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REVIEW ARTICLE

Immunomodulatory Phytocompounds from *Withania somnifera* (L.) Dunal (Ashwagandha) Against COVID-19

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ABSTRACT

Withania somnifera is a famous medicinal plant. It is popularly known as Aswagandha. This plant has been in use in Ayurveda and Unani medicine for ages. The medicinal plant has immense medicinal properties. The plant is rich in potent medicinal phytocompounds. These phytocompounds are known to have potent antioxidant, antiviral, antibacterial and immunomodulatory efficacies. Our immune system is the key player in n fighting back any kind of pathogeni attack on us. *Withania somnifera* extract and certain isolated phytocompounds from the plant are known to boost our immune system. Studies show that the mechanisms of immunomodulatory actions of the bioactive phytocompounds from *Withania somnifera* are by affecting the various cellular signaling pathways. These primarily involve the signaling pathways associated with the receptors present on the vital immune cells like the dendritic cells, T-cells and B-cells. Thus, some of the compounds of *Withania* suppress or activate certain components of the innate and adaptive immune system. Unlike synthetic adjuvants, the natural plant derived phytocompounds and their derivatives, as those from the *Withania* sp. are free from such risk factors. A strong immune system is the best possession to fight back invasions by microbes like bacteria and viruses like the SARS-CoV-2. Detailed and compact knowledge of the compounds from *Withania* sp. and their mechanism of modulating and impacting our immune system may make the ways for development of new supportive therapies against almost all different types of diseases including COVID 19.

Keywords: Aswagandha; *Withania somnifera*; immunomodulatory; side effects; immune system

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1. Introduction

Immune system is the system that is composed of varied types of complex proteins and cells and it defends and protects our body from against foreign invasions by microorganisms primarily[1]. At the same time, the immune system's another vital role is protection of the body's own cells[1]. The innate and acquired immune systems are the two main parts of the immune system other than the physical barrier which is considered as the first line of defense[2]. Abnormalities of the immune system cause disorders like allergy, autoimmune disorders and immunodeficiency leading to susceptibilities to various infections[1]. Factors like frequent infections, exposure to treatments and some kind of medicines that effect the components of the immune system, smoking, genetics, infection by the Human Immune Deficiency Virus, iron deficiency anemia, chronic diseases like diabetes or rheumatic arthritis, organ or bone marrow transplantation, ageing etc., may adversely affect the immune system and lead to a compromised immune system[3]. A compromised immune system means a weak

immune system and the person with a weak immune system is immune-compromised as he lacks the ability of fight back any kind of attack by any foreign pathogen. Reports and studies show that people with immunodeficiency are more susceptible to SARS-CoV-2 infection and develop mild to severe symptoms of COVID-19[3]. Studies till date has revealed 300 types of primary immunodeficiency disorders. Most of these are mild and go unnoticed in an individual he reaches the adult age. Other severe forms of immunodeficiency get noticed at an early age. Primary immunodeficiency disorders have been broadly classified into six major categories based on the components of the immune system that get affected by the disorder. The components of the immune system that may get affected by primary immunodeficiency disorders are T-cell efficiency, B-cell deficiency, combination of T & B cell deficiency, defective phagocytes, complement deficiency and the sith one is idiopathic (unknown)[4]. Treatments with agents that can boost the immune system are helpful in improving the immunity and helps the individual to fight infections and have a better life[4]. Studies reveal that complications and death associated with SARS-CoV-2 infection is linked to an immunosenescence or ageing of the immune system[5]. Ageing is known to cause various physiological changes[5–7]. This result in various types of health ailments including compromised immunity. Ageing is associated with high morbidity and mortality rate with various infections[5]. Studies report that the aged population is at higher risk of developing COVID-19 associated secondary fatal infections like the acute respiratory distress syndrome and are also at higher risk of morbidity and mortality due to COVID-19[8]. Studies show that plant-based foods with immune boosting potency play a vital role to boost and enhance the immunity of people and this significantly contributes in the control and management of COVID-19[9]. Herbal remedies have been reported to be effected against other viral infections like influenza[10]. Studies report that various phytoconstituents forming the dietary constituents are capable of protecting against SARS-CoV-2 infection[11]. *Withania somnifera*, Aswagandha, the popular medicinal plant is reported to exhibit immunomodulatory activity *in vitro*[12]. The study reveals that the phytocompounds isolated from the roots of *Withania somnifera* has significant immunomodulatory impact on human neutrophils[12]. The phytocompounds from the *Withania somnifera* (WS) have also been reported to have immunomodulatory effects *in vivo* on mouse[13]. Bioactive phytocompounds like alkaloids, steroidal saponins, steroidal lactones namely withanolides, withaferins etc. have been reported to be present in *Withania* sp. and contribute to the medicinal properties of the plant[2]. Studies report that *Withania somnifera* (WS) significantly modulates several cytokines, enhances T-cell proliferation and promotes functions of macrophages[15]. Study conducted on healthy human subjects reports that the extract of WS significantly improved the immune profile of the individuals by impacting and modulating the innate and adaptive immune systems[2]. Thus WS is recognized as a rich source of potent bioactive phytocompounds with immunomodulating potential. This systematic review summarizes the various immunomodulatory phytocompounds reported from *Withania somnifera* and discusses the prospective of their use against the SARS-CoV-2 infection mediated COVID-19.

2. The traditional medicinal plant Aswagandha, *Withania somnifera*

The plant *Withania somnifera* popularly known as Aswagandha, is in use for treating various health conditions in Ayurveda widely. In WHO monographs on Selected Medicinal Plants, *Withania* appears[16]. The plant is also popularly known as known as “Indian Ginseng” and is also called as “Indian Winter cherry”[17]. Withania is a very important plant in Ayurveda and has extensive uses. In Indian Ayurvedic system of medicine the plant is used as a Rasayan i.e., a tonic[17]. Rasayana is a Sanskrit word which actually is any herbal preparation that promotes youthful state of physical and mental health and is known to expand happiness. In terms of Ayurveda, Rasa provides nourishment to our body, boosts our immunity and helps to keep the body and mind in best of health[18]. *Withania* is known to have life prolonging, sedative and rejuvenating effects[19]. The plant is reported to have extensive use in improving memory and learning in geriatrics. It is also used as a tonic for enhancing general energy and is known as Medharasayana in Ayurvedacharya[19,20]. Aswagandha is known as Indian ginseng. The plant is reported to have traditional use to improve vigor, youthfulness and

for increasing the vital fluids, blood, lymph, fat, muscle, semen and cells. Thus, the plant has a restorative and reparative potential[21,22]. The plant is also helpul in treating anxiety disorder and hypothyroidism and many other health ailments[21]. The plant is also known to treat health conditions like diabetes, hypertension, infections, arthiritis, infertility, depression etc.[17]. Aswagandha is also reported to treat fatigue, weakness, dehydration, premature ageing, muscle tension, debility etc.,[17,21]. Immunomodulatoy activity of Ayurvedic formulation of "Aswagandha curna" is also reported[23]. Thus, Aswagandha has always been a popular and effective medicinal plant and has been in extensive use in traditional medicine.

3. Immunomodulation and Aswagandha

Studies reveal that the plant Aswagandha has pronounced immunomodulatory activities[23]. The immune system consists of various components like the cytokines, cells and antibodies[2]. Immunomodulators are the agents that either stimulate the immune system and are termed as immunostimulants or certain agents that suppresses the immune system and are termed as immunosupressors[24]. The components in WS are reported to work by mobilizing and activating macrophages. WS extract is also known to have immunomodulatory effects by inducing proliferation in the splenocytes of rats[25]. Till date there has not been much detailed study on the immunomodulatory effects of WS at the cellular levels in human. Yet, the studies that have been reported suggest that the immunoregulatory cellular response by WS may open up new avenues in immunotherapy. The immunoregulatory cells induced or stimulated by WS are expected to have various mechanisms of action. These include regulating antigen regulation, controlling immunosuppressive microenvironment and altering the physiological cytokine environment and making it more apt for effector T cell functions[26]. Studies conducted on human subjects shows that WS significantly improved the immune profile of the human subjects. Significant modulatory effects were observed on both innate and adaptive immune systems of the human subjects. Subjects treated with WS extract i.e., the WS test group reported significant enhancement ($p < 0.05$) in Ig's (IgA, IgM, IgG, IgG2, IgG3 and IgG4), Cytokines (IFN-γ, IL4), TBNK (CD45+, CD3+, CD4+, CD8+, CD19+, NK cells)[2]. WS is known to impose therapeutic effects on various disease conditions by virtue of its immunomodulatory potential. It is known to work by modulating immunological markers. WS is reported to have significant role in combating type 2 allergic disease by mitigating type 2 inflammation through its immunomodulatory effects[15]. Excessive type 2 inflammation are recognized to be the driving factor for several allergic reactions like eczema, dermatitis, asthma etc.

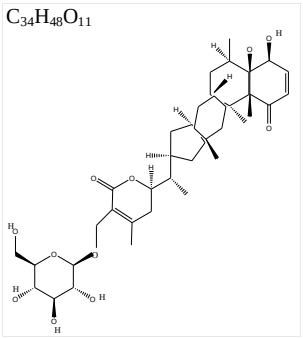
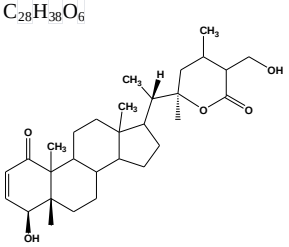
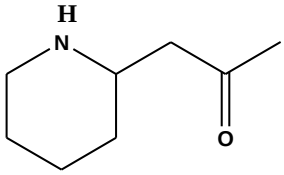
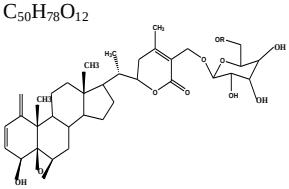
Study shows that WS has the potential to reduce the levels of type 2 cytokines (e.g., IL-4, IL-13) and also the levels of type 2 inflammation markers such as TNF-α and IgE and thus imposes its immunomodulatory effects[27]. Aqueous root extract of Withania is reported to ameliorate LPS-induced inflammatory changes in *in vitro* cell-based and mice models of inflammation[28].

4. Phytocompunds with immunomodulatory potentials from Aswagandha (*Withania somnifera*)

The primary active constituents of *Withnia* have been reported to be steroidal alkaloids and lactones[29]. A glycoprotein named Glycowithanolides (WSG) is recognized to be responsible for the antimicrobial potential of Aswagandha. This glycoprotein is commonly known as *Withania somnifera* glycoprotein[30]. Other active ingredients reported from *Withania somnifera* are alkaloids namely isopelletierine, anaferine; steroidal lactones which includes withanolides, withaferins etc. Steroidal saponins are also known to be present in Aswagandha[31] (**Figure 1** and **Table 1**). Several such phytocompounds from *Withania* have been reported to possess immunomodulatory potential (**Table 1**). Aswagandha has been use in combating various types of health ailments since ages and this mutipotential medicinal property of the plant may be due the immunomodulatory potential of its phytoconstituents. Compounds from the different parts of the entire plant has been explored for their medicinal properties and yet all exact mechanisms have not yet been clear and

hence more research and experimental validation of the medicinal actions of the phytocompounds from *Withania somnifera* is necessary.

Table 1. Phytocompounds from *Withania somnifera* with immunomodulatory activities.

Sl.no.	Name of the compound &PubChem ID	IUPAC name	Structure & Chemical formula	Compound Type	Mechanism of immunomodulatory activities	References
1.	Sitoindoside IX PubChem CID:189586	(1S,2R,6S,7R,9R,11S,12S,15R,16S)-6-hydroxy-2,16-dimethyl-15-[(1S)-1-[(2R)-4-methyl-6-oxo-5-[[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]-2,3-dihydropyran-2-yl]ethyl]-8-oxapentacyclo[9.7.0.02,7.07,9.012,16]octadec-4-en-3-one	$C_{34}H_{48}O_{11}$ 	It is a withanolide saponin that consists of withaferin A attached to a beta-D-glucopyranosyl residue at position 27 by a glycosidic linkage.	In combination with glycowithanolides and sitoindosedes X, it is reported to have immunopotential in experimental rats by having positive effect on the mobilization and activation of peritoneal macrophages.	[32,33]
2.	Withaferin A PubChem CID: 265237	(1*S*,2*R*,6*S*,7*R*,9*R*,11*S*,12*S*,15*R*,16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-2,3-dihydropyran-2-yl]ethyl]-2,16-dimethyl-8-oxapentacyclo[9.7.0.0^{2,7}.0^{7,9}.0^{12,16}]octadec-4-en-3-one	$C_{28}H_{38}O_6$ 	It is a withanolide that is 5,6:22,26-diepoxyergosta-2,24-diene-1,26-dione substituted by hydroxy groups at positions 4 and 27 (the 4beta,5beta,6beta,22R stereoisomer)	Inhibition of TNF-alpha stimulated NF-KappaB in human HEK293 cells transfected with NF-kappaB-Luc incubated for 5 hrs by luciferase reporter gene assay	[34,35]
3.	Isopelletierine PubChem CID:92987	1-piperidin-2-ylpropan-2-one	$C_8H_{15}NO$ 	It is a citraconoyl group. An alkaloid.	Has immunomodulatory potential. Acts via activation of peritoneal macrophages involved in, phagocytosis	[36–39]
4.	Sitoindoside X	[3,4,5-trihydroxy-6-[[2-[1-(6-hydroxy-2,16-dimethyl-3-oxo-8-oxapentacyclo[9.7.0.0^{2,7}.0^{7,9}.0^{12,16}]octadec-4-en-15-yl)ethyl]-4-methyl-6-oxo-2,3-dihydropyran-5-yl]methoxy]oxan-2-yl]methyl hexadecanoate	$C_{50}H_{78}O_{12}$  R=Palmitoyl	It is a withanolide saponin that consists of withaferin A attached to O-(6-O-palmitoyl)-β-D-glucopyranoside glycosidic linkage	It is reported to have immunopotential in experimental rats by having positive effect on the mobilization and activation of peritoneal macrophages when used in combination with glycowithanolides and sitoindosedes IX.	[40–43]

The root of the plant *Withania* is known to contain alkaloids like anaferine, isopelletierine, cuseohygrine, anahygrine, steroidal lactones, withanolides, withaferins and saponins[38] (**Figure 1**). The ariel parts of the plant is known to contain 5-dehydroxy withanolide-R and withasomniferin-A[17,44].

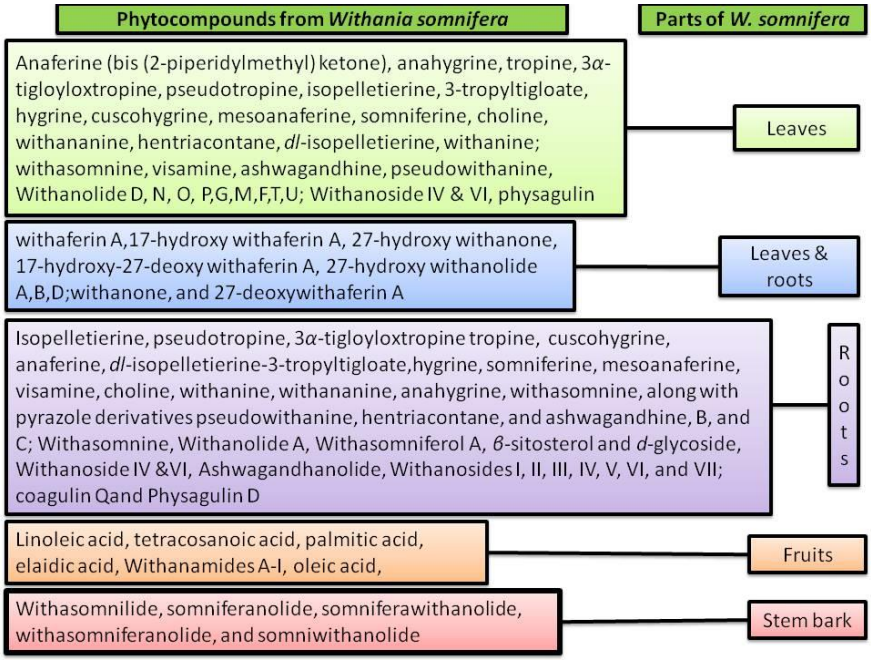


Figure 1. Medicinal phytocompounds from the different parts of *Withania somnifera*.

The two isolated compounds sitoindoside IX (1) and sitoindoside X (2), show potential immunomodulatory activity through the activation of peritoneal macrophages involved in, phagocytosis[39]. The main constituents of the root are withanolide ($C_{28}H_{38}O_6$) and withaferin A ($C_{28}H_{38}O_6$) and these are steroidal constituents which possess immune-stimulatory activity through enhancing the phagocytic activity of peritoneal macrophages[39] (**Figure 1**).

All these phytocompounds isolated from different parts of the plant possess different types of medicinal potency. Among these some are recognized to have immunomodulatory potential. Some of these immunoboosting phytocompounds from *Withania somnifera* have been evaluated against SARS-CoV-2 and many have been found to be effective against the deadly virus[45–59].

5. Mechanism of Immunomodulation by phytocompounds from Aswagandha & COVID-19

It is reported that Withanolides, the alkaloid steroid lactone from *Withania* occupies the receptors in the cell membranes. Thus, they prevent the attachment of the actual hormone to the receptors and prevent the execution of the impacts of the actual hormone. Withanolides are also known to have anti-inflammatory and analgesic activity. Withanolides inhibits cyclooxygenase-2 and impart its anti-inflammatory effects[60]. Aswagandha modulated the cell mediated immune system by the simple mechanism of enhancing the microbes killing properties of the macrophages. Aswagandha increases nitric oxide synthatase activity of the immune cells, macrophages and this increases the microbe killing ability of the macrophages and this in turn boosts the cell mediated immune system[61]. The plant Aswagandha is reported to increase tolerance, strength and dependence and is termed as adaptogen[62]. Administration of WS extract with milk is known to increase the total protein content in the body which leads to healthy gain of body weight[23]. Studies show that treatment with WS extract can counteract Cyclophosphamide-induced immunosuppression. Significant enhancement in hemagglutinating antibody responses and hemolytic antibody responses towards sheep red blood cells is also reported in the same study using WS extract[13,63]. WS is reported to exhibit potent immunomodulatory activity

and is also reported to show effective protection against loss in body weight, viral load and pulmonary pathology. *In vitro* pre-treatment of human and mice neutrophils with WS extract exhibited no adverse effects.WS is expected to impose potential protective effect against the SARS-Cov-2 by virtue of its broad immunomodulatory effects[64].

Studies show that the key immunomodulatory component of *Withania* is the lipopolysachharide of plant associated bacteria. Surprisingly, though this lipopolysachharide is known to have tremendous inflammatory effects, in case of the LPS present in *Withania* this toxicity is not observed. In spite of the presence of the LPS, *Withania* is found not to trigger the inflammatory changes in macrophages. Withaferin A is known as the potent immune-stimulant present in *Withania somnifera*[65]. *Withania somnifera* is known to enhance the nitric oxide synthetase activity of macrophages and thus increasing their immune potential[66].

6. Immunomodulatory compounds from *Withania somnifera* against COVID-19

Certain compounds isolated from Withania have been found to have potent immunomodulatory activity and they have been evaluated to act as protective agents against COVID-19. Certain Withonalides have been investigated and have been reported to be effective as immuneboosters and antiviral agents against the SARS-CoV-2, the virus which causes COVID-19. The *in silico* study reveals that from among several withanolides from *Withnia somnifera* some withanolides namely Withanolide_D, Withanolide_G,

Withanolide_M, and Withanolide_Q (**Table 2**) as the lead hits depending on their drug-likeness score, modulated proteins, and docking score to boost the immune system and also to inhibit the COVID-19 infection[67]. The Withanolides have been found to have high affinity for binding with PLpro, 3CLpro, and spike protein of the SARS-CoV-2 which further establishes the antiviral potency of the compounds[67].

Table 2. WIthanolides from *Withania somnifera* with reported anti-COVID-19 activity.

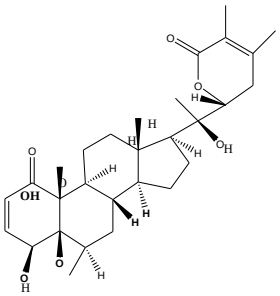
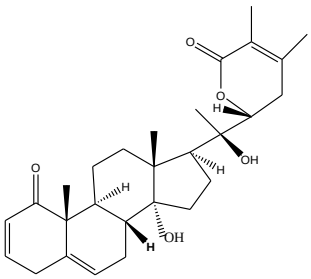
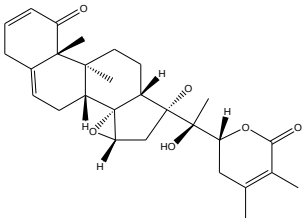
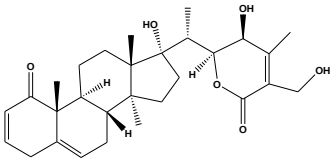
Sl.no.	Name of the compound	Molecular formula	IUPAC name	PubChem ID	Structure	Occurs in the part of *Withania somnifera*	References
1.	Withanolide_D	$C_{28}H_{38}O_6$	(1*S*,2*R*,6*S*,7*R*,9*R*,11*S*,12*S*,15*S*,16*S*)-15-[(1*R*)-1-[(2*R*)-4,5-dimethyl-6-oxo-2,3-dihydropyran-2-yl]-1-hydroxyethyl]-6-hydroxy-2,16-dimethyl-8-oxapentacyclo[9.7.0.0^{2,7}.0^{7,9}.0^{12,16}]octadec-4-en-3-one	161671		Shoots and roots	[68]
2.	Withanolide_G	$C_{28}H_{38}O_5$	(2*R*)-2-[(1*R*)-1-hydroxy-1-[(8*R*,9*S*,10*R*,13*R*,14*R*,17*S*)-14-hydroxy-10,13-dimethyl-1-oxo-7,8,9,11,12,15,16,17-octahydro-4*H*-cyclopenta[a]phenanthren-17-yl]ethyl]-4,5-dimethyl-2,3-dihydropyran-6-one	21679023		Shoots	[69,70]

Table 2. (*Continued*).

Sl.no.	Name of the compound	Molecular formula	IUPAC name	PubChem ID	Structure	Occurs in the part of *Withania somnifera*	References
3.	Withanolide_M	$C_{28}H_{36}O_6$	(1R,2R,4S,6R,7R,10S,11R)-6-[(1S)-1-[(2R)-4,5-dimethyl-6-oxo-2,3-dihydropyran-2-yl]-1-hydroxyethyl]-6-hydroxy-7,11-dimethyl-3-oxapentacyclo[8.8.0.02,4.02,7.011,16]octadeca-13,16-dien-12-one	25090669		Leaves	[70,71]
4.	Withanolide_Q	$C_{28}H_{38}O_6$	(2S,3S)-3-hydroxy-2-[(1R)-1-[(8S,9S,10R,13S,14S,17S)-17-hydroxy-10,13-dimethyl-1-oxo-7,8,9,11,12,14,15,16-octahydro-4H-cyclopenta[a]phenanthren-17-yl]ethyl]-5-(hydroxymethyl)-4-methyl-2,3-dihydropyran-6-one	101281365		Leaves	[72,73]

Besides, Withanolides, certain other compounds like the Withanones from *Withania somnifera* have been found to be immuneboosting and effective in combating COVID-19[74]. Studies conducted on humanoid zebra fish model reports that Withanone from *Withania somnifera* has the potential to mitigate SARS-CoV-2 RBD and Host ACE2 interactions to rescue spike protein induced pathologies in the organism[74].

7. Generalized chemical composition, structure, biological activities, and health-promoting effects of *Withania somnifera*

Some of the potent and primary immunomodulatory phytochemnicals from Withania somnifera, their structures and mode of immuneomodulations have been described in **Table 1**. The plant is rich in biologically active phytocompounds and those primarily belong to the categories of steroidal lactones and alkaloids[29]. Such phytocompounds isolated from the plant's leaves, roots and fruits have been reported to have antioxidant and antibacterial activities[75]. Studies also reveal that the plant extract has antitumor, antibacterial, aphrodisiac, antiviral, and cardiovascular protection activities[76]. Studies show that *W. somnifera* is rich in several pharmacologically active steroidal lactones namely withanolides[22]. Other than alkaloids, the plant has also been reported to be arich source of other pharmacologically active compounds that include flavonoids,steroids, saponins, phenolics, phytophenols, glycosides etc.,[77,78]. Other phytochemicals reported from *Withania* are somniferinine, 14-α-hydroxywithanone, somniferiene, tropanol, 6,7β-Epoxywithanon etc.,[79–83]. The plant extract is known to have antipyretic, analgesic, adaptogenic, and anti-inflammatory uses in traditional medicine and folk medicine since ages[22]. The plant is also reported to have potent neuroprotective potential by the virtue of certain phytocompounds[44,84–86].The plant has anxiolytic, anti-depressantactivities by the virtue of phytoocmpuns like glycowithanolides[84]. Sitoindosides VII and VIII from Withania are reported to impart anti-stress activities[85]. The plant is also known to have over all health promoting potential[86]. The alkaloid, steroidal lactones and Acylsterylglucoside compounds from Withania are known to protect against neurodegenerative diseases like Huntington's disease, Parkinsonism, Alzheimer's diseases. GABA mimetic action of the phytocompounds are reported to promotes dendrites formation and this is the basic underlying mechanism of neuroprotective activity of the extract of *Withania somnifera*[87,88].

8. Antiviral and antibacterial effects of *Withania somnifera*

Withania somnifera is known to have potent antimicrobial activities[89]. Studies conducted *in vivo* in Guinea pigs report that extract of leaves and roots of *Withania somnifera* has antibacterial activity against *E.coli*[90]. The plant extract has been reported to inhibit the growth of bacteria in a dose dependent manner[91]. Studies also reveal that the plant extract has antibacterial activities against Gram negative bacteria like *Salmonella typhi* and *E. coli*[92,93]. Methanolic extract of *Withania somnifera* has been reported to exhibit potent antibacterial activity against Gram-positive bacteria clinically isolated from pus. These bacteria were found to be more resistant against antibiotics like co-trimoxazole, ampicillin, and erythromycin[94]. Thus the challenge of combating bacterial infections due to increasing antibacterial resistance now days is being addressed to some extent with the promising antibacterial potentials of the extracts of *Withania somnifera*. The plant extract is reported to have immune boosting nd antiviral potentials[95]. Withanone from *Withania somnifera* has been reported to have potent antiviral potentials[96]. With potent antiviral and immune boosting potential, *Withania somnifera* has been recommended for possible therapeutics and clinical management of SARS-CoV-2 infection[97].

Withania somnifera extract is known have impacts on the various components of the innate and adaptive immune system (**Table 3**).

Table 3. Effects of *Withania somnifera* (WS) on the innate and adaptive immune system.

Serial number	Effects of *Withania somnifera* (WS) on the immune system		References
	Effects on Innate Immune system	**Effects on Adaptive Immune system**	
1.	WS root and leaves extract can increase general immunoglobulins	WS root and leaves extract can increase IFN-gamma and T-cells CD3+ and CD4+	[98,99]
2.	Whole plant extracts of WS increases immune cell such as macrophges activities	WS extract increases the expression levels of T-helper 1 (Th1) cytokines	[98,100]
3.	WS extract enhances the production of white blood cells	WS extract enhances natural killer (NK) cell activity in a dose-dependent manner with the prompt recovery of CD4+ T cells in immune-suppressed animals	[101,102]
4.	WS extract augments the phagocytic activity of macrophages	WS is reported to stimulate the expression of interferon-gamma and B cells while enhancing the expression of T cells CD3+, CD4+, and CD8+, along with co-stimulatory CD80 and integrins	[101,102]

9. Conclusion

Withania somnifera is a rich source of potent phytocompounds with pronounced medicinal properties. The plant is known to have several medicinal properties. One most significant such medicinal property of *Withania somnifera* is its ability to boost the immune system when consumed in right dose. Certain compounds present in the aerial parts, root and stem of the plant have immune-stimulatory potential have potent ability to alter the components of the immune system. Studies report wide and successful clinical applications of herbal extracts, including that of *Withania somnifera* as immuno stimulating agents[103]. (1 → 3)-, (1 → 4)-α glucan from an edible mushroom Polyporus grammocephalus has been reported to have potent immunomodulatory effect[103]. A clinical study conducted as a randomized, double-blind, placebo-controlled trial on healthy participants, revealed immunostimulatory impats of *Withania* extact[104]. The study reveals that Ashwagandha extract has the potential to significantly increase the cytokine levels an natural killer cell activity in comparison to that of placebo[2,14]. Studies show that *Tinospora cordifolia* extract has potent Immunomodulatory effect in human immuno-deficiency virus positive patients[105]. The plant extract is reported to significantly effect the symptoms of HIV in the patints[105]. Studies recommend use of the Aswagandha in enhancing the immune ability of an individual. The plant has been used and recommended strongly to boost the immune system of an

individual and to strengthen the fight against the SARS-CoV-2. Thus, *Withania* gained a lot of popularity as a safe herbal remedy for preventing COVID-19. Studies report that some of the compounds from *Withania* possess more than one medicinal potency like immunomodulatory activity, antiviral activity, antioxidant activity and by virtue of this they act to combat COVID-19. Though, enough experimental and clinical validation is necessary for adaptation of these highly potent immunomodulatory phytocompounds from *Withania somnifera* to fight against SARS-CoV-2.

Author contributions

Conceptualization, DG and PSS; methodology, PSS and RG; software, DG; validation, DG, PSS and RG; formal analysis, DG and RG; investigation, DG and PSS; resources, PSS; data curation, DG; writing—original draft preparation, DG; writing—review and editing, PSS and RG; visualization, DG and PSS; supervision, DG; All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

WHO	World Health Organisation
WS	*Withania somnifera*
COVID-19	Coronavirus Disease 19.
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IgG2	Immunoglobulin G2
IgG3	Immunoglobulin G3
IgG4	Immunoglobulin G4
IFN-γ-	Interferon-gamma
IL4	Interleukin 4
TBNK	T and B Natural Killer Cells
NK cells	Natural Killer Cells
IL-13	Interleukin 13
TNF-α	Tumor necrosis factor alpha
ACE2	Angiotensin-converting enzyme 2
RBD	Receptor-binding domain

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