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REVIEW ARTICLE

Ashwagandha (Withania Somnifera): A Natural Remedy

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ABSTRACT

Ayurvedic practitioners have relied on ashwagandha root for more than three thousand years. In Ayurvedic medicine, ashwagandha is a common component. Among its traditional uses in Ayurveda are the treatment of fever, discomfort, gout, infections, asthma, cough, neurological disorders, and poisons. Ayurvedic practitioners believe that ashwagandha, an adaptogen, can increase one's lifespan, sharpen one's memory, improve fertility in both sexes, help one sleep better, and alleviate general weakness, particularly during old age or convalescence. Traditional medicine has made extensive use of the herb Withania somnifera, also known as Ashwagandha, for thousands of years, most notably in Ayurvedic procedures. Aphrodisiac, diuretic, anti-helminthic, narcotic, tonic, and stimulant are some of the pharmacological effects of the plant's root. Furthermore, ashwagandha's health benefits and possible enhancement of longevity are due in part to the plant's various parts, such as its leaves, shoots, seeds, and berries. The plant's abundance of bioactive chemicals gives it a wide range of beneficial health effects. Recent studies on ashwagandha's bioactivities have shown encouraging effects in a variety of therapeutic contexts, including anticancer, antioxidant, and anti-inflammatory actions.

Keywords: *Ashwagandha, Withania somnifera, Adaptogen, Antioxidant, Anti-inflammatory*

INTRODUCTION:

Fig No.1 Ashwagandha (Withania somnifera)

Southern Europe, the Middle East, Africa, and portions of Asia, especially central China, India, and Myanmar, are the original habitats of the ashwagandha plant (Withania somnifera (L.) Dunal; Solanaceae). The ashwagandha plant is native to dry, stony areas. Perennial and woody, it has berries that are orange-red and bloom with a vivid greenish-yellow colour. Vegetation can reach a maximum height of 150 cm. Ayurvedic practitioners have relied on ashwagandha root for more than three thousand years. In Ayurvedic medicine, ashwagandha is a common component. Among its traditional uses in

Ayurveda are the treatment of fever, discomfort, gout, infections, asthma, cough, neurological disorders, and poisons. Ayurvedic practitioners believe that ashwagandha, an adaptogen, can increase one's lifespan, sharpen one's memory, improve fertility in both sexes, help one sleep better, and alleviate general weakness, particularly during old age or convalescence. As ashwagandha became known for its ability to alleviate tension, anxiety, and other ailments, it found its way into Ayurvedic therapy. One of the most well-known herbs for the treatment of specific neurodegenerative illnesses, such as Alzheimer's, this plant is also known as an anti-inflammatory drug [2]. (3), (4) A number of cancers, including cell carcinoma, have benefited from ashwagandha's radio sensitising and anticancer properties. The plant's root extract is supposedly used to cure erectile dysfunction, performance anxiety, sexual weakness, and aphrodisiac symptoms in males. [6] Also, the plant's chemical constituents have shown antiviral activity, potentially effective against coronavirus, according to their discernible actions on viral receptors. [7, 8] There are hundreds of different formulations in folk medicine that include powdered plant roots or extracts of roots and leaves. [9]

A compound of the Sanskrit words ashwa and gandha, the common term ashwagandha means "horse's smell" in reference to the roots' perspiration-like aroma, which is reminiscent of a horse. (9, 10) For its medicinal qualities, this plant is also known as "Indian ginseng," "winter cherry," or poison gooseberry. [8]

As a rejuvenating substance that may promote health, increase physical energy, and maybe assist lengthen life, ashwagandha is called a "Rasayana" in Ayurvedic medicine. Alkaloids, steroidal lactones (especially withanolides and withaferins), saponins, glycol-withanolides, and other bioactive phytochemical substances are found in this medicinal plant. [9]
The medicinal properties of the roots make them widely used. Roots, blossoms, leaves, and seeds aren't the only elements of the plant that are good for you. Withanolides are a notable phytochemical component due to their well-documented pharmacological properties. Because of its many bioactivities, including immunomodulatory, anti-inflammatory, anti-angiogenic, antioxidant, pro-apoptotic, and anti adipogenic characteristics, the plant withanolide withaferin A has gained considerable attention [10]. Roots, blossoms, leaves, and seeds aren't the only elements of the plant that are good for you. Withanolides are a notable phytochemical component due to their well-documented pharmacological properties. Among the many bioactivities exhibited by the plant withaferin A—a withanolide—are its immunomodulatory, anti-inflammatory, antiangiogenic, antioxidant, pro-apoptotic, and anti-adipogenic capabilities.

Here we take a look at ashwagandha's bioactivity, including its antioxidant, anticancer, and anti-inflammatory effects, as well as its bioactive components, dosage recommendations, and safety profile [11].

Botanical description of Ashwagandha (*Withania somnifera*)
The Solanaceae family includes the little, usually upright, woody shrub, unarmed bush known as ashwagandha. Its maximum height is two feet. A fleshy, bristly-covered root system that is light brown in colour. For medicinal purposes, the plant's roots are the most important component. The leaves are opposite, tiny, smooth, petiolate, and basic in shape. In axillary, umbellate cymes, you'll find unremarkable flowers that are greenish or yellow. The fruit is a tiny, globose berry that becomes orange-red when ripe and is encased in a persistent calyx. The seeds are reniform and yellow. Gathering the crimson fruit in the late autumn allows for the drying of the seeds, which are then planted in the spring [12].

Fig.No.2 Botanical description of Ashwagandha (Withania somnifera)

Geographical distribution Ashwagandha (*Withania somnifera*)
It grows in the subtropical and arid regions of India. It can reach elevations of up to 1500 meters and is widespread in northwestern India, particularly in the states of Bombay, Gujarat, Rajasthan, Madhya Pradesh, Uttar Pradesh, and Punjab, as well as in certain mountainous regions like Himachal Pradesh and Jammu. [13] Islamabad, Afghanistan, Israel, Egypt, Jordan, Morocco, Spain, the Canary Islands, the Eastern African Congo, and South Africa are just a few of the various nations where you can find this species. [14]

Phytochemical constituents of Ashwagandha (*Withania somnifera*)

Researchers are perpetually intrigued by the phytochemicals found in Withania somnifera. Researchers have extracted and identified groupings of compounds from this species, including steroidal lactones, alkaloids, flavonoids, and tannin. (pp. 15–16) More than thirteen alkaloids, one hundred and thirty-eight withanolides, and a number of sitoindosides—a withanolide that contains a glucose molecule at carbon twenty-seven—have been extracted from the aerial parts, roots, and berries of Withania somnifera. (pages 17–25) An unanticipated shift in secondary metabolic profile could result from environmental changes. [26] in The primary chemical components of this plant, known as withanolides, are mostly found in its roots and leaves. Their component concentration ranges from 0.001% to 0.5 % by dry weight. These C28-steroidal lactones are based on an ergostane structure that has a six-membered lactone ring formed by oxidising C-22 and C-26. The 'withanolide skeleton' is the fundamental building block. in references 27–29 The structural formula for withanolide is 22-hydroxyergostan-26-oic acid, 22-lactone. As a result of adjusting the carbocyclic skeleton or side chain, new structural variations involving anolides surface. Researchers have found enzymes in these polyoxygenated compounds that can oxidise every carbon atom in the steroid nucleus, according to plant studies. Steroids of the ergostane type and withanolides share the identical C8 or C9 side chain with a lactone or lactol ring, as shown in [30]. The carbocyclic portion of the molecule is fused with the six-membered lactone ring via an oxygen bridge or a C-C bond. Bond scission, new bond creation, ring aromatisation, and countless additional configurations leading to unique structures are all possible outcomes of the oxygen side chain. 30 and 31 While Withaferin A is the main component of Withania somnifera, W. coagulants contains a significant quantity of coagulin L. The plant ashwagandha has a rare thio-dimer of withanolide. [32]

W. coagulants isolated from withanolides have a 14,20-epoxide bridge that is unique to them. The number 33. Isolated from W. somnifera recently was a new chlorinated withanolide, 6achloro-5b,17a dihydroxy withaferin A. on page 34 Nicotine, somniferinine, withanine, pseudowithanine, tropine, 3a-tigloyloxytropane, choline, cuscohygrine, dl-isopelletierine, and new alkaloids anaferine and anhygrine are among the many other chemical components that have been documented. 35 and 36 In addition to acylsteryl glucosides, starch, hantreacotane, and ducitol, the plant contains a number of chemical components, including amino acids, glycine, glutamic acid, tryptophan, proline, tyrosine, alanine, glycine, cysteine, and iron. [37]

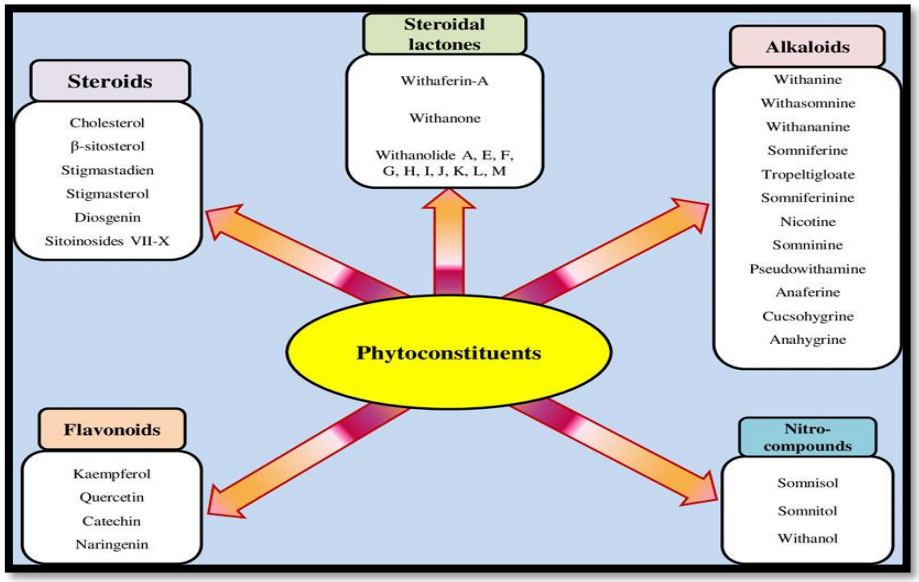

Fig.No.3 Phytoconstituents of Ashwagandha (Withania somnifera)

The main constituents of ashwagandha are withanolides, withaferins and withanosides, which are steroidal lactones. Several alkaloids (eg ashwagandine, ashwagandinine and others) have also been isolated from ashwagandha. Evidence from preclinical studies suggests that most pharmacological activities are attributable to withanolides A and D, and with aferin A; several other constituents have also been reported to be bioactive. [38]

Ayurvedic view on Ashwagandha *(Withania somnifera)*

Important in Ayurveda is the herb ashwagandha, whose scientific name is Withania somnifera. This herb has a long history of use in Ayurvedic medicine, where it is considered a Rasayana that promotes overall health. 37 and 40 According to ayurveda, the Rasapanchaka of Ashwagandha is displayed With a Kapha (water and earth) and Vata (air and space) sedative effect, ashwagandha is a powerful herb. The "Vata" constitution, associated with space and air, is the most typical patient for whom this plant is used for therapeutic purposes. It keeps the Vata energy steady, which in turn keeps the skin and joints pliable, the weight steady, the endurance high, the cerebral ability high, and the sensory system in good working order. [41] The As a tonic for hormonal capacity and memory endurance, the rasayana plant is used. There are various therapeutic uses of this plant which is shown in curing Murchha (syncope), Apasmara (epilepsy), Shosha (cachexia), Unmada (craziness/psychosis), Karshya (weakening), Arsha (heaps), Prameha Pidika (diabetic carbuncle), Arbuda

(tumour), Gandamala (cervical lymphadenitis), Bhagandara (fistula-in-ano), Guhya-vrana (ulcer in genitalia), Vatarakta (gout), Kushtha (illnesses of skin), Kilasa (vitiligo), Asthibhanga (bone break), Katigraha (stiffness in lumbo-sacral area), Gridhrasi (sciatica), Hanugraha (jaw spasming), JanStabdhata (firmness of the knee), Hrudgraha (cardiovascular disappointment), Yoni dosha (issues of female genital lot) and Vidradhi (ulcer)[42]. Some important Ashwagandha benefits according to Ayurveda Increases desire for sexual activity (Vajikara) Boosts Energy Levels with Rasayani Balya cultivates power Improves sperm quality and quantity; ati shukrala Shwitrapaha is effective in removing white spots from the skin. Shothahara—An effective method for treating oedematous disorders and aiding in the elimination of Ama, or toxins, from various parts of the body. Kshayapaha - Beneficial in dietary situations and for alleviating lethargy. References [43,44]

Ashwagandha (Withania somnifera): A contemporary perspective

More than half of the medications in use today are based on herbal plants or chemical components obtained from plants. The pharmaceutical business is crucial to global economic growth. [45] An innovative treatment has transformed the drug discovery process. A major worry over the processing and adulteration of herbal medications arises whenever the topic of their development is brought up. Separate chemicals derived from these The chemical processes or synthesis that natural plants go through change them. Eighty percent of the medications used today to treat infections, heart conditions, and immunosuppression come from plants. The pharmaceutical industry has found numerous medicinal applications for withania somnifera, including sports nutrition, memory, anti-aging, immunological support, and weight management. There are primarily three market segments that it enters: dietary supplements, cosmetics, and beverages. Dietary supplement sales have also increased in the US. As a result of these market-driving factors, manufacturers are continuously releasing new herbal products, which leads to an increase in the adulteration rate and a compromise in the quality of the herbal formulation. [46]

The physiologic effects of ashwagandha

In order to learn about the medicinal and pharmaceutical properties of this plant, numerous investigations have been carried out. Clinical trials on a larger scale are still required to confirm this herb's effectiveness, particularly in stress-related illnesses, neurological disorders, and malignancies. [1]

An array of beneficial effects have been documented in preclinical research on various ashwagandha root extracts and powders, including antioxidant, anti-cancer, anti-aging, anti-diabetic, anti-stress, adaptogenic, immunomodulatory, cardioprotective, and neuroprotective properties. Researchers have looked at the benefits of ashwagandha root (and occasionally leaf) extracts in a number of conditions, such as stress, anxiety, sleeplessness, schizophrenia, diabetes, male infertility, hypothyroidism, and obsessive-compulsive disorder. [47]

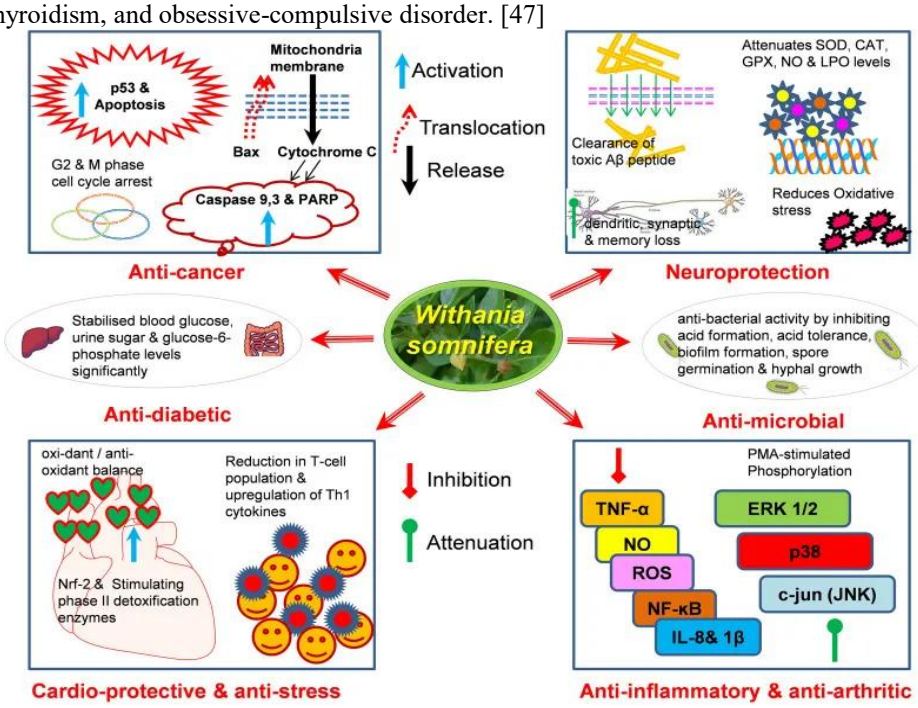

Fig.No.4 Biological uses of Ashwagandha (Withania somnifera)

Anticancer Activity

Bioactive components of Withania somnifera have shown promising results in improving a range of cancers and cancer-related alterations in cell lines. Because it targets numerous oncogenic pathways at once, thanks to its pleiotropic mechanism of action, it has proven to be an effective anticancer drug [48,49]. Withania somnifera has the potential to combat cancer in a number of ways. To begin with, its anti-inflammatory properties make it a promising adjuvant treatment that may lessen the side effects of radiation and chemotherapy. Furthermore, its radio- and chemo-sensitization characteristics make it a potential addition to traditional chemotherapeutic regimens, which could enhance the therapeutic benefits of radiation and chemotherapy in a synergistic manner [50].

By interacting with cancer cells through at least five different signalling pathways—apoptosis, granulocyte-macrophage colony-stimulating factor, death receptor, p53, and the G2-M DNA damage checkpoint—ashwagandha's leaf extract and its constituents exhibit cytotoxic effects. By stimulating the production of reactive oxygen species (ROS), withaferin-A was able to induce cell death in melanoma cells, thereby demonstrating its anticancer efficacy. Upstream of cytochrome-C release and nuclear translocation of apoptosis-inducing factor, withanolides contribute to ROS generation and mitochondrial membrane potential perturbations. Along with downregulating the expression of the pro-apoptotic factor, withaferin-A promotes overexpression of the tumour necrosis factor receptor (TNFR)-1. Make a bid. In human lymphoma cells, withaferin-A induces apoptotic processes through the mitogen-activated protein kinase (MAPK) signalling cascade, caspase-3 activation, B-cell lymphoma-2 (Bcl-2) down-regulation, reactive oxygen species (ROS) production, and enhanced poly-ADP-ribose-polymerase PARP cleavage. in the text.
Many investigations, both in the lab and in living organisms, have shown that ashwagandha has potential as a breast cancer treatment, especially for ER/PR positive and triple-negative breast cancers. In the context of breast cancer, preclinical evidence suggests that ashwagandha has chemo-preventive potential. On the other hand, there have been limited clinical trials that have investigated its effectiveness as an auxiliary treatment for breast cancer, and the results have shown that it may improve patients' quality of life. [51] The therapeutic effects of Withania somnifera extracts have been evaluated in recent randomised, double-blind, placebo-controlled trials at doses ranging from 200 mg/kg to 1000 mg/kg. The results show that Withania somnifera is effective at these dosages, and participants report no side effects or adverse reactions. Research on both the plant and its main ingredient, withaferin-A, has shown promise in the fight against cancer. This includes both human cancer cell lines and animal models. [50]

Antioxidant Activity

The impact of ashwagandha on changes in antioxidant indicators has been demonstrated in numerous research. [52] The plant's antioxidant and free radical scavenging capabilities make it a popular adaptogen and energy enhancer. Withaferin-A, withanone, withanolide-B, withanoside-V, and 1,2-deoxywithastramonolide are the main withanolides responsible for its antioxidant and free radical scavenging properties. The crucial impact of these bioactive chemicals in reducing oxidative stress and improving physiological resilience has been proven. in the 53rd. In addition to its effect in altering immune system function, ashwagandha has demonstrated strong antioxidant characteristics and the ability to scavenge free radicals. Researchers have shown that some of the bioactive components in ashwagandha can help fight against the free radicals that are associated with Alzheimer's disease. Axon, dendrite, and synaptic degeneration in the hippocampus and cerebral cortex can be inhibited by withanolide-A, according to in vitro and in vivo investigations. On top of that, withanolide-A improves memory problems in mice. By inhibiting the production of free radicals in human embryonal neuroblastoma cells, research showed that extract from Withania somnifera had antioxidant characteristics [54]. In addition, withaferin, a plant extract, significantly reduces amyloid formation and the expression of the gene for neuro-inflammatory chemicals. [55] The Antioxidants include glutathione S-transferase, glutathione peroxidase, superoxide dismutase, catalase, and glutathione reductase have their activity increased at various doses of Withania somnifera, according to previous research. Researchers found that the plant's antioxidant properties helped preserve the integrity of the spinal cords of elderly mice. Also, research has shown that the plant extract successfully blocks lipid peroxidation, a pathway associated with human heart disease. [56] Previous studies have shown that methanol extracts of ashwagandha roots have the strongest radical scavenging activities, and that there is a correlation between the antioxidant activity and the total polyphenolic content of the extract. Strong antioxidant, hydrogen peroxide, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, metal chelating, and superoxide-anion scavenging properties have been found in the methanolic extract of Withania somnifera, suggesting that it may have significant therapeutic value. [57]

Anti-inflammatory activity

The anti-inflammatory properties of ashwagandha have been supported by numerous research. This could be because of the synergistic action of the plant's alkaloids and withanolides, which are present in it. [58] Diabetes mellitus, cardiovascular disease, autoimmune diseases, cancer, neurodegenerative diseases, and pulmonary illnesses are only some of the inflammatory-related conditions that have been studied for potential treatment with this plant. Experimental studies have demonstrated that the plant can regulate mitochondrial activity and cell death, and it can reduce inflammation by blocking the production of nitric oxide, inflammatory indicators like cytokines (including TNF-α and Interleukin (IL)-6), and reactive oxygen species. Further, ashwagandha's ability to decrease inflammatory biomarkers and pro-inflammatory cytokine expression while increasing anti-inflammatory cytokine expression has made it an attractive therapeutic target for proteinuria, nephritis, rheumatic disorders, and skin inflammation. [59, 60].Multiple illness models have demonstrated that withania somnifera has strong anti-inflammatory properties. By reducing swelling, neutrophil infiltration, and necrosis in inflammatory bowel illness caused by trinitrobenzene sulfonic acid, the root extract showed anti-inflammatory and much-restorative effect. In a mouse lupus model, the root powder had a significant inhibitory effect on some inflammatory indicators, including proteinuria and nephritis. It also reduced levels of nitric oxide and reactive oxygen species and cytokines including IL-6 and TNF-α. in the text. Also, ashwagandha suppresses the production and release of pro-inflammatory cytokines, and it lowers blood levels of these cytokines, according to animal experiments. [61] in The anti-inflammatory effects of a water-soluble ashwagandha extract were shown in a study that examined how C-C Motif Chemokine Ligand 2 (CCL2) and C-C Motif Chemokine Ligand 5 (CCL5) genes were affected by stimulation with TNF-α or Lipopolysaccharide (LPS). A possible correlation between this impact and a decrease in NF-Kb activity has been

found. Based on these results, ashwagandha has the potential to be a powerful botanical remedy for the treatment of renal failure. [62]

The inhibition of inflammatory biomarker generation by ashwagandha was found to be dose-dependent. [63] The ability to suppress the pro-inflammatory cytokines IL-1β and TNF-α in human monocytes generated by Lipopolysaccharide (LPS) and Tamm Horsfall Protein-1 (THP-1) and to generate superoxide in human monocytic cells caused by Phorbol 12-myristate 13-acetate (PMA) is demonstrated in a dose-dependent manner. These results point to a decrease in neuroinflammation, which may explain why Withania somnifera is effective in reducing anxiety. The antioxidant role through superoxide inhibition and strong inhibitory effects on IL-1β and TNF-α production were highlighted by the in vitro investigation, which may highlight its positive roles on anxiety caused by chronic unexpected stress (CUS). Animal models of stress-induced anxiety and CUS-induced physiological changes were successfully treated with Withania somnifera, according to subsequent in vivo investigations. [60]

Anti-stress
Metabolites derived from White Willow have reportedly shown promise in treating a range of neurological conditions, including insomnia, anxiety, epilepsy, catalepsy, depression, and epilepsy. The extract increased serotonin levels in the hippocampus by suppressing corticosterone stimulating choline acetyltransferase, according to the study. When cultured neurones were exposed to Aβ 25-35, withanolide A, and withanoside IV administered into rats, it resulted in an increase in neurite outgrowth. Sominone, an aglycone of withanoside IV, was also identified as the primary metabolite responsible for the central nervous system activity. I have read [64,65]

Anti-microbial
The ethanolic extract of the leaves or whole plant of W. somnifera was used to isolate chemical constituents withanolides which demonstrated anti-microbial properties. The experimental study on mice showed antimicrobial activity of aqueous fruit extracts which were administrated orally against salmonella infection. It was also found that extract increased survival rate in mice as well as decreased the bacterial load in various vital organs. [66-68]

Immunomodulatory
Research on animal models revealed that ashwagandha significantly reduced immunological reactivity. Researchers used cyclophosphamide, azathioprine, prednisone, and ashwagandha to suppress the immune system in mice. The levels of haemoglobin, red blood cells, platelets, and overall body weight were all shown to be considerably elevated in mice that were given ashwagandha. [69] It was also shown that compared to the group treated with just cyclops hosphamide (CTX), animals given Ashwagandha extract had a much lower incidence of leucopenia and a higher concentration of a-esterase positive cells in their bone marrow. [70] When tested on human B and T cells as well as thymocytes from mice, withaferin A and withanolide E both showed a distinct immunosuppressive impact. [71] The In contrast to withaferin A, which impacted both B and T lymphocytes, withanolide E produced an effect that was exclusive to T lymphocytes. Pages 72–75

Hepato-protective
Various studies showed that the extract of roots of W. somnifera have hepatoprotective activity. The extract influenced the levels of lipid peroxidation and therefore provided the hepatoprotection.[76] In another study it was reported that roots of W. somnifera consist of different flavonoids and neurotransmitters that activates the neuroendocrine system, resulting in hyperactivity of the endomembrane and exit out of molecules via exocytosis.[77]

Anti-arthritic
When administered topically, W. somnifera alleviates neuralgic pain. [78] Research has shown that W. somnifera can alleviate arthritis symptoms. [79] is a Its antipyretic and analgesic properties are well-known. The hot plate approach was used to elicit heat analgesia in rats, according to a study. After 2 hours, the analgesic efficacy of W. somnifera administration was found to be 78.03%. Paracetamol, on the other hand, showed no effects. [80]

Anti-ulcer
It was observed that W. somnifera significantly safeguard against 18 hours immobilization, cold, immobilization and aspirin induced gastric ulcer. Hence the plant was proved to possesses that anti-ulcer property. [81]

Hypocholesterolemic and Hypolipidemic
A study was reported that root powder of W. somnifera decreases total lipid, cholesterol, and triglycerides in hypercholesterolemia animals. W. somnifera showed hypocholesterolemic activity in male albino rats and it could have also mediated through an increased bile acid synthesis for elimination of body. [82]

Anti-ageing
A clinical trial study was carried out to observe the anti-ageing properties of W. somnifera. In the trial, root powder (0.5 g) was given orally to 101 normal healthy males (50-59 years) for three times in a day for a year. Results showed increase in Hb, RBC, hair melanin and seated stature in treated group in comparison to placebo group. So, after this study the plant is also known for anti-ageing effects.[83]

Neurodegenerative diseases

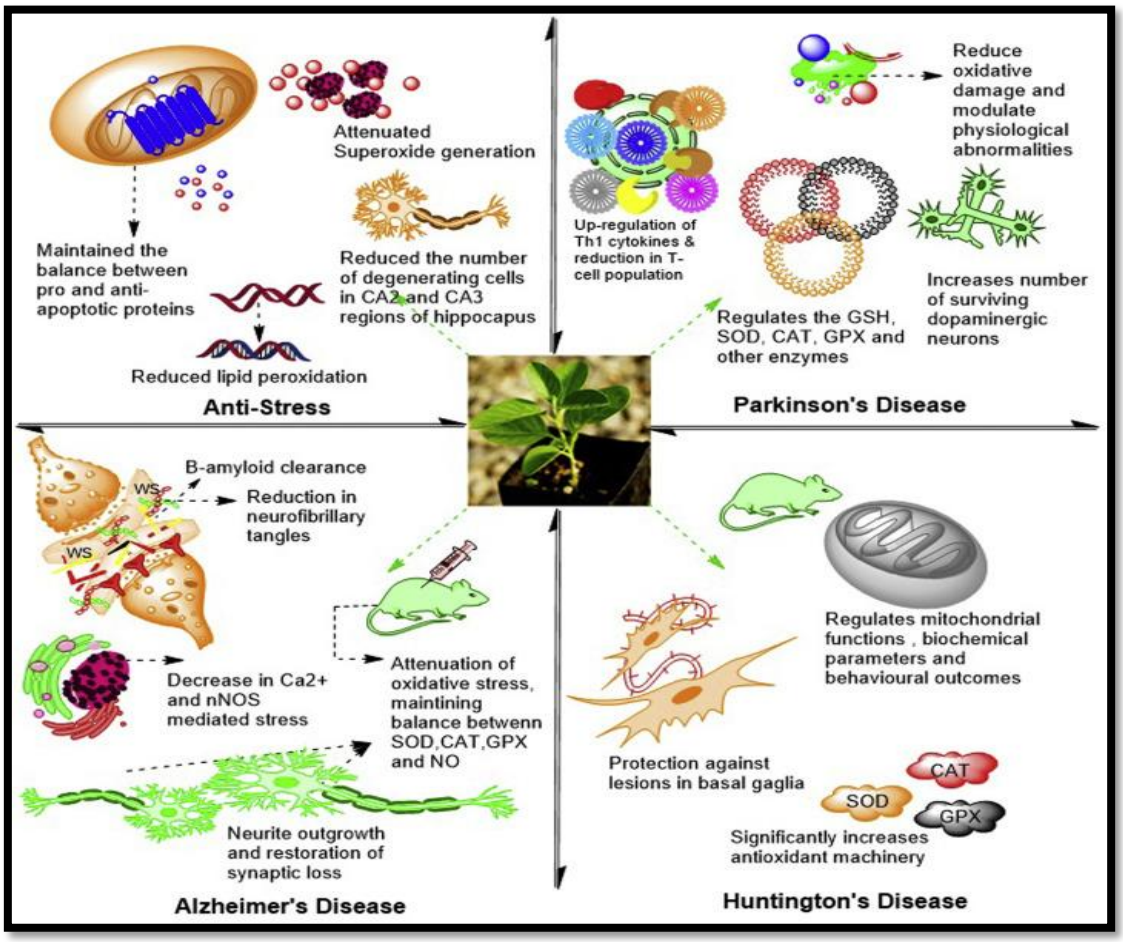

Fig.No.5 Effect of Ashwagandha on Neurodegenerative diseases

Patients with Alzheimer's diseases having cognitive impairment caused by neuriticatrophy and synaptic loss.[84] as per neuropathological post-mortem studies of the brain. The atrophy of neurites has also been observed as an important part of the etiology in the patients suffering with Parkinson's disease, Huntington's disease, and Creutzfeldt– Jakob disease. There are number of studies which showed that Ashwagandha slows, stops, reverses or removes neuritic atrophy and synaptic loss. Glycowithanolides withaferin- A and sitoindosides VII-X extracted from the roots of Ashwagandha significantly reversed ibotenic acid induced cognitive defects in Alzheimer's disease model. [85,86]

Ashwagandha's Dosage and Toxicity

Previous studies investigating the toxicity of various formulations, such as methanolic extracts, decoctions, root pastes, seed powders, and hydroalcoholic extracts, have shown that the active ingredients are present in different portions of the plant in varying concentrations. A recent study evaluated the acute and sub-acute oral toxicities of ashwagandha in animals; the results indicated that all the animals showed a gradual weight gain, and there were no signs of intoxication or significant alterations in blood biochemistry as well as the histo pathological examinations of the organs remained within normal limits. The plant root powder extract shows no significant abnormalities, even with repeated doses of up to 800 mg/kg, which is five-fold higher than the recommended dose for humans. [87,88]

Another study analyzing the toxicity profile of ashwagandha indicated that it is safe in mice at doses of 2000 mg/kg and 500 mg/kg in acute and repeated dose toxicity, respectively, with a low oral bioavailability.[89] Similarly, ashwagandha root and leaf extract at 1,000 mg/kg for 90 days showed no harmful effects on treated rats as well as it was found that the hematological and biochemical profiles were comparable to controls, and major organs appeared normal in histopathological examinations.[90] Furthermore, no adverse outcomes were reported for a methanolic extract standardized to 4.5% withaferin-A when administered to rats at doses of 500, 1,000, and 2,000 mg/kg per day for 28 days.[91]

A human study demonstrated that the plant extract, when administered in capsule form as an aqueous solution, was found to be well-tolerated at gradually increasing dosages ranging from 750 to 1250 mg per day. The formulation was tested to assess hematological and biochemical organ function and found to be safe. Furthermore, in line with its historical use, this study showed improvements in sleep quality, reductions in lipid levels, and enhancements in muscle strength.[92]

A recent clinical study conducted on eighteen healthy male subjects aimed to assess the tolerability and safety of standardized capsules of the ashwagandha root extract at 1000 mg/day dose upon oral administration found that following four weeks of administration, no appreciable changes or anomalies were seen in safety metrics such as kidney, liver, and thyroid functions, and the participant's hematological, biochemical, and physical features were all normal.[93]

In recent years, its application as a dietary supplement has increased in Western countries, often used for unverified indications related to mental health disorders and as an ergogenic aid among fitness enthusiasts. This report involves eight cases of hepatotoxicity associated with ashwagandha supplementation. All patients had preexisting hepatic conditions, and the observed mortality rates weresignificantly elevated due to delays in liver transplantation.[94]

In another study, five liver injury cases were associated with the ashwagandha dietary supplement. The liver injury pattern was consistent among all cases, showing a mixed and cholestatic profile, along with significant hyperbilirubinemia. Each patient was subjected to a thorough and detailed diagnostic evaluation, and a confirmation of all cases was conducted individually by a committee of experts in the field, utilizing the Drug-Induced Liver Injury Network structured expert opinion causality assessment method.[95]

Similarly, a study concluded that while glutathione detoxifies with withanone, which is a metabolite of ashwagandha, low levels of glutathione may contribute to DNA damage. This could explain the reported liver damage linked with ashwagandha use.[96]

Adverse effects

Limited data from small clinical trials indicate that ashwagandha is generally well-tolerated: non-serious, mild gastro intestinal symptoms are the most frequently reported adverse effects. However, comprehensive investigation of the clinical safety profile of ashwagandha and its important constituents when used in a pharmaceutical/medicinal con text, including long-term use, is required. Spontaneous reports of adverse reactions associated with ashwagandha include diarrhoea, vomiting, nausea, abdominal pain, jaundice, pruritus and others; causality has not necessarily been established in these cases. In September 2023, the Netherlands pharmacovigilance center (Lareb) published a safety signal relating to the potential risk of liver toxicity with products containing ashwagandha after receiving four reports of hepatitis, abnormal hepatic function and jaundice, cholestasis and transaminitis in patients who had used ashwagandha for 3–10 months.[47] Causality has not been established definitively in these cases: three patients used other herbal, and/or non-herbal supplements, and/or other medication, concurrently. Also, the possibility that the adverse reactions are due to poor-quality products could not be ruled out. VigiBase, the World Health Organization's (WHO) global database of individual case safety reports of suspected adverse drug reactions, maintained by the Uppsala Monitoring Centre on behalf of WHO, contains 15 reports of hepatobiliary disorders and investigations associated with ashwagandha. Published case reports and case series have also described liver injuries associated with ashwagandha. To date, hepatotoxicity and abnormalities in liver enzyme concentrations have not been reported in clinical trials.

Evidence for efficacy

Preclinical studies testing different ashwagandha root extracts (including ethanolic, methanolic, and/or standardized extracts) and root powder have described antioxidant, anti-cancer, anti-ageing, anti-diabetic, anti-stress, adapto genic, immunomodulatory, cardioprotective, and neuroprotective effects. [1] Clinical studies of ashwagandha root (and, sometimes, leaf) extracts have explored effects in various indications, including stress, anxiety, insomnia, schizophrenia, obsessive- compulsive disorder, diabetes, male infertility, and hypo thyroidism. [1,38,47] Many of these studies reported benefits with ashwagandha across several different outcome measures. However, typically, these studies involved small numbers of participants and had other methodological limitations, hence, at present, there is no definitive evidence for efficacy in these conditions. In addition, different formulations, doses and dosages of ashwagandha were tested in the studies. KSM-66 ® , an ashwagandha root extract manufactured in India, was the most frequently investigated product. Across all studies, the risk of bias was considered low for those exploring the effects of ashwagandha on stress, anxiety, and physical performance, while studies in sexual function and fertility carried some risk of selection and reporting bias.[97]

A meta-analysis of randomized controlled trials of ashwagandha for stress and anxiety indicated that ashwagandha significantly reduced anxiety (SMD: −1.55, 95% CI: −2.37, −0.74; P = 0.005, I 2 2 = 93.8%, 8 studies, 540 participants) and stress (SMD: −1.75, 95% CI: −2.29, −1.22; P = 0.005, I = 83.1%, 7 studies, 286 participants), compared with placebo.[98]

CONCLUSION

Ashwagandha (*Withania somnifera*), a cornerstone herb in Ayurvedic medicine, demonstrates a unique integration of traditional knowledge and modern pharmacological evidence. Its wide array of bioactive constituents—principally withanolides, alkaloids, sitoindosides, and steroidal lactones—provide the molecular basis for its diverse therapeutic properties. These compounds collectively contribute to adaptogenic, anti-inflammatory, immunomodulatory, neuroprotective, and anti-stress activities, which have been documented in both preclinical and clinical studies. Such findings not only validate its long-standing traditional uses in promoting vitality, cognitive function, and stress resilience

but also position the herb as a promising candidate for integrative and complementary medical practices. However, the therapeutic potential of Ashwagandha should be considered alongside its safety profile. Although the herb is generally well tolerated, emerging reports of gastrointestinal upset, allergic reactions, potential thyroid modulation, and hepatotoxicity in sensitive individuals highlight the need for prudent dosing and patient-specific assessment. Variability in plant chemotypes, extraction methods, and formulation standards can also influence pharmacological outcomes and safety, underscoring the necessity for standardized preparations and rigorous quality control. In light of these considerations, Ashwagandha represents a compelling model of how traditional medicinal plants can be scientifically evaluated and incorporated into modern healthcare. Continued research—particularly large, well-designed clinical trials—will be essential to fully elucidate its mechanisms of action, establish optimal therapeutic regimens, and define its long-term safety in diverse populations. By balancing evidence-based benefits with potential risks, Ashwagandha can continue to bridge the gap between traditional and contemporary medicine, offering a natural, multi-targeted approach to improving human health and well-being.

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