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A Study of Withania somnifera and Nyctanthes arbortristis : SARS-CoV-2 Immune System Boosting

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Abstract

Throughout history, infectious illnesses with pandemic potential have frequently emerged and spread. Pandemics and epidemics of great proportions, including the plague, cholera, flu, and severe acute respiratory syndrome coronavirus (SARS-CoV-2) have already afflicted humanity. Via the cell-surface receptor ACE2, Covid-19 viruses attack certain human cells and quickly begin replicating inside the body. Antibodies binding to the spike head and blocking connections to the ACE2 receptor can lower the amount of virus that enters cells.The precise vaccine to stop the spread of this virus will be the subject of numerous studies.However, no vaccination or particular treatment has yet been developed, which is causing major problems all across the world. During this epidemic, strengthening your immune system is the best defence against the virus. Ayurveda has a long history of being the most effective immune system builder for mammals and animals. Withania somnifera and Nyctanthes arbor-tristis L. are examples of herbal plants that have good anti-inflammatory, anti-tumor, anti-oxidant, and anti-carcinogenic qualities. These plants also include essential compounds such Withaferins, various alkaloids, steroids, and amino acids. The brief explanation of the pharmacological properties, active components, and prospective therapeutic uses of these medicinal plants forms the basis for this review. Ayurveda has a long history of being the most effective immune system builder for mammals and animals. Withania somnifera and Nyctanthes arbor-tristis L. are examples of herbal plants that have good anti-inflammatory, anti-tumor, anti-oxidant, and anti-carcinogenic qualities. These plants also include essential compounds such Withaferins, various alkaloids, steroids, and amino acids. The brief explanation of the pharmacological properties, active components, and prospective therapeutic uses of these medicinal plants forms the basis for this review.

Keywords: Withania somnifera; Ayurvedic; SARS-CoV-2; Nyctanthes arbor-tristis L.; Immunomodulators; Immune system.

1. Introduction

The super community spreader SARS-CoV-2 (acute respiratory syndrome corona-virus 2 has affected over worldwide, that is responsible for the death of lakhs of people. To date, there is no specific drug and vaccines registered to combat the disease. This novel SARS-CoV-2 is also known as COVID-19. This COVID-19 patient is suffering from fever, Cough, Tiredness, shortness of breath or difficulty breathing and other symptoms, like blue lips or face, persistent chest pain or pressure, heart attack, loss of taste or smell etc. These can cause diseases associated with the central nervous system, respiratory problems (upper and lower) and gastrointestinal-tract infections [1]. This virus infection is very dangerous for the people having diabetes, kidney and heart diseases. During a viral infection, the anti-viral therapy is based on the attacking way of virus into the host cell [2]. Corona viruses spread infections into the specific human cells through cell-surface receptors. The entry of virus can be secured by targeting the viral receptor-binding site with neutralizing antibodies (nAbs). The surface of the Corona virus is surrounded by many spike proteins. The entry of virus is interposed by the Receptor Binding Domain (RBD) of the spike head(S1, S2), which attaches to the host cell receptor Angiotensin-Converting Enzyme 2 (ACE2). After the connection between virus and the receptor has been established, the human body activates the TMPRSS2 enzyme. The TMPRSS2 enzyme is a protein cutting enzyme that helps to cut the head of the spike and the structure of the virus begins to change. In this process the membranes of the virus and the cell come very closer and the entry of virus into the cell takes place by endocytosis process [3]. Action of Antibody can reduce the entry of virus into the cell by binding with the spike head and prevent to connect with ACE2 receptor. Immune system of our body plays an important role to produce Antibody on the detection of antigens. To reduce spreading and fast rehabilitation, many researches are going on. In this current study, the priority is given to emphasis the immune system of the human body to fight against this COVID-19 pandemic period. The different kind of concept to increase the immunity and resistance power of body to fight with many diseases is Ayurveda that is widely used in ancient times across the world. According to Ayurveda the balancing of vayu, pitta and kaf plays an important role in our body. Imbalance of these three arises many diseases and decreases our immunity power. The immune system is the capacity of our body that protects us against microbes.

There are remarkable benefits of Ayurveda in India and also worldwide. Many parts of several plants are used as medicines and to increase immunity from ancient days. Villagers of India mainly use many types of medicinal plants to cure several diseases even for cancer, diabetes, malaria, cough, common cold and viral fevers etc. Many types of plant products are used for various diseases like Aswagandha (Withania somnifera), parijat (Nyctanthes arbor-tristis L.), Tulsi, Turmeric, Black pepper etc. Recently, the researchers found the key role of Withanone (Wi-N) present in Withania somnifera to block the viral replication [4].

In many parts of India people are using Nyctanthes arbortristis L. leaf to cure large no. of diseases like diabetes, flu, even for malaria fever, Cancer and HIV. Many researches were done to know the benefits and increament of immunity power by consuming leaf of Nyctanthes arbor-tristis L. [5]. This tree is generally 8-10 m height, which does not require any special caring and

can be plant in any place. Harshringar the common name of Nyctanthes arbortristisis belongs from Oleaceae family. The name Nyctanthes is derived from Greek words 'Nykhta' and 'anthos' means "Night Flowering". This tree is known by several names in various states of India like Night-flowering Jasmine, Harshringar, Seoli, Parijataka, Sephalika. Etc. The leaves are generally opposite, 2.4–4.8 inch long and 0.78–2.56 inches broad, with an entire margin. The pleasant smelled flowers are orange centered with a 5-8 lobed white corolla. The loamy soils are perfect for healthy growth of this plant. This plant needs environment differing from partial shade-full sunlight and requires a frequent supply of water. Flowering usually takes place from the month of July- October. All the parts of this plant are very advantageous in medicinal chemistry.

Withania somnifera (Ashwagandha) is also a good medicinal plant that can boost our immune system as well as lower the blood pressure and help help to calm the brain. It Is also known as Winter Cherry, Punir, Ghodakun, Fatarfoda, Asgund, Chirpotan etc. This can be used for longer time by all age-group and both genders as well as at the time of pregnancy with no side-effects [6]. Withania somnifera , commonly known as Aswaganda, Winter cherry, Withania is a woody small shrub belongs to Solanaceae family. This can grow about 2 feet in height and generally found in Africa, the Mediterranean, and drier parts of India. This shrub has stout fleshy roots, simple, ovate opposite leaves and flowers inconspicuous, greenish or lubrid-yellow, in axillary, umbellate cymes. The roots are very useful parts and used as medicines. All the Parts (Whole plant, roots, leaves, stem, green berries) of this medicinal shrub are also valuable. Table-1 shows the taxonomical classification for both Nyctanthes arbortristis sand Withania somnifera.

Table-1: Taxonomical classification for both Nyctanthes arbortristis L. and Withania somnifera

Botanical name	**Kingdom**	**Eudicots Division**	**Order**	**Family**	**Genus**	**species**
Nyctanthes arbor-tristis L.	Plantae	Angiosperm	Lamiales	Oleaceae	Nyctanthes	N. arbortristis
Withania somnifera (Ashwagandha)	Plantae	Angiosperm	Tubiflorae	Solanaceae	Withania	Somnifera Dunal

2. Chemical constituents and Importance

Table-2 shows the useful chemical constituents present in both the plants. The extraction of Nyctanthes arbor-tristis L. seeds with ethyl Acetate (Ny-El) has 206.81 ± 1.11 mg of total phenolic content, excellent scavenging action on DPPH (2, 2-diphenyl-picrylhydrazyl) I.e. IC50 459.91±1.40 μg/mL, hydroxyl (IC50 363.32±1.58 μg/mL), nitric oxide (IC50 545.03 ± 1.69 μg/mL) and superoxide (IC50 338.82 ±1.72 μg/mL) groups, and high reducing power [7]. The seeds and the leaves are important parts of this plant contain iridoid-glycosides. Flower has also medicinal properties and presence of essential oil like jasmine. The leaf contains mannitol, beta-amyrin, beta-sitosterol, benzoic acid, astragalin, nicotiflorin and acids like oleanolic and nyctanthic.

Withania somnifera roots are an important part of this plant and widely used as medicines [8]. The roots contain different types of alkaloids, amino acids, steroids, and reducing sugars as well as glycosides\. Withania somnifera roots, there are present 21- 25 % of crude fibre, 6.09 - 9.46 mg/g of starch, 0.39 - 0.82 mg/g of tannins, various minerals such as potassium (K), manganese (Mn), sodium (Na), iron (Fe), zinc (Zn) etc., 2.52 - 9.52 mg/g of total sugars, 0.15-2.10 mg/g of reducing-sugars and 2.37 - 7.62 mg/g of non reducing-sugars [9].

Table-2: Phytochemistry of Nyctanthes arbor-tristis L. and Withania somnifera

Plants	**Presence of chemical constituents**
Nyctanthes arbor-tristis L.	Flavonoids; Steroids; Tannins; Alkaloids and Glycosides; D(-)mannitol; beta-sitosterole; Flavanol-glycosides (like- Astragaline, Nicotiflorin, methyl salicylate and acids such as Oleanolic acid, ascorbic acid, Nyctanthic acid, tannic acid, etc.) [10].
Withania somnifera	Alkaloids- isopellertierine, anferine; steroidal compounds and steroidal-lactones (like- ergostane, withaferin A, withanolides A-y); withasomniferin A, withasomidienone; withasomniferols A-C; acylsteryl glucosides comprising sitoindosides VII and VIII; reducing-sugar, and different amino acids (aspartic acid, proline, tyrosine, alanine, glycine, glutamic acid, cystine, tryptophan) [11].

Alkaloids

Alkaloids are obtained from various plants. Alkaloids are physiologically active basic nitrogenous compounds. The Raw plants contain most of the alkaloids in the form of organic acids (salts). Alkaloids have various pharmacological activities including antimalarial, antiasthma, anticancer, cholinomimetic (*e.g.* galantamine), vasodilatory, antiarrhythmic etc. [12].

Flavanol-glycosides

Flavonoids are generally obtained from plants. Besides the anti-oxidant behavior, flavonoids have many therapeutic activities such as anti-allergic, antiviral, anti-cancer, anti-inflammatory etc. The antiinflammatory activity of flavonoids are the management of inflammatory disorders, behave as cytokine modulators. Other than these it is beneficial drug to cure oxidative stress, wound (scratch), inflammation, ageing, cancer, arteriosclerosis, and ischemicand neuro-degenerative disorders. It is proven from epidemiological studies that the regular consumption of flavonoids reduces the mortality, hyperpiesis, risk of heart related problems as well as cure coronary diseases [13].

D(-)mannitol

Mannitol has a great property that it is crudely reconsumption from the renal tubule and freely strained by the glomerulus. So it causes an enhancement in osmolarity of the glomerular filtrate, that limits the tubular reconsumption of water, sodium, chloride, and additional solutes as well as promotes diuresis. Except these mannitol also enhances blood plasma osmolarity and the flow of water from tissues into interstitial fluid and plasma [14].

Beta-sitosterol

Beta-sitosterol is known as "plant sterol ester." As it is found in plants. This is a very essential compound that mostly used in medicines and imilar to cholesterol. It helps to reduce cholesterol levels by limiting the absorption of cholesterol by the body. It has also inflammation property that binds to the prostate to help reduce swelling [15].

Withaferin A

The withaferin A (WFA) is a most abundant biological active constituent in Withania somnifera plant with highly oxygenated withanolide. WFA stimulates osteoblast proliferation, mineralization and stimulus of ALP (Alk Phos.) action. WFA has the property to inhibit directly osteoclastogenesis, and indirectly generate osteoblast to control osteoclastogenesis [16].

Amino acids

Amino acids are the “building blocks” of protein as it helps to produce proteins. The amino acids cannot be manufactured by the body sufficiently. So, from outside supplements human body can get different amino acids. Enzymes and hormones are made by utilizing amino acids that supports the biochemical activities, and influencses the body’s metabolism. Amino acids are also used to make hemoglobin and antibodies that are help to oxygen transfer inside the body and fight infections by increasing the immunity [17].

3. Immunomodulators activities

Clinically, there are three types of Immunomodulators like immuneadjuvants, Immunostimulants, and Immunosuppresants. Immunoadjuvants are utilized to improve the potency of vaccines and therefore could be considered specific immunestimulants. It is suggested that Immunomodulators can be used as selectors among cellular and humoral immune helper T1 (Th1) T2 (Th2) cells, immunology activities and reagenic IgE vs. IgG type immunoresponses causing a big issue for design vaccines [18].
The non specific nature of Immunostimulants is playing a key role by enhancing resistance of a body against various infections. They can behave as adaptive and also inborn (natural) immune-responses. The immunostimulants are expected to serve as prevent diseases and promote the immunity in healthier body. That means they act as immunopotentiators by increasing the primary level of immune-responses [19].

Immunosuppressants are a heterogeneous class of drugs on the basis of both structural and functional manners. These are sometimes simultaneously regulated in combination autoimmune diseases and regimens to treat different rejection of organ transplantation [20]. Many types of medicinal plants are employed to increase resistance power of animals and mammals, which is traditionally known as 'Rasayana' in India. The interesting medicinal properties of these plants have attracted many researchers worldwide.

Nyctanthes arbor-tristis L. is a medicinal plant, that has Anticancer [21], Immuno-Stimulant [22], Hepatoprotective (Srivastava, 2018a), Antiviral [24], Antimicrobial And Antifungal [25], Anti Allergy [26], Anti-Diabetic [27], Anticholinesterase [28] properties against several diseases. Nyctanthes arbor-tristis L. has the capacity to stimulate the immune-system, pretends both humoral and cell-mediated immunities as have been analyzed its effect in the indirect hemagglutination test and serum immunoglobulin levels [29]. The leaf juice of this plant is used to cure many deseases like- to get rid of roundworms and threadworms, to treat loss of appetite and nausea, liver and bile-duct related diseases, piles, chronic disorders and fever like malarial, obstinate the irritation of the sciatic nerve, rheumatoid arthritis diseases, and as a diaphoretic. Garden- fresh leaf juice, honey and common salt mixed doses have been recommended to be secure laxative for infants. Two ounce infusion doses are beneficial in fever and rheumatic diseases as diuretic and medicinal drug . For snake bite and bronchitis treatment the bark is very useful. The Indian tribal people utilize different parts of Nyctanthes arbortristis to get cure from cough, hiccup, dysentery, snakebite and sores. To destroy parasitic worms (anthelmintic) this plant is used widely in Nepal. Along with the above activities, Nyctanthes arbortristisis is also used as immunotoxic, antiallergic, antihistaminic, purgative, antibacterial and ulcerogenic activities [30].

Withania somnifera is a very attractive medicinal plant with many healing properties. In other words, it is a blessing plant for human life. Withania somnifera is very useful on the bone marrow cellularity and a-esterase positive cell, on circulating antibody titre, on antibody producing cells, on phagocytic action of peritoneal macrophages. The extraction of W.somnifera is noticed that it increases the circulation of antibody titre and cells that form antibody. It is also proved that by treating animals with Withania, there is an outstanding growth of the bone-marrow cells [31]. Withanolides contain have activities like anti-inflammatory and analgesic because of cyclooxygenase-2 diffidence behavior. Use of **t**his plant also increases the 'NO' (nitric oxide) synthatase activity of the macrophages. That increases the CMI (Cell Mediated Immune) response due to enhancement of microbial destroying ability of the immune cells. W. somnifera, a glycol protein known as WSG (Glyco-withanolides) is also liable for anti-microbial activities [32]. Protein and the body weight increase, when Withania somnifera is supplemented with milk. This plant is a treasure of nature due to it's antistress; radio-sensitization activity; advantageous effects on the cardiovascular system and sex hormones; therapeutic behaviors upon Neuro-degenerative symptoms and poisons (like- toxins, snake venom and chemicals). According to charak-sahmita Withania somnifera has Immunostimulatory,anti-inflammatory,anti-stress, anti-rheumatic properties [33]. Recently, the researchers attacked the leading SARS-CoV-2 enzyme for breaking up proteins, identified as the Main protease (Mpro). Mpro plays an important role in moderating viral replication. Withanone (Wi-N) obtained from Withania somnifera and Caffeic Acid Phenethyl Ester (CAPE), an active constituent of New Zealand Propolis, has the potential to interact with and block the activity of Mpro.

4. Other Immunomodulatory herbal plants

Worldwide, there are a vast number of medicinal plants that are used to cure many diseases and enhance the immune system. Table-3 represents some plants those have high Immunomodulators activities other than Nyctanthes arbor-tristis L. and Withania somnifera.

Table- 3 medicinal plants that are used as Immunomodulators

Sl.No.	Botaniacal name	Common name	Properties
1	Allium Sativum	Lahsuna	Antibacterial, Antiviral [34]
2	Desmodium gangeticum	shalaparni	Antiviral, Antiasthamatic [35]
3	Terminalia belerica	Bahera	Immunostimulant [36]
4	Tinospera cordifolia	Guduchi	Immunostimulant, anti-rheumatic, anti-allergic [37]
5	Abrus precatorius	Gunja	Immunostimulant [38]
6	Allbizzia Lebbeck	Shirisha	Immunostimulant [39]
7	Andrographis paniculata	kalmegh	Immunostimulant [40]
8	Aristolochia Indica	Isharmul	Immunostimulant [41]
9	Berberis aristata	Dar-hald	Immuno-suppressor,antibacterial [42]
10	Catharanthas roseus	Sada Bahar	Immunostimulant, Induces antibody production [43]
11	Clitoria ternatea	Aparajita	Immunostimulant [44]
12	Cymbopogon martini	Gandh	Immunostimulant [45]
13	Hyoscyamus niger	parsikaya	Immunostimulant [46]
14	Nardostachys jatamansi	Jatamansi	Immunostimulant [47]
15	Ocimum sanctum	Tulsi	Antiviral, Antifungal, Antiasthamatic, anti-inflammatory [48]
16	Piper betel	Paan	Antiviral, antiseptic [49]
17	Zingiber officinal	Adrak	Antiviral, anti-oxidant [50]
18	Claviceps purpurea	Ergot	Immunomodulates TNF [51]
20	Phellodendron amurense	Amur cork tree	Immunosuppressant [52]
21	Dioscorea japonica	Japanese mountain yam	Immunostimulant [53]
22	Boerhaavia diffusa	punarnava	Immunomodulator [54]
23	Acacia catechu	Senegalia **catechu**	cell mediated, humoral immunity [55]
24	Jatropha curcasL.	**Barbados nut**	Immunomodulato [56]
25	Achillea wilhelmsii	Achillea wilhelmsii	Immunomodulatory [57]

26	Picrorhiza Scrophulariiflora	Picrorhiza Scrophulariiflora	Immunostimulatory [58]
27	Schisandra arisanensis	**Schisandra**	Immunomodulatory [59]
28	Curcuma longa	Turmeric.	Immunostimulatory, anti-inflammatory [60]

5. CONCLUSION

The extraction of different plants and herbs are very helpful in obtaining higher protective antibody against various infections and also to produce and develop more productive cell mediate immune system. These are beneficial to protect from different bacterial, viral and other infections with no/lower toxic property. So that Herbal formulation is the best way for positive immunomodulator. These drugs are very high potential therapeutic with high efficacy, low toxicity and cost effective. Nyctanthes arbor-tristis L. and Withania somnifera have excellent immunomodulatory, antiinflammatory, antitumour, inhibition of oxidant, carcinopreventive properties with important chemicals like Withaferins, different alkaloids, steroids, amino acids. These are secure the body from cumulative damage by oxidations and diseases. In conclusion,this research paper gives the therapeutic awareness about Withania somnifera, Nyctanthes arbor-tristis L. and other medicinal plants , which are used widely across the world. Although, the conclusion from this review are utterly convenant for the utilization of these plants as an immunomodulators and benign medicinal agents and to improve immune system during COVID-19.

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