An insight to curative effects of *Ashwagandha* (*Withania somnifera*), an Ayurveda herb

Rashi Jain and Komal Mathur

Abstract

Ayurveda is the oldest form of medical sciences treats with the plant extracts. The plant produces secondary metabolites (phytochemicals). They pose as bioactive component act on many physiological mechanisms to treat disorders of the human body with zero side effects. Thus, they are being used to develop phyto-medicines and Ayurveda to become global health care system. This review focuses on re-emergence of Ayurveda and the recent studies on *Ashwagandha* (*Indian Ginseng*) showcasing it’s potential as rejuvenator, nerve tonic, anti-carcinogenic and anti-rheumatic agent and even in combating Covid-19 infection. The major active ingredients were involved withaferin-A, withanolide-D, withanone, withanosides, sitoindosides and includes various alkaloids, steroidal lactones and saponins. These phytochemicals are studied on the basis of their mechanism of action, how they influence the activity of target enzymes or proteins. Through understanding the biochemical pathways of *Ashwagandha* produced by their secondary metabolites, it will be reasonable to justify its further research and application in drug formulation.

Keywords: *Ashwagandha*, Ayurveda, phytochemicals, plant extracts, rejuvenator

Introduction

History of Ayurveda

Ayurveda, the traditional Indian medicine system is considered to be an eternal scientific knowledge imparted for the benefit of mankind. The term coined by two Sanskrit words: the science (*Veda*) of life (*Ayur*). The fact is believed truthful upon various ancient scriptures and manuscripts that were written about 5,000 years ago by some few of the majestic *rishis* or saints living in India. It is the precious field of expertise which contains essential knowledge on how to achieve a balanced body and mind with the help of invaluable gifts of nature, the plants. The medicinal plants contain such chemical compounds that directly or indirectly affect the mechanisms of the human organ system. The evidence of such great knowledge and scientific facts was recorded in the sacred texts, called the *Veda*s. They are the world’s oldest form of literature, written in Sanskrit, mother of all the languages in the world. (Singh Pal A., 2005) [4]. Acharya Charaka had a major role to present the first concept of disease immunity. He was the first to study the human body system and defined three systems of the human body; the *Vata*, *pitta*, and the *Kapha*. They circulate through the bodily fluids and control a person’s physiological operations. Therefore, Acharya Charaka is known as the Father of Ayurveda. The beautiful heritage started by rishis to perform the duty of radiating the knowledge of Ayurveda to whole mankind is still ongoing since thousands of years and will continue to move on till the human life exists on earth. (Andrew T., 2007) [7]

Many communities around the world have been inspired by the Indian Ayurveda system and practiced it later in their native places with their medical system. E.g., Greek, Middle Eastern, South American, European, Chinese, Arabian civilization. In India, the knowledge and expertise is transmitted through generations in the form of songs and poems. The first university to introduce Ayurvedic medicine was at the University of Banaras in 500 BC, teaching the great Charaka Samhita (encyclopedia of medicine). Later on, two more great literature were discovered, called Sushruta Samhita and then Ashtanga hridaya, altogether build the foundation of the Ayurveda system. (Fakeem A., 2006) [3].
Ayurveda is being practiced in mostly developing countries since ages, till around 20th century, when the branch of pharmacology emerged. It is the branch of modernized medicines through western science involved the synthesis of capsules through chemicals artificially. Since ages, many people from the countryside or developing countries use traditional remedies of which they may not understand the scientific logic behind, they know from their own and elders experiences. For them these medicinal plants are the best healing agents when used in right way with no side effects at all. Many people don’t accept the fact that modern allopathic medicine system has its foundation from ancient medicine only, that’s why there is the great possibility in future that the novel medicine would be discovered and adapted by following the traditional knowledge and experiences. (Fakeem A, 2006) [3]

In developed countries, mainly in cities, the use of medicinal plants is often considered as wrong, illegal practice and superstition, because people preaching it did not have the scientific insight to explain the therapeutic action. Moreover, some people were actually preaching it wrong due to lack of education and wrong intentions to earn money. Therefore the emergence of modern science and allopathy shattered the integrity of Ayurveda system at the beginning of the 20th century. However, for the past two decades, the severe side effects and chemical toxicity intolerance of allopathy were shooting up at very fast rate and people started looking for no side effect medicines. Thus Ayurveda came back into the picture as a cool, organic way to fight diseases. People all around the world started cooking dishes in Indian style and are including medicinal herbs and spices in their daily dietary intake as health supplements, e.g., turmeric latte or golden tea, neem and tea tree essential oils for skin and hair, etc., which Indian households been using since ages. Scientists are also even conducting researches to cure deadly cancer through Ayurveda throughout the world. People call it an organic way, the natural way with no side effects and comparable very low cost of the treatment. Many developed countries after scientifically proven researches have started to acknowledge Ayurveda as a safer and better alternative compared to synthetic drugs. (Singh R., 2015) [19]

However, the production of Ayurvedic medicines at the industry level is facing the major challenge that is the treatment is customized for each unique patient. Therefore, generalized medicines produced at large scale are called as nutrient supplements or health boosters, not curable for a specific disease. Each person gets personalized treatment according to their system doshas. The five basic elements combine and manifest in the human body as three basic humors are known as Vata, Pitta and Kapha collectively called tridoshas.

1. **Vata**: governs the movement, associated with the nervous system, directs nerve impulses, circulation, respiration, and elimination. Vata is cold, dry, and light and resembles the element air.

   \[ Vata = \text{Ether} + \text{Water} \]

2. **Pitta**: governs body temperature and energy, associated with metabolism, endocrine function, and digestion, also concerned with intelligence and understanding. Pitta is oily, hot and light and corresponds to the element fire.

   \[ Pitta = \text{Fire} \]

3. **Kapha**: governs biological structure, immunity, production of body fluids, also assists with wound healing, general vigor, and memory retention. Kapha is wet, cold, and heavy and resembles the element water.

   \[ Kapha = \text{Water} + \text{Earth} \]

4. These guidelines offered in Ayurveda for preserving health throughout life are not only scientific but practical...
and entirely workable with a common-sense approach. They are highly relevant today when Mankind is suffering from the ravages of highly artificial lifestyles consequent to modern civilization, urbanization, and technology explosion, severe competition and extreme mental stress in daily life. (Goyal M. et al., 2012) [12]

Major diseases around the world today and tomorrow
The imbalance of tridoshas in the body system causes a state of disease or sickness. According to Ayurveda, daily healthy food intake, physical exercise, meditation, and specific treatment approaches can prevent or cure most of the diseases of the world, even cancer. The kind of disease and age of death depends on the economy of the country. In wealthy countries, most people would reasonably expect to die in older age whereas, in low-income countries, children aged under 5 years are the most at risk. Around 56-58 million people die annually around the globe combined due to communicable, non-communicable diseases, and injuries. In the coming future, the real battle is with non-communicable diseases and cancers, they will become a global threat in the future with no vaccines available, resistance to most of the synthetic drugs. Lifestyle disorders would be more common in the future. The scope of treatment relies upon in an organic way, the Ayurveda way in the future. Therefore, scientists again going back to the roots, are trying the effort to create the fusion method connecting modern medicine with the ancient medicine system. Herbal medicine are made up of bioactive component extracted from plants. It contains secondary metabolites that do not have any function in their growth and metabolism. They are produced in certain tissues or during developmental stages of plant include terpenoids, nitrogen fixing metabolites, amines, cyanogenic glycosides, glucosinolates, alkaloid, and phenolics. These phytochemicals possess specific action on human physiology to heal the illness. Immense research on these secondary metabolites of plants is going on around the world, due to their many human friendly benefits such as potent therapeutic efficacy, no side effects, and low cost of production. (Shakya A., 2016) [17]

Some medicinal plants mentioned with their active ingredient (secondary metabolites) and common uses below:

Table 1: List of popular medicinal plants with their active ingredient and uses

<table>
<thead>
<tr>
<th>Medicinal Plant</th>
<th>Active Ingredient</th>
<th>Common uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashwagandha</td>
<td>Withaferin A</td>
<td>Treat rheumatism and arthritis</td>
</tr>
<tr>
<td>Brahmi</td>
<td>Bacosides</td>
<td>Brain tonic improves learning and memory</td>
</tr>
<tr>
<td>Giloe</td>
<td>Berberine</td>
<td>Immuno booster</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Curcumin</td>
<td>anti-bacterial, antiseptic</td>
</tr>
<tr>
<td>Guggal</td>
<td>Guggalsterones</td>
<td>Treat atherosclerosis, acne, act as hypolipidaemic</td>
</tr>
<tr>
<td>Long Pepper</td>
<td>Piperine</td>
<td>Improves appetite and digestion</td>
</tr>
<tr>
<td>Neem</td>
<td>Azadirachta</td>
<td>Treat heart disease, skin diseases, liver problems</td>
</tr>
<tr>
<td>Ashoka</td>
<td>Tannins</td>
<td>Used as a uterine sedative</td>
</tr>
<tr>
<td>Curry leaves</td>
<td>Monoterpenes</td>
<td>Treat diabetes and weight loss</td>
</tr>
<tr>
<td>Tulsi</td>
<td>Oleancolic acid</td>
<td>Treat cough, flu, heart problems</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Saponins</td>
<td>Treat skin problems, indigestion</td>
</tr>
<tr>
<td>Ginger</td>
<td>Gingerols</td>
<td>Provide immunity, treat muscle pain</td>
</tr>
<tr>
<td>Nomi</td>
<td>Octanoid acid</td>
<td>Provide immunity, treat high blood pressure</td>
</tr>
<tr>
<td>Triphala</td>
<td>Gallic acid</td>
<td>Used for indigestion and gastric problems</td>
</tr>
<tr>
<td>Cloves</td>
<td>Eugenol</td>
<td>Used for dental disorders</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Bisabolol</td>
<td>Used in cosmetics and aromatherapy</td>
</tr>
<tr>
<td>Garlic</td>
<td>Allicin</td>
<td>Used to lower cholesterol, act as an anti-inflammatory</td>
</tr>
<tr>
<td>Flax seeds</td>
<td>Linolenic acid</td>
<td>Used as a cardiac tonic, helps in weight loss</td>
</tr>
<tr>
<td>Tea tree</td>
<td>Terpinenol</td>
<td>Used as antibacterial, antifungal, treat skin diseases</td>
</tr>
<tr>
<td>Peppermint</td>
<td>Menthol</td>
<td>Used to treat indigestion and give a cooling effect</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>Cinnamaldehyde</td>
<td>Act as anti-inflammatory, anti-oxidant</td>
</tr>
<tr>
<td>Sandalwood</td>
<td>Santolol</td>
<td>Used as antiseptic, antistringent</td>
</tr>
<tr>
<td>Bhringraj</td>
<td>Ecliptine</td>
<td>Promotes hair growth and prevent baldness</td>
</tr>
<tr>
<td>Mustard</td>
<td>Allyl isothiocyanate</td>
<td>Used for painful joints, treat arthritis</td>
</tr>
</tbody>
</table>

Withania somnifera (Ashwagandha)
Ashwagandha, also known as Indian Ginseng or winter cherry belongs to the family Solanaceae. It is one of the versatile herbs and holds a special space in Ayurvedic traditions. In India, it is grown mainly in Madhya Pradesh, Rajasthan, Gujarat, Haryana, Maharashtra, Punjab and Uttar Pradesh.
1. Medicinal Values
It is one of the best health tonics and energy restorative agents to treat lassitude, general debility and stress-induced fatigue. Studies have shown its rejuvenating and growth promoting effect on whole body, specifically for the muscles and bone marrow by promoting mitochondrial health. It is used as an immunomodulator to treat arthritis. The roots are mainly used to create drugs that act as aphrodisiacs (stimulates sexual desire), gives sedative effect, and deobstruent (removes obstruction in secreting ducts). Leaves are used as anti-inflammatory, hepatoprotective, and antibacterial. Fruits and seeds are used as a diuretic to increase urine output. (Ramar S. et al., 2008)[17] The active ingredient of *Withania* has shown cytotoxic effect on cells which means this property can be used as potential anti-carcinogenic agent in the treatment of various tumours. It has good cognitive effect to improvise memory in children and old adults. It is also seen as useful medicine to treat neurodegenerative diseases. The active ingredient also act as GABA molecule to fit in its receptor to accelerate the formation of dendrites. Thus we can say that Ashwagandha is also a very potent nerve tonic. (C.F. Khare, 2007) [9]

![Fig 5: Ashwagandha plant showing red colored fruits and flowers](image)

2. Active Ingredients
The major active ingredients of *Withania somnifera* includes withaferin-A, withanolide-D, withanosides, withanones, sitoindosides, anaferine, isopelletierine, and includes various other alkaloids, steroidal lactones and saponins which have a therapeutic role as anti-stress agents or rejuvenating tonic. It is also rich in mineral iron needed for formation of RBCs to carry out more oxygen to the various organs, hence improvising energy levels in body.

Mechanisms of phytochemical action on the human system are being verified from the ongoing research studies of
- Receptor site of drug action,
- Environment of interaction,
- Nature of the drug-receptor interactions

![Fig 6: Chemical structures of major withanolides – Withanone and Withaferin A](image)

The structure of withanolides is based on an ergostane (tetracyclic triterpene) backbone. The withanolides have C28 steroidal nucleus with C9 side chain, having six membered lactone ring. (Kulkarni S.K. *et al.*, 2007) [16]

3. Mode of action of the active ingredients
Withaferin A and withanone, component of biologically active steroidal lactones which are majorly responsible for treating disorders like rheumatism, arthritis, fatigue, cancers, cardiac and brain disorders. It improves various physiological functions by simply acting as mimic molecule or increase/decrease the amount of target biomolecules by acting in directly proportional, in response to them. The bioactive compounds trigger specific enzyme activity inducing desired physiological response.

![Fig 7: Major therapeutic actions of Ashwagandha herb](image)

**Anti-oxidative activity**
It emits anti-oxidative activity by increasing levels of various anti-oxidant enzymes like superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase, NADPH dehydrogenase which reduces free radicals or stress formed in the affected cells and provide healthy mitochondrial function. This function is proved in many recent studies by simply testing treated and non-treated mouse models and human cell lines. The cellular oxidative damage was far better reduced in treated cells with Withaferin A. (Ahmad M *et al.*, 2015) [1] Comparative anti-carcinogenic assays were conducted in human cells which have shown to induce p53 dependent apoptosis, LC3B autophagy marker and Na+ K+ ATPase activity to accelerate killing of abnormal cells. P53 is tumor suppressor gene which detects oxidative stress in cells and kill them. LC3 is a central protein needed for autophagoy pathway where it functions in autophagosome biogenesis. It recruits unwanted cells to the autophagosomes. Increases in reactive oxygen species (ROS) can oxidize the Na/K-ATPase α/β subunits. The high oxidation levels can inhibit its activity and promotes its degradation by proteasomal and endosomal/lysosomal proteolytic pathways. The active biochemical acts as an excellent antioxidant which is shown to protect and increase Na/K-ATPase activity. Thiobarbituric acid reactive substances (TBARS) are formed as a byproduct of lipid peroxidation which get increased in ROS enriched cells.

The active ingredient is also helpful to decrease the levels of TBARS in tumor cells. It is experimentally shown to treat breast, cervical, ovarian, prostate, oral, lung, colorectal and pancreatic cancers. It also prevent proliferation of harmful cells by regulating cellular division through activating cyclin-dependent kinases (CDKs), signal transducer and activator of transcription 3 (STAT3), and proliferating cell nuclear antigen (PCNA) for regulating DNA replication and repair. It also has major role in suppressing epidermal growth factor receptor (EGFR) responsible marker for lung cancer, human epidermal growth factor receptor 2 (HER2) responsible marker for breast cancer, thus preventing various kind of cancers. (Sivasankarapillai *et al.*, 2020) [20]
Withaferin A, Withanolide D and its triacetate derivatives have been particularly found to possess anti-carcinogenic activities. (Chowdhary K., 1975) WFA acts as an inhibitor of the chaperon p97. The chaperone-like p97 is a member of the AAA + ATPase enzyme family. P97 has been broadly studied in mammals and numerous investigations highlighted that this protein is post-translationally regulated, interacts with cofactors that direct it to distinct cellular signalization pathway including protein quality control and degradation, cell cycle regulation, genome stability, vesicular trafficking, autophagy and immunity. WFA along with its analogues can be a proteostasis modulator by retaining p97 activity and cytostatic activity in vitro. Recently, a scientific study have been reported the synthesis and cytotoxicity of semisynthetic Withalongolide analogues where 24 compounds were tested on five cancer cell lines (IMAR, MDA-MB-231, SKMEL-28, DRO81-1, and MRC-5). WFA treatment leads to apoptosis, evasion of anti-growth signalling and immune system along with sustained proliferative signalling and interactions with the tumour microenvironment. (Dutta R. et al., 2019) Despite of all these basic and mechanistic studies, the potential of WS extracts do not now promise to cure cancer completely especially at later stages but can be used as daily dietary supplement or secondary treatment to decrease treatment related fatigue and improved quality of life of cancer patients.

**Anti-inflammatory activity**

It also produces anti-inflammatory effects by showing inhibitory action on overexpression of pro-inflammatory modulators like tumour necrosis factor – alpha (TNF-α), prostaglandin (PGE2) synthesis. It also inhibits cyclooxygenase-2 (COX-2) and nitric oxide production by inhibiting nitric oxide synthase (iNOS). The release of reactive oxygen species (ROS), interleukins (IL-8 & 1β) and nuclear factor κ light chain enhancer of activated B cells (NFκB) causes arthritis and rheumatism which is treated by Withania action. Also, it increases the amount of p38 in macrophages which enhances production of anti-inflammatory cytokine IL-10 and enhances activation of c-jun (JNK) and ERK1/2 which are members of MAPK pathways responsible for anti-inflammatory responses causes anti-arthritic effects in humans. (Dutta R. et al., 2019) Rheumatoid Arthritis (RA) is a chronic autoimmune disease where unnecessarily mechanism of inflammation is inflated when own antibodies trigger joint tissues due to several internal and external factors and causes overexpression of...
inflammatory responses. Several studies shown that action of *Withania* causes suppression of such pro-inflammatory proteins and responses and treat the disorder. Also increase in C-Jun protects cells from inflammation induced apoptosis, and it cooperates with NF-xB to prevent apoptosis induced by TNFa. The protection from apoptosis by C-Jun requires serines 63/73 (involved in phosphorylation of Jun). Both Jun and its dimerization partners in AP-1 formation are subject to regulation by diverse extracellular stimuli, which include pro-inflammatory cytokines, oxidative stress. Also, the c-Jun activities can be regulated by the ERK pathway which is the part of MAPK pathway to control immunity and inflammation. The p38 pathway is also the part of the MAPK signalling pathway. It functions in the control of apoptosis and the release of cytokines by macrophages and neutrophils. It is strongly activated by environmental stresses and inflammatory cytokines. Its activation contributes to the regulation of inflammation and apoptosis. (Ahmad M. *et al*, 2015)[1].

**Anti-stress activity/ rejuvenating activity**

Withanoids also emits anti-stress activity by activating various cell killing mechanism like BCL2-associated X protein (Bax), Death receptor 5 (DR5), protease-activated receptor 4 (PAR-4), tumour suppressor proteins (p53 and p21), T-cell production and major caspases (−3, −8 and −9), thus eliminating toxic and aged cells by inducing apoptosis to restore healthy cells in the body and to slow down the process of aging. (Kulkarni S.K. *et al.*, 2007)[16]

It is also successfully studied to decrease the amount of adrenal cortisol produced after stressful activity, thus rejuvenating the whole body. Often adrenal cortisol is called the “stress hormone,” released by adrenal glands during and after stressful conditions, cortisol cause increase in heart rate and blood pressure. It is a natural “flight or fight” response to maintain normality. But after stressful situations, cortisol tends to remain in bloodstream which causes pressure on heart and blood vessels, leading to rapid ageing of tissues and feeling of continuous tiredness in the body. It is also proven to have inhibitory effect on granulation (tumorous) tissue by uncoupling oxidative phosphorylation, the reduction in levels of ADP/O observed in the mitochondria of tumorous tissue. Further, trigger of Mg2+ dependent ATPase activity in muscle mitochondria was found to promote good cardiovascular activity, overall boosting energy levels in the human body. It is also clinically proven that administration of *Ashwagandha* to the patients with anxiety and depression shown anxiolytic effect. It was successful to reduce brain levels of tribulin, endogenous monoamine oxidase (MAO) which act as endocoid marker of clinical anxiety. Thus it also works as mood stabilizer. (Singh N. *et al.*, 2011)[18]

The famous “forced swim test” conducted on mice several times to prove rejuvenating and anti-depressant properties of *Ashwagandha* when fed to mice prior to swimming. The energy levels and cardiac rate was being continuously monitored and got results significantly higher in *Withania* fed mice in comparison to non-fed mice. The forced swim test is nothing but behavioural test used for evaluation of novel or unidentified rejuvenating antidepressant drugs. Mice are placed in an inescapable water filled transparent tank and their mobility behaviour is measured with time. The forced swim test is simple, straightforward to conduct reliably and it requires minimum equipment. Here, when Withanoside X is fed at minimal dose also, it lead to good energetic results and these mice were able to survive far better and longer than non-fed mice. It is shown it to be effective in increasing the stamina (physical endurance) and preventing stress induced gastric ulcer, carbon tetrachloride (CC14) induced hepatotoxicity and mortality. (C.P. Khare, 2007)[9]

The results indicate a significant increase in the plasma corticosterone level, phagocytic index and T- cell cytokines index in rats subjected to cold swimming stress. In the rats pre-treated with the drug, these parameters were near control values and an increase in the swimming time was observed. These results indicate that *Withania somnifera* used in the crude form is a potent anti-stress agent. The results of above studies lend support to the hypothesis of tonics, revitalizers and rejuvenators of Ayurveda which indicate clinical use of *Withania somnifera* in the prevention and treatment of many stress induced diseases like arteriosclerosis, premature ageing, arthritis, diabetes, hypertension and malignancy. *Ashwagandha* was also found to be useful in the prevention of stress-induced ulcers of the gastrointestinal tract. It also showed good anabolic effect as there was a significant increase in the body weights of the *Ashwagandha* treated group as compared to control for a period of 3 months in rats. (Singh N. *et al.*, 2011)[18]

**Neuroprotection activity**

It also provides anti-neurodegenerative activity by producing cognitive promoting effects and neuronal production. It actually belongs to subgroup of rasayana, called medhyarasayana. Medhya literally refers to the mind and mental capacity. There are many scientific studies that proven that *Ashwagandha* slows down, stops, reverses neurotic atrophy and synaptic loss. Thus, it can be used to treat Alzheimer’s, Parkinson’s, Huntington’s and other neurodegenerative diseases at earlier and middle stages of the disease. *Ashwagandha* has been described as a potent nerve tonic in Ayurveda and that is why it is a common ingredient of Ayurvedic tonic. Tonics, rejuvenators and vitalizers of Ayurveda appear to allay disease and induce immunity and longevity in the users. (Basist P., 2020)[22] *Withanoloids also are known to inhibit acetylcholinesterase*
and butyrylcholinesterase in a dose dependent manner. The cholinesterase inhibitory potential along with calcium homeostasis ability of Withania somnifera has made it a suitable drug candidate to treat Alzheimer’s disease and associated problems. In Alzheimer’s, there is disruption of Ca2+ homeostasis, extracellular deposition of amyloid, free radicals production, intracellular deposition of neurofibrillary tangles (NFT) which are aggregates of hyperphosphorylated tau protein, known as a primary marker of Alzheimer’s disease. The Withania extracts uplifts the Ca2+ levels which is responsible for several neuronal functions, such as neurotransmitter synthesis, release, neuronal excitability, phosphorylation. Ca2+ initiate and regulate responses of central nervous tissues to combat brain tissue damage and injury. Thus, Ca2+ homeostasis supports brain physiology maintaining neural integrity. (Zahiruddin S., 2020) [21]

Ibotenic acid is used as powerful neurotoxicant to study brain-lesions effect. When injected directly into the brains of mice, rats, or monkeys, it causes profound destruction of basal forebrain cholinergic neurons. In recent studies, Glycowithanolides, withaferin-A and sitoindosides were proven to significantly reverse ibotenic acid induced cognitive defects in Alzheimer’s disease model.

Pre-treatment with Ashwagandha extract was found to prevent all the changes in antioxidant enzyme activities, catecholamine content, dopaminergic D2 receptor binding and tyrosine hydroxylase expression induced by 6-hydroxydopamine (6-OHDA) in rats (an animal model of Parkinson’s disease) in a dose-dependent manner. It increases the levels of catecholamine which help the body to respond to stress and prepare the body for “fight-or-flight” reactions. Oxidopamine, also known as 6-hydroxydopamine (6-OHDA) acts as a neurotoxic used by researchers to selectively destroy dopaminergic and noradrenergic neurons in the brain. The main use for oxidopamine in scientific research is to induce Parkinsonism in laboratory animals. The Withania extracts were proven to significantly reverse 6-OHDA induced neuron damage in Parkinson’s disease model. Thus, these results suggest that Ashwagandha may be helpful in protecting the neuronal injury in Parkinson's disease.

Also being a potent cognitive promoting agent, different clinical research gave confirmations to progress in cognitive functions which will be useful in improving the inability in dyslexia. Dyslexia is reading and learning disorder, mostly diagnosed in small children. They have problem in neurons of left hemisphere of brain. In 2001, it was reported that improvement in memory-consolidated induced by electroconvulsive shock in mice receiving Ashwagandha root extract (Zahiruddin S., 2020) [23].

Withanoloides also act as GABA (aminobutyric acid) receptor agonist which acts as ion channels that are permeable to chloride ions which decreases neuronal excitability, thereby having sedative effects on the CNS. Synthetically designed benzodiazepine have also similar sedative function but causes lot of side effects including addiction, also it has different binding sites on GABA receptor. But Withanoloides being structurally similar to GABA molecule act as exact mimic bind at GABA binding sites only, exerting natural sedative effect with no side effects at all. Also, it helps to promote new neurons formation. Withanoxide IV is metabolized into sominone, which induced marked recovery in neurites and memory which enhanced axonal and dendritic outgrowth and synaptogenesis. Also methanol extract of Withania proven to promote formation of dendrites. (Tohda C. et al., 2000) [21].

Ashwagandha against COVID-19

New studies suggest that Withaferin-A can help fight against the novel coronavirus. Four AYUSH formulations are being tested against the novel coronavirus infection. The Indian government has initiated trial to determine whether Ashwagandha can be a suitable alternative to anti-malarial drug Hydroxychloroquine for prevention against COVID-19. The clinical trials are being carried out by a group of scientists and researchers from the Ministry of AYUSH, Ministry of Health and Family Welfare, University Grants Commission (UGC) and Indian Council of Medical Research (ICMR). It is being proved that Withaferin-A demonstrate as a therapeutic agent to treat or prevent the spread of COVID-19 due to the reported interference in viral S-protein to host receptor binding and its lack of effect on ACE2 expression in the lungs. (Alex R. et al, 2020) [21]

Also, in a collaborative study between IIT-Delhi and National Institute of Advanced Industrial Science and Technology – Japan, they claimed that Ashwagandha might prove to be beneficial in fighting against COVID-19. They discovered that Ashwagandha having natural compound, Withanine can block the activity of Mpro or Main protease – a type of protein essential for the reproduction of the coronavirus. Withanine is also predicted to block cell membrane receptor required for entry of virus into cells. Same therapeutic role is seen with CAPE of Propolis (bee glue). Withanine is also
predicted to block human cell surface receptor TMPRSS2, required for virus infection. The team described that Withanone is particularly enriched in Ashwagandha stem. Therefore, Ashwagandha and Propolis although easily available and affordable globally, one needs to be conscious about the content of active ingredients for further testing in laboratory. Natural compounds Withanone from Indian Ashwagandha and CAPE from New Zealand Propolis may holds upcoming vaccine and inhibit viral main protease Mpro that is required for viral replication in host cells. Without specific antiviral agent discovered or due to very long time in vaccine production for the coronavirus infection, researchers are now exploring the ancient medicine system in an attempt to find a cure for the dreaded illness.

Fig 14: Hindrance in interaction of viral S-protein and human ACE2 receptor caused by Withaferin A

Fig 15: Withanone and CAPE to block the viral protein Mpro required for its replication (https://www.thehindubusinessline.com)

Commercial preparations
The various commercial products of Withania somnifera, their manufacturers along with their claimed therapeutic effects have been summarized below.

Table 2: List of commercial products, their manufacturer along with therapeutic effect

<table>
<thead>
<tr>
<th>Product name</th>
<th>Manufacturer</th>
<th>Therapeutic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stresswin</td>
<td>Baidyanath Ayurved Bhawan</td>
<td>Anti-stress, anti-anxiety</td>
</tr>
<tr>
<td>Wellness Pure Herbs Ashwagandha</td>
<td>Himalaya Pvt. Ltd.</td>
<td>Anti-ageing, boost immunity</td>
</tr>
<tr>
<td>Health Vit Natural Ashwagandha Powder</td>
<td>West Coast Pharmaceutical Works Ltd</td>
<td>Anti-stress and cardio protective</td>
</tr>
<tr>
<td>LoveMax</td>
<td>BACFO Pharmaceuticals Pvt. Ltd.</td>
<td>Vigour and vitality promotion</td>
</tr>
<tr>
<td>Brento</td>
<td>Zandu Pharmaceuticals Works Ltd.</td>
<td>Nerve tonic</td>
</tr>
<tr>
<td>Vital Plus</td>
<td>Mukhti Pharma</td>
<td>Rejuvenating effect</td>
</tr>
<tr>
<td>Ashwagandharista</td>
<td>Baidyanath Ayurved Bhawan</td>
<td>Nerve tonic</td>
</tr>
<tr>
<td>Ashwagandha powder</td>
<td>Jain Lifesciences Pvt Ltd</td>
<td>Rejuvenating effect</td>
</tr>
<tr>
<td>Ashwadi pills</td>
<td>Dehlvi Remedies</td>
<td>Anti-stress, anti-depressant</td>
</tr>
<tr>
<td>Ashwagandha tablets</td>
<td>Organic India Pvt. Ltd</td>
<td>Improves sleep, relaxant</td>
</tr>
<tr>
<td>Stresscom</td>
<td>Dabur India Ltd</td>
<td>Anti-anxiety, anti-depressant</td>
</tr>
</tbody>
</table>

Conclusion
This review article summarises the importance and re-emergence of Ayurveda and its medicinal plants, especially focussing on Ashwagandha herb. The therapeutic effects of Ashwagandha on various cancers, rheumatoid arthritis, lethargy, ageing, cardiac stress and brain related disorders like Alzheimer’s, Parkinson’s and dyslexia are being discussed. It is now even considered to treat COVID-19 infection which is the need of the hour. Ashwagandha has gained interest from last three decades for its potential. The combination of advanced medical sciences with an ancient remedy system is very essential for many reasons such as to down regulate newly formed diseases for which there is no vaccine for now, to treat people who have become drug-resistant, to treat people who experience lot of side effects of synthetic medicines, to improve quality of life for some deadly last stage diseased patients and also not all people can afford the expensive medicines. The preservation and cultivation of most of the Ayurveda medicinal plants will also conserve the balance of the ecosystem. It is very important for now to promote and invest in Ayurveda research and its teachings. As it has the full capability to become one of the global health care system in these upcoming pandemic situations. The ancient medicine system can save us from this unpredictable
world pandemic if the people accept it with pure intention and trust. Thus, it is high time to exploit newer opportunities to create jobs, fuel the Indian economy, and meet the demands of Ayurveda through India for India and the rest of the world.

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