and potency of Ayurvedic medicines in treating COVID-19 infection in combination with ICMR approved hydroxyl-chloroquinone. This regime is meticulously designed with clinical relevance for the ayurvedic intervention therapy on war footing to cope with COVID-19 infection.

Dosage Forms

1.	Tablet *Swasari Ras*	:	(500 mg)
2.	Tablet *Pure Ashwagandha Extract*	:	(500 mg)
3.	Tablet *Pure Giloy Extract*	:	(500 mg)
4.	Tablet *Pure Tulsi Extract*	:	(500 mg)
5.	*Anu Taila* (Nasal drop)		

In the morning:

At-least 60 mins before break-fast	:	4 drops of *Anu Taila* (Nasal drop), in each nostril.
At-least 30 mins before break-fast	:	2 Tablets *Swasari Ras* (with luke-warm water)
At-least 30 mins after break-fast	:	2 Tablets *Pure Giloy Extract* 1 Tablet *Pure Ashwagandha Extract* 1 Tablet *Pure Tulsi Extract* (with luke-warm water)

In the evening:

At-least 30 mins before dinner	:	2 Tablets *Swasari Ras* (with luke-warm water)
At-least 30 mins after dinner	:	2 Tablets *Pure Giloy Extract* 1 Tablet *Pure Ashwagandha Extract* 1 Tablet *Pure Tulsi Extract* (with luke-warm water)

Note: In case of excessive mucous and cough,

* 2 Tablets of *Swasari Ras* could also be given 30 minutes before lunch.
* 4 drops of *Anu Taila* (Nasal drop) could be administered in each nostril 60 minutes before meals.

Patient Classifications for the Ayurvedic Treatment Regime

A. COVID-19 Positive Patients

Inclusion Criteria

- Asymptomatic patients
- Mildly symptomatic patients
- Moderately symptomatic patients
- Age 15-80 years of age (Doses as per previous page)
- Age 6-14 years of age (Half of doses as per previous page)
- Patients able to give Informed consent and follow instructions
- Agree to follow at 14 days and 30 days after testing positive for COVID-19

Exclusion Criteria

- Severely symptomatic patients (SaO_2 <90%)
- Acute Respiratory Distress Syndrome (ARDS)
- Life expectancy less than 1 year due to other co-morbid conditions

B. Prophylactic Treatment

- COVID-19 negative patients
- Medical and Paramedical staff engaged in COVID-19 patients care

Inclusion Criteria

- Patients at the screening OPD with flu like symptoms who test negative for COVID-19
- Medical and Paramedical staff engaged in COVID-19 patients care
- Age 15-80 years of age

Exclusion Criteria

- Acute Respiratory Distress Syndrome (ARDS)
- Life expectancy less than 1 year due to other co-morbid conditions

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