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RESEARCH ARTICLE

From Ancient Herb to Modern Medicine: The Therapeutic Promise of Ashwagandha (*Withania somnifera*) in Human Health — A Review

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ABSTRACT

Withania somnifera is an Crucial Rasayana herb and widely considered as Indian ginseng in Ayurveda. In traditional system of Indian medicine, In Ayurvedic preparations, various parts of the plant have been used to treat variety of disorders that affect the human health Ws is a potent neuronal tonic and has been used in animal models to treat a number of neurological conditions, including Parkinson's disease, epileptic, memory loss and depression It has pharmacological action in almost all systems of the human body. It has also some side effects and contraindication. Number of pharmacological studies have been conducted and a wide range of biological activities have been observed such as anti inflammatory property, hepato-protective activity, infertility activity, anti bacterial activity, immune-modulator activity, Haemopoitic effect, Antbiotic activity, Anti-hyperglycemia, Cardio-tonic activity, Anti-tumour activity, Anti-Carcinogenic activity, Snake venom neurotoxicity were carried out previously that showed its anti-oxidative effect, synergistic effect with other medicinal herbs and its efficiency to increase catecholamines level and regulation of apoptotic processes Extensive studies are needed to prove its therapeutic efficacy in neuronal disorders.

Keywords: kAshwagandha, Withania somnifera, Ayurveda, Rasayana herb, Neuroprotective activity, Antioxidant activity, Anti-inflammatory activity, Immunomodulatory activity, Antibacterial activity, Antitumor activity.

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INTRODUCTION

"Indian Ginseng" and "Indian Winter Cherry" are the two most popular names for ashwagandha (Withania somnifera, fam. Solanaceae) [1,2]. Many ailments, such as stress [3], anxiety [4], arthritis [5], and other disorders affecting the central nervous system (CNS), such as Parkinson's [6,7] and Alzheimer's [8], can be effectively treated with this indigenous medicinal plant. Ashwagandha has been shown to improve memory and the functioning of the brain and nervous system. Sexuality and reproductive stability are promoted by its enhancement of the reproductive system. It is a powerful adaptogen, meaning it makes the body more flexible while under stress. This increases cell-mediated immunity, which fortifies the body's protections against disease. Ashwagandha's potent antioxidant properties can outweigh defense against free radical-induced cellular damage [9]. Chemical components that are biologically active include steroidal lactones (withanolides, withaferins), alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), and saponins [10]. It has immunomodulatory effects in many of its constituent elements [11]. Ws aerial parts are used to create 5-dehydroxy withanolide-R and withasomniferin-A [12]. Ashwaganda extract pretreatment in rats prevented all the changes caused by 6-hydroxydopamine (6-OHDA), an animal model of Parkinson's disease, in antioxidant enzyme activities, catecholamine content, dopaminergic D2 receptor binding, and tyrosine hydroxylase expression. Consequently, our research indicates that ashwagandha

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might help stop Parkinson's disease-related neuronal degeneration [13].As stated by Gupta LG and Rana AC (2007), the entire plant, roots, stem, seeds, leaves, and fruits of Ws were utilized for a number of experimental studies to elucidate their medicinal applications. Ws's roots are the main plant parts that are utilized medicinally. Dried roots of ashwagandha have been shown to help treat neurological and sexual disorders [14,15]. Ws extract's biological properties demonstrated its capacity to act as an antioxidant and scavenge free radicals [16]. Additionally, Ws is a potent neuronal tonic and has been used in animal models to treat a number of neurological conditions, including Parkinson's disease [6], epileptic [17], memory loss [18], and depression [5].

Indication described in Ayurvedic Medicine

According to Ayurvedic literature, ashwagandha is advised for the following ailments: Guhya-vrana (genital ulcer), Guhya-vrana (syncope), Apasmara (epilepsy), Shosha (cachexia), Unmada (mania/psychosis), Karshya (emaciation), Arsha (piles), Pramehapidika (diabetic carbuncle), Arbuda (tumor), Gandamala (cervical lymphadenitis), Katigraha (stiffness in the lumbo-sacral region), Gridhrasi (sciatica), Hanugraha (lockjaw), Janustabdhata (kne), Hrudgraha (cardiac failure), Yonidosha (disorders of the female genital tract), and Vidradhi (abscess) [19–20].

Taxonomical Classification

The plant belongs to Division-Angiosperma, Class-Dicotyledons, Order- Tubiflorae, Family Solanacae, Genus -Withania and Species- somnifera[21].

Morphology

Approximately two feet in height, Withania somnifera is a tiny, woody shrub belonging to the Solanaceae family. Among the regions where it flourishes are Africa, the Mediterranean, and India. In the drier parts of India, this upright, evergreen tomentose shrub thrives in waste areas and on bunds. Its height is between 30 and 150 cm. Sturdy, fleshy, white-brown roots; simple, ovate, glabrous leaves, with smaller, opposite leaves in the floral region; undetectable, lubrid-yellow or greenish flowers in axillary, umbellate cymes; small, globose, orange-red berries when fully grown, enclosed in the persistent calyx; yellow, reniform seeds.

The entire plant, including roots, leaves, stem, green berries, fruits, seeds, and bark, was used for medicinal purposes, with the roots being the main component used, and the seeds dried for growth the next spring after the bright red fruit is harvested in late fall [21].

Geographical Distribution

The main Indian states that produce ashwagandha are Rajasthan, Punjab, Haryana, Uttar Pradesh, Gujarat, Maharashtra, and Madhya Pradesh. In Madhya Pradesh alone, ashwagandha is grown on over 5000 hectares. Given that the country's expected production is over 1500 tonnes and the annual demand for ashwagandha roots is over 7000 tonnes, more cultivation and production are needed [22].

Plant pathology

There are several diseases and pests that might affect Withania somnifera. In the plains of Punjab, Haryana, and Himachal Pradesh, Alternaria alternata is the primary cause of the most prevalent disease, leaf spot disease. When leaf spot disease strikes, there have been reports of the pharmaceutically active chemicals biodeteriorating [23] The rot of the stem and leaves of Withania somnifera is induced by Choanephora cucurbitarum [24]. They seem brown, rough, and woody due to a treehopper that eats the apical portions of the stem. The plant slowly withers away as the apical leaves fall off [25]. 4. In India, carmine red spider mites (Tetranychus urticae) are the most prevalent pest of the plant [26].

Phytochemicals

Chemical Components of Withania somnifera Plant extract and active components, both in the whole plant and in specific parts (roots, stems, and leaves), have been used to cure a wider range of human ailments. The main ingredients of ashwagandha include alkaloids and steroidal lactones. Among its chemical components are withanine, somniferine, somniferinine, withananine, pseudo-withanine tropane, pseudo-tropine, choline, anaferine, anahydrine, and isopelletierine. Steroid lactones known as "withanolides" are present in the leaves. A lot of attention has been focused on withaferine A's antibacterial and antitumor qualities. A paste made from its leaves is used to treat inflammation of the tubercular gland. Fruits and seeds have a diuretic impact [27].

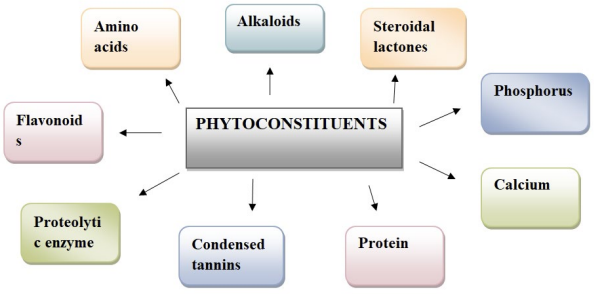

Fig 1: Phytoconstituents of Ashwgandha.

The green berries include amino acids, flavonoids, a proteolytic enzyme, and condensed tannins.They include a large number of free amino acids, including proline, valine, tyrosine, alanine, glycine, hydroxyproline, aspartic acid, glutamic acid, cystine, and cysteine. The presence of the proteolytic enzyme chamase may be the cause of the berries' high content of amino acids. The tender shoots are rich in crude protein, calcium, and phosphorus and are not fibrous. They have allegedly been found to contain scopettin. The stem contains condensed tannins and flavonoids. The bark contains a variety of free amino acids [28].

Pharmacological effects of Withanolides

Withania somnifera's many pharmacological properties are mostly due to its active ingredients, withanolides [29]. Its anti-aging [31], anti-oxidant properties [30], and anti-cancer [32] properties have made Ws root extract a useful pharmaceutical ingredient. Clinical observation by Andallu B and Radhika B.2000 [33] demonstrated that diabetic, diuretic, and hypocholesterolemic chemicals may be present in Ws roots. Sitoindosides VII–X and withaferin-A, the two active components of ashwagandha, have shown strong antistress efficacy in a range of stress-induced paradigms [34] and high antioxidant activity in a rat model [35]. As hormone precursors, the withanolides can be converted into human pathophysiological hormones when needed [36]. As per Ahmed M. et al. (2005), [37] Ws extract pretreatment was found to decrease all changes in antioxidant enzyme function, catecholamine content, dopaminergic D2 receptor binding, and tyrosine hydroxylase expression in a dose-dependent manner in the Parkinson's disease rat model (Parkinson's triggered by 6-hydroxydopamine (6-OHDA)). By occupying cell membrane receptors and preventing the binding of actual hormone, Ws thus seems to have a concentration-dependent pharmacological activity. As shown by Kobuyama T et al. (2002) [38], withanolide A, which is isolated from the root of Ws, can regenerate neurites and repair synapses in severely damaged neurons in mice. One of the main ingredients in physiologically active steroids, withaferin A, has demonstrated potent anti-inflammatory properties [39] and anti-cancer [40] effects among Ws withanolides. As a result, the study showed the pharmacological potential of Ws, which could be applied to future PD therapy approaches.

Pharmacological evidences

Shown in Fig 2

Anti inflammatory property

The alcoholic extract considerably lowers inflammation in both acute and chronic forms. The root extract had a potent anti-inflammatory activity when administered orally against inflammation induced by carrageenin [41]. Using experimental models of chronic inflammation and CCl4-induced liver damage in albino rats, the leaf extract showed anti-inflammatory action [42]. Ashwagandha shown a potent anti-inflammatory effect on protein denaturation in vitro. The impact was most likely caused by the amounts of withanolide and alkaloids in ashwagandha [43]

Hepatoprotective activity

The significant suppression of CCl4-induced alterations in transcription factors activity and pentobarbitone sleeping time by an alcohol-based extract of the plant's leaves suggested the presence of hepatoprotective activities. Investigations using histopathology confirmed this [44].

Infertility activity

In mice, roots result in infertility; they slowed down the processes of oestrus and mating but did not completely prevent them. Tuber roots can cause infertility and smaller litters, and they have no uterus stimulating effects on separated guinea pig uteri [45].

Anti bacterial activity

The antibacterial and antifungal properties of the leaves were demonstrated. Both gram-positive bacteria and the fungus Helminthosporium sativum were effectively combatted by it [46]

Immuno-modulator activity

In animal models, ashwagandha significantly alters immunological reactivity. When ashwagandha was administered, it showed similar effects to immunosuppressive medications such as prednosolone, azathioprin, and cyclophosphamide. Mice treated with ashwagandha showed a substantial increase in body weight, RBC count, platelet count, and Hb concentration [47].Leucopenia brought on by cyclophosphamide (CTX) treatment was shown to be

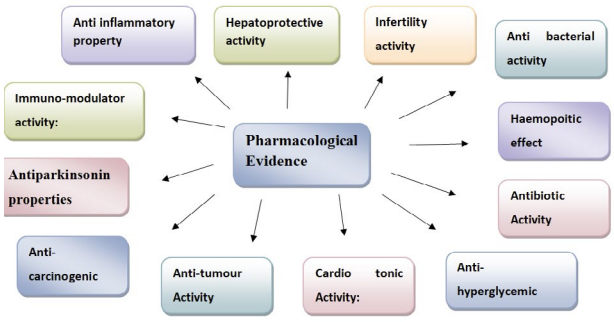

Fig 2: Pharmacological evidence of Ashwgandha

considerably reduced by the administration of asgandh extract. Compared to the group treated with CTX alone, the number of animals treated with Asgand extract increased [48]. It was discovered that administering asgand extract considerably decreased the sublethal dosage of gamma radiation caused by leucopenia [49]

Haemopoitic effect

Three doses of ashwagandha and ginseng (Panax ginseng) were given orally to rats for ninety days. Improved hemopoiesis was noted, along with a notable rise in body weight, food intake, and liver weight [50].

Antibiotic Activity

Ashwagandha's roots and leaves have been shown to have antibiotic activity; at a concentration of 10µg/ml, Withaferin A inhibited the growth of various Gram-positive bacteria, acid-fast and aerobic bacilli, and pathogenic fungi; it was also active toward Micrococcus species pyogenes var aureus and also partially inhibited the activity of Bacillus subtilis glucose-6-phosphate-dehydrogenase; it inhibited Ranikhet virus; the shrub's extract is active against Vaccinia virus and Entamoeba histolytica [51–53]; Asgand demonstrated a protective effect against systemic Aspergillus infection, likely due to the activation of macrophage function, as evidenced by the observed increases in phagocytosis and intracellular killing of peritoneal macrophages in mice [54] The unsaturated lactone ring in Withaferin A is what gives it its antibiotic properties. The lactone exhibited a somewhat higher therapeutic effect than penicillin in rabbits with artificially generated abscesses. In the indigenous medical system, it supports the leaves' reputation as a remedy for ulcers and carbuncles [55].

Anti-hyperglycemic Effect

It has been claimed that asgand, when combined with additional substances in a composite formulation called Transina, reduces the hyperglycemia that streptozocin (STZ) causes in rats. Given that the hyperglycemic activity of STZ results from a decrease in pancreatic islet cell super oxide dismutase (SOD) activity, which causes an overproduction of degenerative in nature oxidative free radicals in islet-beta cells, this anti-hyperglycemic effect might be caused by the pancreas islet free radical scavenging activity [56]

Cardio tonic Activity

It has been shown that the components of withania, which structurally resemble digoxin, have cardiotonic activity and improve CHF [57].

Anti-tumour Activity

At doses of 10, 12, and 15 mg/kg body weight, withaferin A, withanolide D, and E demonstrated strong antitumor activity against human epidermoid carcinoma of nasopharynx (KB) cells in vitro as well as against Ehrlich's ascites carcinoma, Sarcoma 180, Sarcoma, also Black (SBL), and E 0771 mammary adenocarcinoma in mice. More than half of the mice that lived for 100 days without showing any signs of tumor growth had Ehrlich ascites carcinoma growth totally stopped. Additionally, they functioned as a mitotic toxin, stopping the growth of human laryngeal carcinoma cells in culture during metaphase and in HeLa civilizations in a manner akin to star metaphase. Withaferin A caused mitotic arrest in embryonic chicken fibroblast cells. Methylthiodeacetyl colchicines potentiated the effect of Withaferin A. the presence of an unsaturated lactone in the side-chain to which an allelic primary alcohol group is attached at C25 and the highly oxygenated rings at the other end of the molecule may well suggest specific chemical systems possessing carcinostatic properties[58-60]. Withaferin A has been shown to possess growth inhibitory and radio-sensitizing effects on experimental mouse tumours31. Administration of Withaferin A in mice inoculated with Ehrlich ascites carcinoma cells was found to inhibit tumour growth and increase tumour-free animal survival in a dose dependent manner. In vivo, the plant's dried roots' alcoholic extract and its active ingredient, withaferin A, demonstrated strong antitumor and radiosensitizing properties against experimental tumors without causing any discernible systemic harm. Withaferin A treatment at a non-toxic level of 2.1 µM for one hour prior to irradiation markedly increased cell death. For the in vitro cell death of V79 Chinese hamster cells, withaferin A provided a sensitizer enhancement coefficient (SER) of 1.5 at a non-toxic dose of roughly 2 µM. Drug dosage increased SER [61,62]

Hypoglycemic Effect

The risk of cardiovascular illnesses is significantly increased by hyperglycemia. Withania improves glycated hemoglobin, liver enzymes, and urine and blood glucose levels in diabetic rats [63-68].

Anti-carcinogenic activity

According to reports, ashwagandha has anti-carcinogenic properties. The herb suppresses the interstitial tumor necrosis factor, increases apoptotic signaling in malignant cell lines, and lowers nuclear factor kappa B levels, according to studies conducted on animal cell cultures. [69]The ability of ashwagandha to combat cancer by shrinking tumor size is among its most intriguing

potential applications [70]. Researchers have examined the anticancer effects of the plant Withania somnifera to look at its potential use in treating different types of cancer. In one study, adult male mice with lung tumors produced by urethane were used to test the herb's anti-tumor properties.The histopathological appearance of the lungs of animals that received ashwagandha after seven months of administration was comparable to that of the lung of the control animals [71].

Antiparkinsonian properties

The neurodegenerative condition known as Parkinson's disease is typified by the selective death of dopamine (DA) neurons in the substantia nigra pars compacta. However, the mechanisms causing and/or mediating the loss of nigral DA neurons are yet unknown. For many years, medicines have been screened for Parkinsonism using an animal model of neuroleptic-induced catalepsy. Mice with catalepsy were dramatically affected by the administration of either reserpine or haloperidol. WS dramatically reduced catalepsy brought on by haloperidol or reserpine and offered hope for Parkinson's disease treatment [72]. In another study, one of the most popular experimental animals for Parkinson's disease is 6-hydroxydopamine (6-OHDA).

The literature provides strong evidence that oxidative stress is the mechanism by which 6-OHDA produces its harmful effects. Because of its strong antioxidant, antiperoxidative, and free radical quenching qualities, WS extract has been shown to provide antiparkinsonian benefits in a variety of medical disorders. For three weeks, rats were given the WS extract orally as a pretreatment. On day 21, the vehicle was given to the sham-operated group, and 6-OHDA was injected into the right striatum. Rats were examined for neurobehavioral activity three weeks following 6-OHDA injections. for the assessment of lipid peroxidation, decreased glutathione content, glutathione-S-transferase, glutathione reductase, GPX, SOD, and CAT activities, catecholamine content, dopaminergic D2 receptor binding, and tyrosine hydroxylase expression, and were killed five weeks after lesioning.WS extract reversed all the parameters significantly in a dose-dependent manner [73]. In a study by Naidu et al [62] tardive dyskinesia is one of the major side effects of long-term neuroleptic treatment. The pathophysiology of this disabling and commonly irreversible movement disorder is still obscure. Vacuous chewing movements in rats are widely accepted as an animal model of tardive dyskinesia. Oxidative stress and products of lipid peroxidation are implicated in the pathophysiology of tardive dyskinesia. Repeated treatment with reserpine on alternate days for a period of 5 days significantly induced vacuous chewing movements and tongue protrusions in rat Animals treated with reserpine showed a significant and dose-dependent reduction in reserpine-induced vacant gnawing activities and tongue protrusions after receiving WS root extract for four weeks. The pathophysiology of reserpine-induced aberrant oral motions may be significantly influenced by oxidative stress [74]. In another investigation, the beginning of the neuroleptic TD was reduced by WS glycowithanolides (WSG) given concurrently via haloperidol for 28 days. Vitamin E, an antioxidant, also reduced haloperidol-induced TD, whereas sodium valproate, a GABAmimetic antiepileptic drug, had no effect. Both treatments were given for 28 days, just like WSG. WSG has been shown to have an antioxidant impact instead of a GABA-mimetic function in preventing TD caused by haloperidol [75].

Snake Venom Neurotoxicity

The poisonous effects of snake poison are caused by the enzymes known as phospholipases A-2 (PLA2). They exhibit a variety of harmful effects, such as inflammation, neurotoxicity, and injury to muscle tissue [94]. Attempts have been attempted to separate chemicals from medicinal herbs that can function as antagonists of PLA2 enzymes and, therefore, operate as medications to snake bites, according to the assertions of traditional medical systems in several tropical Asian and African nations. Consequently, it was discovered that a glycoprotein isolated from WS (WSG) inhibited cobra venom phospholipase and counteracted its cytotoxicity, myotoxicity, and edema, but it was unable to stop neurotoxicity.

Given that the glycon component of WSG was not discovered to be involved in the inactivation of the snake enzyme, it appears that the complex that forms within the the WSG and the snake phopholipase is what inhibits cobra venom phospholipase [95]. In contrast, WSG inhibited a postsynaptic neurotoxin PLA2 that was made from the venom of the Indian cobra Naja. Additionally, it neutralized the toxicity of the cobra and snake venom PLA-2 protease and numerous of their forms, suppressed their activities, and extended the survival of the experiment mice, thereby confirming the medical potential of WS as a medicine against snake bite, as stated in Ayurvedic scriptures [96]. Through the destruction of the victim's tissue intracellular matrix, WSG was discovered to work by blocking the venom hyaluronidases of cobras and vipers, which mediate the spread of the venom poisons [97].

Effect of Ws on Oxidative stress

Neurodegenerative diseases including Parkinson's disease

have been linked to weaker anti-oxidative defense systems and a rise in oxidative free radical production. Catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD) are the main enzymes that scavenge free radicals. A buildup of harmful free radicals and the ensuing degenerative course of the disease are caused by these enzymes' malfunctions [76]. The anti-oxidant enzymes SOD, CAT, and GPX were reported to have higher cortex and striatal concentrations when exposed to the potent glycowithanolides [77]. Using a rotenone is (ROT) model of the Drosophila melanogaster species (Oregon-K), Manjunath be MJ and Murlidhara.2013.,[78] examined the neuroameliorative consequences of wax. Ws provided notable defense against ROT-induced lethality, and the survivor flies had enhanced locomotor characteristics. Additionally, biochemical studies showed that Ws considerably reduced the oxidative damage caused by ROT. One of the most popular rat models for Parkinson's disease is 6-hydroxydopamine (6-OHDA), which causes oxidative stress and accompanying harmful symptoms. Ws extract's anti-parkinsonian action was assessed, and it was found to have strong antioxidant, anti-peroxidative, as well as free radical quenching qualities in a range of medical situations. In comparison to the 6-OHDA rat model, Ws extraction was found to dramatically and dose-dependently reversed the amount of decrease in glutathione, GPX, SOD, and CAT [79]

Additionally, Prakash J et al. (2013) [80] reported that Ws root extract had a neuroprotective effect against dopaminergic neurodegeneration caused by ManebParaquat (MB-PQ) in PD mouse models. Their research indicates that Ws extract can both increase the number of Tyrosine Hydroxylase-positive cells in the SN region of the brain of MB-PQ-induced PD mice and reduce the oxidative stress that occurs in nigrostriatal tissues. Because it resists neurodegeneration, Ws's powerful antioxidant capability and ROS scavenging ability are crucial in preventing Parkinson's disease.

Effect of Ws on Catecholamines level

Dopamine (DA), a neurotransmitter, is essential for motor control and movement. In Parkinson's disease (PD), neurodegeneration is caused by oxidative stress and decreased catecholamine levels [81], which results in the loss of motor abilities in PD patients [82,83]. The striatum of Ws-treated and untreated PD mice was examined for catecholamines, including dopaminergic (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA), by RajaSankara S et al. (2009)

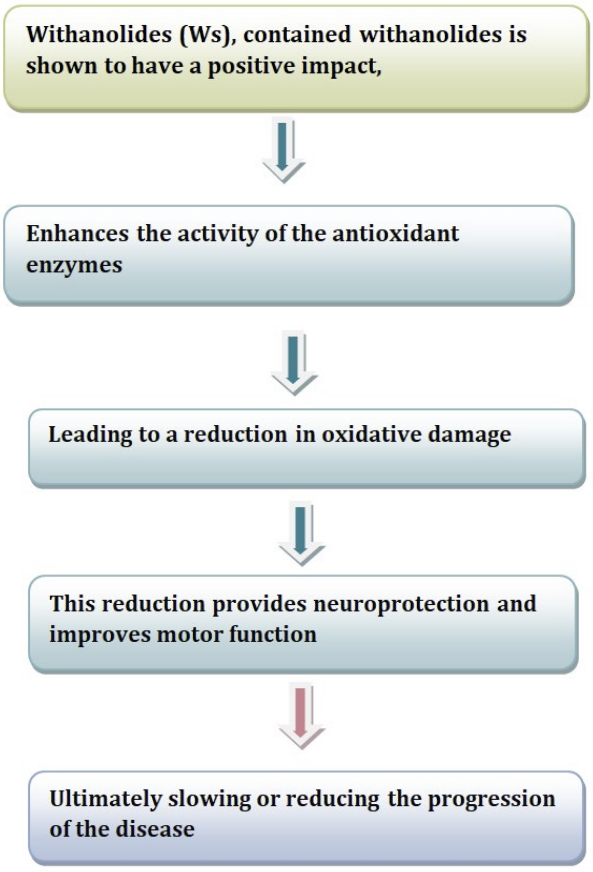

Fig 3: Effect of Ws on Oxidative stress

[84]. Oral administration of Ws root extract (100 mg/kg body weight) to PD mice for either 7 or 28 days increased the levels of DA, DOPAC, and HVA in the corpus striatum, according to Rajasankara.As a result, they concluded that the Indian traditional herb Ws has therapeutic benefits by enhancing the catecholamines and antioxidants and preventing peroxidation of lipids in the corpus striatum of Parkinson's disease (PD) rats. In the SN area of PD mice, Prakash J et al. (2014) [85] investigated the impact of Ws on dopamine and its metabolites. PD mice's brains showed lower levels of dopamine and its metabolites than controls. Additionally, compared to untreated PD mice, dopamine, DOPAC, and HVA levels were considerably improved after 9 weeks of Ws therapy. Therefore, it is evident that Ws has the ability to raise catecholamine levels and combat problems similar to Parkinson's disease.

Effect of Ws on Apoptotic Pathways

Programed cell death, also known as apoptosis, is a strictly controlled process that causes cells to actively

commit suicide in specific situations. Defective control of programmed cell death has been identified as one of the primary causes of neurodegenerative disorders [86]. An anti-apoptotic protein called Bcl-2 prevents cell death by blocking the function of the proapoptotic protein Bax. Thus, the ratio of Bcl-2 to Bax determines either the cell is going to survive or die. Fascinatingly, a study has proposed that Bcl-2 overexpression aids in reducing MPTP-induced neuronal cell death [87].

In a PD MB-PQ model, Prakash J et al. (2014) [85] demonstrated that Bax expression was dramatically upregulated and Bcl-2 expression was significantly downregulated. Additionally, in the MB–PQ model of Parkinson's disease, it was found that Ws therapy raised the level of anti-apoptotic (Bcl-2) proteins and lowered the level of pro-apoptotic (Bax) proteins. As a result, Indian ginseng, also known as ashwagandha, has gained recognition for its ability to control the levels of the apoptotic proteins Bax and Bcl-2. It is now evident that Ws possesses the capacity to overcome neurological conditions such as Parkinson's disease.

Synergistic Effect of Ws

Girdhari LG and Avtar CR.2009.,[88] investigated the synergistic impact of Ws and L-dopa in preventing mice from developing catalepsy brought on by haloperidol. The polyphenols in Ws that directly scavenge free radicals and reduce lipid peroxidation in the central nervous system may be the cause of its anti-cataleptic activity. Due to the presence of L-DOPA in Mp seed powder and withanoloides in Ws root extract, Ws and Mucuna pruriens (Mp) are traditional herbal herbs that are known to have neuroprotective effects [89]. In Parkinsonian mice that were chronically exposed to 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) [90] and Paraquat (PQ), Prakash J et al. (2013), [89], the synergistic effect of Ws and Mp was thus investigated. It was discovered that all neurochemical variables, oxidative stress, and physiological abnormalities were significantly improved in comparison to the brains of untreated PD mice. Prakash J et al. (2013) reported that exposure to PQ raises the nitrite concentration in the nigrostriatal area [89]. They therefore shown in their work that Mp + Ws coexposure changes the amount of nitrite in PQ-treated mice, and that this decrease in nitrite content by Mp + Ws may be due to the antioxidant properties of plant extracts of Mp [91] and Ws [92]." Additionally, malondialdehyde (MDA), a byproduct of lipid peroxidation, has been employed as an indicator of oxidative damage [93]. Through their studies, Prakash J et al. (2013) [89] shown that mice treated with PQ had significantly higher MDA levels than controls. Nevertheless, following the Mp + Ws co-treatment, MDA levels were markedly reduced. Therefore, compared to Mp and Ws treatments alone, the combination therapy of Mp + Ws shown a substantial effect. Consequently, the groundbreaking research on the synergistic effects of Ws with Mp and L-Dopa, respectively, provided insight into the effectiveness of Ws in the treatment of Parkinson's disease.

Safety of Use

Ashwagandha's lengthy history of usage in medicine is largely evidence of its effectiveness and the body's high tolerance to it. However, a lot of researchers are working to allay worries about its application these days. Liver damage has been reported recently, which is concerning. In both domestic and foreign pharmaceutical markets, herbal supplements make up a sizable and expanding portion. As a result, keeping an eye on its safety is becoming increasingly crucial. The first instance of Ashwagandha being linked to liver illness was found in Japan in 2004 [97].

" In this case, a 20-year-old male with congestive liver damage recovered without any problems following two months of ursodeoxycholic acid and phenobarbitone symptomatic treatment and ashwagandha discontinuation. Ptomatic therapy with ursodeoxycholic acid and phenobarbitone was described by Björnsson et al. [98]. According to Björnsson et al. [99], five occurrences of liver injury were linked to ashwagandha. These instances highlight ashwagandha's propensity for hepatotoxicity. Liver damage typically manifests as cholestatic or in combination with serious jaundice and itchiness, but it resolves on its own and liver test results return to normal in one to five months. Additionally, a case was reported in the UK where a 39-year-old lady took an over-the-counter herbal medication incorporating Ashwagandha root extract and was diagnosed with nausea and jaundice [100].Additionally, a 41-year-old lady who was taking progesterone and ashwagandha extract was reported to be eligible for a liver transplant because of her worsening health [101]. Triiodothyronine, thyroxine, and TSH blood levels were also measured to track thyroid function; however, no discernible variations in these hormone levels were found [102]. The lack of substantial impacts on the number of red blood cells, white blood cell proportion, ESR value, bilirubin, and plasma protein levels is confirmed by another study conducted on a smaller sample of volunteers (18 participants). Nonetheless, there was a drop in blood urea nitrogen levels and a rise in serum creatinine. The concurrently noted boost to muscle tissue during the investigation was the reason given by the researchers for this event." Aqueous extracts of vitania sluggard root were

administered to volunteers in increasing doses over a 10-day period, beginning with an amount of 6 g and concluding with the equivalent of 10 g [103]. Although the plant has several advantages, it should not be consumed when pregnant or nursing. The safety of using ashwagandha-based preparations during such delicate times in life is still not fully supported by evidence. The effects of vitania sluggard extract on pregnant rats are studied to provide some light on this safety concern. The period from day 5 to day 19 of pregnancy was the main emphasis. Crucially, because of the fetus's enhanced organogenesis and histogenesis, this is an especially delicate stage.The maximum dosage, which was given orally, was 2000 mg/kg/day. The study did not reveal any harmful consequences, and there were no alterations in the pregnant women's body weight, corpus luteum count, or embryo implantation. Additionally, no skeletal, visceral, or exterior fetal abnormalities were seen [104].

Contraindications

Ashwagandha root phytotherapy is growing in popularity, but it's crucial to remember that not all patients should use the preparations until their other therapies are under control. This group may include hyperthyroidism patients who exhibit symptoms like irritability, restlessness, anxiety, palpitations, hand shaking, psychomotor disorder, muscle weakness and exhaustion, and diminished libido. Although vitania sluggard root preparations have been shown to be effective in reducing the aforementioned symptoms, it is not recommended for usage in individuals with hyperthyroidism since they worsen the condition's consequences. According to research, this raw material raises the levels of tetraiodothyronine (T4) and 3,3',5-triiodothyronine (T3), which is detrimental in hyperthyroidism [105]. Indian ginseng root extract has been used to treat male infertility, but it should not be used by men who have hormone-sensitive prostate cancer. Studies have shown that the plant may enhance the production of testosterone [106], which accelerates the disease's progression. Because greater doses of Ashwagandha root extract can cause miscarriage, the serum is specifically prohibited for patients who are planning or already pregnant [107]. Because methanolic extract from Ashwagandha root has been shown to affect dopaminergic neurons in the ventral tegmental area via GABA-A receptors, sluggish vitania should be used very carefully when taking medications that act via the indicated receptor (particularly those from the benzodiazepine and barbiturate groups) for fear of intensifying the effects of the medications. [108].Ashwagandha root may have synergistic effects with sedative, sleep aids, myorelaxants, and anti-anxiety medications. When used with barbiturates, benzodiazepines, and anticonvulsants, the raw material shows additive effects that may exacerbate their side effects, including headaches, sleepiness, muscular tremors, decreased libido, and impaired motor coordination [109]. Clinically significant raw material–drug interactions may result from studies of ashwagandha root extracts, which indicate that the raw material may be a CYP3A4 inducer or a CYP2B6 inhibitor [110]. As a direct result of this phenomena, the medication's side effects could worsen or it can stop working in the course of treatment.Additionally, people with autoimmune illnesses, hypoglycemic, hypotensive, or immunosuppressive medications, and others should speak with a physician about the potential benefits of ashwagandha therapy. Sluggard is a safe plant for both short-term and long-term use, according to the research that is currently available on both humans and animals. Ingestion of the raw material or its preparations has not yet been demonstrated to cause any notable negative consequences. Hypersensitivity reactions to plants belonging to the Solanaceae family, or specifically to this species, would be the primary contraindications [111,112].

CONCLUSION

In the ancient system of Indian medicine, Withania somnifera is used as Rasayana herb for more than 2500 years W. somnifera participate as an active ingredient and are prescribed for treating various ailments that affects human health. Different parts of the plant has also been widely studied for their various pharmacological activities like anti inflammatory property, hepato-protective activity, infertility activity, anti bacterial activity, immune-modulator activity, Haemopoitic effect, Antbiotic activity, Anti-hyperglycemia, Cardio-tonic activity, Anti-tumour activity, Anti-Carcinogenic activity, Snake venom neurotoxicity novel mechanism of action makes ashwagandha a suitable drug candidate for the treatment of various diseases more clinical trials should be conducted to support its therapeutic use Parkinson's groups provided valuable insights into the associated pathways and protein-protein interactions. Collectively, the findings strongly suggest the potential use of Withaferin-A as a treatment option for Parkinson's disease

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