



Optimal^{Rx}

Withania somnifera

WITHANIA



**BOTANICAL NAME:**

Withania somnifera

COMMON NAME:

WITHANIA

OTHER NAMES:

Ashwaganda, Indian Ginseng, Winter Cherry, Queen of Ayurveda, Amukkrang Kilangu (Tamil)

 It is interesting to note that the species name somnifera means 'sleep inducing' in Latin.

BOTANICAL FAMILY:

Solanaceae

PARTS USED:

Root

**TASTE AND CHARACTER:**

Sweet and astringent with secondary bitter qualities.

HISTORY

Withania or Ashwaganda is one of the most utilized herbs in Ayurvedic medicine holding a position of importance similar to that of ginseng in China. Ayurvedic practitioners consider Ashwaganda a powerful 'rasayana' herb or potent tonic to promote greater vitality and longevity. Ashwaganda is believed to balance 'vata' and 'kapha' in Ayurvedic medicine. Traditionally it is used to treat a myriad of conditions and it is found to:

- Increase strength
- Boost stamina and relieve fatigue
- Enhance sexual energy
- Rejuvenate the body and slow the aging process
- Strengthen the immune system
- Promote recovery after illness
- Strengthen sickly children
- Soothe and calm the nerves without drowsiness (low - moderate doses)
- Mildly sedating and hypnotic in higher doses
- Clear the mind and improve memory

Ashwaganda, in Sanskrit literally means "horses smell" which refers more to its ability to impart horse-like strength and stamina than to the odour of the herb itself.

Every part of the plant can be used, with the young shoots and seeds used in food and as a thickener in the making of vegan cheese. The fruit can be used as a substitute for soap and the leaves can be used as an insect repellent. Ashwaganda is commonly combined with other herbs to enhance its rejuvenating effects.



ACTIONS

- Adaptogen
- Tonic
- Sedative
- Nervine tonic
- Anti-inflammatory
- Immunomodulatory
- Hemopoietic
- It has also been shown to exert a positive influence on the endocrine, cardiopulmonary and central nervous system.

INDICATIONS

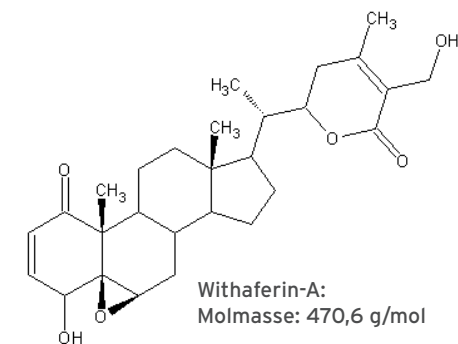
- Anaemia
- Convalescence
- Chronic diseases, especially of an inflammatory nature
- Emaciation, weakness and wasting disorders, especially in children and the elderly
- Impotence due to stress and poor vitality
- Debility
- Nervous exhaustion
- May have some preventative role in cancer

CONSTITUENTS

The major constituents of *Withania* are alkaloids, steroidal saponins and steroidal lactones including withanolides and withaferins. Twelve alkaloids and forty withanolides have been isolated and studied as well as several sitoindosides. Sitoindoside is a withanolide containing a glucose molecule at carbon 27.

There are two main withanolides, withaferin-A and withanolide D which are thought to be responsible for much of *Withania*'s pharmacological activity.ⁱ *Withania* is also rich in iron.ⁱⁱ Below is a diagram of the chemical structure of withaferin-A.

Withaferin-A





ANTI-INFLAMMATORY PROPERTIES

Withania is considered an anti-inflammatory herb in Ayurvedic medicine and has traditionally been used for arthritis and asthma. It seems that Withania exerts its positive effects on arthritis through a direct anti-inflammatory, antioxidant and chondroprotective effect. It is thought that Withania's anti-inflammatory and antioxidant actions also combine to contribute to its anti-tumour properties.

- Animal studies have shown that Withania has an anti-inflammatory effect comparable to that achieved by the use of 5mg/kg of hydrocortisone which was believed to be due to the presence of withaferin-A.ⁱⁱⁱ
- An induced asthma animal trial was studied with Withania and its anti-inflammatory effect. It was found that Withania produced a marked reduction in inflammatory markers including eosinophils and when combined with selenium Withania significantly reduced the white cell count confirming its anti-inflammatory activity.^{iv}
- In vitro studies have shown that Withania provided a statistically significant decrease in nitric oxide release in a subset of patients with chronic osteoarthritis.^v
- Several genes that involve cellular proliferation, carcinogenesis, metastasis and inflammation are regulated by the activation of Nuclear Factor- κ B (NF- κ B). NF- κ B are proteins that are involved in the control of a large number of cellular processes including immune and inflammatory processes, developmental processes, cellular growth and apoptosis. Withanolides, which are constituents of Withania has been shown in clinical studies to directly suppress the activation of NF- κ B induced by a number of inflammatory and carcinogenic agents including Tumor Necrosing Factor (TNF) and Interleukin 1 β .^{vi}

ADAPTOGENIC AND TONIC EFFECTS

- Withania has a reputation of having a wide range of nonspecific actions that contribute to its potent adaptogenic activity. Although little is known of the exact adaptogenic mechanisms of Withania, on reviewing the literature it has indicated there are several possible contributing factors including:
- Withania is known to have an effect on the HPA axis including cortisol levels which are known to modulate the stress response and either improve or hinder adaptation.
- Withania has also been shown to suppress and down regulate IgE antibody response - IgE hypersensitivity response is an example of poor adaption to stress.
- It has been postulated that Withania's mechanism of action may be due to its effect on the up-regulation of anabolic processes and its activity on catecholamines and mitochondrial processes which have been demonstrated in trials of animals under physical stress.
- Anabolic activity of Withania was attributed to the presence of steroidal lactones called withanolides. It has also been postulated that the anabolic effects may be due to the anti-serotonergic activity which would lead to an increase in appetite and therefore weight gain.^{vii}
- The potent antioxidant action is also thought to contribute to Withania's adaptogenic effects.
- The adaptogenic effects of Withania were studied in a clinical trial using a rat model of chronic stress produced by random regular foot shock. The chronic stress induced significant hyperglycaemia, glucose intolerance, increased cortisol levels, immunosuppression and gastric ulceration. Withania administered 1 hour before footshock was found to attenuate these effects and demonstrated significant anti-stress and adaptogenic activity similar to that of Panax Ginseng.^{viii}



ANTI-TUMOUR ACTIVITY

- Withania has a reputation as being a powerful tonic for debility and wasting conditions in Ayurvedic medicine, and its potential anti-tumour action has been the subject of much attention in the scientific community leading to many clinical trials.
- Several genes involved in cellular proliferation, carcinogenesis, metastasis and inflammation are regulated by NF- κ B. In vitro studies on human cancer cells were undertaken to ascertain if the anti-tumour activity of withanolides is mediated through the modulation of NF- κ B activation. It was found that withanolides inhibited activation and expression of NF- κ B and enhanced the apoptosis induced by TNF and chemotherapeutic agents. Withanolides were found to suppress cellular TNF- induced invasion and receptor activation of NF- κ B ligand-induced osteoclastogenesis. This mechanism of action may explain the ability of withanolides to enhance apoptosis and inhibit invasion and osteoclastogenesis. It was also found that withanolides suppressed NF κ B activation in a dose dependant manner, with complete inhibition occurring at 5 μ mol/L dose. ^{ix}
- In vitro trials of the effect of withaferin-A on human cells lines of estrogen dependant (MDA-MB-231) and estrogen responsive (MCF-7) breast cancer cells were conducted. It was shown that withaferin-A decreased the cell division cycle and induced mitotic arrest. The results of this study indicated that cell cycle arrest may be an important mechanism in the anti-proliferative effect of withaferin-A against human breast cancer cells. ^x



CONTINUES



- A recent in vitro study of withanolides effect on human promyelocytic leukemia cells has shown that withanolides activate the apoptotic cascade through cytochrome C release from the mitochondria, inducing apoptotic cell death in leukemia cells. ^{xi}
- In vitro cell studies have identified withanone (a constituent of Withania) as a cancer inhibitory factor (i-factor). Ongoing animal studies have confirmed that withanone has an effect on apoptosis signaling, p53 signaling, GM-CFS signaling, cell death receptor signaling and G2-M DNA damage regulation, all contributing to its anti-carcinogenic effects. ^{xii}
- Animal studies of Withania's anti-tumour activity have shown that after 17 weeks of treatment Withania significantly decreased the chemotactic activity of murine macrophages and markedly reduced the production of Interleukin-1 (IL-1) and Tumour Necrosing Factor (TNF). The primary role of TNF is in the regulation of immune cells where it induces apoptotic cell death and inflammation. ^{xiii}
- Withania is thought to exert its anti-tumour activity via multiple pathways. Most recently in clinical trials using human cancer cells lines it was shown that Withania possesses anti-cancer and Th-1 immune up-regulatory activities. Withania produced cytotoxicity in vitro. The mechanism of cytotoxicity was investigated and it was found that Withania induced apoptosis via the activation of intrinsic and extrinsic signaling pathways. It induced early generation of reactive nitrogen and oxygen species (RNOS) thus producing oxidative stress, mediated mitochondrial membrane potential (MMP) loss leading to release of cytochrome C to the mitochondria and apoptosis inducing factor to the nuclei of cells. Further animal studies performed by the same research team showed it inhibited greater than 50% tumour growth in mouse tumour models and demonstrated that Withania selectively stimulated Th-1 immunity by enhancing the secretion of INF- γ and IL-2. ^{xiv}



FURTHER IMMUNE ACTIVITY

- Withania is known for its ability to restore health and immune function after periods of stress. Chronic stress is known to suppress immune function and disturb homeostasis, bringing about changes in behaviour, endocrine and immune function. Recent animal studies have investigated the effects of Withania on chronic stress-induced alterations in T-lymphocytes and corresponding cytokine secretion patterns. It was found that administration of Withania caused significant recovery of stress induced depletion of T cell population, causing an increase in cytokines associated with Th-1 helper cells and a decrease in the concentration of cortisone in stressed experimental animals. It also showed a reversal of stress -induced increase of ALT, AST and hepatic lipid peroxidation as well as an improvement in the stress- induced decrease of hepatic glutathione and glycogen levels thus demonstrating significant anti-stress and immunomodulating activity.^{xvi}
- Withania's immunomodulatory effects have also been demonstrated in clinical trials using animal models to investigate its effects on IgE antibody response. Withania was shown to exert a significant suppression of IgE antibody production when administered with ovalbumin (OVA), a classic antigen. It was also able to produce the same effects when administered 24 hours prior and 6 hours after administration of OVA. It was found to suppress and down-regulate IgE antibody production and be effective against other allergens tested.^{xvii}
- A small human trial investigating Withania's effects on the activation of lymphocytes found that it produced a significant increase in the number and activation of CD4 cells after 96 hours. Overall the mean values of receptor expression for all measured receptor types were increased over baseline indicating a major change in immune cell activation across the sample.^{xviii}

ADJUVANT TO CANCER TREATMENT

A comprehensive review of 218 articles has found that Withania reduces tumour cell proliferation while increasing overall survival time in animal trials. It has been shown to enhance the effectiveness of radiation therapy while potentially mitigating undesirable side effects. Withania also reduces the side effects of chemotherapeutic drugs including cyclophosphamide and paclitaxel without interfering with the tumour reducing actions of the drugs. These effects were demonstrated in in vitro human cancer cell lines and in vivo on animal subjects.^{xv}

ANTIVIRAL ACTION

Withania has also been shown to have some effects on viral replication in in vitro studies using cells from monkeys infected with the HS-1 virus. Exposure to an aqueous extract of Withania was shown to induce 100% cell death induced by cytotoxic effects after 96 hours at concentrations ranging from 7.8 µg/ml to 500 µg/ml.^{xix}



ANTIOXIDANT ACTIVITY

- Withania's mode of action in many disease states is thought to be explained by its potent antioxidant activity. Many clinical trials investigating its neuroprotective and cardioprotective actions have found that its antioxidant activity plays a major role in its protective action.
- In vitro studies assessing Withania's antioxidant activity has found that the root possesses both non- enzymatic (ascorbic acid, α -tocopherol and reduced glutathione) and enzymatic (superoxide dismutase, ascorbate peroxidase, catalase, peroxidase and polyphenol oxidase) activity.^{xxii}
- Animal studies have demonstrated that Withania has potent antioxidant activity and produces a significant decrease in lipid peroxidation. Liver peroxidation and antioxidant status of mice with adjuvant induced arthritis were tested before and after administration of Withania. It was found that Withania produced a significant decrease in the level of lipid peroxides. Withania was found to have modulated the lipid peroxidation and antioxidant status to near normal levels.^{xxiii}

NEUROPROTECTIVE EFFECTS AND EFFECTS ON COGNITION

- Withania is one of the major herbal components of geriatric tonics in Ayurvedic medicine and is used to treat memory decline related to aging and has a reputation for clearing the mind and improving memory. A recent animal study assessed the potential neuroprotective effects of Withania in cognitive impairment and altered the levels of oxidative defence in induced rat brain damage. It was found that treatment with Withania over 14 days significantly restored glutathione and restored acetylcholinesterase levels in striatum, cortex and hippocampus regions of the brain.^{xxiv}
- Another recent trial investigated the potential anti-dementia effects of Withania and its effects on neuronal networks in the damaged brain. Using an animal model they found that Withania was able to significantly improve memory deficits and prevented loss of axons, dendrites and synapses.^{xxv}



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ANTIBACTERIAL ACTION

- Withania is also known to have some antibacterial action with clinical studies testing extracts of Withania from root and leaves against pathogenic bacteria. Both aqueous and alcoholic extracts of Withania were found to possess significant antibacterial activity against a range of bacteria. They also tested Withania's antibacterial effects in animal trials with mice infected with salmonella. Oral administration of Withania obliterated the salmonella infection, increased survival rates and reduced bacterial load in various vital organs of the treated animals.^{xx}
- Methanol and hexane extracts from the roots and leaves of Withania have also been shown to have potent antibacterial effects in vitro.^{xxi}



- ➔ Withanoside IV significantly induced axonal and dendritic regeneration and synaptic reconstruction. Their data suggested that withanoside IV may ameliorate neuronal dysfunction in Alzheimer's disease. ^{xxvi}
- Withania has been reported to have potent antioxidant, anti-peroxidative and free radical quenching properties which are considered to contribute to its neuroprotective effects. The neuroprotective and potential anti-Parkinsonian effects of Withania have been investigated in animal trials. It was found that Withania given three weeks prior to an agent inducing brain damage and producing symptoms of Parkinson disease was found to reverse significantly all parameters in a dose dependant manner. These included lipid peroxidation, reduced glutathione, activities of glutathione -S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase, dopaminergic binding and tyrosine hydroxylase. This trial demonstrated the neuroprotective effects of Withania and its potential to protect against neuronal injury in Parkinson's disease. ^{xxvii}

WITHANIA'S POTENTIAL ROLE IN DRUG WITHDRAWAL

Withania is well known as a potent adaptogen and nervine tonic and is often used as a supportive treatment during drug withdrawal. Its potential in drug withdrawal has been studied with clinical trials focusing on the potential neuritic regeneration and synaptic reconstructive properties of withanolides. Most recently a clinical trial investigated Withania's effects on morphine withdrawal. Withania was administered 30 minutes prior to morphine, daily over a period of 14 days; this concomitant administration of Withania significantly reduced the severity of withdrawal symptoms. In addition, treatment with Withania in the 14 days leading up to withdrawal fully prevented brain and spinal changes seen in control animals. Withania was also given to another group of animals during the withdrawal period only and it was found that it had no effect in reducing the symptoms of withdrawal. This study suggests that treatment with Withania in the weeks leading up to a planned opiate withdrawal would be beneficial. ^{xxx}

WITHANIA'S ROLE IN SLEEP REGULATION

In Ayurvedic medicine Withania is known to soothe and calm the nervous system without drowsiness. Western herbalists use Withania as a calming nervine tonic which helps to improve the quality of sleep. High doses are considered sedating and mildly hypnotic. Clinical trials have confirmed its ability to regulate sleep via its effects on the modulation of GABA. Animal studies have found that pre-treatment with Withania shortened sleep latency, decreased waking, increased REM and total sleep time in sleep disturbed rats. They found that Withania induced sleep promoting effects by involving GABAergic modulation. ^{xxx}

CARDIOPROTECTIVE EFFECTS

Withania is known to have potent antioxidant activity and adaptogenic action leading to its widespread use in the recovery from illness. A clinical trial was undertaken to evaluate the cardioprotective potential of Withania using an animal model of induced myocardial necrosis in rats. Withania was found to exert a strong cardioprotective effect by augmenting endogenous antioxidants, maintaining the myocardial antioxidant status and significantly restoring the altered hemodynamic parameters. 50mg/kg dose produced maximum cardio-protective effects. ^{xxxiv}



EFFECTS ON MALE FERTILITY

- Withania is known as an aphrodisiac in Ayurvedic medicine and is often used to promote vitality and treat fertility in men. Stress is known to be a causative factor in male infertility. Withania's proven adaptogenic effects, antioxidant action and its ability to modulate the stress response and therefore improve male fertility has been the subject of human clinical trials. The trial subjects consisted of 121 infertile men with normal semen profiles that were further categorized into three groups - heavy smokers, men under psychological stress and infertility of unknown aetiology. The participants were given Withania root powder at 5g/day for 3 months. Various biochemical and stress parameters were measured before and after treatment. Treatment resulted in a decrease in stress, significant decrease in cortisol levels, increase in testosterone, regulation of other reproductive hormones and improvement in overall semen quality in a significant number of individuals. The treatment resulted in pregnancy in the partners of 14% of trial subjects. The authors concluded that Withania promoted fertility by balancing hormone levels, reducing oxidative stress, directly and indirectly, modulating the stress response and possibly improving detoxification processes in the body. ^{xxxii}
- Another recent prospective study was conducted to investigate the impact of Withania on semen profile, oxidative biomarkers and levels of reproductive hormone levels of infertile men. The study included 75 healthy fertile men (control subjects) and 75 men undergoing infertility screening. Before and after treatment seminal plasma biochemical parameters, antioxidant levels and serum testosterone, LH, FSH, and prolactin were measured. It was found that Withania inhibited lipid peroxidation and improved sperm count and motility, improved antioxidant levels and significantly increased serum testosterone and LH and reduced levels of FSH and prolactin. They concluded that Withania effectively reduced oxidative stress and regulated reproductive hormones having a significantly beneficial effect on overall fertility. ^{xxxiii}

NERVINE TONIC EFFECTS

- Withania has traditionally been used in Ayurvedic medicine as a tonic to soothe and calm the nerves and it is prized by Western herbalists for its anxiolytic activity and nervous system tonic effects. An animal trial which investigated Withania's anxiolytic and potential anti-depressant effects used glycowithanolides isolated from the root of Withania. It found that glycowithanolides administered once daily for 5 days produced a potent anxiolytic effect comparable to that elicited by the benzodiazepine Lorazepam. Both Lorazepam and glycowithanolides reduced rat brain levels of tribulin, an endocrine marker of clinical anxiety. It also achieved results in the anti-depressant trials comparable to that of the tri-cyclic anti-depressant imipramine. These investigations support the use of Withania as a mood stabilizer in clinical conditions of anxiety and depression in Ayurvedic medicine. ^{xxviii}
- As a potent adaptogen Withania is known to moderate the stress response, hence its reputation as a nervine tonic. A recently discovered withanolide (withanolide 1-oxo-5 β , 6 β -epoxy-witha-2-ene-27-ethoxy-olide) was the subject of animal trials to ascertain its adaptogenic activity on stress indices using the cold-hypoxia-restraint model. It was found that pre-treating animals with the new withanolide caused significant decrease in stress markers including; serum creatinine phosphokinase activity, serum lactate dehydrogenase activity, serum corticosterone levels and serum lipid peroxidation in comparison to controls. ^{xxix}



HYPOGLYCAEMIC AND HYPOLIPIDEMIC EFFECTS

- Withania is not commonly used for lipid and blood glucose dysregulation in Western herbal medicine, although its potent adaptogen action is well established. Animal studies investigating Withania's potential hypocholesterolaemic effect found that Withania root added to the diet at 0.75 and 1.5 gm/day of hypercholesterolaemic rats, produced a significant decrease in total lipids (-40.54%; -50.69%), cholesterol (-41.58%; -53.01%) and triglycerides (-31.25%; -44.85%) in plasma, and significantly increased plasma HDL-cholesterol levels (+15.10%; +17.71%).^{xxxv}
- Another animal study of hypercholesterolaemic and hyperglycaemic Alloxan-induced diabetic rats investigated Withania's effects on cholesterol and blood glucose. It showed that treatment with Withania reduced lipid and blood glucose back to normal levels after eight weeks of treatment.^{xxxvi}
- Withania's effect on insulin sensitivity in non-insulin dependent diabetes mellitus (NIDDM) has been studied in animal trials. It was found that Withania reduced elevated levels of blood glucose and insulin and produced a significant improvement in overall glucose tolerance. Insulin sensitivity was assessed for both peripheral insulin and hepatic insulin resistance and was found to be significantly improved. It was concluded that Withania helps to normalize hyperglycaemia by improving insulin sensitivity.^{xxxvii}

INTERACTIONS:

According to Braun, 2007 there has been no controlled studies conducted on any interactions with Withania. Any evidence stated is theoretical and is speculative.

BARBITURATES, BENZODIAZEPINES and Withania may lead to an additive effect. This could be beneficial however it would require observation.

The effects of Withania in animals undergoing chemotherapy has been observed. It was found that the neutropenia caused by the anti-cancer drugs was reversed by the administration of Withania via prevention of bone marrow depression.^{xxxviii}

SIDE-EFFECTS:

Withania is generally well tolerated and is safe at high doses. If used at the recommended dosage there should be no side-effects or contraindications.

Withania does contain iron and may potentially increase levels of haemoglobin. Therefore a high consumption of Withania should be avoided in patients with haemochromatosis.

Withania may increase the effects of barbiturates and sedative drugs.

Rare cases of individual specific hypersensitivity have been reported.



DOSE:

3-6 gm per day, equivalent of the dried root or 6 to 12mL of 1:2 fluid extract

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