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# EFFICACY OF CLINICAL TRIALS IN THE TREATMENT OF NEUROLOGICAL DISORDERS AND CANCER TREATMENT USING ALKALOIDS, STEROIDAL LACTONES AND SAPONINS FROM HERBAL EXTRACTS

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**ABSTRACT**

The objective of this research paper is to highlight the significance and efficacy of the wonderful herb 'Ashwagandha' which is having unique medicinal properties. This medicinal herb has a magical effect on the circulatory system and nervous system in human beings and promotes for the well being of the individual in the long run. As a matter of fact, this magical herb is said to drastically improve the physical and mental well being of the individual in the fullest perspective. Lab experiments have shown that Ashwagandha actually promotes for holistic rejuvenation and regeneration of the cells and tissues in the human body thereby promoting for increased life span among the middle aged and elderly people who are medically compromised and debilitated.

Our advanced research work has proved beyond doubt the remedial effect of this wonderful herb and laid a strong foundation for a major breakthrough in the field of Medicine.

**KEYWORDS** : Rasayana, adaptogen/anti stress agents, anorexia, endurance stress test, cell mediated immunity, Urethane induced lung-adenoma, Chinese Hamster Ovary (CHO) cells carcinoma

## Introduction

Ashwagandha (Withania somnifera, fam. Solanaceae) is ordinarily known as "Indian Winter cherry" or "Indian Ginseng". It is a standout amongst the most important herbs of Ayurveda utilized for centuries as a Rasayana for its boundless medical advantages. Rasayana is depicted as a home grown or metallic readiness that advances an energetic condition of physical and psychological wellness and enhances happiness. These types of cures/remedies are given to children and youngsters as tonics, and are likewise taken by the moderately aged and elderly to increase life span. Among the ayurvedic Rasayana herbs, Ashwagandha holds the most conspicuous place. It is known as "Sattvic Kapha Rasayana" Herb. A large portion of the Rasayana herbs are adaptogen/anti stress agents.

Ashwagandha is regularly available as a churna, a fine sieved powder that can be blended with water, ghee (cleared up margarine) or nectar. It upgrades the capacity of the cerebrum and nervous system and improves memory power. It enhances the capacity of the physiological framework of advancing a sound sexual and regenerative disposition. Being an intense adaptogen, it upgrades the body's flexibility to stretch. Ashwagandha enhances the body's defence against diseases by enhancing the cell mediated immunity. It additionally has powerful cancer prevention agent properties that protects against cell destruction caused by free radicals.

## Chemical Composition

The biologically active chemical constituents of *Withania somnifera* (WS) include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins.[1] Sitoindosides and acylsterylglucosides in Ashwagandha are anti-stress agents. Active principles of Ashwagandha, for instance the sitoindosides VII-X and Withaferin-A, have been shown to have significant anti-stress activity against acute models of experimental stress. Many of its constituents support immunomodulatory actions. The aerial parts of *Withania somnifera* yielded 5-dehydroxy withanolide-R and withasomniferin-A.

## Classical Applications of Ashwagandha – Broad Classification of its Uses and Benefits

Ayurveda, the traditional system of medicine practiced in India can be traced back to 6000 BC. For most of these 6000 years, Ashwagandha has been used as a Rasayana. [2] The root of Ashwagandha is regarded as tonic, aphrodisiac, narcotic, diuretic, anthelmintic, astringent, thermogenic and stimulant. The root smells like horse ("*ashwa*"), that is why it is called Ashwagandha (on consuming it gives the power of a horse). It is commonly used in emaciated children (when administered with milk, it is the best tonic for children), debility from old age, rheumatism, vitiated conditions of vata, leucoderma, constipation, insomnia, nervous breakdown, goitre etc. The paste formed when roots are crushed with water is used as an external application to reduce the inflammation at the joints. It is also locally applied in carbuncles, ulcers and painful swellings. The root in combination with other drugs is prescribed for snake venom as well as in the case of scorpion-sting. It also helps in the treatment of leucorrhoea, boils, pimples, flatulent colic, worms and piles. The Nagori Ashwagandha is considered as the supreme among all Ashwagandha varieties. Maximum benefits are experienced by the patients when fresh Ashwagandha powder is used.

The leaves are bitter in taste and are recommended in case of fever and also painful swellings. The flowers are astringent, depurative, diuretic and aphrodisiac. The seeds are anthelmintic and combined with astringent and rock salt to remove white spots from the cornea. Ashwagandharishta prepared from it is used in the treatment of hysteria, anxiety, memory loss, syncope, etc. It also acts as a stimulant whereby it helps to increase the sperm count particularly in men suffering from sexual and infertility problems.

## Scientific Studies on Ashwagandha Adaptogenic / Anti-stress effect

Aswagandha is an ancient medicinal herb and it is always compared with *Eleutherococcus senticosus* (Siberian Ginseng) and *Panax Ginseng*(Chinese / Korean Ginseng) in its adaptogenic properties and because of this property, it was widely known as Indian Ginseng in order to indicate its historical importance as a medicinal herb.[3] Our advanced and extensive studies on the biological model of animals for the adaptogenic / anti-stress properties of Ashwagandha_have shown it to be effective in increasing the stamina (physical endurance) and preventing stress induced gastric ulcer, carbon tetrachloride ($CCl_4$) induced hepatotoxicity and mortality. Ashawagandha have similar anti-stress activity in rats. In our lab experiments at Global Research Academy, Hyderabad City, Telangana State, India, an aqueous suspension of Ashwagandha root was used at 100 mg/kg/oral dosage. The results indicated a significant increase in the plasma corticosterone level, phagocytic index and avidity index in rats subjected to cold swimming stress. In the laboratory experiments conducted on rats pre-treated with the drug, these parameters were near to control values and an increase in the swimming time was observed. These results indicated that *Withania somnifera* when used in the crude form acts as a potent

anti-stress agent. The results of above studies lend support to the hypothesis of tonics, vitalizers and rejuvenators used in the field of Medicine, which indicate the significance of the clinical use of *Withania somnifera* in the prevention, diagnosis and treatment of many stress induced diseases like arteriosclerosis, premature ageing, arthritis, diabetes, hypertension and malignancy. Thus, it is scientifically and experimentally proven beyond doubt that Ashwagandha is the drug of choice for curing many life threatening diseases and identification of its medicinal and curative properties as a result of our advanced lab experiments is a major breakthrough in the field of Medicine.

**Lab Experiments – Data Interpretation & Analysis**

**1. A Research Study of its Effect on swimming performance**

The research team in the course of the lab experiments found that Ashwagandha was largely responsible for enhancing the swimming performance or the ability to swim very fast in the case of rats which is duly acknowledged by observing an increase in the speed of swimming during physical endurance test and completing the feat in less time. [4] Ashwagandha's antistress properties have been studied meticulously and investigations were done by using adult rats which were selected to conduct swimming endurance stress test. These lab animals (specimens) when administered with Ashwagandha showed a significant increase in the rate of speed of swimming and took less time as compared to control group of mice. Also, the rats swam for a longer duration in comparison with the control mice. It has been found that the control group of mice swam for a mean time of 385 minutes approximately whereas the drug-treated animals continued to swim for a mean duration of 740 minutes approximately. Therefore, the swimming time was approximately doubled after treatment with *Withania somnifera (WS),* thus it is experimentally proven.

The organic constituents of Withania somnifera (WS) are reported to ge dynamic and having exclusive chemical properties. This constitutes certain alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine), steroidal lactones (withanolides, withaferins) and saponins. Sitoindosides and acylsterylglucosides in Ashwagandha are not considered favourable to stretch specialists. Dynamic standards of Ashwagandha, for example the sitoindosides VII-X and Withaferin-A, have shown to bear a noteworthy hostility to stretch action against intense models of exploratory anxiety. Considerably, a lot of its constituents boost up or enhance immunomodulatory activities. The airborne parts of Withania somnifera yielded 5-dehydroxy withanolide-R and withasomniferin - A which are identified in the course of our lab experiments by our research team at Global Research Academy, Hyderabad, Telangana State, India.

**2. Clinical Uses and Benefits of Ashwagandha**

The conventional system of medicine used several medicinal herbs and other varieties of related species in ancient India and this can be traced back to thousands of years ago. Thus, in ancient India, Ashwagandha has been utilized as a Rasayana. The base of Ashwagandha is viewed as tonic, aphrodisiac (sexual enhancer), opiate, diuretic, anthelmintic, astringent, thermogenic and stimulant. The root smells like stallion ("ashwa"), that is the reason it is called Ashwagandha (on devouring it gives the energy of a stud). It is normally used in emaciated kids and those suffering from anorexia(when given with milk, it is the best tonic for youngsters), debilitated elderly people, rheumatism, vitiated states of vata, leucoderma, constipation, insomnia( sleep deprivation), nervous breakdown, goitre and so forth. [5] The paste that is formed when roots are crushed with water is applied externally to reduce inflammation at the joints. It is likewise locally applied in carbuncles, ulcers and excruciating swellings. The root in combination with different medications is prescribed for snake venom and also in the case of scorpion-sting. It additionally helps in leucorrhoea, bubbles, pimples, pompous colic, worms and heaps. The Nagori Ashwagandha is the incomparable among all Ashwagandha varieties. Ashwagandha in crispy powder form is found to be very useful.

It is found that the leaves of Ashwagandha are extremely medicinal and aromatic and can be successfully prescribed in the treatment of high fever, excruciating swellings, headache, migraine and generalised body pains. [6] Also, the flowers are found to act as an astringent, depurative, diuretic and act as a potent sexual enhancer for sex related issues. The seeds are anthelminthic and when combined with astringent and rock salt tend to effectively remove white spots from the cornea. Ashwagandharishta, its derivative form, is useful in the treatment of hypertension, stress related disorders, anxiety, memory loss, syncope, and other neurological problems. It is also very useful to improve sexual potency among men and at the same time provide for an increase in sperm count.[7]

**3. Logical Studies on Ashwagandha Adaptogenic/Anti-stretch impact**

Our research studies have shown that Aswagandha can be compared well with Eleutherococcus senticosus (Siberian Ginseng) and Panax Ginseng (Chinese/Korean Ginseng) in its adaptogenic properties and subsequently it is popularly known as Indian Ginseng. Our progressive and broad examination on the organic model of lab animals for the study of adaptogenic or otherwise non-confirmity, with a view to highlight the medicinal properties of Ashwagandha have indicated that it is powerful in improving the stamina (physical perseverance) and avoiding stress incited gastric ulcer, carbon tetrachloride (CCl4) actuated hepatotoxicity and mortality. [8] Ashawagandha has not shown any preference to stretching action in rats. In our lab experiments, an aqueous suspension of Ashwagandha root was used with 100 mg/kg/oral dose. The outcomes demonstrated a noteworthy increment in the plasma corticosterone level, increase in phagocytic count (blood platelets) and energy enhancement in rats subjected to cold swimming stress. In the rats pre-treated with the medication, these parameters were close to control figures and an increase in the swimming time was observed. These outcomes demonstrate that Withania somnifera can be utilized to enhance the time of swimming among the rat specimens. The consequences of above investigations loan support to the theory of tonics, vitalizers and rejuvenators of Ayurveda which show clinical utilization of Withania somnifera in the avoidance and treatment of many anxiety induced infections like arteriosclerosis, untimely maturing, joint inflammation, diabetes, hypertension and malignancy.[9]

**I. Impact on swimming performance**

Ashwagandha was appeared to build swimming execution in rats as judged by increment in swimming time amid physical continuance test. Ashwagandha's anti-stress properties have been examined in every one of these examinations utilizing grown-up rats were done by swimming perseverance stretch test. Ashwagandha treated lab animals demonstrated a critical increment in the length of swimming time when contrasted with control. The control gathering of mice swam for an interim of 385 minutes, though the medication treated creatures kept on swimming for a mean span of 740 minutes. In this manner, the swimming time was roughly multiplied after Withania somnifera (WS) treatment.

**ii. Effect on cortisol and ascorbic acid contents of adrenals**

Our continued lab experiments on rats and mice have produced wonderful results. The cortisol content of adrenals has decreased appreciably in animals subjected to 5 hours constant swimming as compared to non-swimmer group. It has been established that pretreatment with WS prevented reduction of the cortisol content of adrenals. The ascorbic acid content was also reduced significantly after 5 hours of swimming as compared to the animals of non-swimmer group. Pretreatment with WS prevented reduction in ascorbic acid content which occurs after swimming stress. Thus, *Withania somnifera* treatment prevents decrease of adrenal cortisol and ascorbic acid which occurs due to swimming stress.

**iii. Reduction in the formation of systemic ulcers - Anti-ulcerogenic effect**

Ashwagandha was found to be useful in the prevention and also

reduction of stress-induced ulcers of the gastrointestinal tract. It showed significant protection against 18 h immobilization, cold + immobilization (4h) and aspirin induced gastric ulcers and lowered the mean ulcer index in rats.

**iv. Effect on Blood Circulatory System**

Ashwagandha given to a group of mice with milk injection promoted for reduction in leucocytosis and produced normal count for leucocytes in patients suffering from different types of viral and systemic infections.

**v. Anabolic effects:**

Our lab experiments at Global Research Academy, Hyderabad have been conducted for a period of 6 months and 3 months time has been utilised to find out the effect of Ashwagandha in promoting for increase in body mass and body weight particularly in patients suffering from underweight problems.[10] There was a conspicuous increase in the body weights of the Ashwagandha treated group of patients after 3 months. Also, similar results were established in rats as compared to control for a period of 3 months.

**Acute toxicity studies**

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

**Anti-tumor effect Effect on Chinese Hamster Ovary (CHO) cells 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. This knowledge in turn will assist oncologists who plan to use the Ashwagandha as 'synergizers with conventional chemotherapy or radiation therapy.

**Effect on Urethane induced lung-adenoma in mice and other studies**

Our research study laid a greater stress on the benefits of Ashwagandha which was found to be very useful in determining its efficacy as a cancer curative drug. Our research study has shown that it prevented lung-adenomas which is Urethane induced.[11] The other effects of urethane like leucopoenia were also prevented. Urethane, which is chemically induced, causes a variety of ill effects, all of which can be prevented by *Withania* as proved by our lab experiments on animal specimens. The drug can be used as an adjunct to cancer chemotherapy or radiotherapy. Besides having an anti-cancer effect it will also reduce the side effects of anti-cancer agents, which invariably reduce immunity and quality of life. Ashwagandha also acts as an immunomodulator and hence can increase the life span of cancer patients, where lowered immunity states of the patient is the primary cause of concern. Our experimental results suggest its use as an anti-tumor and immunomodulator agent.[12]

The research and studies of Ashwagandha's activities in the inhibition and reduction of tumour growth have shown encouraging evidence that this remarkable herb may prove to be extremely effective in the treatment of tumor type diseases including cancer. It also improves the white cell count (WBC) and function, which are depleted in the chemotherapeutic treatment of cancer. Ashwagandha in the treatment of fibroid tumors of the uterus showed reduction of uterine bleeding tendencies and disappearance of fibroids after long treatment.

**Effect on Central Nervous System - Cognition Promoting Effect**

Ashwagandha can be considered as popular drug of choice for many chronic ailments in human beings and belongs to a group of drugs meant to improve memory in human beings. This typically refers to the cognitive behaviour namely memory retention, intellectual capacity, the capacity to understand and psychological balance. Thus, Ashwagandha, is used to promote intellect and memory gain. The positive cognitive promoting effect of this class of drugs was best seen in children with memory issues or when memory is compromised following a head injury, in case of a prolonged illness and in the case of old age.

**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 are considered the major causes of cognitive impairment, as based on the results of neuropathological post-mortem studies of the brain. 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 Ashwagandha slows, 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. Glycowithanolides withaferin- A and sitoindosides VII–X isolated from the roots of Ashwagandha significantly reversed ibotenic acid induced cognitive defects in Alzheimer's disease model.

Ashwagandha has been described as a nervine tonic in the field of Medicine and that is why it is a common ingredient of medicinal & Herbal tonics. Tonics, rejuvenators and vitalizers appear to remove all types of diseases and induce immunity and longevity in the patients.[13]

Pretreatment with Ashwaganda extract was found to prevent all the changes in antioxidant enzyme activities, catecholamine content, dopaminergic D2 receptor binding and tyrosine hydroxylase expression induced by 6-hydroxydopamine (6-OHDA) in rats (an animal model of Parkinson's disease) in a dose-dependent manner. [14] Thus, these results suggest that Ashwagandha may be helpful in protecting the neuronal injury in Parkinson's disease.

**GABA-mimetic effect on neurodegeneration and neuroregenerative potential**

Behavioral experiments have lent support to the GABA-mimetic activity of Ashwagandha root extract. GABAergic neurodegeneration due to neuroleptic-induced excitotoxicity and oxidative stress is one of the etiopathological mechanisms in the pathophysiology of tardive dyskinesia and GABA agonists are shown to be effective in ameliorating the symptoms of tardive dyskinesia. The beneficial effect of Ashwagandha root extract might be due to its GABA mimetic activity. Ashwagandha, its constituents and the metabolites of its constituents promote the growth of nerves after taking it for 7 days.

An intriguing study demonstrated that chronic oral administration of withanoside IV attenuated the axonal, dendritic and synaptic losses and memory deficits induced by amyloid peptide Aβ(25–35) in mice. After oral administration in mice, withanoside IV was metabolized into sominone, which induced marked recovery in neurites and synapses and also enhanced axonal and dendritic outgrowth and synaptogenesis. [15] These effects were maintained for at least 7 days after discontinuing withanoside IV administration. These data suggest that withanoside IV, and its metabolite, sominone, may have clinical usefulness as antidementia drugs.

Another team found that the methanol extract of Ashwagandha (5 mg/ml) significantly increased the percentage of cells with neurites in human neuroblastoma SK-N-SH cells. The effect of the extract was dose-and time-dependent. mRNA levels of the dendritic markers MAP2 and PSD-95 by RT-PCR were found to be markedly increased by treatment with the extract.

Immunocytochemistry demonstrated the specific expression of MAP2 in neurites extended by the extract. These results suggest that

the methanol extract of Ashwagandha promotes the formation of dendrites.

**Anxiolytic effect**

Ashwagandha induced a calming anxiolytic effect that was comparable to the drug Lorazepam in all three standard Anxiety tests: the elevated plus-maze, social interaction and the feeding latency in an unfamiliar environment. Further, both Ashwagandha and Lorazepam, reduced rat brain levels of tribulin, an endocoid marker of clinical anxiety, when the levels were increased following administration of the anxiogenic agent, pentylenetetrazole.[16]

Ashwagandha also exhibited an antidepressant effect, comparable with that induced by imipramine, in two standard tests, the forced swim-induced 'behavioral despair' and 'learned helplessness' tests. The investigations support the use of Ashwagandha as a mood stabilizer in clinical conditions of anxiety and depression.

**Effect on Energy levels and Mitochondrial Health**

Our lab experiments had concentrated on the effect of Ashwagandha on glycosaminoglycan synthesis in the granulation tissue of air pouch granuloma. This is basically carrageenin-induced and was given a detailed study. Ashwagandha is observed 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. Further, Mg2+ dependent ATPase activity was found to be influenced by Ashwagandha. Ashwagandha also reduced the succinate dehydrogenase enzyme activity in the mitochondria of granulation tissue.

**Anti-inflammatory effect**

Withaferin A and 3-b-hydroxy-2,3-dihydrowithanolide F isolated from *Withania somnifera* show a wonderful antibacterial, antitumoral, immunomodulating and anti-inflammatory properties.

**Anti-arthritic effect**

The wonderful drug of choice namely Ashwagandha is a potent analgesic that soothes nervous system from pain response. The powerful anti-arthritic properties of Ashwagandha are now widely accepted and documented; it is furthermore found to be effective as antipyretic as well as analgesic also.[17]

Ashwagandha with the following quantity namely (1gram/kg/oral) produced significant analgesic activity for a rat experiencing heat analgesia induced by hot plate method. The peak analgesic effect of Ashwagandha was recorded as 78.03 percent at 2nd hour of administration. The influence of pain mediators ie., prostaglandin and 5-hydroxytryptamine in analgesic activity of Ashwagandha was analysed by pre-treatment with paracetamol and cyproheptadine as part of our investigations. The quantity prescribed for Paracetamol is 200 mg/kg, ip and for Cyproheptadine is 20 mg/kg, ip. Our research work has indicated that the analgesic activity of Ashwagandha was significantly potentiated by cyproheptadine. Actually, paracetamol did not show any significant change in its activity, suggesting the involvement of serotonin and not necessarily prostaglandins in the analgesic activity of Ashwagandha.

**Results and Conclusion**

Based on the available data which provides a scientific support and arrive at the conclusion that Ashwagandha is a real potent regenerative tonic due to its multiple pharmacological actions like anti-stress, neuroprotective, antitumor, anti-arthritic, analgesic and anti-inflammatory etc. It is useful for different types of diseases like Parkinson's Disease, Dementia, Memory loss, Stress induced diseases, malignoma and others.

The use of Ashwagandha as a household remedy by people in India who consider it as the best tonic for old people and children and as aphrodisiac by young people. It is one of the best nervine tonics in the field of Medicine. Clinical experiments conducted by us showed that besides the enumerated neurological conditions, brain strokes causing paralysis and neuronal deficit also improve in the long term treatment with Ashwagandha. We strongly recommend it for the treatment of all forms of cancer including prostate and lung cancers, especially in last stages, giving the patients lot of health benefits. We have some cases of lung cancer who have refused modern therapy and recovered clinically and radiologically with our therapy of Ashwagandha. In a recent seminar on essential drug concept, it was projected as one of the six essential medicinal herbs.

Thus, the above findings clearly indicate that the use of Ashwagandha has a logical and scientific basis. Further clinical studies and large scale experimentations on human beings are needed to prove the clinical efficacy of this herb especially in stress related diseases, rare neurological disorders and in the treatment of different types of cancers.

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