

A Review on Medicinal Plants *Withania somnifera* and *Nyctanthes arbor-tristis*: Boosting of Immune System During SARS-CoV-2

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Abstract: The worldwide epidemic of SARS-CoV-2 has created a panic situation in human beings. Covid-19 viruses spread infections into the specific human cells through cell-surface receptor ACE2 and start viral replication speedily inside the human body. The action of antibodies can reduce the entry of the virus into the cell by binding with the spike head and prevent to connect with ACE2 receptor. Many types of research are going to find the exact vaccine to control the spread of this virus. But still, now there is no vaccine and specific medicine invented still now, which is a big headache across the world. At this pandemic period, boosting of the immune system is the best way to fight against this virus. From ancient times, Ayurved is known as the best immune booster for animals and mammals. The herbal plants, such as *Nyctanthes arbor-tristis* L. And *Withania somnifera* has excellent immunomodulatory, anti-inflammatory, antitumor, inhibition of oxidants, carcinopreventive properties with important chemicals like Withaferins, different alkaloids, steroids, amino acids. This review is based on a brief discussion of the pharmacological behaviors, active ingredients, and potential therapeutic applications of these medicinal plants.

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

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1. Introduction

The super community spreader SARS-CoV-2 (acute respiratory syndrome corona-virus 2 has affected over worldwide. This coronavirus pandemic is the defining health and wealth crisis of our time and the greatest challenge we have faced since world war two. 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 people having diabetes, kidney, and heart diseases. During a viral infection, antiviral therapy is based on the attacking way of the virus into the host cell [2]. Coronaviruses spread infections into specific human cells through cell-surface receptors. The entry of the virus can be secured by targeting the viral receptor-binding site with neutralizing antibodies (nAbs). The surface of the Coronavirus is surrounded by many spike proteins. The entry of the virus is interposed by the

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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 the 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 the virus into the cell takes place by the endocytosis process [3]. The action of antibodies can reduce the entry of the virus into the cell by binding with the spike head and prevent to connect with the ACE2 receptor. The immune system of our body plays an important role in producing antibodies on the detection of antigens. To reduce spreading and fast rehabilitation, many types of research are going on. In this current study, the priority is given to emphasize the immune system of the human body to fight against this COVID-19 pandemic period. The different kinds of concepts to increase the immunity and resistance power of the 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 kapha 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 arbor-tristis* 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 increment 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 planted in any place. Harshringar, the common name of *Nyctanthes arbor-tristis* belongs from *Oleaceae* family. The name *Nyctanthes* is derived from the 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 the healthy growth of this plant. This plant needs an 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 to calm the brain. It is also known as Winter Cherry, Punir, Ghodakun, Fatarfoda, Asgund, Chirpotan, etc. This can be used for a 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 Ashwagandha, Winter cherry, *Withania* is a small woody shrub belongs to the *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* and *Withania somnifera*.

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

Botanical name	Kingdom	Eudicots Division	Order	Family	Genus	species
<i>Nyctanthes arbor-tristis</i> L.	Plantae	Angiosperm	Lamiales	Oleaceae	<i>Nyctanthes</i>	<i>N. arbortristis</i>
<i>Withania somnifera</i> (Ashwagandha)	Plantae	Angiosperm	Tubiflorae	Solanaceae	<i>Withania</i>	<i>Somnifera</i> 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-EI) has 206.81 ± 1.11 mg of total phenolic content, excellent scavenging action on DPPH (2, 2-diphenyl-picrylhydrazyl), i.e., $IC_{50} 459.91 \pm 1.40 \mu\text{g/mL}$, hydroxyl ($IC_{50} 363.32 \pm 1.58 \mu\text{g/mL}$), nitric oxide ($IC_{50} 545.03 \pm 1.69 \mu\text{g/mL}$) and superoxide ($IC_{50} 338.82 \pm 1.72 \mu\text{g/mL}$) groups, and high reducing power [7]. The seeds and the leaves are important parts of this plant contain iridoid-glycosides. The flower also has medicinal properties and the presence of essential oil like jasmine. The leaf contains mannitol, beta- amyrin, beta-sitosterol, benzoic acid, astragaline, 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 fiber, 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
<i>Nyctanthes arbor-tristis</i> 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].
<i>Withania somnifera</i>	Alkaloids- isopellertierine, anferine; steroidal compounds and steroidal-lactones (like-ergostane, withaferin A, withanolides A-y); withasomniferin A, withasomnidienone; 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].

2.1. 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].

2.2. *Flavanol-glycosides.*

Flavonoids are generally obtained from plants. Besides antioxidant behavior, flavonoids have many therapeutic activities such as antiallergic, antiviral, anticancer, anti-inflammatory, etc. The anti-inflammatory activity of flavonoids in the management of inflammatory disorders behaves as cytokine modulators. Other than these, it is a beneficial drug to cure oxidative stress, wound (scratch), inflammation, aging, cancer, arteriosclerosis, and ischemic and neurodegenerative disorders. It is proven from epidemiological studies that the regular consumption of flavonoids reduces the mortality, hyperpnea, risk of heart-related problems as well as cure coronary diseases [13].

2.3. *D(-)mannitol.*

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

2.4. *Beta-sitosterol.*

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

2.5. *Withaferin A.*

The withaferin A (WFA) is the 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].

2.6. *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, the human body can get different amino acids. Enzymes and hormones are made by utilizing amino acids that support the biochemical activities and influences the body’s metabolism. Amino acids are also used to make hemoglobin and antibodies that are helping 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 immune adjuvants, immunostimulants, and immunosuppressants. Immunoadjuvants are utilized to improve the potency of vaccines and, therefore, could be considered specific immune stimulants. It is suggested that immunomodulators can be used as selectors among cellular and humoral

immune helper T1 (Th1) T2 (Th2) cells, immunology activities, and reagent IgE vs. IgG type immune responses causing a big issue for design vaccines [18].

The non-specific nature of Immunostimulants is playing a key role by enhancing the resistance of a body against various infections. They can behave as adaptive and also inborn (natural) immune-responses. The immunostimulants are expected to serve to prevent diseases and promote immunity in a 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 with autoimmune diseases and regimens to treat different rejection of organ transplantation [20]. Many types of medicinal plants are employed to increase the 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], immunostimulant [22], hepatoprotective [23], antiviral [23], antimicrobial and antifungal [24], anti allergy [25], anti-diabetic [26], anticholinesterase [27] 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 [28]. The leaf juice of this plant is used to cure many diseases 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 a diuretic and medicinal drug. For snakebite and bronchitis treatment, the bark is very useful. The Indian tribal people utilize different parts of *Nyctanthes arbor-tristis* to get a 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 arbor-tristis* is also used as immunotoxic, antiallergic, antihistaminic, purgative, antibacterial, and ulcerogenic activities [29].

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 titer, on antibody-producing cells, on phagocytic action of peritoneal macrophages. The extraction of *W. somnifera* is noticed that it increases the circulation of antibody titer and cells that form antibodies. It is also proved that by treating animals with *Withania*, there is an outstanding growth of the bone-marrow cells [30]. Withanolides contain many activities like anti-inflammatory and analgesic because of cyclooxygenase-2 diffidence behavior. The use of this plant also increases the 'NO' (nitric oxide) synthetase activity of the macrophages. That increases the CMI (Cell-Mediated Immune) response due to the enhancement of the microbial destroying ability of the immune cells. *W. somnifera*, a glycol protein known as WSG (Glyco-withanolides) is also liable for anti-microbial activities [31]. Protein and the bodyweight 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 (a Sanskrit

text on Ayurveda), *Withania somnifera* has Immunostimulatory, anti-inflammatory, antistress, anti-rheumatic properties [32]. 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 that have high Immunomodulators activities other than *Nyctanthes arbor-tristis* L. and *Withania somnifera*.

Table 3. Medicinal plants that are used as Immunomodulators.

Sl.No.	Botanical name	Common name	Properties
1	<i>Allium Sativum</i>	Lahsuna	Antibacterial, Antiviral [33]
2	<i>Desmodium gangeticum</i>	shalaparni	Antiviral, Antiasthmatic [34]
3	<i>Terminalia bellerica</i>	Bahera	Immunostimulant [35]
4	<i>Tinospora cordifolia</i>	Guduchi	Immunostimulant, anti-rheumatic, antiallergic [36]
5	<i>Abrus precatorius</i>	Gunja	Immunostimulant [37]
6	<i>Allbizzia Lebbeck</i>	Shirisha	Immunostimulant [38]
7	<i>Andrographis paniculata</i>	kalmegh	Immunostimulant [39]
8	<i>Aristolochia Indica</i>	Isharmul	Immunostimulant [40]
9	<i>Berberis aristata</i>	Dar-hald	Immuno-suppressor, antibacterial [41]
10	<i>Catharanthas roseus</i>	Sada Bahar	Immunostimulant, Induces antibody production [42]
11	<i>Clitoria ternatea</i>	Aparajita	Immunostimulant [43]
12	<i>Cymbopogon martini</i>	Gandh	Immunostimulant [44]
13	<i>Hyoscyamus niger</i>	parsikaya	Immunostimulant [45]
14	<i>Nardostachys jatamansi</i>	Jatamansi	Immunostimulant [46]
15	<i>Ocimum sanctum</i>	Tulsi	Antiviral, Antifungal, Antiasthmatic, anti-inflammatory [47]
16	<i>Piper betel</i>	Paan	Antiviral, antiseptic [48]
17	<i>Zingiber officinal</i>	Adrak	Antiviral, anti-oxidant [49]
18	<i>Claviceps purpurea</i>	Ergot	Immunomodulates TNF [50]
20	<i>Phellodendron amurense</i>	Amur cork tree	Immunosuppressant [51]
21	<i>Dioscorea japonica</i>	Japanese mountain yam	Immunostimulant [52]
22	<i>Boerhaavia diffusa</i>	punarnava	Immunomodulator [53]
23	<i>Acacia catechu</i>	Senegalia catechu	cell-mediated, humoral immunity [54]
24	<i>Jatropha curca sL.</i>	Barbados nut	Immunomodulator [55]
25	<i>Achillea wilhelmsii</i>	Achillea wilhelmsii	Immunomodulatory [56]
26	<i>Picrorhiza Scrophulariiflora</i>	Picrorhiza Scrophulariiflora	Immunostimulatory [57]
27	<i>Schisandra arisanensis</i>	Schisandra	Immunomodulatory [58]
28	<i>Curcuma longa</i>	Turmeric	Immunostimulatory, anti-inflammatory [59]

5. Conclusions

The extraction of different plants and herbs are very helpful in obtaining a 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 a positive immunomodulator. These drugs are very high potential therapeutic with high efficacy, low toxicity, and cost-effectiveness. *Nyctanthes arbor-tristis* L. and *Withania somnifera* have excellent immunomodulatory, anti-inflammatory, antitumor, 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 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 is utterly convenient for the utilization of these plants as immunomodulators and benign medicinal agents and to improve the immune system during COVID-19.

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Conflicts of Interest

The authors declare no conflict of interest.

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