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# HERBAL FORMULATION (IMMUHELP) IN THE MANAGEMENT OF UPPER RESPIRATORY TRACT INFECTION.


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**ABSTRACT** The Upper respiratory tract infection is mainly attributed to viral infections so focus should be given to inhibition of viral-host interaction, their entry and replication in the host cells and release of inflammatory cytokines, resulting physiological disturbances. The host's immune system is the 1st line of defence against such threats so multi-targeted herbal immune-boosters, with antioxidant, anti-inflammatory and tissue repair potential would be preferred. The natural cocktail of medicinal plants has shown promising results both by using bioinformatics based drug docking studies, in animal experiments and in clinical trials. Here we have reviewed the 6-medicinal plants, used in making **"Immuhelp"**, towards their established role in management of viral-host interaction, activation of innate and adaptive immunity, inhibition-potential against release of inflammatory cytokines, immunosuppressive and chemoattractant agents and antioxidant potentials.

**KEYWORDS :** Respiratory disease, Immunity, Lung, Medicinal plants, AYUSH, Imuhelp

## INTRODUCTION:

The physiological function of URT is to provide the air-conditioning, filtering, sensory monitoring of the ambient environment, microbial defense, sensation, and phonation. The particulate matter, larger than 1 µm in diameter is trapped in the mucous blanket, by ciliary epithelial layer, which gets directed to alimentary. The activation of the resident immune cells provides antimicrobial effect, which is attributed to release of some defense proteins. It inhibits the attachment and entry (by action of proteases) of these microbes to the inner epithelial cells. The innermost cellular layer of URT is the epithelial lining, which is covered with mucus layer, rich in antimicrobial proteins, host friendly microbiome and the immune cells. This epithelial barrier plays as the 1st line of defense, but in the compromised state, infection spreads to other parts. The upper respiratory tract diseases (URTD), are mostly attributed to infection and allergens. The decreased epithelial barrier-activity, decreased mucociliary clearance, excessive mucus production, decreased epithelial innate immune responses and inhibitory effect of Th2 cytokines on the production of antimicrobial peptides are some of the causes. The degree of these changes are attributed to the immune system and epigenetic factors like lifestyle, food-habits, mental performance, stress, anxiety and gaseous hygiene, but it needs scientific validation in terms of their effects on histone modifications and changes in the microRNAs (miRNAs) population.

The mucus layer consists of water, mucins, and antimicrobial peptides. The mucins are large glycoproteins released by goblet cells, club cells, serous cells, and mucous cells. Since mucin is a negatively charged proteins, so it is capable of hosting positively charged proteins like IgA (IgA), antimicrobial peptides, lysozyme, and collectins [1]. Further the ion channels such as the Cystic fibrosis transmembrane conductance regulator (CFTR) and ENaC regulate the volume and composition of airway secretions, which are important contributor of mucus layer and peri-ciliary layer (PCL). The antimicrobial peptides (AMPs) of mucin belong to the family of defensin and cathelicidin proteins, produced by AECs. The defensin consists of 6 cysteines, forming three intra-molecular disulphide bonds. The mucosal layer is also rich in host-friendly microbiome, which serves a strong defense against pathogens in the respiratory tract. In response to stimulus from external environment, it gives signals to neighboring cells to alter their native secretions, to increase body defense. Initially at birth-time, this microbiota is acquired from the mother, but later on, it develops in response the environmental and life style linked factors [2].

In the medical terms, the URTD are defined as Acute-nasopharyngitis, sinusitis, pharyngitis, tonsillitis, laryngopharyngitis, laryngitis or tracheitis, obstructive laryngitis, epigolottitis, upper respiratory infections of multiple and unspecified sites, Vasomotor or allergic rhinitis, Chronic rhinitis, nasopharyngitis or pharyngitis, rhino sinusitis, Silent sinus syndrome, Cyst or mucocele of nose or nasal sinus, Deviated nasal septum, Hypertrophy of nasal turbinates, Chronic laryngitis, Diseases of vocal cords, Nasal polyps, Abscess of upper respiratory tract. These diseases are commonly defined as the cold and cough but self-limiting within 14 days. Various pathogens have different incubation time for expression of their disease symptoms. Most of the viruses have 4-7 days incubation time, but Diphtheria has this

time up to 10 days and whooping cough (Pertussis) has incubation time up to 21 days and Epstein-Barr virus (EBV) has incubation time between 4-6 weeks. The COVID-19 has the span of 14 days. Their symptoms broadly include dyspnea, edema, and hemoptysis, nasal congestion, running nose with clear, white or green discharge, nasal breathing, sneezing, scratchy throat, painful swallowing (odynophagia), cough, low fever, but sometimes with rare symptoms like foul breath, reduced ability to smell (hyposmia), headache, erethmia, sinus pain, conjunctivitis, feeling of nausea or vomiting diarrhea and body ache. These symptoms are due to release of toxins resulting inflammation, which is induced by immune system to fight against infection.

In case of viral infection, there are four phases defined as Prevention, Infection, Inflammation and Recovery. During viral infection, several pathways get activated e.g. Lactin pathway—direct activation; Classical pathway immune complex; Alternative pathway—TLR activation. The host activates adaptive immune responses against the structural antigens of these viruses like Spike-glycoproteins located in the viral envelope (S proteins). They activate the T cells and develop the humoral and cellular immunity. Further, the infection of macrophages and dendritic cells leads to an aberrant cytokine/chemokine expression pattern. The spread of viral infection is also reported in lymphoid organs such as spleen, thymus, Peyer plaques and mesenteric lymph nodes, resulting depletion of lymphoid tissue mass and compromised function for lymphocyte maturation and Antibody release. The depleted level of circulating CD4+ T lymphocytes for longer period has been reported in such infections. Under the defence mechanism, the epithelial cells produce ROS (reactive oxygen species) by activation of NADPH oxidases (DUOX1 and DUOX2), lacto peroxidase (LPO) for imparting anti-microbial function, but if produced in large amount and for longer period then it causes oxidative stress and associated cell damage. So, those drugs which may not directly show anti-viral activity may show protection by enhancing the expression of these interferons. The production of antimicrobial peptides by upper airway AECs is triggered by bitter receptors (T2R) is also important factor to regulate human upper respiratory innate immunity.

The asymptomatic COVID patients show different symptoms at different stages of infection, so different lines of treatments are recommended. The 1st stage involves immune activation and 2nd stage involves antiinflammation. Since the viral infection may evade the innate immune response and kill macrophages, so they can result to blunted antigen presentation, delaying and diminishing activation of the adaptive immune response[3].In 1st stage, type I interferons (IFN), complement system proteins and other innate immune mediators limit viral spread. This process also helps in the development of the subsequent adaptive immune response[4],proinflammatory cytokines in serum (e.g., (interleukin IL) IL-1β, IL-6, IL-12, interferon-γ (IFNγ), Interferon-inducible protein 10 (IP10), and monocytic chemotactic protein 1 (MCP1)) were associated with pulmonary inflammation and extensive lung damage in patients with Severe Acute Respiratory Syndrome (SARS). But hyperactive innate immune response is not good, and it may result to subsequent tissue damage, so its time dependent regulation is very important. This situation helps in deciding the choice of drug depending on the condition of the infection, which is determined through activation of Toll-like receptors (TLRs), including TLR3, TLR7, TLR8 and TLR9, [5] and activation of complement system, which is responsible for the development of pro-inflammatory reactions[6]. These situations activate the viral replication at higher rate in the host, along with release of chemokines, infiltration of immune cells in the pneumocytes, and increase in neutrophilic infiltration in the lungs. These activities must be controlled to reduce the disease burden[7]. Since C3 is one of the first proteins, which is synthesized by the complement system in the innate immune cascade, so C3/C5 blockage would help in disease control. Drugs like AMY-101 are being investigated on these lines[8].

There are 4 ways to control viral infection. i.e. use of direct antiviral drugs, anti-inflammatory drugs, immune-modulators, detoxiofication drugs, antioxidants, and drugs for repair of tissue damage. Based on this classification, the drugs for management of viral infection can be grouped in to categories like (1) direct inhibition of the viral attachment to the host cells, (2) control of viral replication in the host cell, (3) Inhibition of NFkB, PLA2, iNOS, inflammatory cytokines release and other signaling pathway involved in inflammation, (4) modulation of immune response by increased expression of (a) defencine peptides, (b)TLRs, other pathogen pattern recognition peptides, (c) interferons, (d) activation of NK cells, (e) activation of phagocytic cells, (f) detoxification and antioxidant enzyme activation, (g) repair of damaged cells and (h) activation of antiapoptotic enzymes, NRF-2 signaling pathway proteins, and (i) high expression of HSP-70, cytoprotective proteins and (j) enzymes of melatonine signaling pathway (k) activation of phagocyting cells like mast cells, dendritic cells, macrophages, neutrophils, eosinophils, and basophils; mucous sentinel cells and (l) increase in Adaptive immunity including T cells and MHC proteins, B cells and antibodies.

**Immune System In Respiratory Tract:**

When we talk of immune system in relation to upper respiratory tract, then it needs to consider the cells like (1) Dendritic cells, (2) Myeloid dendritic cells( dominates) (3) Plasmacytoids dendritic cells, (4) Resident airway mucosal DCs (AMDCs)-responsible for immune surveillance, (5) Macrophages, (6) Mast Cells, (7) Plasma Cells, (8) T cells-CD4, (9) T cells- CD 8 and (10) B cells, which are embedded below the layer of epithelial cell lining. The newly identified innate immune cell in URT are myeloid-derived suppressor cells, MAIT cells, and ILC, which add to the complexity of innate host defense shields in the pulmonary mucosal environment. All these cells collectively release several antimicrobial substances like complement, collectins, lysozyme, lactoferrin, secretory leukocyte protease inhibitor, and defensin etc, helping in host defence. The macrophages play important role as it engulfs the pathogen to degrade them by phagocytosis; it also presents the antigenic part of pathogen on its surface (APC) which is capable to interact with helper T cells, activating it to further proliferate into TH-1 or Th2 cells, responsible for release of different kind of cytokines, having different functions. The cytokines of TH1 cells activate the cytotoxic T cells, which get matured and lyse the infected host cells to stop propagation. This is called cell mediated immunity. The cytokines of the TH2 activated lymphocytes induce the humoral immunity by interaction of CD40 ligands of B lymphocytes. It expresses the B cell receptors to interact with antigen proteins to produce specific antibodies (mature B cells). More precisely, the PAMP of pathogens interacts with PRR of host cells, described above, which may be grouped under epithelial cells, endothelial cells, hematopoietic cells, circulatory leukocytes, stromal cells and activates the cellular signals related to TLR, NLR (NOD like receptors), B cell receptors, T cell receptors. These signals include ions and transcription factors like NFkB, AP-1, IRF-3/7, which finally regulate the transcription of growth factors, interferons, inflammatory cytokine like IL-1, IL-6 and TNF alpha; chemokines like IL-8, RANTE; and adhesion molecules like e-selectin; antigen presenting proteins. These signals, depending on the cell types activate the expression of receptor proteins, release of free radicals by neutrophils, phagocytosis by macrophages, differentiation of monocytes, activation of NK cells and release of IFN-alpha to lyse the infected cells.

Besides, some secretions induce activation, maturation of antigen specific T cell and B cell response, T cell differentiation, Cα++ signaling and IgG production. Different types of T helper cells are having different secretions and functions, e.g. TH-1 releases type-1 IFNs (TNF-alpha and Betα) acting on MyD-88, which activates the adaptive immunity, through differentiation of B lymphocytes, DC maturation, and activation of pathogen specific T cells. The matured DC cells are antigen presenting cells (APC) migrate to Lymph-node and interact with MHC of lymphocytes. The TH-2 releases type-2 IFN, which is IFN-γ, which activates macrophages to clear the pathogens by phagocytosis. It also kills extra-cellilar protozoα at mucosal surface involved in allergic response through IL-4, IL-5 and IL-13. The Th-17 plays the role in autoimmune disorders and certain bacterial infections. In the entire process, the post-transcriptional stability of mRNA is also essential, which is mediated by P-38, MAPK, micro-RNA mediated pathways. The down regulation of AU rich element (ARE) is also essential. The role of epithelial cells towards innate immunity is attributed to the secretion of osteopontin (OPN), which further stimulates the dendritic cells (DCs), to induce type-1 T-helper (TH-1) and type-17 T-helper (TH-17), to undergo differentiation to produce type-1 (Tc-1) and type-17 (Tc-17) cytotoxic T cells. The release of IL-8, MCP-1, RANTES and IP-10 by the epithelial cells acts as chemo-attractant resulting high pathogen accumulation and high secretion of inflammatory cytokines.

The neutrophils are 2nd line of defense to sense the invading pathogen, which further alerts the resident lymphoid cells through the secretion of several cytokines like IL-1α, IL-1β, ILs-12,23,25,33 and all types of IFNs, described above. It also produces Thymic stromal lymphopoietin (TSLP) and TGFβ (Transforming growth factor betα).. These secretions react with lymphocyte, Natural killer cells and tissue resident memory cells, to further produce these cytokines, interferons. and AREG etc. Collectively they help in recruiting and activating the effector-cells to kill and expel the foreign particles. [9]. Similarly, the neutrophils can facilitate viral clearance and dampen inflammation. It is important to note that classically activated (macrophages (M-1) and DCs contribute to disease pathogenesis, while alternatively activated macrophages (M-2) dampens the virus-induced inflammation It is mediated by activation of nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ)[10].

Another alarming situation in post infection challenges, where alveolar macrophages get desensitized, showing lower response of NK cells (TNF producing cells)[11], α state of compromised immune system. This can be targeted by reducing the TH1-type immune responses of the viral infection, which is known to produce IFNγ. It is reported that in influenzα virus infection, secondary bacterial infection can be controlled by neutralizing the IFNγ, which restores the level of MARCO expression by macrophages. Contrary to this, the increased expression of the CD200 receptor (CD200R), suppresses alveolar macrophage activation in response to secondary bacterial challenge, thus lowering the threshold of lung innate-immune cell-activation, finally altering the host's susceptibility to secondary bacterial infection[12]. Further the decreased translocation of nuclear factor-κB (NF-κB) has also been attributed to reduce expressing of cytokines and chemokines.

These drugs are collectively called as "adaptogens" and plant products are the best suited agents because of their multi-targeted action, attributed to presence of hundreds of phytochemicals as natural cocktail in the water extract of these plants. The adaptogens can be useful in prophylaxis and treatment of viral infections at all stages of progression of inflammation as well as in aiding recovery of the organism by (i) modulating innate and adaptive immunity, (ii) anti-inflammatory activity, (iii) detoxification and repair of oxidative stress-induced damage in compromised cells, (iv) direct antiviral effects of inhibiting viral docking or replication, and (v) improving quality of life during convalescence. Both activation and inhibition of various components of innate immune system [13][14] by numerous natural compounds have been reported in the literature. Now bioinformatics based drug docking studies are supporting this hypothesis.

At the molecular biology point of view, the key elements of innate immunity stimulation include activation of IF-γ and TLR followed by inhibition of NF-κB and inflammation mediated by proinflammatory cytokines. Adaptogens activate adaptive signaling pathways by upregulating gene expression-encoding phosphatidylinositol 3-kinase (PI3K), protein kinase C (PKC), and mitogen-activated protein kinases (MAPKs) [15], which are upstream of transcription factors (Nrf2, HNF1, CCAAT, C/EBPβ, and PXR), FXR and peroxisome proliferator-activated receptors that promote the induction of phase II enzymes and phase III transporters involved in metabolic detoxification process, clearance of breakdown products[16] and overall defense response to pathogens.

However, since the behavior of immune responses are different between severely and moderately infected persons, so line of treatment should also be different for resolving the symptoms. In Ayurveda it is called "Samprapti Vighatan". For this characterization of the disease stage, the measurement of (α) number of activated CD4+ helper T cells, (b) CD8+ killer T cells, (c) follicular helper T (Tfh) cells, (d) antibody-secreting cells (ASCs) and (e) level of IgG **(Immunoglobulin G)and IgM (Immunoglobulin M) could be detected**. On the other hand, in severely infected patients, lymphocytopenia is α common denominator with substantial fall in numbers of natural killer cells, B cells, CD3+ T cells, CD4+ helper T cells, CD8+ killer T cells along with the increase in neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein levels[17].

The host cells have inbuilt defense mechanism acting on various steps of viral infection like lytic, chronic, latent or immortalizing, through involving the biological or chemical barriers, which is considered as the 1st layer of defence. However, when they get weaker or compromised then 2nd line of "Immune defence" plays important role by activating Natural killer (NK) cells, monocytes, Dendritic Cells (Dcs), type I interferon (IFN), neutralizing antibodies, and T cells. When DC interacts with NK cells the innate immunity is activated and when DC interacts with T cells then adaptive immunity is activated. However, the infecting agent adopt several devices to overcome the host's defense system, which may include modulation in the (1) Pattern Recognition Receptors (PRRs), (2) low production of type I IFNs, (3) inhibition of DCs mediated immune activation. Since viral infection is difficult to manage because of lack of direct antiviral drugs, so immunotherapy by strengthening the cells involved in this process, would be an effective strategy to control the viral infection mediated upper respiratory tract diseases. Currently, development of vaccines focusing induction of $CD8^+$T cell responses is in progress, but this process to produce more IFN-gamma mediated promotion of Th1-biased $CD4^+$T-cell response, by using medicinal plant based food supplements or herbal drugs would be effective in quick control of infection.

**Treatment Guidelines:**

The mechanism behind induction of respiratory-immune tolerance, changes in lung structure, the influence of genetic background and environmental factors, and the impact of the aging on respiratory health, are important to understand for developing novel therapeutic modalities. The use of antibiotics, anti-allergy, immunotherapy, steroid inhalers, antihistamine-drugs and decongestants, are some of the recommended treatments. It is reported that glucocorticoids

are effective therapy for asthma, but its use for longer time is associated with several side effects, as osteoporosis and metabolic disorders. The Inhaled glucocorticoids are reported to inhibit the epithelial expression of inflammatory proteins. Thus, it can be concluded that glucocorticoids enhance innate immunity while suppress the adaptive immunity[18].

The immunotherapy to promote antigen-specific tolerance to ameliorate allergic responses is also in practice [19]. Since viral infection suppresses Treg activity in the lung, thus enhancement in allergic responses and number of pulmonary macrophages are able to induce the development of Tregs and to down-regulate allergic responses Since nutrition also affects regulatory pathways, with the number of FoxP3+ T cells as it has been correlated with the levels of Vitamin D in the circulation and its higher level was found to be effective in patients of steroid-refractory asthma.[20]

The **current treatment strategies include** Cidofovir and ribavirin as antiviral therapy in immune-compromised individuals. Brincidofovir is a lipid-linked derivative of cidofovir that has enhanced oral bioavailability. Other potential drugs could be those, which inhibit adenoviral cysteine enzyme (Ex- ritonavir); soluble virus receptor trap (Ex-soluble CAR-Fc); Suppressor of adenoviral replication by using siRNA, virus receptor trap (Ex-sCAR-Fc and Cidofovir), donor-derived adenoviral specific T infusion[21].

**Post Viral Infections and their management:**

Further, it has been clinically noticed that viral infections are generally followed by bacterial infections. This is due to broken epithelial barrier, inefficient micro biome, and failure of localized immune system. The increased vascular resistance in pulmonary organs may result to accumulation of neutrophils, which further regulate the immune responses via secretions of proteases and free radicals. The process of fibrinogenolysis on allergic responses is also an important factor to be considered[22].

Now, when we talk of coronavirus disease 2019 (COVID-19) infection, it affects both upper and lower respiratory tract. Here, most of the patients get recovery within 14 days, but some may enter to critical stage of acute respiratory syndrome (ARDS). Depending on the severity of the disease the patients have been classified in to stage I, II and III and finally multi-organ failure. In these patients, it is a time dependent process, sequentially involving airway, lung parenchymal, pulmonary vascular and respiratory neuro-muscular junctions in brain, liver and kidney. [23].

In Ayurveda, rasayan chikitsa and targeting the cause behind symptoms (Samprapti Vighatan) are the recommended approach for treatment. A patented formulation, consisting of water-soluble extract of following plants would be a better option to treat this pathogenesis. The selections of these medicinal plants are based on a rational developed by tools of bioinformatics. It appears that this formulation would be highly effective in management of pre COVID, during the COVID and also the post COVID stage. In Ayurveda, this aspect of wellness is well defined as it advocates for (1) diet, (2) sleep and (3) code of conduct, as the 3 basic pillars for keeping good health. When we talk of diet, then it has been considered as the best medicine and it has been defined in terms of quality and quantity of food along with proper timing of feeding. In yoga also 8 branches of *astang yoga* are directly related in maintaining the immune system and other physiological aspects, responsible for good health. Besides the yogic practices, saline wash, steam inhalation is also effective. Preventive measures include regular use of saline sprays or wash, keeping the nose moist, use of humidifier in dry indoor environments and abstaining from cigarette smoke, pollen allergens, swimming in chlorinated water pools etc.

Since body physiology is in equilibrium with external environment so seasonal changes, environmental conditions, psychological wellbeing, and age are also important factors [24]. Some of these factors are beyond the control of human being but some can be controlled. However, for scientific validation of impact of all non-pharmacological factors and the modulating effect of diet and drug has not been done till date, and requires further studies.

The development of novel drugs, interfering with the signaling pathways of these processes is the demand of time. The bioinformatics tools may be helpful in identifying the secondary metabolites of those medicinal plants, which are described in ancient texts of Ayurveda and being clinically used in management of respiratory disorders and enhancing the immune system [25]. So, the use of phytoconstituents of different medicinal plants, which are already in clinical use by Ayurvedic physicians, may be explored to enhance the potential of this way of treatment. Here, the medicinal plant-based food supplements and drugs may prove to be better, as they are multi-targeted. In addition to drugs, the lifestyle, hygiene genetic makeup of an individual also plays important role, which supports the concept of individualized/ personalized medicine. Since, in infants the infection is mainly localized in URT, which is auto-resolved with time, but sometimes it may migrate to lower respiratory tract, causing severe symptoms [26]. However, the defense system needs to be strengthened to avoid frequent infection because opens the pathway of several lung-diseases in adult age also. Major phytochemicals involved with therapeutic activity of viral infection are described here.

Terpenoids: most of the plant terpenoids have been found to control viral spread in the host, by acting at different levels. Some of them like thymoquinone of *Nigella sativa, t*he Salvinorin A derived from *Salvia divinorum*, Bilobalide and Ginkgolide A extracted from *Gingko biloba*, citral from *Backhousia citriodora*, menthol from *Mentha*, Noscapine extracted from Papaveraceae family, Forscolin from *Plectranthus barbatus* and Beta Selinene from *Apium graveolens,* Betulinic acid from bark of white *Betula alba* var. *pubescens* tree, have been reported to suppress the virus protease enzyme activity[27].

The Polyphenols are other group of phytochemicals, are reported to increase the number of immune cells[28]. The flavonoids are reported to inhibit the cellular receptor kinases like MAPKs, the serine/threonine-specific protein kinase (Akt) and the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3-K), resulting down regulation of cellular signal transduction cascades,[29][30]. Quercetin, a flavone shows Hemagglutinin Inhibitory Activity, thereby inhibiting virus-cell fusion. Quercetin also treats Influenza Virus. Other flavonoid show inhibition of neuraminidase activity (NA) of influenza virus. Quercetin are the flavonols, reported to be effective against influenza virus[31].Shikimic acid, one of the primary components of oseltamivir, is effective through its anti-inflammatory potential by modulating the expression of IL-6 and IL-8 in the peripheral blood mononuclear cells (PBMCs).

Similarly Chymotrypsin, a bioactive Dipeptides is reported to inhibit coronavirus. The Aurantiamide, is a plant derivative extracted from *Piper aurantiacum*, has been reported to an efficient protease inhibitors against COVID-19. The Sulphated polysaccharides are structurally multifaceted class of biomolecules having diverse physiochemical characteristics . They are the richest and most traditional pool of structurally and functionally assorted biopolymers, easily biodegradable and plays vital role in manufacturing of various medicines, cosmetics and food derivatives[32]. Guduchi or Giloy herb is suggested to contain various diterpene compound and polysaccharides including

arabinogalactan polysaccharide (Subhose et al., 2005), collectively attributing to immunomodulating and adaptogenic properties. They enhance the IgG in the serum and activate the macrophages, resulting activation of both cell mediated and humoral immunity. These plants have been widely reported for their potential antiviral activity against H1N1 flu and as an immunostimulator.

Since, high ACTH (Adrenocorticotrophic Hormones) secretion, resulting more activity of stress hormones like adrenaline, non-adrenaline and glucocorticoids is reported to supress the immune system of the body, so special precaution should be taken to balance their normal level. Several medicinal plants have been reported to target this pathway, both directly and indirectly through regulation of optimum sleep, which reorganizes the T-cells towards lymph nodes and boosts their immunogenic memory respon. Controlling the level of high glucose or $CO_2$ within blood is also immunoboosting, as these pathologies causes hypercapnia and inhibits the normal macrophage activity towards pathogen clearance. Besides, regular physical exercise, proper intake of muti-vitamins is also helping in immunoboosting.

Impact of PAK-1 blockers: budding therapeutics against coronavirus: PAKs belong to mammalian kinases family also known as RAC/CDC42-activated kinases, are reported to be hyperactive in several diseases like cancer, inflammation, malaria, dengue, conditions of immuno-suppression. Strikingly, PAK1-blockers (naturally existing) such as caffeic acid, its esters, bee-product propolis have been observed to be effective antiviral agents[33]. A herbal formulation mainly triterpenes or steroid named 'triptolide' derived from thunder god vine is also reported to inhibit the RAC followed by blocking PAK1 route[34]. One category of anti-influenza drugs are the neuraminidase-inhibitors (NAI). The Oseltamivir and zanamivir belong to this group and reported to reduce the viral shedding within the respiratory tract. Similarly, the M2 channel blockers like amantadine and rimantadine, are reported to block the viral-RNA uncoating within infected cells, thereby preventing their replication. They disrupt the transmembrane domain of the viral M2 protein. Since excessive production of NO, mediated by IFN-$\gamma$, together with $O_2$-, which forms more reactive peroxynitrite, may be the most important pathogenic factors in influenza virus-induced pneumonia, so drugs blocking iNOS would be effective in controlling the viral symptoms. The ROS at one hand activate viral replication via activation of NF$\kappa$B, and on the other hand they decrease the CD4+ T cell count by inducing apoptosis, so antioxidants would be effective. They may direct neutralizing the free radicals or induce the expression of genes of antioxidant enzymes within the host cells.

With these backgrounds of pathogenesis and active phytochemicals in mind, here we have reviewed the secondary metabolites of the plants of **Imuhelp (Fig 3.)** affecting the innate and adaptive immune system (Fig 2). It contains the water-soluble extract of 6 medicinal plants having major phytochemicals as shown in Table-2. Individually these plants belong to group of rejuvenation drugs (Rasayana) and detoxifying drugs (Vishaghna). As per Ayurvedic literature and guidelines for treatment of respiratory disorders the use of agad-dravyas, sthavar-visha and sthavar-upvisha, has been recommended[35]. These medicinal plants are supposed to remove them from the body by neutralizing them on chemical basis. The biochemical basis behind the rational of developing this combination is to target the pathways involved in immune modulation related cells, and to regulate the metabolic pathways involved in producing toxins, oxidative stress, and inflammatory cytokines. We have used the key words like *in-silico* studies, docking studies, bioinformatics, therapeutic claims with each plant and the paper shorted out were carefully reviewed to select the phytochemicals having high binding and stability status with the selected proteins, involved in pathogenesis of URTI, to make a search in Google, Pubmed, Web of Science. The rationale behind the use of each plant has been described below separately.

(1)**Amla** (*Phyllanthus emblica*): Its fruit contains ellagic acid, gallic acid, quercetin, kaempferol, emblicanin, flavonoids, glycosides and proanthocyanidins. Phyllantine, phyllantidine, Vitamin C (ascorbic acid or ascorbate), tannins (e.g., emblicanins A and B), phyllemblic acid, gallic acid, lipid, emblicol, colloidal complexes, micic acid, amino acids and minerals, fixed oil, essential oil and phophatides and flavonoids present in amla have very powerful immunomodulatory, antioxidant and anticancer activities. It shows anti-microbial, antimutagenic, anti-inflammatory, antipyretic, analgesic, antidiabetic, hepatoprotective, anti-anaemic, pro-wound healing, anti-respiratory disorders.

**(2) Ashwagandha** (*Withania somnifera* (L.) Dunal (Solanaceae)), commonly known as 'Indian Ginseng' categorized as a rasayana (rejuvenator) is being used as antiaeging, immunomodulant and neuroprotective [36]. Other experimental and clinical data supports its claim as anti-inflammatory, anti-diabetic, antimicrobial, analgesic, anti-tumour, anti-stress, neuroprotective, cardio protective, rejuvenating and immunomodulatory effects[37][38][39] . Recently based on in-silico studies it has being claimed as antiviral specially with reference to COVID-19 [40].Its major active ingredient includes withanolides, Withaferin-A, Withanolide D, steroidal saponin, alkaloids, and steroidal lactones. [41].Its anti-inflammatory properties have been attributed to inhibition of Nf-kb. Thus its use in management of URTD seems logical.

**(3) Tulsi** *(Ocimum sanctum)* as a sanctified herb used for its medicinal property as per Ayurvedic scriptures. It's multiple therapeutic action comprises of adaptogenic, immunomodulatory, antimicrobial, cardio protective, and anti-inflammatory effects, anti- viral, anti- fungal and anti-bacterial activity, also possess anti-diabetic, analgesic, antifertility, anticancer, antispasmodic, antiemetic diaphoretic and hepatoprotective actions[42]. Their leaves are beneficial for the treatment of rheumatism, bronchitis, and pyrexia and considered as 'Elixir of life' for its healing power [43]. By the enhancement of both cellular and humoral immunity, it strengthens the immune response[44]. The Eugenol and Ursolic acid are its main phytoconstituents and show interaction with SARS CoV- 2Mpro, and other target proteins (S, E, N) of COVID-19.[40] It has been reported that Dihydrodieuginol B and Tulsinol A, B, C, D, E, F, G of O. sanctum could be used as potential inhibitors for Papain-like Protease and SARS Coronavirus Main Protease.[45]

(4). **Guduchi or Giloy:** *(Tinospora cordifolia)*, is a medicinal plant which has been used for its remedial purpose for thousands of years in Ayurvedic system of medicine. Its extracts have alkaloids, glycosides, steroids and polysaccharides[46]. It is well known for its immunomodulatory, antidiabetic, antioxidant, antihepatotoxic and cytotoxic effect.[47] The active phytoconstituents, Tinocordioside, Cordifolioside A, Magnoflorine, and Syringin are known for its immunomodulatory effect.[48]

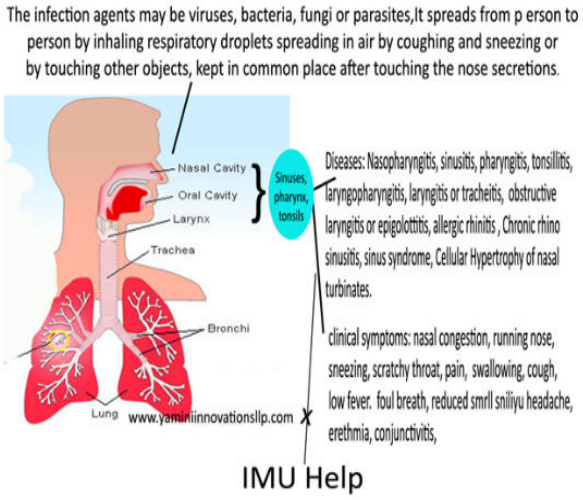
**(5) Kalmegh** *(Andrographis paniculata)* also called King of bitters/ Indian Echinaceae, is a drug of preference of liver disorders, skin diseases and digestive system. It has shown anti-bacterial and anti-fungal potentials[49] and is a potent modulator of the immune system. It's prominent secondary metabolites includes andrographolide[50] and its other derivatives, which are attributing to it anti-dengue, anti-swine

flu, anti-hepatitis C, anti chickengunia, anti-influenza, anti-Epstein-Barr virus (EBV)and anti-herpes simplex virus 1 (HSV-1).[51][52] The 14-deoxy-11, 12-didehydroandrographolide has been found to be most effective against COVID-19, based on bio-informatics tool of binding energy and drug likeness[53].It is reported to be involved in the pathway of chemokine signaling, Rap1 signaling, Cytokine-cytokine receptor interaction, MAPK signaling pathway, NF-kappa B signaling pathway, Ras signaling pathway, p53 signaling pathway, HIF-1 signaling pathway, and Natural killer cell-mediated cytotoxicity.

So plant extract of *A paniculata*, proves it's multi-target action in control of infection mediated respiratory disorder, mainly by modulating the immune cell functions.

**(6) Yashthimadhu:**

(*Glycyrrhiza glabra)*, (licorice or liquorice) is perennial legume. It has been attributed to several biological properties related to antioxidants, anti-inflammatory, anti-aging potentials. This herb has proven to be effective in treating respiratory disease such as COPD, asthma, bronchiolitis and whooping cough Liquiritin, glycyrrhizic acid, glycyrrhizin , its saponins and glycosides; and glabridin , Glucobrassicin, a glucosinolate, Ursolic acid, Hederagenin, Apigenin, Oleanolic acid and Rosemarinic acid are some of the important phytochemicals, which have been reported to have better interaction with COVID-19 protease protein.[54][55]




**Figures 1:** Graphical abstract of Imuhelp showing potential therapeutic claims for different upper respiratory tract disorders (URTD)

## CONCLUSION:

It appears that **Imuhelp** is a herbal formulation, made by mixing the water soluble extract of 6 medicinal plants, having established claims for treating respiratory distress of lower and upper tract in ancient Ayurvedic texts and further validated by various experimental and clinical studies conducted globally. It's mechanism of action may be attributed to its multi-targeted action as immune stimulant, antioxidant, anti-inflammatory, protease inhibitors, and antihistaminic.It can inhibit signaling pathway involved in vasoconstriction and helps in stimulation of factors responsible for vasodilation. **Immuhelp** constituents can inhibit the signaling pathway responsible for worsening of the condition as well as decrease the cytokines responsible for inflammatory storm along with improvement of lung physiology in disease and distress.

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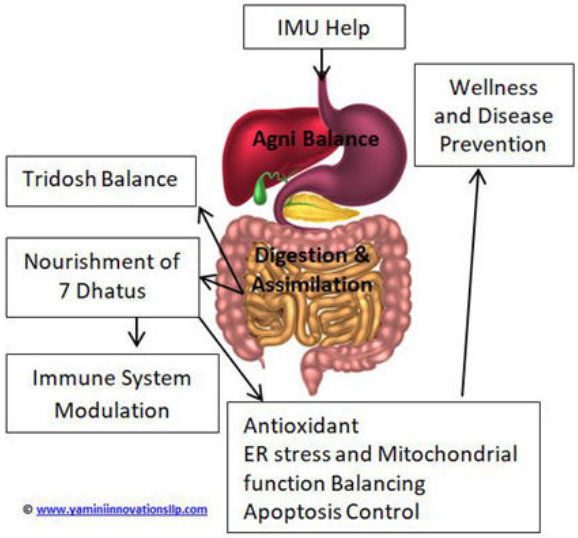


**Fig -2:** Role of Imuhelp in overall health of the patient, in addition to management of URTD, based on the principles of Ayurveda

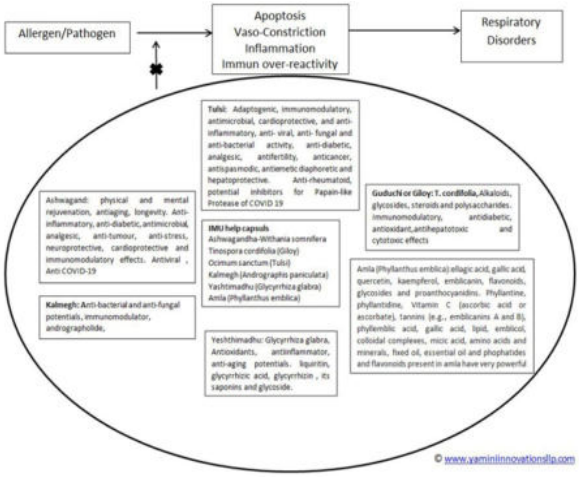


**Fig 3:** Summary Of Different Pharmacological Claims Of Constituent Plants Of Imuhelp And Their Collective Role In Management Of URTD

**Table-1: Name Of Common Diseases Of Upper Respiratory Tract**

| S.No. | Diseases | Description |
|---|---|---|
| 1. | Croup | Predominantly in children, defined as swelling in neck, voice box (larynx) and trachea, resulting symptoms of barking cough, breathing difficulties with lethargic tendency, whistling sound when breathing, fever, running nose etc mostly at night, and persists from 3-7 days.. The causative factors include viral/bacterial infections, allergens or stomach- reflux. Preference of treatment includes the use of inhalers, inject-able steroids, antipyretic and anti-inflammatory drugs. |
| 2. | Epiglottitis | Defined as inflammation in epiglottis, due to Haemophilus inuenzaetype B (Hib), borne infection. Hypersensitive children for this bacterium need preventive measures. General vaccination is the usual practice in developed countries. Antibiotics, steroids along with treatment for pain and fever are recommended. |

| | | |
|---|---|---|
| 3. | **Influenza** | Due to flu viruses, which are of 3 types-A,B and C. The 1st two are more common and spread like pandemic, usually in winter, having high fever, body aches, a cough, and respiratory unrest. It usually persists for 6 to 9 days and sometimes results to pneumonia. It spreads through sneezing or coughing, so touching the infected fixed objects in the house or use of common eating and drinking utensils. So cleanliness is the main path to step to stop its spread. The flu symptoms are different than common cough and cold. Antipyretic, antiviral and anti-inflammatory drugs are effective. The antibiotics are only given to control the secondary infection. Electrolyte imbalance should also be managed properly. Yearly flue-vaccines are common practice in developed countries. |
| 4. | **Sinusitis** | It is broadly divided in to 3 types i.e. short (<12 weeks), long (>12 weeks) or recurrence. It is infection in sinuses, usually happens after cough and cold or allergy. Anatomically, the sinuses, of 4 types, the air space around the nose, lined with mucous membranes. When this air space is filled with body-fluid, then it allows infection mostly with Streptococcus pneumonia, Haemophilus influenza and Moraxella catarrhalis. Its common symptoms include, headache, stuffy nose, thick coloured drainage from nose, cough, slight fever and loss of smell. Blocking the opening of sinus is the main etiological factor. Allergy mediated inflammation, tooth-infection, nose injury, gastroesophageal reflux (GERD), cystic fibrosis and immune deficiency are also important factors to precipitate sinusitis. |
| 5. | **Stridor** | Defined as the high-pitched sound during breathing. It is due to partial blockage of upper airway organs involving nose, mouth, sinuses, voice box (larynx), or trachea. The other causative factors may include congenital defects in airway, infections, as described above, swallowing toxic-substances, blockage of upper airway during swallowing of food, Injuries to the jaw or neck, nervous control of breathing, tumor in airway and allergic reactions. |
| 6. | **Whooping cough (pertussis)** | It is an infectious disease caused by Bordetella pertussis bacteria, which causes swelling of the airways and mucus. It causing fits (paroxysms) and coughing, mainly in babies. Vaccination is the treatment of choice for prevention. |
| 7. | **The common cold(upper respiratory infection)** | Most common illnesses in children happen due to viral (rhinoviruses) infection, causing irritation in the lining of the nose and throat. Child with low immunity is more prone to this infection. Dry nose in winter with lesser humidity is a suitable climate for catching cold. Its incubation time is 1-3 days. It may be accompanied by ear infection, sinus infection, throat infection and pneumonia. |
| 8. | **Rhinitis** | A reaction that happens in the eyes, nose, and throat when air bound allergens trigger the release of histamine from the mast cells, causing itching, swelling, and fluid accumulation in the fragile linings of nasal passages, sinuses, and eyelids.<br>The symptoms include ear-infections, snoring, breathing through mouth, dark circles under the eyes, and swollen tissue inside the nose. |

**Table-2: Major Phytochemicals Of Constituent Plants Of Imuhelp**

| Plant | Botanical Name | Reported major phytoconstituents |
|---|---|---|
| Ashwagandha | *Withania somnifera* | withanolides(triterpene lactones), withaferin A, alkaloids,steroidal lactones,tropine, and cuscohygrine[56] |
| Giloy | *Tinospora cordifolia* | Tinosporide,Tinosporine,Giloin,Giloinsterol,Mangloflorine,Berberine[48] |
| Tulsi | *Ocimum sanctum* | Oleanolic acid, Ursolic acid, Rosmarinic acid, Eugenol, Carvacrol, Linalool, and β-caryophyllene[42] |
| Kalmegh | *Andrographis paniculate* | Andrographolide, a bicyclic diterpenoid lactone and Kalmeghin[57] |
| Yashtimadhu | *Glycyrrhiza glabra* | Glycyrrhizin, Glycyrrhetinic (glycyrrhetic) acid.——[58] |
| Amla | *Phyllanthus emblica* | Ascorbic acid,gallic acid, ellagic acid,rutin and quercetin[59] |

**Table-3: Pharmacological Claims Of Different Phytochemicals Of Constituent Plants Of Imuhelp**

| Phytoconstituents | Reported Activity | Reference |
|---|---|---|
| **Tulsi** | | |
| Oleanolic acid | 1. Anti-inflammatory, Analgesic and potential anti-arthritic activity.(In-vivo and in-silico inhibition of COX-1,COX-2,IL-1 and TNF-α)<br>2. Anti-cancer activity(alters multiple cell signaling pathway)<br>3. Antidiabetic,Antimicrobial,Hepatoprotective,Anti-hypertensive,Antiparasitic | [60]<br>[61]<br>[62] |
| Ursolic acid | 1.Anticancer activity(Breast cancer,Colon cancer)<br>2. Treatment for obesity mediated and muscle mass mediated metabolic consequences.<br>3. Manage Neurodegenerative and Psychiatric disorders | [63]<br>[64]<br>[65] |
| Rosmarinic acid | 1. Anti-inflammatory<br>2. Anti-diabetic potential<br>3.Alleviates lipid accumulation<br>4. Anticancer potential<br>5.Hepatoprotective<br>6.Treats ocular neovascularization | [66]<br>[67]<br>[68]<br>[69]<br>[70]<br>[71] |
| Eugenol | 1.Anticancer<br>2.Antimicrobial<br>3.Anti-inflammatory and Hepatoprotective | [72]<br>[73]<br>[74] |
| Carvacrol | 1.Neuroprotective<br>2.Reduce adipogenic differentiation<br>3.Antimicrobial<br>4.Antiviral efficacy<br>5.Anti-inflammatory and immunomodulation in Asthma | [75]<br>[76]<br>[77]<br>[78]<br>[79] |

| | | |
|---|---|---|
| Linalool | 1. Antifungal | [80] |
| **Kalmegh** | | |
| Andrographolide | 1. Hepatoprotective activity<br>2.Anti-tumour activity in liver damage<br>3.Immunoprotective potential<br>4.Accelarates intestinal absorption and digestion of carbohydrate | [81]<br>[82]<br>[83]<br>[84]<br>[81] |
| Kalmeghin | 1. Natural Inhibitor against Influenza A (H1N1)(in-silico)<br>2. Antioxidant activity | [85]<br>[86] |
| **Yashthimadhu** | | |
| Glycyrrhizin | 1.Anti-cancer | [87][88][89] |
| | 2.Covid 19 | [90] [40] |
| Glycyrrhetinic acid | 3.Anti-Inflammatory | [91] [92][93] |
| | 4.Anti-Cancer | [94] |
| | 5.Anti-Allergic | [95] |
| | 6.Anti-Viral | [96] |
| | 7.COVID-19 | [97][98] |
| **Giloy** | | |
| Berberine | Anti-oxidant | [99] |
| Tinosponone | COVID-19 | [100] |
| Tinocrdside | COVID-19 | [101] |
| Tinosponone | Anti-inflammatory | [102] |
| Cordifolioside-A | Cardioprotective and cytoprotective | [103] |
| Jatrorrhizine | Anti-cancer | [104] |
| Palmatine | Anti-cancer | [105] |
| Berberine | Anti-cancer | [106] [107] |
| Mangloflorine | Anti-cancer | [107] |
| **Ashwagandha** | | |
| Withanoside-V Somniferine | Anti-viral(COVID-19) | [40][44] |
| Sitoindosides VII-X | Antioxidant | [39] |
| Withaferin A | Anticancer<br>Anti-inflammatory,<br>Anti-angiogenesis, Anti-metastasis activities | [108].<br>[109] |
| Sitoindoside X | Anti-stress activity | [110] |
| **Amla** | | |
| Pentagalloylglucose | Anti-viral | [111] |
| Emblicanin<br>Ellagic acid<br>Phyllaemblicin B | Cardio protective | [112][113]<br>[114] |
| Mallotusinin ,mucic acid 1,4-lactone 3-Ogallate<br>Gallic acid | Anticancer | [115].<br>[116] |
| Ellagic acid | Anti-diabetic | [117] |

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