Innovating Across Boundaries: Bridging Science, Technology, and Humanities
September 2024
ISBN Number: 978-93-95305-66-2

WITHANIA SOMNIFERA L.: AN OVERVIEW

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Abstract

Withaniasomnifera L. is a member of solanaceae, also known for thousands of years by Ayurvedic practitioners. *Withaniasomnife*ra root contains flavonoids, alkaloids, steroid and many active functional ingredients (Kumar *et al.,* 2015). *Withaniasomnifera* having small white flowers mainly in rainy and winter seasons that can be develop into fruit during the winter seasons. Plants products can be obtained from the roots, leaves, and branches, by using many different biological techniques. Withania which is also known as Ashwagandha having effectiveproperty can also used in blends and supplements which are designed to show many multiple effects. It is described as an herbal tonic and health food in Vedas and considered as 'Indian Ginseng' in traditional Indian system of medicine (Singh *et al.*, 2001).

Introduction

The meaning and origin of the word *Withania* is doubtful, whereas *somnifera* refers to the narcotic property of the leaves of plant. *Withaniasomnifera* is an erect, evergreen (green in whole year), branching, and tomentose shrub of 30 to 150 cm in height. Leafs are simple, petiolate with the leaf blade varying in shape from elliptic-ovate to broadly ovate, entire along margins, acute to obtuse at apex, oblique at base, clothed with a persistent grayish tomentum on sides, 4-10cm long and 2-7cm broad (Mirjalili*et al.,* 2009).

Leaves on vegetative shoots are alternate and large and those on floral branches are opposite, arranged somewhat laterally in pairs of one small leaf and one large leaf, bearing in their axil a cymose cluster of 4-25 inconspicuous pale green monoceous flowers. It produces flowers indeterminately round the year with a peak of flowering between March and July (Mirjalili*et al.,* 2009). In Sanskrit it is called ashvagandha (asva_'horse', gandha_'smell') which means 'smell of the horse', because the root of the infected plant has the smell of the horse urine, but in general the meaning of the name is: 'what gives the energy and the sexual vitality of a horse'.

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Other synonymous are: Varada (vara_'choosing', 'desiring'; 'offering', 'producing') that means 'granting wishes', 'conferring a 'a; Vajigandha (vaji_'strength', 'vigour'; gandha_'smell') i.e. 'smell of the strength'; Vajikari (kari_'causing', 'accomplishing') that means strengthening', 'producing virility'; Vajiini (_'a mare') i.e. 'what promotes pregnancy'; Palashparni (palasa_'cruel', 'toxic'; parna_'leaf') with reference to the poisoning leaves. In Ayurveda Withania is used as tonic, aphrodisiac, sedative, as Medharasayana (Nadkarni 1993; Monier-Williams 1997). Vernacular names Sanskrit, Ashvagandha, Ashvakandika, Balada, Balaja, Gandhapatri, Vajigandha, Vajikari, Vajiini, Palashaparni; Hindi, Asgandh; English, Winter cherry; Italian, FalsoAlchechengi; Japanese, Ashwagandha; AasogandaNepalese; Singalese, Amukkara; Arabic, Bahman; Tibetan, Ba-dzigandha (Kirtikar*et al.,* 1993).

Distribution:-The genus Withania is restricted and related to the old World; rather it closely belongs to the genus Physalis, the gooseberries. Withania possesses a natural occurrence, most probably in the drier and humid areas, spread from the Mediterranean region to throughout tropical region of Africa to South Africa and also from the Cape Verde Islands and Canary region to the Arabia and Middle East region like India, southern China and Sri Lanka.

Ashwagandha is propagated and cultivated in gardens in the warmer and drier regions of Europe and became a natural herb in New South Wales and South Australia. Generally it is cultivated in India and in many other places as a medicinal crop (Govindaraju*et al.,* 2003), most probably for its fleshy roots. Ashwagandha is globally known but is not so common in all regions of South Africa, Botswana, Namibia, Lesotho and Swaziland. It is total absent in the western half of the Western and Northern Cape regions. It develops and cultivated in a wide range of vegetation types in dry and warm areas to areas with usually high humid region with high rainfall like coastal vegetation, savanna, grassland, scrubland, karoo, woodland, and mostly in margins of forests and thickets, besides water also, as on the river banks. Its presence is also observed in light shaded dark places as well as in full sun places, mostly among rocks where the roots are being kept cool.(Kapoor 1990).

Habitat:-Ashwagandha grows in dry areas in India, on the Himalayas under 1600m, Beluchistan, Sri Lanka and in the Mediterranean area: spontaneous in Sicily and Sardinia Kirtikar*et al.,* 1993). Used parts root, leaf, seed *Withaniasomnifera L.*Dunal is a common herbaceous evergreen shrub of 30-150cm height. It grows as a weed along road sides and in open waste places. It is distributed throughout the drier parts of India. It is now cultivated at different parts of the country due to its medicinal importance. The plant is

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usually clothed with minutely stellate tomentum. The leaves are 5-10 cm long, simple alternate, ovate, entire, thin with cuneate/connate base and are densely hairy with reticulate venation. However, near the inflorescence leaves are opposite with adnate.(Kapoor 1990).

1. **Morphology**

According to the Datta*et al.*,2011 based on its cultivation in experimental field plots of the University of Kalyani, West Bengal plains, elevation on 48 feet above sea level, sandy loamy soil, organic carbon0.76%, soil pH 6.85 during the period of September to February, (max. temperature 24.03-32.17 ºC, Min. temperature 11.24-25.51 ºC, rain fall 0.0-12.46 mm; relative humidity max. 93.96- 98.28% min. 44.43-86.85%).

The species is perennial (can be sown twice a year , in march to August and September to Feb (Das *et .al.*, 2009), branched, terrestrial herb (plant height: 69.58-75.22 cm); tap root , long(17.52 to 19.28 cm), unbranched, 2-3 cm thick, terate,rootlets many, confirmed within 1-5 cm, angular and branched; stem terate, hairy to the younger part and glabrous at maturity; leaves alternate, simple, ovate to broadly ovate (7.0-12.0 cm long; 5.0-7.0 cm broad), acute at apex entire, broad as well as cuneate at base, herbaceous, unicostate with 4-5 pinnate secondaries, hairy on both surface, green, petioles slender 1-2 cm long, hairy; flowers auxiliary in fascicles of 2-5 often 2-3 developed complete, bisexual, hypogynous, actinomorphic, pentamerous, pale green, pedicillate ; pedicel 2 to 3 mm long hairy lobes, triangular acute, about 1 mm long, tubular part about 2 mm long, hairy throughout, persistent and accrescent at maturity covering the whole fruit increased up to 1.5-1.8 cm long; corolla tubular, campanulate; petals 5, ovate triangular about 1.5 mm long, hairy on both surface, tubular part about 2 mm long, stamens 5, filaments slender, epipetalous and alternipetalous attached below the middle of the corolla tube, white glabrous; anthers oblong, two celled dorsifixed, dehiscence longitudinal- latrose, white; pollen grains prolate spheroidal (**as per Erdtman 1952**) fertility 59.96-71.05 %, size 21.67 µm× 18. 67 µm (18.5 pollen grain per microscopic field: 85564 μm^2; carpels 2 syncarpous; ovary oblong about 1.2 mm long, greenish, glabrous: style one terminal, terete about 1-5 mm long, glabrous; stigma rounded, ochre (16283); ovary two chambered with many ovules per chamber in axile placentation; fruits berry, subglobose to rounded, coloured at maturity, many seeded 4 to 5 mm across, glabrous with varied seed colour, fully covered with accrescent calyx; seeds flate about 1.0mm across, surface reticulate, g;labrous, light brown to yellowish brown.

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Fig.Plant of *Withaniasomnifera.*

Fig. Stem and fruits of *Withania somnifera*

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2. Anatomy

- **Stem**

Transverse section (4.0-5.0) of stem (main stem, 75 days old plant at vegetative stage; hand sectioned and double strained as per **Johansen 1940**) showed the lowing features: epidermis 1 cell layer thick, cells more or less rounded to barrel shaped rarely rectangular, medianly thick walled, cells compact arranged: hypodermis 1 cell layered thick, cells compact, rounded, medianly thick, smaller than the epidermal cells, at maturity hypodermal layer may be indistinct: cortex 6-8 cell layered thick, cells rounded, smaller towards stele, thin walled loosely arranged with intercellular spaces: stele consisting of a ring of vascular structure having pith to the centre, siphonostelic: outer phloem layer few cell layered thick, continuous as well as in patches: cambium 2-3 cell layers thick, inconspicuous: xylem layer with medullary rays: inner phloem in discrete patches: pith cells alike to cortical cells (**Johansen 1940**).

Fig. Stem of *Withania somnifera.*

- **Roots**

Fig. Roots

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Transverse section (main root of 75 days old plant, 5-6 cm below the top; double stained) of root documented the following: periderm (phellem, phelogen and phelloderm: 3 layers evident) present; phellem 3-5 cell layered thick, tetra to polygonal, thin walled, compactly arranged with contents within; phelogen 2-3 cell layered thick, rectangular, compactly arranged; phelloderm 5-7 cell layered, rectangular thin wall, compactly arranged; cortex 7-10 layer thick, polygonal to rounded often with brownish content within; pericycle and endodermis indistinct due to secondary growth; stele prominent with distinct xylem and ray cells; primary vascular bundle tetra-arched, centrally placed with metaxylem and phloem arranged radially. (Datta*et al.*,2010).

Roots of ***Withaniasomnifera.*** **Seeds of *Withania somnifera.***

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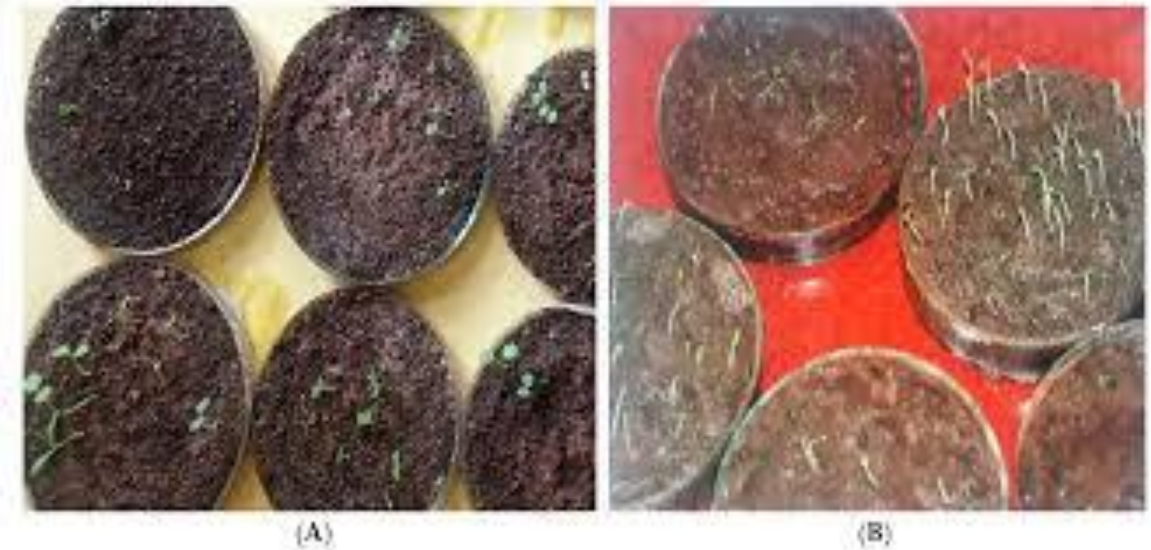
Fig. Seeds of Ashwagandha

3. Seed Germination



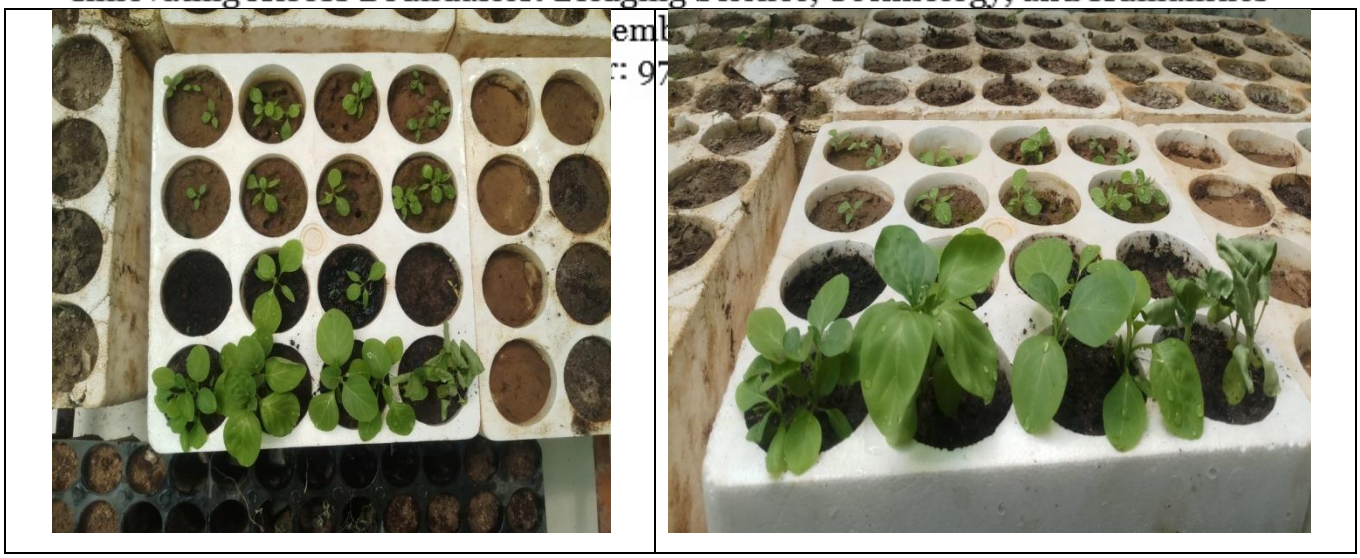


Fig. Seed germination and seedling

The germination of the ashwagandha seed is irregular and takes more than 15 days, so there is urgent need to study on germination aspect of this crop. In order to have better germination and seedling quality parameters of ashwagandha, it is necessary to conduct germination treatments for breaking the dormancy in the laboratory conditions. The irregular and low germination is the main problem in the propagation of many medicinal plants which can be enhanced by application of biofertilizers . The present investigation was conducted to study the effect of different dormancy breaking treatment methods and different growth hormones, chemical treatments and biofertilizer treatments on seed germination, quality enhancement and other quality parameters in Ashwagandha(Changhadi , 1938).

Some research on physico-chemical treatments like storage, temperature, photoperiod and growth regulators (GA3, IAA, IBA, 2–4 D and BA) on germinability were also done by different researchers and they found that the most effective treatment is GA3 at 150 µg/ml concentration at 25 °C. The optimal temperature for germination is 25 °C and continuous light favored germination showing that photoperiod has a significant role. The seedlings derived from seeds performed well when grown in a glasshouse.

The seed germination of *W. somnifera* can be enhanced by pretreating seeds with GA3 500µg/l for 24 hours before sowing. This increased germination percentage as well as reduced the mean germination time .The mechanically scarified seeds also showed a much favorable result. This suggest that mechanical scarification of seeds can be applied as a very suitable, cost–effective and eco-friendly method which is easy enough to be used by local, unskilled farmers to combat seed dormancy of Ashwagandha seeds and hence improve seed germination.

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The mechanical scarification for two minutes recorded highest germination percent and seedling parameters compared to control. The maximum germination per cent was attained biofertilizer Phosphorous Solubilizing Bacteria culture recorded the highest seedling germination and its attributing parameters followed by Bio NPK .

Seed treatments like sand paper scarification and pin pricking and hot water treatment for Ashwagandha, Depending on the availability, KNO_3 (1. 0%) can be recommended for seed treatment to assure good germination and emergence in the field.

The 5-minutes' treatment of $NaHClO_3$ and glasshouse condition yielded maximum emergence in Ashwagandha. However, seedlings growth and biomass in open condition were comparable to that in glasshouse condition.

Filter paper had the highest germination percentage (94%) at dark condition, less than 50% of the seeds were able to germinate under light conditions at both B5 media and Plain agar, on the other hand, at light condition germinated seeds in filter paper (46%) were more than B5 media (25%) and Plain agar (37%).

The results of some studies revealed that some varieties, like *Posida,* Indore general. Having low seed germination and higher fungal infection. There is necessity of treatment of different growth hormones, fungicides, nutritional sources and efficacy plant parts. So as to increase the productivity this plant Ashwagandha production is need to be increase day to day.

The application of bio-fertilizers, in the treatment combinations of *Azospirillumlipoferum*, *Pseudomonas striata* and *Pseudomonas fluorescens* recorded maximum plant growth, yield and survivability of garden rue seedlings than single application and untreated.

Black, plastic mulch significantly increased the seed yield obtained from field plantation and accelerated fruit ripening, rising the percentage of seeds capable of germinating in the yield (GraŜynaObidoska,*et al.*,., 2004).

In Polish climatic conditions the field yield of *Withaniasomnifera* seeds capable of germinating, was to a great extent dependent on weather; especially at the end of the vegetation season (September-October) (GraŜynaObidoska, *et al.*,., 2004).

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The results of Some study depicted synergistic activity of temperature, Gibberellic acid and light indicated by improved seed germination, that can be exploited to obtain uniform seed germination under controlled conditions for raising large populations of desired accession for commercial cultivation **(Khanna*et al.,.,2013).***

4. Allelopathic Potential

Withania extract has been found to be effective as bio-herbicide against Partheniumhysterophorus. However, its role against Ageratum coenyzoides, Chenopodium album and Achyranthusaspera has not been tested. The rationale of the study is to to use allelochemicals as a control measure for weed distribution in Himalayan areas. The present study was premeditated to evaluate the herbicidal activity of Withaniasomnifera using plant extracts against germination and growth of noxious weeds of Himalaya i.e. Ageratum coenyzoides, Chenopodium album and Achyranthusaspera in a laboratory and foliar spray bioassay so as to present a bioherbicidal method for the management of weeds in the Himalayan regions.

An experiment revealed the fact that many medicinal plants can be used as a bio herbicide to control some weeds as well as invasive weeds. The phyto-chemical present in plants act as allelochemicals for the weeds and provide a safe and natural meanof weed management. Earlier initiatives have been proved successful, for examples, Artemisinin, a sesquiterpene lactone from the Artemisia annumL. is a patent plant growth inhibitor. Leptospernone is a known allelochemical from which the triketone class of herbicides was produced. Similarly, 1,8, coneole, a monoterpene, has been identified as one of the most potent allelochemical released by Artemisia spp. and a synthesise analog, cinmethylinia, being sold as a herbicide in Europe. As medicinal plants like Withaniasomnifera are a rich repository of phytochemicals and have a herbicidal effect over weeds, there is a possibility to commercialise its extracts as herbicide which will prove a milestone in the weed management in the Himalayan region. **(Sharma *et al.,.,2017)***

Numerous medicinal values of *W. somnifera* have been reported and its allelopathic potential has also been declared by many researchers (Jabran*et al.,*. 2010; Javaid*et al.,*. 2011; Chandra *et al.,*. 2012; Khaliq*et al.,*. 2013; Sharma *et al.,*. 2017). The hydro alcoholic extract of ashwagandha mainly at higher concentrations demonstrated promising allelopathic properties by significantly affecting seed germination and radical elongation of both *Cicerarietinum L.* and *Triticumaestivum L.* in a concentration dependent manner. Triticumaestivum was found to be more sensitive than C. arietinum**(Chandra *et al.,*. 2012).**

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The aqueous extract and alkaloid fraction of *Withaniasomnifera* and *H. mutcus* showed an inhibitory allelophathic effect on the germination of wild chicory and the inhibitory effect depended on the concentration. Phytochemical analysis showed the plant contain different class of phytochemical compounds GC-Ms analysis of aqueous extract revealed the presence of hydroxyl cinnamic acid and methyl ferulate and other phenolic compound which may have a major role in germination inhibition also alkaloid fraction have many compounds which consider as alellochemical finally we can recommended by use these plant extracts as a pest side after further studies.**(Eman Ramadan Elsharkawy, 2019).**

5. Secondary metabolites

Medicinal plants are a source of naturally active compounds used extensively by tribal people worldwide for many ailments. *Withaniasomnifera* (WS) is one such plant used to treat many ailments from the time of Ayurveda. Extraction of the bioactive plant constituents from the whole plant or from the different parts of the plant has always been a challenging task. As the dried roots of WS are widely used in the treatment of many disorders, the current study aimed at extraction and detection or screening of active phytochemical compounds from different extracts of WS root. Phytochemical screening of different extractions revealed the presence of phenols, flavonoids, tannins, saponins, alkaloids, steroids, terpenoids, glycosides and reducing sugars which could account for its varied medicinal properties like anti-inflammatory, anti-spasmodic, anti-analgesic, neuroprotective and diurectic effects.
Various preparations and forms of Withaniasomnifera (Linn) Dunal (Ashwagandha) i.e. powder, decoction, oil, smoke, poultice etc. have been advised for the cure of various disorders such as skin disorders, nervous disorders, intestinal affections, venereal diseases, rheumatism, emaciation of children and as a tonic for all kinds of weakness and in geriatrics. It also promotes vigor and stamina and is regarded as aphrodisiac and rejuvenator.

Withaferin A and Withanolide D are two main withanolides contribute to the most of biological actions. 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, psychotropic/anti anxiety activity, anti convulsant activity, skin care activity, healthy hair activity, immune-modulator activity, anti peroxidative action, anti ageing effect, macrophage activating effect, haemopoitic effect, antibiotic activity, antitumour activity, anti-

ISBN Number: 978-93-95305-66-2

hyperglycemic effect, morphine tolerance and dependence-inhibiting effect, cardio tonic activity, hypo lipidemic, anti-atherogenic activity, positive inotropic activity, hypoglycemic effect, anti-oxidant activity, anti-carcinogenic activity etc. This review presents morphology of the plant, geographical distribution, cultivation and market value, plant pathology, Ayurvedic properties, chemical ingredients, medicinal uses in Ayurveda, side effects and contraindications, pharmacological evidences of Withaniasomnifera (Linn) Dunal (Ashwagandha). Some of the uses of W. somnifera according to different researchers are reviewed here. This review will help to know all the medicinal properties of Ashwagandha.

6. Medicinal properties

Withania somnifera is a medicinal plant extends over a large area, from the Atlantic Ocean to South East Asia and from the Mediterranean region to South Africa. The medicinal plants are widely used by the traditional medical practitioners for curing various diseases in their day to day practice. In traditional systems of medicine, different parts (leaves, stem, flower, root, seeds, bark and even whole plant) of Withaniasomnifera (Ashwagandha), a small herb seen throughout India, have been recommended for the treatment of aphrodisiac, liver tonic, anti-inflammatory agent, astringent, and more recently to treat bronchitis, asthma, ulcers, emaciation, insomnia, and senile dementia etc. Clinical trials and animal research support the therapeutic use of ashwaganda for anxiety, cognitive and neurological disorders, inflammation, and Parkinson's disease. Ashwaganda'schemopreventive properties make it a potentially useful adjunct for the patients undergoing radiation and chemotherapy. Ashwaganda is also used therapeutically as an adaptogen for patients with nervous exhaustion, insomnia, and debility due to stress, and as an immune stimulant in patients with low white blood cell counts in blood. The major biochemical constituents of ashwaganda root are steroidal alkaloids and steroidal lactones in a class of constituents called withanolides.

i. Adaptogenic / Anti-stress effect

Aswagandha is compared well with Eleutherococcussenticosus (Siberian Ginseng) and Panax Ginseng (Chinese / Korean Ginseng) in its adaptogenic properties, and hence it is popularly known as Indian Ginseng (Singh *et al.,*., 2010). The extensive studies on the biological model of animals for the adaptogenic / anti-stress properties of Ashwagandha (Abbas and Singh, 2006; Kalsi*et al.,*., 1987; Singh *et al.,*., 1976, 1977, 1981, 1982, 1993a, 1993b, 2003; (Singh, 1995a, 1995b, 2006, 2008) have shown it to be effective in increasing the stamina (physical endurance) and preventing stress induced gastric ulcer,

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carbon tetrachloride (CCl4) induced hepatotoxicity and mortality. Ashawagandha have similar anti-stress activity in rats (Archana&Namasivayam, 1999).

An aqueous suspension of Ashwagandha root was used at 100 mg/kg/oral dosage. The results indicate a significant increase in the plasma corticosterone level, phagocytic index and avidity index in rats subjected to cold swimming stress. In the rats pretreated with the drug, these parameters were near control values and an increase in the swimming time was observed. These results indicate that Withaniasomnifera 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 Withaniasomnifera in the prevention and treatment of many stress induced diseases like arteriosclerosis, premature ageing, arthritis, diabetes, hypertension and malignancy (Singh, 1986, 2005; Singh and Misra, 1993).

Effect on cortisol and ascorbic acid contents of adrenals

The cortisol content of adrenals was reduced significantly in animals subjected to 5 h constant swimming as compared to non-swimmer group. Pretreatment with WS prevented reduction of the cortisol content of adrenals. The ascorbic acid content was also reduced significantly after 5 h of swimming as compared to the animal of non-swimmer group. Pretreatment with WS prevent reduction in ascorbic acid content which occurs after swimming stress. Thus, *Withaniasomnifera* treatment prevents, decrease of adrenal cortisol and ascorbic acid which occurs due to swimming stress.

Anti-ulcerogenic effect

Ashwagandha was found to be useful in the prevention of stress-induced ulcers of the gastrointestinal tract (Singh *et al.*,. 1982). It showed significant protection against 18 h immobilization, cold + immobilization (4h) and aspirin induced gastric ulcers and lowered the mean ulcer index in rats.

Effect on leucocytosis

Ashwagandha given to a group of mice with milk injection produced reduction in leucocytosis.

Anabolic effects:

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.

Acute toxicity studies

In acute toxicity studies the LD50 of *Withaniasomnifera* was found to be 1750 mg (p.o.) in albino mice.

Anti-tumor effect

Effect on Chinese Hamster Ovary (CHO) cells

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Carcinoma Withania roots caused the inhibitory effect of about 49% on colony forming efficiency of CHO cells. It inhibits the cell growth and prevents the cell attachment. It induced long term growth inhibition of CHO cells which was dependent on the cell density and duration of Ashwagandha exposure (Sumantran*et al.,*. 2007). This knowledge in turn will assist oncologists who plan to use the Ashwagandha as 'synergizers with conventional chemotherapy or radiation therapy.

Effect on Central Nervous System

Cognition Promoting Effect

Ashwagandha is a well knownAyurvedicRasayana, and belongs to a sub-group of Rasayanas known as Medhyarasayanas. Medhya typically refers to the mind and mental/intellectual capacity. Thus, MedhyaRasayana like Ashwagandha, is used to promote intellect and memory. The cognition-promoting effect of MedhyaRasayanas is best seen in children with memory deficits, or when memory is compromised following head injury, or a prolonged illness and in old age (Singh and Udupa., 1993).

Effect on neurodegenerative diseases such as Parkinson's, Huntington's and Alzheimer's diseases

In patients with Alzheimer's disease, neuritic atrophy and synaptic loss (Dickon and Vicker, 2001) are considered the major causes of cognitive impairment, as based on the results of neuropathological post-mortem studies of the brain (Dekosky&Scheff, 1990). In the brains of patients suffering from other neurodegenerative diseases such as Parkinson's disease, Huntington's disease, and Creutzfeldt– Jakob disease, the atrophy of neurites has also been observed as a significant part of the etiology.

There are dozens of studies that show that Ashwagandhaslows, stops, reverses or removes neuritic atrophy and synaptic loss. Therefore Ashwagandha can be used to treat Alzheimer's, Parkinson's, Huntington's and other neurodegenerative diseases at any stage of the disease, even before a person has been diagnosed and is still in the state of mild forgetfulness, etc.

Ashwagandha has been described as a nervine tonic (Singh *et al.,*., 1988, 1993) 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 (Singh *et al.*,., 1986) and longevity in the users.

Effect on Energy levels and Mitochondrial Health

The effect of Ashwagandha on glycosaminoglycan synthesis in the granulation tissue of carrageenin-induced air pouch granuloma was studied. Ashwagandha is shown to exert significant inhibitory effect on incorporation of ribosome -35S into the granulation tissue. The uncoupling effect on oxidative phosphorylation (ADP/O ratio reduction) was also observed in the mitochondria of granulation tissue.

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Further, Mg_2^+ dependent ATPase activity was found to be influenced by Ashwagandha. Ashwagandha also reduced the succinate dehydrogenase enzyme activity in the mitochondria of granulation tissue **(Begum &Sadique, 1987).**

Nootropic effect

Effects of sitoindosides VII-X and withaferin isolated from aqueous methanol extract of roots of cultivated varieties of WS were studied on brain cholinergic, glutamatergic and GABA ergic receptors in rats. The compounds slightly enhanced acetylcholinesterase (AChE) activity in the lateral septum and globuspallidus, and decreased AChE activity in the vertical diagonal band. These changes were accompanied by enhanced M1-muscarinic-cholinergic receptor binding in lateral and medial septum as well as in frontal cortices, whereas the M2- muscarinic receptor-binding sites were increased in a number of cortical regions including cingulate, frontal, parietal, and retrospinal cortex. The data suggest the compounds preferentially affect events in the cortical and basal forebrain cholinergic-signal transduction cascade.

The drug-induced increase in cortical muscarinic acetylcholine receptor capacity might partly explain the cognitionenhancing and memory-improving effects of WS extracts in animals and in humans **(R. Schliebs*et al.*,.,1997).**

In a study by Zhao *et al.*,**(J. Zhao *et al.*,., 2002)**Withanoside IV (a constituent of WS; the root of WS) induced neurite outgrowth in cultured rat cortical neurons. Oral administration of withanoside IV significantly improved memory deficits in Abeta-injected mice and prevented loss of axons, dendrites, and synapses.

In another study reserpine treated animals also showed poor retention of memory in the elevated plus maze task paradigm. Chronic WS administration significantly reversed reserpine-induced retention deficits **(P.S. Naidu *et al.*,.,2006).**

Potential Benefits of Leaves of Ashwagandha

Several recent studies have explored the potential of leaves of this plant for their therapeutic value as it offers several advantages over root such as their ecofriendly and bio-friendly base. There is no need to sacrifice the plant to prepare the extract, unlike root-based preparations. Additionally, recent reports have used **G. Kaur*et al.*,.**419 water-based crude formulations of leaves as compared to root based alcoholic extracts with an aim to scientifically validate the traditional use of Ashwagandha as an ayurvedic

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supplement. Moreover, the use of powder or water based extract is convenient, safe and easy to prepare with no need to use organic solvents for extraction procedure.

Some Pre-clinical Studies on AshwagandhaNeuroplasticty is the ability of brain to synthesize and reorganize synaptic and neuronal connections in response to any environmental stimulus or injury. Neuroprotection is the event that leads to regeneration of damaged neurons or connections resulting in recovery of the neuronal function. Any compound that has the ability to confer neuroprotection can be classified as a neuroprotective agent. The neuroprotective and neuroplasticty inducing potential of Ashwagandha has been explored in numerous in vitro and in vivo studies.

Similar effects of withanoside IV were observed with injured neurons wherein it enhanced synaptogenesis and neurite outgrowth in the brain **(Kuboyama*et al.*,. 2006).**Tohda and **Kuboyama group (2000)** investigated the effects of methanol extracts of Ashwagandha on neurite outgrowth using an in vitro culture system and found the neurite outgrowth-promoting activity of Ashwagandhamethanolic extract in human neuroblastoma SK-N-SH cells and rat cortical neurons.

Withanolide A, withanoside IV, and withanoside VI were identified as active constituents behind the neurite outgrowth promoting activity of the methanol extract **(Zhao *et al.* 2002; Kuboyama*et al.*,. 2002).** They also studied the effect of these phytochemicals on an in vitro axonal atrophy and synaptic degeneration model established using an active partial fragment of Aβ such as Aβ 25–35. Each of these 3 compounds induced axonal growth and synaptic densities even in the presence of Aβ 25-35 in both in vitro and in vivo model of Alzheimer's disease **(Kuboyama*et al.*,. 2005, 2006).**

Tohda andJoyashiki 2009; Joyashiki*et al.*,. 2011). A novel compound "denosomin" an analogous derivative of sominone was synthesized by **Matsuya *et al.*,. (2009)** and showed axonal growth activity comparable to sominone in cultured cortical neurons. Recently this group also investigated the effects of denosomin on spinal cord-injured mice and found that consecutive oral administration of denosomin for 14 d one hour after contusion injury at the L1 spinal cord facilitated axonal growth in the injured center and recovered hind limb motor function. Additionally, it was found that Vimentin-secreting GFAP-positive reactive astrocytes also increased in the injured center that helps in axonal growth and motor function recovery in spinal cord-injured mice **(Teshigawara*et al.*,. 2013).**

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Some Pre-clinical Studies on Ashwagandha

Neuroplasticty is the ability of brain to synthesize and reorganize synaptic and neuronal connections in response to any environmental stimulus or injury. Neuroprotection is the event that leads to regeneration of damaged neurons or connections resulting in recovery of the neuronal function.

Any compound that has the ability to confer neuroprotection can be classified as a neuroprotective agent. The neuroprotective and neuroplasticty inducing potential of Ashwagandha has been explored in numerous in vitro and in vivo studies. In human neuroblastoma cell line, root extract of Ashwagandha increased the percentage of the neuronal population with significant neurite outgrowth in a dose-dependent manner.

The study demonstrated up regulation in the expression of synaptic and neuronal growth markers MAP2 (Microtubule-associated protein) and PSD95 (post synaptic density protein) (**Tohda***et al.,*. 2000) with the Ashwagandha treatment. Further, standardized dose of withanoside IV (steroidal saponin isolated from WS root extract) improved memory in Amyloid β (25–35) injected mice model of Alzheimer's disease. Similar effects of withanoside IV were observed with injured neurons wherein it enhanced synaptogenesis and neurite outgrowth in the brain (Kuboyama*et al.,*. 2006).

Tohda and Kuboyama group (2000) investigated the effects of methanol extracts of Ashwagandha on neurite outgrowth using an in vitro culture system and found the neurite outgrowth-promoting activity of Ashwagandhamethanolic extract in human neuroblastoma SK-N-SH cells and rat cortical neurons.

-A novel compound "denosomin" an analogous derivative of sominone was synthesized by **Matsuya** *et al.,*. (2009) and showed axonal growth activity comparable to sominone in cultured cortical neurons.

Recently this group also investigated the effects of denosomin on spinal cord-injured mice and found that consecutive oral administration of denosomin for 14 d one hour after contusion injury at the L1 spinal cord facilitated axonal growth in the injured center and recovered hind limb motor function. Additionally, it was found that Vimentin-secreting GFAP-positive reactive astrocytes also increased in the injured center that helps in axonal growth and motor function recovery in spinal cord-injured mice (**Teshigawara***et al.*,. 2013).

Ashwagandha: Modulator of Behavioral Plasticity

Both basic and clinical studies have explored the potential of this plant in improvement of physiological and cognitive functions of the body in wide range of neurological conditions. Ashwagandha is known for sleep inducing and memory enhancing potential among its diverse range of other biological roles.

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Somnifera as the species name of the plant means sleep inducing. A recent study by **Manchanda***et al.,*. (2017) reported the beneficial role of Ashwagandha in preventing memory dysfunction in acute sleep deprived (SD) Wistar rats.

Oral administration of semi-purified root extract of Ashwagandha predominant in withanolides and withanosides to transgenic mice model of Alzheimer's disease has been shown to reverse behavioral deficits, and Aβ plaque pathology (**Sehgal***et al.,*. 2012). The study proposed that Ashwagandha mediates its neuroprotective role by upregulation of liver LRP (lipoprotein receptor related protein) and targeted the periphery for clearance of Aβ.

Methanolic extract of Ashwagandha applied in CA1 neurons of hippocampus region of brain was observed to exert a neuroprotective role in mice and may be important in process of memory (**Bhattarai and Han** 2014). The study reported that Ashwagandha causes activation of synaptic/extrasynaptic GABA (gammaAminobutyric acid) receptors type A, suggesting a link between WS mediated neuroprotection and GABA signaling. Ashwagandha has been known to promote overall health and vitality by exhibiting a pleiotropic action.

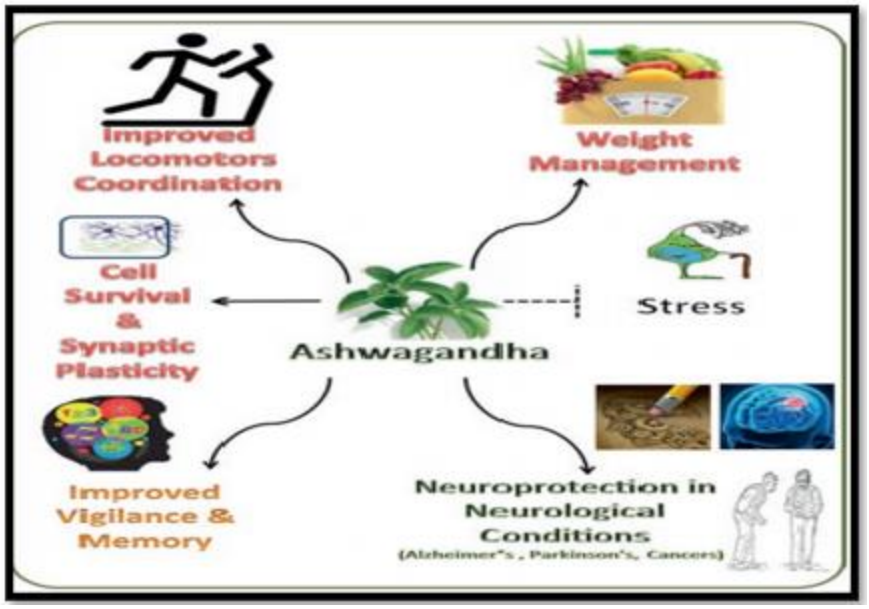
A randomized study reported the use of root extract of Ashwagandha as a precognitive agent used as an adjunct with the medication in bipolar patients **(Chengappa***et al.,*. 2013). The study tested patients' cognitive ability for different domains such as reaction time, social cognition and working memory and Ashwagandha extract appears to improve cognitve capacity in all three domains in bipolar patients.

In addition, a clinical study by **Choudhary***et al.,*. (2015) has reported the efficacy of root extract of Ashwagandha in improving cardiac endurance and physical performance in a mixed population of athletic adults, thereby improving their quality of life. Another recent clinical study **G. Kaur***et al.,*. 423 has reported the efficacy of Ashwagandha root extract in improving muscle strength by exercise based evaluation of muscle strength. The study proposed that extract supplementation reduces exercise-induced muscle injury by downregulating serum creatine kinase levels (**Wankhede***et al.,*. 2015).

Role of *W. somnifera* in Anxiety

Many recent studies have investigated anxiolytic properties of *W. somnifera* in laboratory settings. The plant has been reported to curb anxious behavior in both rats **(Baitharu*et al.,*. 2013)** and humans **(Chandrasekhar *et al.,*. 2012; Khyati and Anup 2013; Pratte*et al.,*. 2014).** Aqueous concentrate of roots of *W. somnifera* (commercially available from Dabur), after extraction with chloroform and spray drying, has shown anxiolytic properties in a dose-dependent manner **(Bhattacharya *et al.,*. 2000).**

ISBN Number: 978-93-95305-66-2



The graphical abstract depicting pleiotropic roles of Ashwagandha in neuroplasticity mediated by modulation of multiple pathways such as synaptic plasticity, cell survival, senescence/ apoptotic cell death. → indicates activation and —| indicates inhibition

The anxiolytic property of *W. somnifera* was similar to lorazepam, a drug belonging to benzodiazepines family of drugs that have been used for the treatment of anxiety disorders. The anxiolytic effect of this extract has been attributed to the GABAmimetic effect of glycowithanolides of the plant, which have been identified as withaferin and sitoindosides VII-X by HPTLC. Recently, pre-supplementation of hydro-alcoholic root extract of *W. somnifera* for 30 days (300 mg/kg body weight) in rats has shown improvement in behavioral deficits caused due to middle cerebral artery occlusion (MCAO) in model of ischemic stroke **(Sood*et al.*,. 2016).**

In a recent study by **Dey*et al.*,. (2016),** a commercially available root extract of the plant with 2.7% (w/w) withanolides (Natural Remedies Pvt. Ltd., Bengaluru, India) has been shown to be instrumental in suppressing marble burying behavior in electric foot shock induced stress in mice. This activity has been attributed to phytochemicals other than withanolides that have been characterized in W. somnifera such as Withalongolide-A, an analogue of Withaferin-A **(Kumar *et al.*,. 2015)** and Withanamides**(Mirjalili*et al.*,. 2009).**

In another model of chronic stress, rats were given mild, unpredictable footshock, administered once daily for 21 days **(Bhattacharya and Muruganandam 2003).** Aqueous: ethanol (1:1) extract of two-year old

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thin roots of *W. somnifera* was further extracted with chloroform and was spray dried. The dry powder mixed in 0.3% carboxymethyl cellulose was used for the study. *W. somnifera* was administered one hour before footshock daily for 21 days. *W. somnifera* administered rats showed reduced levels of behavioral depression as evident from Porsolt's swim stress-induced behavioral despair test. Chronic stress led to significant increase in the immobility period and number of escape failures with decrease in number of avoidance response in the swin stress-induced behavioral despair test, but *W. somnifera* significantly reversed these effects in a dose-dependent manner owing to its adaptogenic properties.

Fig.Root and leaf extracts of W. somnifera possess anxiolytic properties, which has been validated under different paradigms.

Role of W. somnifera in Inflammation Different pharmacological experiments both in vitro and in vivo models have demonstrated the ability of Withaniasomnifera to exhibit anti-inflammatory, antioxidative, anti-microbial, anti-anxiety, immunomodulatory activities lending support to the rationale behind its traditional uses.

Anbalagan and Sadique (1981) reported that *W. somnifera* is an effective anti-inflammatory agent with higher activity as compared with hydrocortisone, a commonly prescribed anti-inflammatory drug. In another study by **Anbalagan and Sadique (1984),***W. somnifera* was found to inhibit the α2-macroglobulin, an indicator of anti-inflammatory activity in dose dependent manner in serum of rats.

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Begum and Sadique (1988) reported the effect of oral administration of *Withaniasomnifera* root extract before the injection of inflammatory agent.

Paw swelling and bony degenerative changes were seen in Freund's adjuvant induced arthritis. It was reported that this plant cause the significant reduction in both paw swelling and degenerative changes better than the reference drug, hydrocortisone.

A1-hindawi *et al.,*. (1992) also found that *W. somnifera*inhibited the granuloma formation in cotton pellet implantation in rats comparable to hydrocortisone sodium succinate treatment. **Sumantran*et al.,*. (2008)** evaluated the effects of *W. somnifera* roots aqueous extract and glucosamine sulphate (GlcS) on the levels of nitric oxide (NO) and GAGs secreted by the knee cartilage of chronic osteoarthritis patients using validated explants model of in vitro cartilage damage.

7. Cultivation

In natural conditions *W. somnifera* occurs on disturbed soil, along roadsides, in cultivated land, on termite mounds in grassland, in open woodland and riverine vegetation, from sea level up to 2300 m altitude. It is grown in areas with 600- 750 mm annual rainfall and prefers well drained soil; water logging is harmful **(Patra*et al.,*2004).** It grows well in sandy loams and stony red clay soils with pH 7.5-8.0 (**Thomas *et al.,*2000).** However, Obidoska and Sadowska (2003) suggested the preference of the species to acidic soil. It thrives in full sun but tolerates some shade (**PROTA 2008**).

Patra*et al.,*(2004) suggested that the species is a rainfed crop requiring dry season (1-2 winter rains are conducive for root development) and grows well in semi-arid subtropical areas receiving good rainfall. The species can be cultivated between 600-1200 m altitudes. **Misra*et al.,*(2001**) suggested that *W. somnifera* is a potential cash crop greening dry-land zones and making waste land more productive. **Das *et al.,*(2009**) successfully cultivated 'Poshita' and 'Jawahar 22' (recommended varieties) in West Bengal plains (Bidhan Chandra KrishiViswavidyalaya, Mohanpur campus).

Soil for *Withania Somnifera*

Ashwagandha is usually grown in fields which are not well covered by the irrigation systems. This is due to requirement of dry season during its growing period. The field on which food crops cannot be taken profitably due to lack of irrigation facilities may be used for Ashwagandha cultivation. Ashwagandha grows well in sandy loam or light soil or black soil, having pH 7.5-8.0 with well Drainage.

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Fig. Soil

Climate for *Withania somnifera*

Ashwagandha requires relatively dry season during its growing period, because, Ashwagandha is rainfed crop. Rainfall requirements is 650-750 mm is suitable for *Withania somnifera* cultivation. A temperature requirement of Ashwagandha is 20°C to 35°C are ideal for Ashwagandha growth. This crop even tolerates temperatures as low as 10°C. Late winter rains are conducive for the proper development of the plant roots. That's why the root of ashwagandha develops to their full strength after 1-2 late winter seasons.

Land Preparation

During land preparation the soil is nourished with plenty of organic matter while the manures or composts must be well decayed and should not have any city waste or human excreta. Around 10-20 tons/ha of farm yard manure (FYM) be supposed to be combined to the soil during last ploughing moment and then field is leveled by planking.

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Propagation

Propagation of Ashwagandha is commonly done by the seeds. The crop can be directly sown either by broad casting or line sowing. Line to line method of sowing is preferred because it increases root production and also helps in performing intercultural operation properly. Row to Row spacing of 25 to 30 cm and Plant to Plant spacing is 10 cm. and transplanting is also a viable option for Ashwagandha cultivation. In this method, time of sowing is just before the onset of the rainy season the seeds are sown in the nursery @ 5kg/ha and covered with light soil. These seeds will germinate within 6-7 days after sowing. When seedling attain the age of 25-35 days then it should be transplanted in the main field with marinating spacing of 60 x 60 cm. Seed rate: For sowing, 10-12 kg/ha seed is sufficient.

Nursery Managements

High quality and disease free seeds should be selected and sown in well prepared nursery beds. Transplanting method is preferred for better quality for *Withania somnifera* cultivation. About 5 kg of seeds is required for planting in one hectare land of main field. Nursery should be raised in the month of June and July and about 35 to 40 days old seedlings can be transplanted in the main field.

Fig. Seedling of Ashwagandha

Manure and Fertilizer Application

The medicinal plants have to be grown without chemical fertilizers by using organic manures like, Farm Yard Manure (FYM), Vermicompost; Green Manure etc. may be used as per requirement of the species. Ashwagandha need only (10-12 tons/ha) of well decomposed farm yard manure (FYM). Or 1-1.5 ton vermicompost per 1 hectare plantation. But in recent times, fertilizer have to apply on soil test value for

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keeping the optimum plant population in marginal land (poorly fertile land). In this case, additionally NPK @ 20:20:0 kg/ha is used as nutrition for the Ashwagandha plants.

Pest and Diseases Management of *Withania somnifera*

Seed rotting, seedling blight and leaf blight are common diseases affecting Ashwagandha. And Aphids, Mites, insect attack and Seedling rot and blight. However, there is no serious pest found in these crops. By spraing Dithane M-45@ 3g/l at the interval of 7-10 days can be minimized and Bio- pesticides could be prepared from Neem, Chitrakmool, Dhatura and Cow's urine and crop rotation, having proper soil drainage will reduce the impact of any diseases**.**

Fig. Pest and Disease of Ashwagandha

Harvesting of *Withania somnifera*

The Ashwagandha plants start flowering and bearing fruits from December onwards. The crop is ready for harvest in January-March at 150 to 170 days after sowing. The maturity of crop is judged by drying out of leaves and yellow red berries/fruit**.** The entire plant is uprooted along with roots.

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Fig. Harvesting of Ashwagandha Plants

Post Harvest

After harvesting, the roots are separated from aerial parts by cutting the stem 1-2 cm above the crown with the help of knife and then it is washed. The roots are then cut transversely into small pieces (7 to 10 cm) and dried in the sun or shed with up to 10-12 % moisture content, the dried roots have to be further cleaned, trimmed and graded; the berries plucked from the dried plants are threshed to obtain the seeds.

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Fig. Cleaning and washing

Grading

On the basis of length and girth of root pieces, Ashwagandha are sorted out into following grades:

A grade: Root pieces up to 7 cm in length, 1-1.5 cm in diameter, solid cylindrical with smooth external surface and pure white from inside.

B grade: Root pieces up to 5 cm in length, 1 cm or less in diameter, solid, brittle and white from inside.

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C grade: Solid root pieces up to 3-4 cm in length, 1 cm or less in diameter.

D grade: Small root pieces, semisolid or hollow, very thin, yellowish inside and < 1 cm in diameter.

DISCUSSION

Ashwagandha traditionally was used as a rejuvenative tonic for both children and the elderly. It grows in various parts of the world and is readily available, easy to store, and easy to formulate. It is one of the most utilized plants in Ayurvedic medicine and the most studied rasayana. Ashwagandha is widely accepted to be safe though would benefit from further systematic research into the safety profile. It is best administered as a churna mixed with ghee, milk or honey but other formulations are also effective. Standard dosages vary with the most common being 1-2 grams, three times per day. Ashwagandha is formally classified as an adaptogen. The primary pharmacological effect is derived from the roots which contain withanoloids and are attributed with giving the plant its impressive versatility. It is known as the "Indian Ginseng" and may be widely applied to many disorders and imbalances. Most recently it has been studied in the areas of oncology, both for tumor reduction and as a tonic post-chemotherapy, and in the area of neurodegenerative disorders. Ashwagandha's unique properties and the many animal studies performed to date point positively to the fact that it acts as both a neuro-protective agent and as a neuro-regenerator. Human studies in the therapeutic area of neurodegenerative disorders are very limited and further research is needed.

CONCLUSION:

Withania somnifera commonly known as Ashwagandha in Ayurveda medicine possesses numerous pharmacological activities supported by experimental and clinical studies. Further studies will enhance the support of its multifarious action on living organisms.

As modern medicine continues to expand, so do the uses of botanical medicines. Withania somnifera shows great potential as a safe and effective in Immunomodulation and Hematopoiesis. More research is needed to determine if Withania somnifera can duplicate this activity in humans, and to determine an optimal dosage range for achieving these effects. The potential beneficial effects of Withania in anxiety, cognitive and neurological disorders, inflammation, and Parkinson's disease. Experienced natural

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medicine practitioners, working hand-in-hand with oncologists, could increase effectiveness and decrease side effects of conventional treatments with the use of *Withania somnifera.*

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ISBN Number: 978-93-95305-66-2

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