



Review Article

PHYTOCHEMICAL ANALYSIS OF ASHWAGANDHA (*WITHANIA SOMNIFERA*) AND ITS ROLE ON COVID-19 –A QUALITATIVE REVIEW

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ABSTRACT

COVID-19 being a mild to severe respiratory and an infectious disease is caused by a new viral strain named coronavirus 2 (SARS-CoV-2). Though managed with antivirals such as lopinavir, ritonavir and nelfinavir, as well as the antimalarials chloroquine and hydroxychloroquine etc, none of them have provided the promising solution. Amidst these conventional approaches, bioactive natural compounds are being considered due to its good biocompatibility, bioavailability, less toxicity and rich phyto-constituents like phenols, steroids and flavonoid molecules etc. Ayurvedic system of medicine is the ancient medicine that is being practiced since 5000yrs ago and *Ashwagandha* or *Withania somnifera* is being used as a *Rasayana* in traditional medicine systems like Ayurveda, Unani, and Siddha. This has been known for its therapeutic benefits since long period including anticancer properties, neuro-protective, cardio-protective, hepato-protective, anti-inflammatory, anti-diabetic, antimicrobial, anti-arthritis, antistress/adaptogenic, chemo-/radiation sensitizing and immuno-modulatory properties etc. Currently *Ashwagandha* has been extensively studied using molecular docking approaches on Covid-19 due to its immuno-modulatory properties and *Withania somnifera* could be developed as a therapeutic agent against Covid-19 for both management and prevention.

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INTRODUCTION

Derived from the Latin terminology, corona means that has "crown" like shape^[1] with the suffix 2019 novel coronavirus or "2019-nCoV" coronavirus declared by WHO as on 12 January 2020. This novel strain (Coronavirus disease (COVID-19) emerged during an outbreak in Wuhan, China with its first appearance at the end of December 2019. An infectious and a transmissible disease accompanied by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a severe threat to human health.^[2]

On 11 February 2020, this disease was named as Coronavirus Disease-19 (COVID-19) after declaring the outbreak as a Public Health Emergency of international concern as on 30 January 2020 by World Health Organization (WHO) and consequently declared COVID-19 as a global pandemic on 11 March 2020.^[3] WHO reported worldwide 5,593,631

confirmed cases and 353,334 deaths due to SARS-CoV-2 until 28 May 2020.^[4]

SARS-CoV-2 transmission is through direct contact or by contact with the infected surface with touching of the face of humans. It also spreads through respiratory droplets released by coughs or sneezes^[5] and mainly is from human to human. Presentation of coronavirus (SARS-CoV-2) include respiratory symptoms with cough, fever, shortness of breath, and more severe of this infection can lead to pneumonia, severe acute respiratory syndrome, and even death.^[6]

Ever since declaring COVID-19 a global pandemic, it has overwhelmed many healthcare systems and ravaged many countries worldwide. Emergence of new SARS-CoV-2 variants threatens to overturn the significant progress made so far in limiting the spread of this viral illness, despite the

unprecedented speed of vaccine development against the prevention of COVID-19 and robust global mass vaccination efforts.^[7] Currently, a variety of therapeutic preferences are available that include anti-SARS-CoV-2 monoclonal antibodies (e.g., bamlanivimab/etesevimab, casirivimab/imdevimab), antiviral drugs (e.g., remdesivir), anti-inflammatory drugs (e.g., dexamethasone), immunomodulators agents (e.g., baricitinib, tocilizumab) etc are available under FDA issued Emergency Use Authorization (EUA) and is being evaluated in the management of COVID-19.^[8]

The 3-chymotrypsin-like protease (3CL^{pro}) also known as the main protease (M^{pro}) is a key protein required for the proteolytic maturation of the virus.^[9,10] Targeting the main protease may provide an effective treatment against SARS-CoV-2 by inhibition of the viral polypeptide cleavage.^[11] Since this protein is absent in humans, it forms an excellent target for drug discovery. Moreover, there is presently no specific medicine or vaccine available for the treatment of COVID-19 infection caused by SARS-CoV-2.^[4] Bioactive natural compounds are the compounds that have diverse bioavailability, with relatively less non-toxic property. These bioactive natural compounds consists of various phytoconstituents like phenols, steroids, flavonoid molecules etc that have been screened and reported for their possible therapeutic effects against various viral diseases including COVID-19.^[12-15]

Implementation of Complementary Alternative Medicines is showing a remarkable increase in support. The poor compliance^[16] and the long-term side effects of conventional medicines are leading to large CAM users.^[17] The innumerable benefits of the herbal medicines which are naturally available include anti-inflammatory, those works on the hormones and metabolism, and also boost up the immune system. Indian medicinal plants have wide variety of natural compounds and have been widely used for various diseases, to develop drugs and also to provide strength to our immune system. In the present pandemic situation, there is an urgent need to investigate bioactive compounds which have the potency to combat this viral infection and provide immunity and strength to our body to combat SARS-CoV-2.

Ministry of AYUSH in India is conducting different trials of herbal medicines which have been used safely for other ailments, for prophylaxis or treatment of COVID-19, and of all the COVID-19 related clinical trials registered in the Clinical Trial Registry of India (CTRI), about 60% are related to the AYUSH interventions.^[18] *Ashwagandha* (*Withania somnifera*) is one among them and one of the most

valued Indian Ayurvedic medicinal plants that are revered as a biologically active immune-modulator and its ability to energise, rejuvenate balance and revitalise.^[19] *Ashwagandha* comprises a rich source of various phytoconstituents such as, *Withaferin A*, steroidal lactones of the withanolide series, steroidal alkaloids of the withanoside series and some other compounds.^[20-23]

In the current study, the effort was made to explore the medicinal potential of *Withania somnifera* that is described in detail in Ayurvedic science as *Ashwagandha* and to evaluate its effects on Covid-19 by the studies published on the same.

***Ashwagandha* in Ayurveda**

Brahman Grantha

The first description of *Ashwagandha* was found by the name *Asmagandha* (assumed to be *Ashwagandha*) in the *Brahman Grantha*. In *Shatpath Brahman* and *Kaushik sutra* it is advised not to keep the drug "*Asmagandha*" in *Shamshaan Bhumi*. "*Asmagandha*" literally means "bearing smell of rock"

Aranyakas

In *Aranyakas*, the use of juice of the *Ashwagandha* root is mentioned and said to be having *Garbhalambhan* property. Here the juice of root is used as a nasal drop. *Ashwagandha*, derived from the Sanskrit *Ashva* meaning "horse" and *Gandha* meaning "smell", describes the strong aroma of the root which is considered to be reminiscent of a horse's skin, sweat, or urine, depending upon to which authority one refers. The species name *somnifera* refers to the Latin *Somnus* meaning "to sleep", apparently alluding to the use of *Ashwagandha* as a nervine and sedative.

Scientific classification

Kingdom: Plantae, Sub kingdom: Tracheobionta, Super division: Spermatophyta, Division: Magnoliophyta, Class: Mangnoliopsida, Sub-class: Asteridae, Order: Solanales, Family: Solanaceae, Genus: *Withania*, Species: *somnifera* Latin Name: *Withania somnifera* (L.) Dunal.

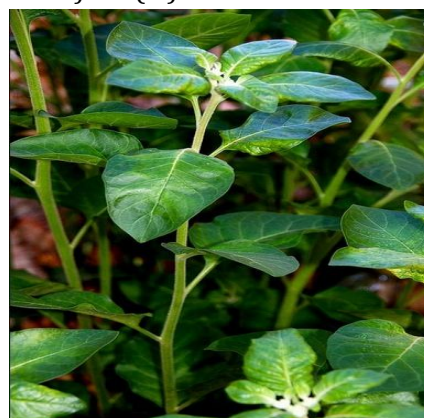


Figure 1: Showing *Ashwagandha* plant



Figure 2: Bunch of Unripe fruits of Ashwagandha



Figure 3: Showing flower of Ashwagandha



Figure 4: Showing fruits of Ashwagandha



Figure 5: Showing root of Ashwagandha

Description of the root

The root system consists of a stout main root 20 to 30cm. long with a few (2 to 3) lateral roots of slightly smaller size. The roots are somewhat

tuberous and attain a diameter of 1 or 2 or 2.5cm. They are occasionally branched. Their distal ends are tapering and slightly woody. The outer surface of the tuberous root is yellowish brown in colour and almost smooth except for a few very shallow short longitudinal fissures. The cut end of a root shows an outer narrow brown ring enclosing a soft white starchy tissue. At the center is the wide cylinder of wood which is not very hard except for the peripheral part and has a light cream colour.

The drug as sold in market is in the form of simple dry slightly woody cut pieces of root 3 to 6cm in length. The diameter of the pieces varies from 4 to 10mm. The cut pieces are of light brown or slightly yellow brown colour. The surface of thin root is almost smooth but it appears shrunken with closely arranged very shallow irregular longitudinal ridges. Cut end of the rootlets are almost noticeable in the pieces, the cut end of these pieces are white in colour.

Chemical constituents

Laboratory analysis has revealed over 35 chemical constituents contained in the roots of *Withania somnifera* - (L.) Dunal. [24] The biologically active chemical constituents are alkaloids (isopelletierine, anferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanoloides with a glucose at carbon 27 (sitonidoside XI and X). *Withania somnifera* - (L.) Dunal. is also rich in iron. The roots of *Withania somnifera*-(L.) Dunal. consist primarily of compounds known as withanolides, which are believed to account for its extraordinary medicinal properties. Withanolides are steroidal and bear a resemblance, both in their action and appearance, to the active constituents of Asian ginseng (*Panax ginseng*) known as ginsenosides. *Ashwagandha*'s withanolides have been researched in a variety of animal studies examining their effect on numerous conditions, including immune function and even cancer. [25]

Chemical analysis of *Ashwagandha* shows its main constituents to be alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent. The other alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropine, choline, cuscohygrine, isopelletierine, anaferine and anahydrine. Two acyl steryl glucoside viz. sitoindoside VII and sitoindoside VIII have been isolated from root. The leaves contain steroidal lactones, which are commonly called withanolides. The withanolides have C28 steroidal nucleus with C9 side chain, with a six membered lactone ring. [26] Twelve alkaloids, 35 withanolides, and several sitoindosides from *Withania somnifera* -

(L.) Dunal have been isolated and studied. *Ashwagandha* pharmacological activity has been attributed to two main withanolides, withaferin A and withanolide D. Further chemical analysis has shown the presence of the following:

Anaferine (alkaloid), Anahygrine (alkaloid), Beta-Sisterol, Chlorogenic acid (leaf), Cysteine (fruit), Cuscohygrine (alkaloid), Iron, Pseudotropine (Alkaloid), Scopoletin, Somniferinine (alkaloid), Somniferiene (Alkaloid), Tropanol (alkaloid), Withanine (alkaloid), Withananine (alkaloid) and Withanolides A-Y (Steroidal lactones). [27-29]

Phytochemical Studies Properties

The presence of various chemical constituents in the different parts of the plant which are as follows:

Root

The roots are reported to contain alkaloids, amino acids, steroids, volatile oil, starch, reducing sugars, glycosides, hentriacontane, dulcitol, withaniol. The total alkaloidal content of the Indian roots has been reported to vary between 0.13 and 0.31 percent, though much higher yields (up to 4.3%) have been recorded elsewhere. [29]

Table 3: Showing the Rasa panchaka of *Ashwagandha* according to different authors

<i>Ashwagandha</i>						
Character	D.N	B.P	M.N	R.N	K.N	P.N
<i>Rasa</i>						
<i>Katu</i>				+		
<i>Tikta</i>	+	+	+	+	+	+
<i>Kashaya</i>	+	+	+		+	
<i>Virya</i>						
<i>Ushna</i>	+	+	+	+	+	+
<i>Vipaka</i>						
<i>Katu</i>				+	+	

Pradhana Yoga of *Ashwagandha* in Brihat Trayi

Charak Samhita

Vajikaran ghrita, Agurvadi taila, Gandha hasti agad, Mahagandha hasti agad, Amrit Ghrita, Kusthadi taila, Rasna tail, Vrishamuladi taila, Mulak taila, Jivakadi Mahasneha.

Sushruta Samhita

Bala taila, Chitrakadi taila, Bhutikadi taila, Dhavadi agad, Ashwagandhadi churna.

Ashtanga Hridaya

Bala taila, Nagar ghrita, Vashisht haritaki rasayan, Dadhik ghrita, Sinhyadi Ghrit, Shringyadi ghrita, Lakshadi taila, Sariwadi ghrita Siddhartthkadi Gutika.

Prayoga of *Ashwagandha* in Other Samhitas

Chakradutta

Chakradutta mentioned the *Vata* alleviating and *Vrishya* properties of *Ashwagandha* and said that its use increases the bulk of muscles. In *Rasayana prakarana* he emphasized on the rejuvenating property of *Ashwagandha*, and advocated its use in patients of weak and poor neurological sequences. Along with that Chakradutta also mentioned its use in *Udara roga* (in *Udara Roga Chikitsa Adhyaya*) and *Vandhyatva* (in *Yonivyapat Chikitsa Adhyaya*).

Vrinda Madhav

Acharya Vrinda also threw light on the *Brmhan karma* of *Ashwagandha* and said that it increases the vigor and strength of body.

Vangasena

Vangasena highlighted somniferous effects of *Ashwagandha*

Rajamartand

One *Pala* of root powder with honey, taken in *Shishir ritu* for one month turns the aged subjects into young ones.

Bhavaprakash

Bhavaprakash mentioned its use in *Hridayagata vata*.

Action and Use [30]

The roots are astringent, bitter, acrid, alexipharmic, somniferous, thermogenic, stimulant, aphrodisiac, diuretic, deobstruent and tonic. They are useful in leucoderma, constipation, insomnia, lumbar pain, nervous disorders, asthma, cardiac disorders, psoriasis, consumption, ulcers, carbuncles, scabies, marasmus of children, senile debility. Leaves are bitter and recommended in fever, painful swellings, inflammation of eye, syphilitic sores, haemorrhoids,

tumours, tuberculous glands. Seeds are reported to be diuretic, hypnotic and are employed to coagulate milk.

Formulation and Preparations

Ashwagandhadhi churna, Ashwagandha rasayana, Ashwagandha ghrta, Ashwagandharishta, Ashwagandha taila, Madhyamanarayana taila, Brihat ashwagandha ghrta, Brihachchhagaladya ghrta, Saraswata churna Bala arista [31] *krsnadi Ashwagandha leha, Aswagandaha ghrta, Aswagandaha curna, Ashwagandhadhi leha,* [32] *Ashwagandhadhi ghrta, Ashwagandharista,* [33] *Ashwagandha ksirapaka, Ashwagandha curna, Ashwagandha rasayana, Sukumara ghrta.* [33,34]

Pharmacological Activity

Hypotensive, bradycardiac and respiratory stimulant, antibacterial, hypothermic, immunosuppressive, immunostimulatory, immunomodulatory, adaptogenic, antitumour, radiosensitising, antistress, anticonvulsant, psychotropic, CNS depressant, antioxidant, anti-inflammatory, antispasmodic, analgesic, antipyretic, antiviral, antiarthritic, sedative, cardiotropic, cardioprotective, anti-coagulant, anti-ageing, cytoprotea. [34]

Some common uses of Ashwagandha

- *Mandukaparni, Shankhapushpi, Ashwagandha* and *Satavari* should be used in order to promote intellect life span, stability and strength. [35]
- One may also take *Sharkara, Ashwagandha* and *Pippali* mixed with ghee and honey to promote body strength. [36]
- Ghee is cooked with one-fourth paste of *Ashwagandha* and ten times milk. It promotes development of body and is useful in emaciated children.
- Well dried material *Ashwagandha* should be crushed to make fine power and sieved through a fine cloth. It is recommended for *Krisa roga*, given internally in a dose of 5-10gm. It is administered with *Ksira, Taila, Ghrta* or *Sukhambu* (warm water) 2-3 times a day for 15 days. [37]
- *Lepa* of leaf paste is indicated in *Apachi, Gandamala, Granthi.* [38]
- *Ghrta* prepared by *Ashwagandha kwatha* is taken in *Ritukala* for conceiving (*Garbha dharana*)
- For insomnia ghee, sugar candy and *Ashwagandha* root powder. [39]
- 4 *tola* root powder of *Ashwagandha* is taken with honey, *Ghrta* and milk for 1 month in *Sisira* ritu gives *Rasayana* effect. [40]
- *Ashwagandha kshara*, honey and *Ghrta* is indicated in *Swasa.* [41]

- In *Granthi, Ashwagandha* root *Kalka* is applied as a hot *Lepa.* [42]
- *Ghrta* prepared by *Ashwagandha kalka* and *Kwatha* and *Chaturguna* milk is *Vata shamaka, Vrishya, Mamsavardhaka* and gives strength. [43]
- *Ashwagandha churna* along with hot water is indicated in *Hridayagata vata.* [44]
- *Ashwagandha* powder with milk, *Taila, Ghrta*, hot water or recommended *Anupana* for 15 days is indicated in *Karshya roga* of child. [43]

Substitutes and Adulterants

Ashwagandha (*Withania somnifera* (L.) Dunal.) is used as a substitute for *Kakoli* and *Kshirakakoli* of *Ashtavarga*,

Part used: Root, Leaf, *Kshara*.

Dose: 0.5-1gm

DISCUSSION

Withania somnifera (WS) usually known as *Ashwagandha* is mainly identified as a *Rasayana* (rejuvenator) anticipated to enrich physical and mental state. It has been reported to have anti-diabetic, antimicrobial, analgesic, anti-inflammatory, anti-tumour, anti-stress, neuroprotective, cardio-protective, rejuvenating and immunomodulatory effects.[45-47] It also rejuvenates the body in weakened situations and upturns longevity.[48] It contains an active ingredient known as 'withanolides', steroidal saponin, alkaloids, and steroidal lactones. Most of the biological actions contributed by *Withaferin-A*, *Withanolide D*, *Withanoside I-VII* and *Withanolide Glycosides* are extracted from its roots.[22]

Ashwagandha, an ancient Indian herb and an immuno-modulator has been used since years due to its numerous advantages. Though there are multiple studies concerning its effectiveness on various diseases, after the emergence of pandemic, this drug has been identified by the AYUSH Ministry as the potential drug that can improve the immunity of Covid-19 patients and also helps in prevention of the same.

A molecular docking study that targeted COVID-19 (SARS-CoV-2) main protease through active phytochemicals of Ayurvedic medicinal plants, suggested that the active phytochemicals from medicinal plants could potentially inhibit M^{pro} of SARS-CoV-2 and further equip the management strategy against COVID-19-a global contagion with *Withania somnifera* (*Ashwagandha*), *Tinospora cordifolia* (*Giloy*) and *Ocimum sanctum* (*Tulsi*).[49] These studies reported that some of the phyto-constituents from above medicinal plants like *Withaferin A*, *Withanolide B*, *Tinocordioside*, *Somniferine A*, *Tinosporide*, *Withanolide*, *Orientin*, *Flavonol glucoside*, *Apigenin*, *Kaempferol*, *Withanone*

shows interaction with SARS CoV- 2 M^{pro}, and other target proteins (S, E, N) of COVID-19. [50] Withaferin A (WFA) is a steroidal lactone isolated from the plant *Withania somnifera*, also known as *Ashwagandha*. [51]

Recent works has demonstrated that COVID-19 infections have a large immune component and can result in the development of cytokine storm, a potentially life-threatening immune reaction in which the body releases too many cytokines into the blood at a rapid rate.[52] Interestingly, at least three independent research groups have suggested that phyto-chemicals found in the plant *Withania somnifera* could be developed as a therapeutic agent against COVID-19 infection using molecular docking approaches. Two of the groups reported that various Withanolides, such as WFA, should be able to bind to the viral S-protein receptor binding domain, thereby blocking or reducing interactions with host ACE2 receptor. [53,54] The third group reported that WFA and a separate withanolide, Withanone, are predicted to interact with the main protease of SARS-CoV-2, although WFA is predicted to have less of a binding affinity than an established N3 protease inhibitor used for baseline docking scores. [55]

Withaferin A. alone or in combination with drugs, such as: hydroxychloroquine, dexamethasone or other treatments (under clinical trials), could be developed into an attractive therapeutic agent for both the general population and cancer patients due to its anti-tumorigenic properties and the preliminary studies showing that it is capable of binding to the S-protein of SARS-CoV-2, thereby potentially inhibiting infection and/or spread of the disease. [56]

In a silico study, the possible inhibitory potential of phytochemicals from *Ashwagandha* was analyzed and these docking studies and the MD pointed out the possible lead-like properties of the phytochemical or bio-actives such as QGRG, Withanoside X, Ashwagandanolide, Dihydro-withaferin A and Withanolide N hold promise in inhibiting the SARS-CoV-2 key viral proteins. [57]

Many studies are being carried out on ashwagandha and are showing its effectiveness in the prevention of Covid-19 by its immuno-modulating properties along with its positive effects on the covid affected patients. There are many numbers of studies being conducted on the same including clinical, in-silico and docking studies etc. This shows the potential of Ayurvedic herbs and its role in the management of Covid-19 which can be administered either alone or in combination of current conventional approach and this provides a novice path to the ancient Ayurvedic medicine to explore its treasure that can be beneficial to the society.

CONCLUSION

When the pandemic, Covid-19 had ravaged the entire world with its extensive devastation in 2020, the entire health community irrespective of modern or traditional medicines, everyone were endeavoring to find the best possible solution to combat the new viral strain. With the conventional management of those affected, the entire human population was trying to improve their immunity with best possible methods using various modalities. Among these *Ashwagandha*, the Indian Ginseng was been advised by the AYUSH ministry to improve the immunity naturally and without any adverse effects and this is being investigated in various research studies and showing promising effects that can be implemented both for the prevention and the management of Covid-19 successfully.

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