Review Article

Health Benefits and Medicinal Potency of *Withania somnifera*: A Review

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ABSTRACT

A herb is a plant is valued for flavor, scent, or other qualities. Herbs are used in cooking, as medicines, and for spiritual purposes. From ancient days to now a day, medicinal plants are a potential and useful for the treatment of several diseases and disorders. *Withania somnifera* (Ashwagandha) is a plant used in medicine from the time of Ayurveda, the ancient system of Indian medicine. This review article is presented to consolidate all the updated information on its phytochemical and pharmacological activities, which were performed by widely different clinical experimental methods. Ashwagandha has long been considered as an excellent rejuvenator, a general health tonic and a cure for a number of health complaints. It possesses antioxidant, anti-inflammatory, hypoglycaemic, hypolipidaemic, anxiolytic, potent immunomodulatory and antibiotic activities. Other effects like antistress, antiaging, antialzheimer's, antiparkinsonian, anticancer, cardioprotective, anticortisol, antidepressant and macrophage-activating effect. These results indicate this herb should be studied more to confirm and reveal other potential therapeutic effects.

Keywords: Herbs, *Withania somnifera*, Ashwagandha, Pharmacological activities.

INTRODUCTION

Since ancient times, plants and herbal preparations have been used as medicine, flavor, scent or other qualities. Research carried out in last few decades has certified several such claims of use of several plants of traditional medicine. The main reason behind the use of medicinal plants is that low toxicity. The efficacy and safety of herbal medicine have turned the major pharmaceutical population towards medicinal plant's research. *Withania somnifera* commonly known as Ashwagandha, Indian ginseng, winter cherry is an important medicinal plant in the solanaceae family that has been used in ayurvedic and indigenous medicine for more than 3,000 years[1]. It got local names like Punir, asgandh (Hindi), Ashwagandha (Bengali), Ghodakun, Ghoda (Gujrati), Pulivendram (Telugu), Amukkura, amkulang (Tamil) etc. Ashwagandha in Sanskrit means "horse's smell" probably originated from the odor of its root, which resembles that of sweaty horse. The species name *somnifera* means "sleep-making" in Latin, attributed to sedating properties[2]. It is a xerophytic plant, found in dried parts of India, Sri Lanka, Afghanistan, Baluchistan and Sind and is distributed in the Mediterranean regions[3]. It can very suitably used for both sexes and even during pregnancy without any side effects. Withanolides, a group of steroidal lactone present in *Withania somnifera* roots attributed to pharmacological effects of Withania somnifera. Also, a number of withanolide steroidal lactones have been isolated from the leaves of Withania somnifera and exhibit antibacterial, antifungal and antitumour properties[4]. Ashwagandha is commonly available as a churna, a fine powder that can be mixed with water, ghee or honey. It increases the function of central nervous system (CNS) and improves the memory[5]. As a rasayana herb, the decoction and extracts of the herb shows excellent immunomodulatory affect by activation of non-specific macrophages, granulocytes, complement systems, natural killer cells and lymphocytes. It also interferes the production of various effecter molecules generated by activated cells (para-immunity), gives protection against different pathogens including bacteria, fungi, viruses etc[6]. Regular consumption considered to arrest senescence, rectify abnormalities of the sense organs and hypotrophy of muscles, rejuvenate the reproductive organs, and increase fertility[7]. It is widely used in the treatment of several ailments, Viz. asthma, bronchitis, inflammatory diseases, ulcer, stomach problems[8]. Steroidal lactones are major phytochemicals of this species[9]. Several in vitro and in vivo studies have convincingly proved the ability of *Withania somnifera* to exhibit anti-inflammatory, anti-oxidative, antimicrobial, anti-anxiety, aphrodisiac, immunomodulation, anti-hyperglycaemic, anticancer, CNS depressant, hepatoprotective, hypolipidemic, cardiovascular protection, diuretic, adaptogenic, anti-stress, anti-epileptic, antiarthritis, impotence and suppressant in HIV/AIDS[8]. Various studies revealed that ashwagandha very effective approach for the treatment of neurological disorders like parkinsonian and alzheimer's[5]. This review aims to highlight the main pharmacological and medicinal properties on *Withania somnifera* is to provide up to date information, in references to botanical, chemical, ethnopharmacological, phytochemical and pharmacological studies.

Vernacular Names

Arabic	: Kaknaj-e-Hindi
Bengaali	: Ashvaganda, Asvagandha
English	: Winter cherry
Gujarati	: Asan, Asana, Asado, Asundha, Ghadaasoda
Hindi	: Asgandh, Punir
Malayalam	: Amukkiram, pevetti
Marathi	: Askandha, Kanchuki, Tilli
Odiya	: Ashgandha
Persian	: Kaknaj-e-Hindi, Asgand Nagaori
Sanskrit	: Ashvagandha, Ashvakandika, Gandhapatri
Tamil	: Amukkira, Asubam, Asuvagandi, Asvagandhi
Telugu	: Asvagandhi, Penneru, Dommadolu
Urdu	: Asgand, Asgand Nagori

TAXONOMY

Kingdom	: Plantae
Subkingdom	: Tracheobionta
Superdivision	: Spermatophyta
Division	: Magnoliophyta
Subclass	: Magnoliopsida
Order	: Solanales
Family	: Solanaceae
Genus	: Withania
Species	: *Withania somnifera*

Plant Description

Ashwagandha is a small, branched, perennial woody shrub that grows usually about 2 feet in height and is naturally found in diverse areas ranging from Africa, the Mediterranean and East into India. Because of its wide range, there is considerable biodiversion like morphological and chemotypical variations in terms of local species. The flowers are small and green, while the ripe fruit is orange-red berry, smooth, oblong and rounded. It has more or less brown tuberous roots which are used for medicinal purposes. The seeds are yellow and scurfy[10].

Origin and Distribution

Withania somnifera grows abundantly in India, especially in Madhya Pradesh, Uttar Pradesh, Punjab and North Western parts of India like Gujarat and Rajasthan. It is also available in Congo, South Africa, Egypt, Morocco, Jordan and Pakistan[11].

Figure 1: *Withania somnifera L.*

Figure 2: *Withania somnifera* root

Source fig 1&2: infertiltyherbal.com

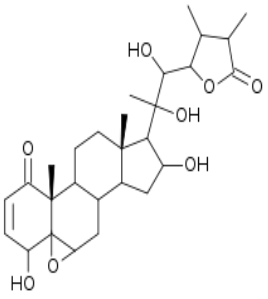
Cultivation and Collection

The morphological and therapeutic properties of *Withania somnifera* depend on its sources. Basically, it is reported that the plants from different sources vary in their morphological and therapeutic properties. *Withania somnifera* is grown as late rainy season crop. Actually semitropical areas are suitable for its cultivation as a rainfed crop. Now-a-days, the cultivation is mainly done in Madhya Pradesh, where about 2000 hectares are under cultivation. The propagation is done by seeds. The propagation is done towards June-July. Nitrogenous fertilizers can be used for the formation of small roots. Hervesting is initiated which lasts upto march. The roots are collected by uprooting the plant[12].

Phytochemistry

Various laboratory studies reported that over 35 chemical constituents are present in the roots of *Withania somnifera*. The major biochenical constituents of Ashwagandha root are alkaloids (isopellertierine, anferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanolides with a glucose at carbon 27 (sitonidoside XI and X). Withanolides and withaferin A, which are attributed to extraordinary pharmacological effect of Ashwagandha[13]. The withanolides act as important hormone precursors that can convert into human physiologic hormone as needed. Chemical analyses on Ashwagandha show its main constituents to be alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent[9]. The other

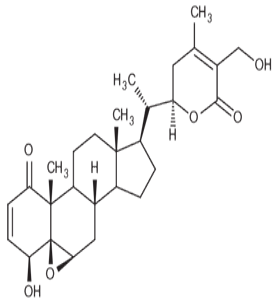
alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropane, choline, cuscohygrine, isopelletierine, anaferine[14]. The total alkaloidal content of the Indian roots has been revealed to vary between 0.13 and 0.31 percent[15]. One biochemical analysis revealed that the leaves of the plant (Indian chemotype) consist of 12 withanolides, 5 unidentified alkaloids, many free amino acids, chlorogenic acid, glycosides, glucose, condensed tannins and flavonoids. The leaves primarily contain withaferin A, a steroidal lactone is the most important withanolide. It is thermostable and slowly inactivated at PH 7.2. The fruits contain amino acids, a proteolytic enzyme, condensed tannins, and flavonoids. They contain a high ratio of free amino acids which are proline, valine, tyrosine, alanine, glycine, hydroxyproline, aspartic acid, glutamic acid, cystine and cysteine. Shoots of *Withania somnifera* primarily contain scopoletin and also they contain protein, calcium and phosphorous. Stem and bark consist of number of condensed tannins, flavonoids and free amino acids[16].



Withanolide A

Mol. Formula = $C_{28}H_{38}O_6$

Mol. Weight = 470.59



Withaferin A

Mol. Formula = $C_{28}H_{38}O_6$

Mol. Weight = 470.606

Pharmacological Activity

Hypoglycaemic activity

Several studies demonstrated that Ashwagandha reduces blood sugar levels. A test tube study found that it increased insulin secretion and improved peripheral tissue sensitivity to insulin. One study revealed that people with schizophrenia, those treated with *Withania somnifera* for 4 weeks had an average reduction in fasting blood sugar levels of 13.5 mg/dl, compared to a 4.5 mg/dl reduction in those who received a placebo[17]. Transina, one ayurvedic formulation which contain Ashwagandha as active ingredient have been reported to decrease streptozotocin (STZ)-induced hyperglycaemia in rats. This hypoglycaemic effect may be attributed to pancreatic islet free radical scavenging activity because the hyperglycaemic activity of STZ is a consequence of decrease in pancreatic islet cell superoxide dismutase (SOD) activity leading to the accumulation of degenerative oxidative free radicals in islet beta cells[18].

Antioxidative activity

Lipids and iron are rich components of the brain and nervous system. That's why they are relatively more susceptible to free radical damage than other tissues. Free radical damage of nervous tissue may be involved in normal aging and neurodegenerative diseases, e.g epilepsy, schizophrenia, Parkinson's, Alzheimer's and other diseases. The free radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) play a very vital role in protective effect on neuronal tissue. Decreased activity of these enzymes leads to accumulation of toxic oxidative free radicals and resulting degenerative effects[19]. In one laboratory analysis reported that glycowithanolides of withania somnifera were given once daily for 21 days, dose related increased in all enzymes were observed[20]. Another study revealed that sitoindosides VII-X and withaferin A actively having antioxidant activity[21].

Hypolipidaemic activity

Withania somnifera effectively help to improve heart health by reducing cholesterol and triglyceride levels. Animals studies have found that it significantly decreases these blood fats. One experimental study in rats found that it lowered total cholesterol by as much as 53% and triglycerides by nearly 45%. In a 60 day experimental study of chronically stressed adults, the group taking the higher dosage of Ashwagandha experienced a 17% decrease in LDL cholesterol and 11% decrease in triglycerides[22].

Withania somnifera root powder reduced total lipids, cholesterol and triglycerides in hypercholesteremic animals. On the other hand, significantly increased plasma HDL-cholesterol levels, HMG-CoA reductase activity and bile acid content of liver[23]. In another study with hydroalcoholic extract of fruits of Withania coagulans to high fat diet induced hyperlipidemic rats for 7 weeks, significantly reduced elevated serum cholesterol, triglycerides and lipoprotein levels[24]. In one study, six mild non-insulin dependent diabetes mellitus subjects and six mild hypercholesterolemic subjects were treated with the powder of roots of *Withania somnifera* for 30 days. Various parameters were assessed in the blood and urine samples of the subjects. Decrease in blood glucose was comparable to that of an oral hypoglycaemic drug. Significant increase in urine sodium, urine volume, significant decrease in serum cholesterol, triglycerides, LDL and VLDL-cholesterol were observed, indicating that root of *Withania somnifera* is a potential source of hypoglycaemic, diuretic and hypocholesterolemic agents[25].

Anti-stress activity

Ashwagandha has been shown to reduce stress in both animal and human studies. It is a very popular herb for reduce stress. Anti-stressor effect of ashwagandha was investigated in rats using cold water swimming stress test. One clinical investigation reported that it blocked the

stress pathway on rat brain by regulating chemical signaling in the nervous system. Several studies reported that it can effectively reduce symptoms in people with stress[26]. A study conducted by the Institute of Basic Medical Sciences at Calcutta University evaluated the effects of Ashwagandha on chronic stress in rodents. Research results showed that Ashwagandha decreased the frequency and severity of stress-induced ulcers, reversed stress-induced inhibition of male sexual behavior, and inhibition the effects of chronic stress on retention of learned tasks[27]. In one experiment, an aqueous suspension of Ashwagandha root was used at 100mg/kg/oral dosage, resulting prevents/decreases adrenal cortisol and ascorbic acid which occurs due to swimming stress. Ashwagandha has been evaluated for its adaptogenic activity[28]. Administration of ashwagandha with other drugs in experimental animals exposed to a variety of biological, physical and chemical stressors was found to offer protection against these stressors[29].

Anti-anxiety activity

Several controlled human studies have shown that it can reduce symptoms in people with anxiety disorders. In one 6 week experimental study revealed that 88% of people who took Ashwagandha results in a reduction in anxiety, compared to 50% who took a placebo[30]. Research conducted at the Department of Pharmacology, University of Texas health science centre indicated that extracts of Ashwagandha produce GABA-like activity which may account for the herbs antianxiety effects. This produces calming effect. Excessive neuronal activity can lead to restlessness and insomnia, but GABA inhibits the number of nerve cells that the fire in brain and helps to induce sleep, uplift mood and reduce anxiety[31].

Anti-aging

Anti-aging properties of *Withania somnifera* was evaluated in a double blind clinical trial. A group of 101 healthy males, 50-59 years old were given the herb at a dosage of 3 grams daily for one year. Decrease in serum cholesterol was more in treated group than in placebo group. The subjects experienced significant enhancement in hemoglobin, red blood cell count, hair melanin, and seated stature. Seventy of the research subjects reported improvement in sexual performance[31].

Immunomodulator activity

In one animal study, Ashwagandha showed a significant modulation of immune reactivity. Administration of Ashwagandha was found to prevent myelo-suppression in mice treated with three immunosuppressive drugs viz. cyclophosphamide, azathioprin, and prednisolone. Treatment with Ashwagandha was found to significantly increase Hb concentration, RBC count, platelet count, and body weight in mice. Administration of Ashwagandha extract was found to significantly reduce leukopenia induced by cyclophosphamide treatment. Administration of Ashwagandha extract increased the number of β-esterase positive cells in the bone marrow of cyclophosphamide treated animals. Withaferin A and Withanolide E showed specific immunosuppressive effect on human B and T lymphocytes and on mice thymocytes[32].

Antialzheimer's and antiparkinsonian activity

Ashwagandha supplements may improve brain function, memory, reaction times and the ability to perform tasks. Animal studies suggest that Ashwagandha may reduce memory and brain function problems caused by injury or disease. Researchers have shown that it promotes antioxidant activity that protects nerve cells from harmful free radicals[33]. In a controlled study, researchers who gave healthy men 500 mg of the herb daily reported significant improvements in their reaction time and task performance, compared to men who received a placebo[34]. Administration of haloperidol or reserpine significantly induced catalepsy in mice. *Withania somnifera* significantly inhibited haloperidol or reserpine induced catalepsy and provide effective approach for the treatment of parkinson's disease. Antiparkinsonian effect of *Withania somnifera* extract has been reported due to potent antioxidant, antiperoxidative and free radical scavenging properties[35]. One clinical investigation revealed that *Withania somnifera* significantly reversed the catalepsy, tardive dyskinesia and 6-hydroxydopamine elicited toxic manifestations and may offer a new therapeutic approach to the treatment of parkinson's disease[36].

It is investigated by the scientists of National Brain Research Centre (NBRC), New Delhi, that an extract of Ashwagandha root administered on mice brought from Jackson Labs in US with Alzheimer's disease could reverse memory loss of the mice. Basing on these findings scientists assumed that administration of Ashwagandha root extract may be effective for the cure of alzheimer's disease in human also[37].

Anti-inflammatory activity

Ashwagandha has been shown to increase natural killer cell activity and decrease markers of inflammation. Several animal studies have shown that Ashwagandha helps reduce inflammation. In one experimental study of humans have found that it increases the activity of natural killer cells, which are immune cells that fight against infection. It also helps to reduce markers of inflammation, such as C-reactive protein (CRP)[38]. Withaferin A showed potent anti-arthritic and anti-inflammatory activities. Anti-inflammatory activity has been attributed to biologically active steroids of which Withaferin A is a major component. It is effective as hydrocortisone sodium succinate dose for dose[39]. *Withania somnifera* has been shown to possess anti-inflammatory property in many animal models of inflammations like carrageenan-induced inflammation, cotton pellet granuloma and adjuvant-induced arthritis[40]. Detailed studies were carried out to investigate the release of serum β-1 globulin during inflammation by two

models of inflammations viz. primary phase of adjuvant induced arthritis and formaldehyde induced arthritis. The experiments showed interesting results as most of the APR were influenced in a very short duration and also suppressed the degree of inflammation[8].

Antibiotic activity

The antibiotic activity of the roots as well as leaves has recently been shown experimentally. Withaferin A in concentration of 10µg/ml inhibited the growth of various gram-positive bacteria, acid-fast, aerobic bacilli, and pathogenic fungi. It was active against *Micrococcus pyrogens* var aureus and primarily inhibited the activity of bacillus subtilis glucose-6-phosphate dehydrogenase[41]. One experimental study reported that Withaferin A inhibited Ranikhet virus[16]. The shrub's extract is active against Vaccinia virus and *Entamoeba histolytica.* Withania somnifera showed the protective action against systemic Aspergillus infection. This protective activity was probably related to the activation of macrophage function revealed by the observed increases in phagocytosis and intracellular killing of peritoneal macrophages induced by Ashwagandha treatment in mice. Antibiotic activity of Withaferin A is attributed to the presence of the unsaturated lactone ring. It is stronger than penicillin[42].

Anticancer activity

Animal and test tube studies have shown that it promotes the death of tumour cells and may be effective against several types of cancer. Animal studies have found that Ashwagandha helps induce the apoptosis or "programmed cell death" of cancer cells. It also inhibits the growth of new cancer cells in several ways. Main mechanism behind the anitcarcinogenic effect of Ashwagandha is generation of reactive oxygen species (ROS), which are toxic to cancer cells but not normal cells[43].

Animal studies suggest that it may be beneficial for treating several types of cancer, including breast, lung, colon, brain and ovarian cancer[44]. In one clinical investigation, mice with ovarian tumor treated with Ashwagandha alone or in combination with an anticancer drug had a 70-80% reduction in tumor growth. The treatment also prevented metastasis. Research on animals revealed that the herb decreases the the levels of the nuclear factor Kappa B, reduces the intracellular tumor necrosis factor, and enhances apoptotic signaling in cancerous cell lines. The most possible uses of Ashwagandha is its capacity to fight cancers by reducing tumour size[45]. In one study, the herb was evaluated for its antitumor effect in urethane-induced lung tumors in adult male mice. Following administration of Ashwagandha over a period of seven months, the histopathological appearance of the lungs of animals which received the herb was similar to those observed in the lungs of control animals[18].

Withaferin A, Withanolide D and E exhibited significant antitumour activity in vitro against cell derived from human epidermoid carcinoma of nasopharynx (KB) and in vivo against Ehrlich ascites carcinoma, sarcoma 180, sarcoma black (BL) and EO771 mammary adenocarcinoma in mice in disease of 10, 12, 15 mg/kg body weight. Withaferin A has been shown to possess growth inhibitory and radio-sensitizing effects on experimental mouse tumors[46].

Antiepileptic activity

Administration of ashwagandha root extract was found to reduce jerks and clonus in 70% and 10% animals respectively with dose of 100mg/kg and reduction in the severity of pentylene tetrazole (PTZ)-induced convulsions was evident from EEG wave pattern. *Withania somnifera* root extract showed reduction in severity of motor seizures induced by electrical stimulation in right basilateral amygdaloid nuclear complex through bipoler electrodes. The protective effect of Ashwagandha extract in convulsions has been reported to involve GABA ergic mediation[47].

Cardioprotective activity

The extract of *Withania somnifera* was evaluated on the cardiovascular and respiratory systems in dogs and frogs. The alkaloids had a prolonged hypotensive, bradycardiac, and respiratory stimulant action in dogs. The cardioinhibitory action in dogs appeared to be due to ganglion blocking and direct cardiodepressant actions[48]. In another study, left ventricular dysfunction was seen as a decrease in heart rate, left ventricular rate of peak positive and negative pressure change and elevated left ventricular end-diastolic pressure in the control group was recorded. *Withania somnifera* showed strong cardioprotective action in the experimental model of isoprenaline-induced myonecrosis in rats[49].

Macrophage-activating effect

The chemotactic activity of macrophages and production of interleukin-1 (IL-1) and tumor necrosis factor (TNF) were significantly reduced in mice treated with the carcinogen ochratoxin A (OTA). Administration of Ashwagandha with other drugs was found to significantly inhibit OTA-induced suppression of macrophage chemotaxis and production of IL-1 and TNF-α by macrophages[50].

Anticortisol activity

Ashwagandha supplements may help lower cortisol levels in chronically stressed individuals. Cortisol is a hormone secreted from adrenal gland and regulates blood sugar levels. Cortisol is known as a "stress hormone" due to adrenal gland release it in response to stress and when blood sugar levels get too low. Cortisol levels may become chronically elevated, which can lead to high blood sugar levels and increased fat storage in the abdomen. Studies have shown that Ashwagandha may help reduce cortisol levels. In a controlled study of the chronically stressed adults, the group that supplements

with Ashwagandha had significantly greater reduction in cortisol than the control group[30].

Increase fertility in men

Ashwagandha helps increase testosterone levels and significantly boosts sperm quality and fertility in men. In a study of 75 infertile men, the group treated with Ashwagandha had an increase in sperm count and motility[51].

Antidepressant activity

One experimental study revealed that Ashwagandha may help reduce severe depression. In a 60-day experimental study in stressed adults, those who took 600mg/day reported a 79% reduction in severe depression. At the same time, the placebo group reported a 10% increase[52].

Nootropic effect

Effects of sitoindosides VII-X and withaferin isolated from aqueous methanol extract of roots of withania somnifera were studied on brain cholinergic, glutamatergic and GABAergic receptors in rats. The compounds slightly enhanced acetylcholinesterase (AchE) activity in the lateral septum and globus pallidus, and decreased AchE activity in the vertical diagonal band. These changes were accompanied by enhanced M1-muscarinic-cholinergic receptor binding sites were increased in a number of cortical regions includind cingulate, frontal, parietal, and retrospinal cortex[53]. In a study by Zhao et al withanoside IV 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. Withanolide IV may ameliorate neuronal dysfunction in alzheimer's disease and that the active principle after metabolism is somninone. In another study of reserpine treated animals also showed poor retention of memory in the elevated plus maze task paradigm[54].

Other Health Benefits

Several studies have also shown Ashwagandha is very effective in the treatment of osteoarthritis[55], inflammation[39], stroke[56], and tardive dyskinesia[57]. Ashwagandha has been shown very potential antifungal[58] and antibacterial activity[59].

CONCLUSION

Since ancient times, natural products have been used for the treatment of different type of diseases in several ways. The plant contains different type of phytoconstituents which showed different pharmacological activities. More than 80% of the world's population in 2001 used herbal medicine for their primary health care. Herbal medicines are used for treatment of various ailments in the world due to the belief of its fewer side effects. Over the years scientists have verified many of the traditional uses of *Withania somnifera* that continue to be an important natural remedy for various diseases. The roots, leaves and fruits possess tremendous medicinal value. Multiple health benefits featured in this herbal supplement makes it as a perfect rejuvenator of physical and psychological health. Ashwagandha formulations are becoming more widely available in the U.S as well as rest of the world and are employed by practitioners of natural health for treatment of diabetes, high cholesterol and triglyceride level, stress, anxiety, neurodegenerative diseases, cancer, various bacterial and fungal infections. We concluded that withania somnifera is a potential herbal in the world. Further studies are required to find many more activities of this plant.

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