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

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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 Vedas. 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 hridya, altogether build the foundation of the Ayurveda system. (Fakeem A., 2006) [3].

Fig 1: Statue of Maharishi Charak situated at Patanjali Yogpeeth, Haridwar, India

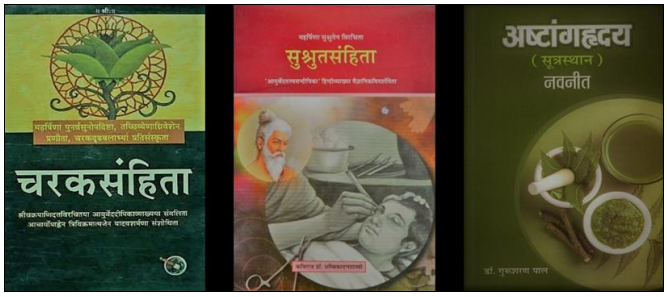

Fig 2: The basic literature of Ayurveda which forms its foundation system

Importance of Ayurveda in modern times

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. Now people have complete wisdom today of how the human body works, and they are in a better state to understand the healing powers of plants due to the study of scientific insight present in plant ingredients. Several scientific research have been done these years that objectively investigated Ayurveda. Scientists are trying to establish the connect between current medicine and Ayurveda in order to validate its theories and principles. (Bansal P., 2009) [8].

Medicinal plants contain various organic chemical compounds which act either individually, additively, or in synergy to combat 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]

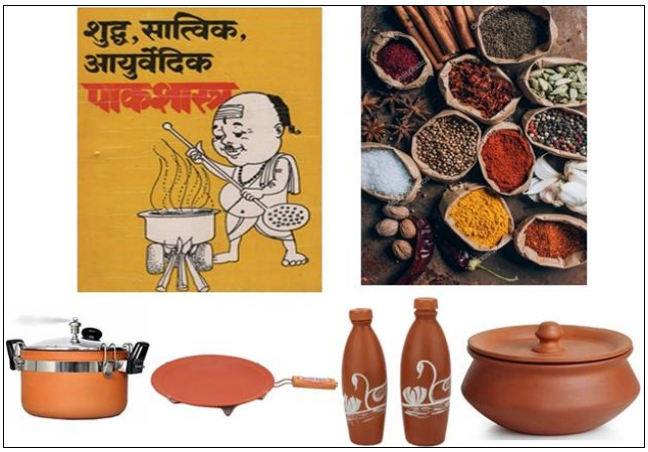

Fig 3: Indian cooking style and cooking ware becoming every health conscious person choice all around the world.

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 = Ether + 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 = 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 = Water + 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.

Fig 4: (a) Turmeric latte (golden milk). (b) Organic handmade soaps and cosmetics. (c) Onion oil for hair damage. (d) Camomile herbal tea to treat stress and insomnia.

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) [7]

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

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

***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 nervine tonic. (C.P. Khare, 2007) [9]

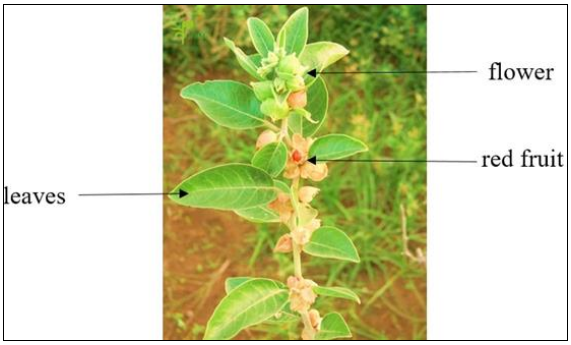

Fig 5: Ashwagandha plant showing red colored fruits and flowers

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

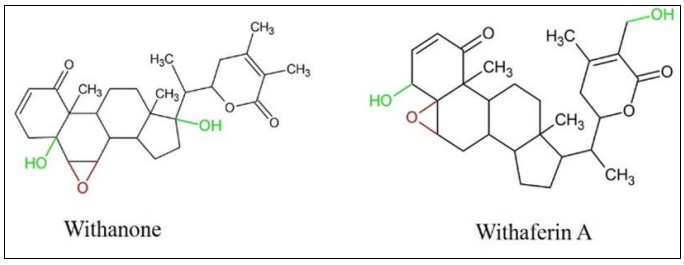

Fig 6: Chemical structures of major withanolides – Withanone and Withaferin A

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.

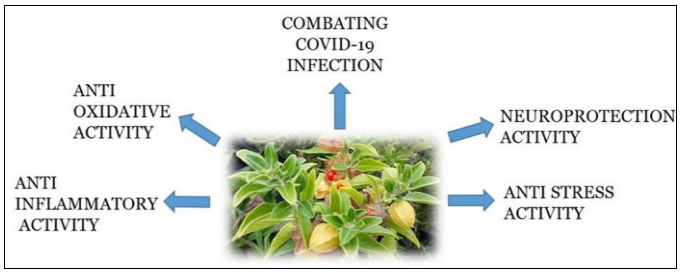

Fig 7: Major therapeutic actions of Ashwagandha herb

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 autophagy 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 (JMAR, 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) [11]

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.

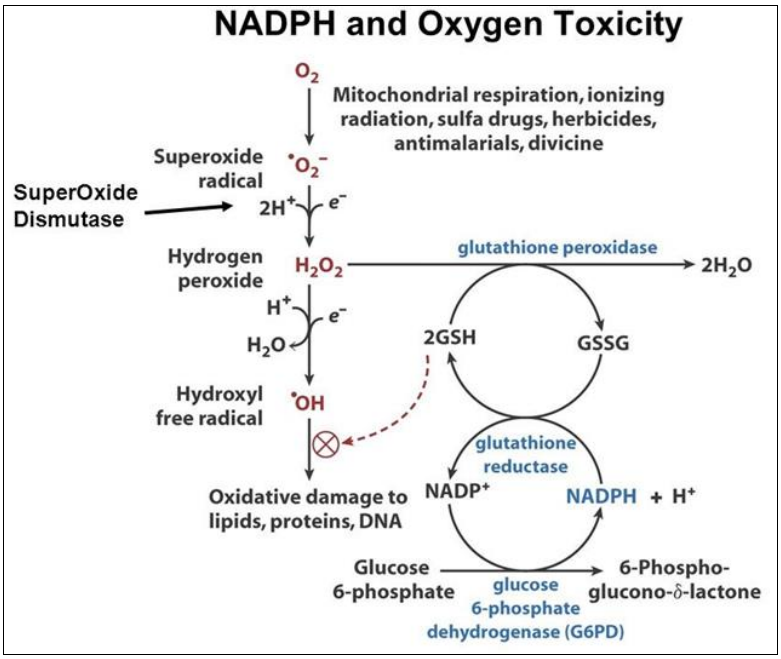

Fig 8: Mechanism of anti-oxidants inhibiting oxidative cell damage

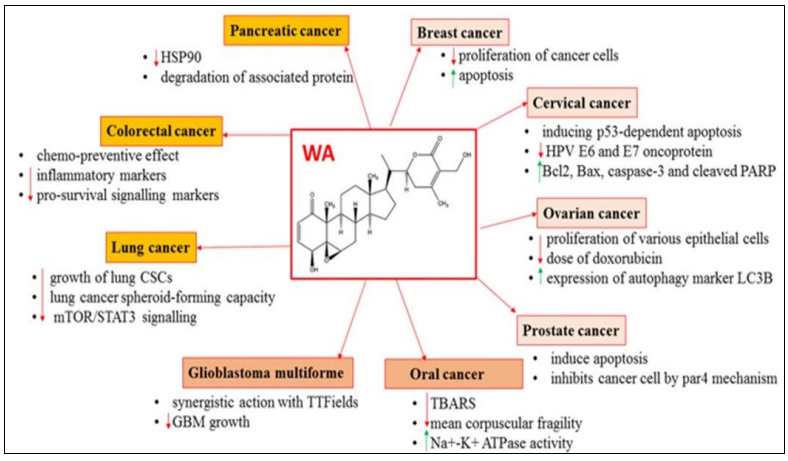

Fig 9: Action of Withaferin-A (WFA) on major cancers

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) [11]

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-κB to prevent apoptosis induced by TNFα. 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].

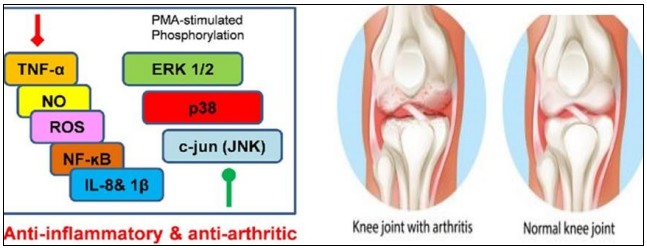

Fig 10: Modulating action of WA on inflammatory agents by directly acting on their enzymes and proteins

Anti-stress activity/ rejuvenating activity

Withanoides 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 (CCl4) 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, vitalizers 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]

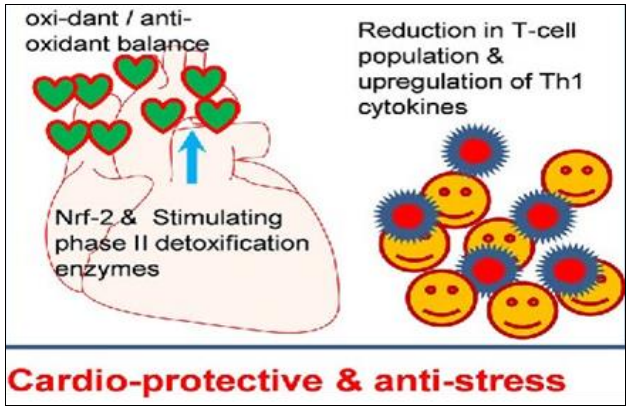

Fig 11: Action of Withania as adaptogen/ anti-stress agent

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 nervine 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) [23].

Withanoloids also are known to inhibit acetylcholinesterase

and butylcholinesterase in a dose dependent manner. The cholinesterase inhibitory potential along with calcium homoestatis ability has made *W. somnifera* a suitable drug candidate to treat Alzheimer's disease and associated problems. In Alzheimer's, there is disruption of Ca2+ homeostasis, extracellular deposition of amyloidα, 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, Ca^{2+} homeostasis supports brain physiology maintaining neural integrity. (Zahiruddin S., 2020) [23]

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 Withanolides 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. Withanoside 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].

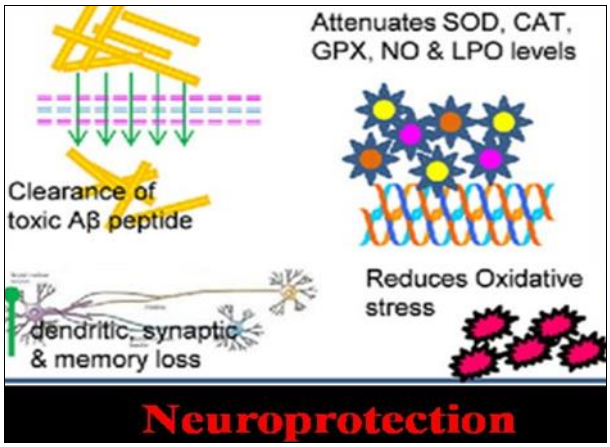

Fig 12: Action of promoting nerves production and reducing neurotoxins, oxidative stress in brain cells

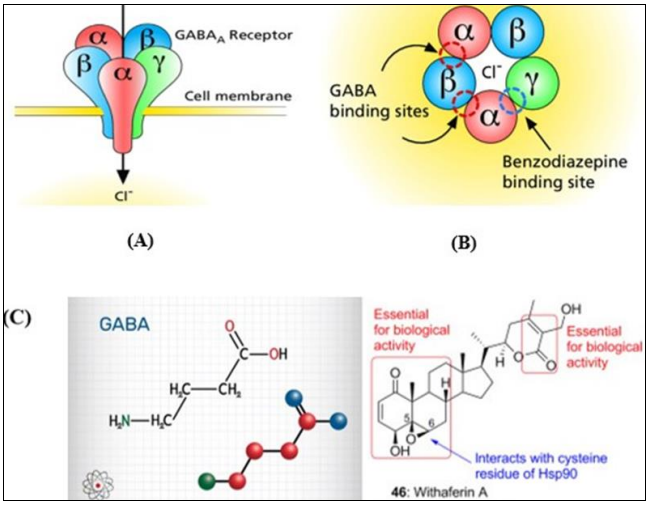

Fig 13: (A) GABA receptor structure, (B) GABA and benzodiazepine binding sites shown and (C) Structural similarity between WA and GABA molecule

Ashwagandha against COVID-19

New studies suggests 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 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, Withanone can block the activity of Mpro or Main protease – a type of protein essential for the reproduction of the coronavirus. Withanone 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). Withanone 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.

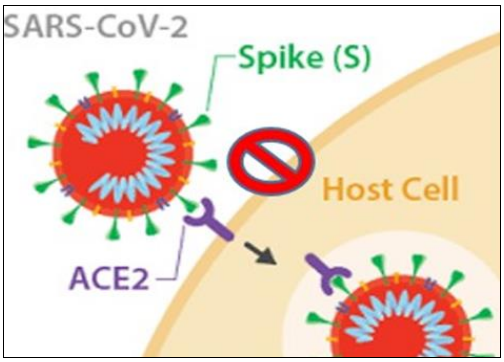

Fig 14: Hindrance in interaction of viral S-protein and human ACE2 receptor caused by Withaferin A

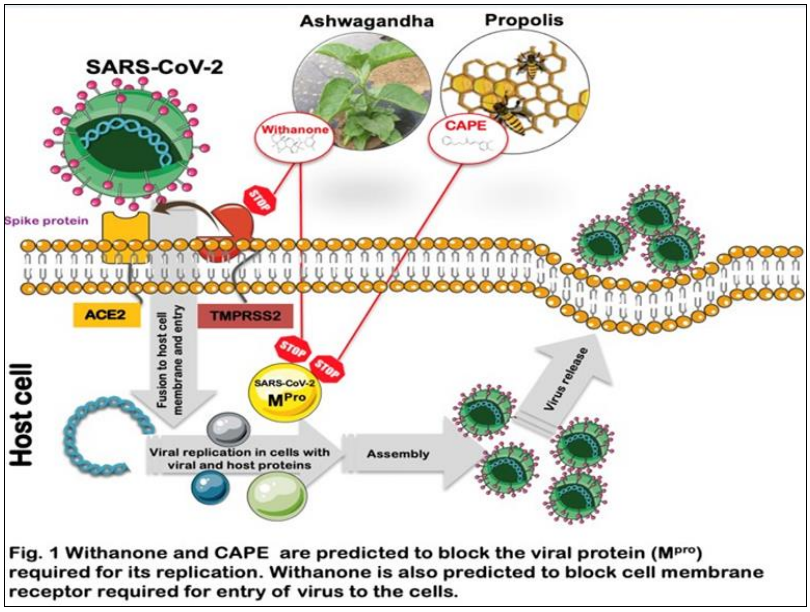

Fig 15: Withanone and CAPE to block the viral protein Mpro required for its replication (https://www.thehindubusinessline.com)

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

Product name	Manufacturer	Therapeutic effect
Stresswin	Baidyanath Ayurved Bhawan	Anti-stress, anti-anxiety
Wellness Pure Herbs Ashvagandha	Himalaya Pvt. Ltd.	Anti-ageing, boost immunity
Health Vit Natural *Ashwagandha* Powder	West Coast Pharmaceutical Works Ltd	Anti-stress and cardio protective
LoveMax	BACFO Pharmaceuticals Pvt. Ltd.	Vigour and vitality promotion
Brento	Zandu Pharmaceuticals Works Ltd.	Nervine tonic
Vital Plus	Mukhti Pharma	Rejuvenating effect
*Ashwagandha*rista	Baidynath Ayurved Bhawan	Nervine tonic
Ashwagandha powder	Jain Lifesciences Pvt Ltd	Rejuvenating effect
Arshadi pills	Dehlvi Remedies	Anti-stress, anti-depressant
Ashwagandha tablets	Organic India Pvt. Ltd	Improves sleep, relaxant
Stresscom	Dabur India Ltd	Anti-anxiety, anti-depressant

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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References

1. Ahmad M, Dar NJ, Hamid A. Pharmacologic overview of Withania Somnifera, Indian Ginseng 2015;72:4445-4460.; *Cellular and Molecular Life Sciences*
2. Alex R. Straughn; Withaferin A: a potential therapeutic agent against COVID-19 infection 2020;13:79.; *Journal of Ovarian Research*
3. Ameenah Gurib-Fakim; Medicinal plants: Traditions of yesterday and drugs of tomorrow; Molecular Aspects of Medicine 2006;27:1-93.
4. Amrit Pal Singh; Promising Phytochemicals from Indian Medicinal Plants; Ethnobotanical Leaflets 2005;9:15- 23.
5. Andrew T. Intergrading Ayurveda and Modern Medicine (Ayurveda Conference presentation) 2007. Budapest
6. Antony B., Aravind A., Benny M., Gupta N., Joseph B., Sebastian A.; Bioactivity Guided Fractionation and Purification of Anti-Depressant Molecule from *Ashwagandha* (*Withania somnifera*), Current Bioactive Compounds 2020;16(5):681.
7. Arvind Kumar Shakya; Medicinal plants: Future source of new drugs; International Journal of Herbal Medicine 2016;4(4):59-64.
8. Bansal P. Plants-herbal wealth as a potential source of ayurvedic drugs; Asian Journal of Traditional Medicines 2006, 4(4).
9. Khare CP. Indian Medicinal Plants: An Illustrated Dictionary; Springer Edition 2007.
10. Chowdary K, Neogy RK. Mode of Action of Withaferin A and Withanolide D; Biochem *Pharmacol* 1975;24(8):919-20.
11. Dutta R, Khalil R, Green R, Mohapatra SS, Mohapatra S. Withania Somnifera (*Ashwagandha*) and Withaferin A: Potential in Integrative Oncology; International Journal of Molecular Sciences 2019;20:21.
12. Goyal M, Sasmal D, Nagori BP. Ayurveda the Ancient Science of Healing: An Insight, Drug Discovery Research in Pharmacognosy, Prof. Omboon Vallisuta (Ed.), In Tech 2012 ISBN: 978-953-51-0213-7
13. http://www.indiahomeclub.com/botanical_garden/medicinal_plants_in_demand
14. https://www.copperh2o.com/blogs/blog/ayurvedic-medicine-origin-history-and-principles
15. https://www.thehindubusinessline.com/news/science/*Ashwagandha*
16. Kulkarni SK, Dhar A. Withania somnifera: An Indian ginseng; Progress in Neuro-Psychopharmacology & Biological Psychiatry 2008;32:1093-1105.
17. Ramar S, Pushparaj P, Gopalakrishnakone P. A compilation of bioactive compounds from Ayurveda; Biomedical Informatics Publishing Group 2008;3(3):100-110.
18. Singh N, Bhalla M, Jager P, Gilca M. An overview on *Ashwagandha*: a rasayana (rejuvenator) of Ayurveda; African Journal Tradition Complement Alternative Medicine 2011;8(S):208-21.
19. Singh R. Medicinal Plants: A Review. Journal of Plant Sciences. Special Issue: Medicinal Plants 2015;3:1-1,50-55.
20. Sivasankarapillai S, Nair RMK, Rahdar A, Bungau S, Zaha DC. Overview of the anticancer activity of withaferin A, an active constituent of the Indian ginseng Withania somnifera; Environmental Science and Pollution Research, Springer Nature; Online Publication 2020.
21. Tohda C, Kuboyama T, Komatsu K. Dendrite extension by methanol extract of Ashwagandha (roots of Withania somnifera) in SK-N-SH cells; Lippincott Williams & Wilkins2000;11:9.
22. Vaishnavi K, Saxena N, Shah N, Singh R, Manjunath K, Muthukumarswamy U *et al*. Differential Activities of the Two Closely Related Withanolides, Withaferin A and Withanone: Bioinformatics and Experimental Evidences; Plos One Journal 2012,7(9).
23. Zahiruddin S, Basist P, Parveen A, Parveen R, Khan W, Gaurav Ahmad S. *Ashwagandha* in brain disorders: A review of recent developments; Journal of Ethno-pharmacology 2020;257:112876.