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(REVIEW ARTICLE)

# Chemical and pharmacological review of *Withania somnifera*

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## Abstract

The Solanaceae family is comprised of 84 genera that include about 3,000 species, scattered throughout the world. Members of this family are generally annual shrubs. The genera Withania and Physalis play an important role in the indigenous medicine of South East Asia, e.g. in the Unani and Ayurvedic systems. *Withania somnifera* (L.) Dunal, (Solanaceae), commonly known as ashwagandha, winter cherry, Indian ginseng, or poison gooseberry. Traditionally it is commonly used in emaciation of children, hindrance from old age, rheumatism, vitiated conditions of vata, leucoderma, constipation, insomnia, nervous breakdown, goiter etc. *W somnifera* and its chemical ingredients are effective in prevention and treatment of different kinds of cancer like colon cancer, lung cancer, blood cancer, skin cancer, breast cancer, renal cancer, fibrosarcoma, prostate cancer and pancreatic cancer. 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. The present study emphasizes the chemical and pharmacological properties of *Withania somnifera*.

**Keywords:** *Withania somnifera*; Chemical; Pharmacological; Anticancer effect

## 1. Introduction

*The Solanaceae family is comprised of 84 genera that include about 3,000 species, scattered throughout the world. Members of this family are generally annual shrubs. The genera Withania and Physalis play an important role in the indigenous medicine of South East Asia, e.g. in the Unani and Ayurvedic systems. The twenty-three known Withania species are widely distributed in the drier parts of tropical and subtropical zones, ranging from the Canary Islands, the Mediterranean region and northern Africa to Southwest Asia. Among them, only two species, W. somnifera and W. coagulans are economically and medicinally significant, being used and cultivated in several regions [1].*

*Withania somnifera* (L.) Dunal, (Solanaceae), commonly known as ashwagandha, winter cherry, Indian ginseng, or poison gooseberry. It is a plant in the solanaceae or night shade family. It is a well-known medicinal plant in Ayurvedic medicine. The principal active compounds include several withanolide-type compounds. Due to the nontoxic and high medicinal value of *W. somnifera* , this plant is widely used all over the world. Roots, and less often leaves and fruits, have been used as phytomedicines in the form of decoction, infusions, ointment, powder, and syrup. Nowadays, this plant is cultivated as a crop to support the high demand of biomass and a sustainable quality for the needs of pharmaceutical industry [2].

Withania, the traditional system of medicine practiced in India can be traced back to 6000 BC. For most of these 6000 years Withania (Ashwagandha) has been used as a Rasayana. 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) [3].

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Ashwagandhais one of the prime drugs of Ayurvedic material medica botanically identified as *Withania somnifera* L Dunal (WS) belonging to Solanaceae family. It is a small evergreen woody shrub that grows to roughly four to five feet tall. In India, it is cultivated, on a commercial scale, in the states of Madhya Pradesh, Uttar Pradesh, Punjab, Gujarat and Rajasthan [4]. This plant is used in more than 200 formulations in Ayurveda, Unani and Siddha. Acharya Charaka included it in Balya and Brimhana-gana and attributed Balya, Vrishya and Rasayana properties to it. Bhavmishra suggested as substitute of Kakoli and Kshirakakoli. Earliest references of use of plants as medicine appear in Rigveda (3500–1600 B.C.) [5].

Leaves are bitter in taste and used as an antihelmintic. Leaves are simple opposite, alternate, petiolate, elliptic ovate to broadly ovate, entire, exstipulate, the tip of the leaf is acute, cuneate or oblique and glabrous up to 8 to 12 cm in length. Flower is shortly pedicillate and 4-6 mm in dia. Flowers are greenish or lurid yellow, small about 1 cm long; few flowers (usually about 5) born together in axillary, umbellate cymes (short axillary clusters). Fruits are globose berries, 6 mm in diameter, orange red when mature, enclosed in the inflated and membranous persistent calyx. Seeds are smooth, discoid, 20-25 seed per fruit. Seeds are yellow, reniform and 2.5 mm in diameter. Roots are stout, fleshy, cylindrical and 1-2 cm thick, straight, unbranched, roots bear fiber like secondary roots, outer surface buff to grey-yellow with longitudinal wrinkles; crown consists of 2-6 remains of stem base; stem bases variously thicked; nodes prominent only on the side from where petiole arises, short and uneven; odour characteristic; taste bitter and acrid. The roots areused as a nutrient and health restorative in pregnant women and old people. The decoction of theroot boiled with milk and ghee is recommended for curing sterility in women. The roots are alsoused in constipation, senile debility, rheumatism, general debility, nervous exhaustion, loss ofmemory, loss of muscular energy and spermatorrhoea [6].

## 2. Plant Description

### 2.1. Classification of the Plant

- Kingdom : Plantae
- Division : Angiosperms
- Class : Dicotiledoneae
- Order : Tubiflorae
- Family: Solanaceae (Nightshade family)
- Genus: *Withania*
- Species: *Somnifera*
- Scientific Name: *Withania somnifera* (Dunal)

### 2.2. Distribution

*Withania somnifera* grows abundantly in India (especially Madhya Pradesh), Pakistan, Bangladesh, Sri Lanka and parts of northern Africa.

### 2.3. Morphology

*Withania somnifera*is an evergreen, erect, branching, tomentose shrub, 30-150 cm in height. Leaves are simple, ovate, glabrous, and up to 10 cm long. Flowers are greenish or lurid yellow, small about 1 cm long; few flowers (usually about 5) born together in axillary, umbellate cymes (short axillary clusters).

Fruits are globose berries, 6 mm in diameter, orange red when mature, enclosed in the inflated and membranous persistent calyx. Seeds are yellow, reniform and 2.5 mm in diameter. The drug Asgand consists of the dried mature roots of the plant which has the following morphological properties: [7]

### 2.4. Macroscopic

The stout fleshy roots when dry are cylindrical, gradually tapering down, straight, unbranched, 10-17.5 cm long and 6-12 mm in diameter. The main roots bear fiber-like secondary roots.The outer surface of the roots is brownish white and interior is creamy white when broken. They have a short and uneven fracture, a strong odor and mucilaginous biter and acrid taste [8].

### 2.5. Microscopic

The young root has a single layered epidermis followed by a parenchymatous cortex of 4-5 layers of cells, the endodermis being conspicuous by the presence of casparian stripes. The cork cambium arises in the outermost layer of the cortex. The endodermis persists even after the secondary growth has taken place [9].

### 2.6. Chemical Composition

The biologically active chemical constituents of *Withania somnifera*include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins. Sitoindosides and acylsteryl glucosides 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 [10].

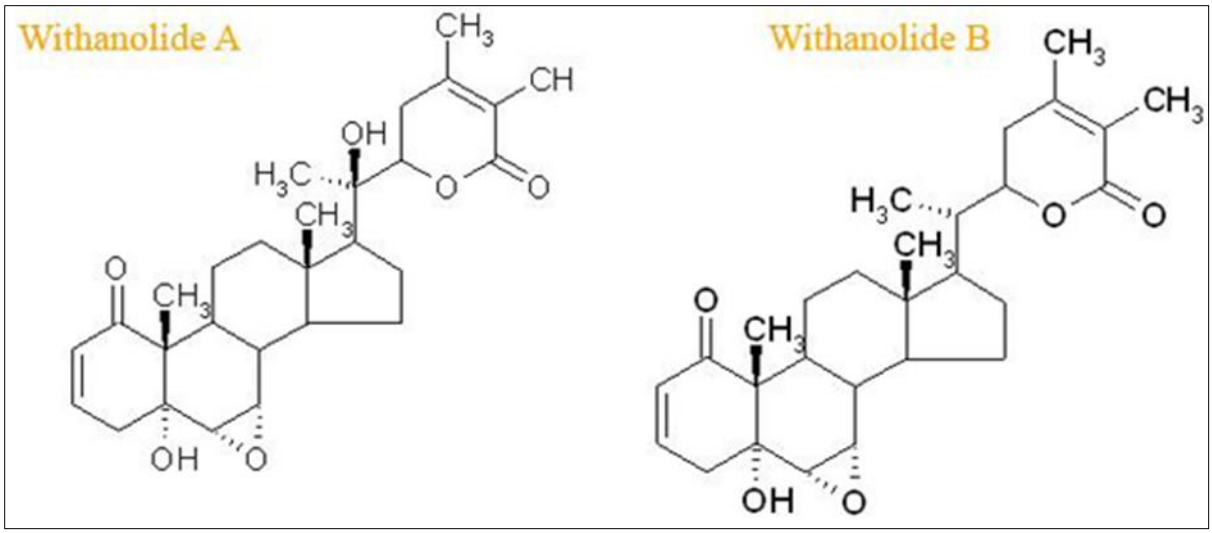


**Figure 1** Common active ingredients of *Withania somnifera*

The roots are reported to contain alkaloids, amino acids, steroids, volatile oil, starch, reducing sugars, glycosides, hentriacontane, dulcitol, withaniol, an acid and a neutral compound. The total alkaloidal content of the Indian roots has been reported to vary between 0.13 and 0.31 percent, though much higher yields (up to 4.3%) have been recorded elsewhere.

The leaves of the plant (Indian chemotype) are reported to contain 12 withanolides, 5 unidentified alkaloids many free amino acids, chlorogenic acid, glycosides, glucose, condensed tannins, and flavonoids [11].

The leaves of the plant from different habitats contain different withanolides–a group of C28 steroids characterized by a 6-membered lactone ring in the 9-carbon atom side chain. Withaferin A, a steroidal lactone is the most important withanolide isolated from the extract of the leaves and dried roots of *Withania somnifera*. It is thermostable and slowly inactivated at pH 7.2. It is insoluble in water and is administered in the form of suspension. For its separation, the leaves are extracted with cold alcohol; the extract is purified and dried, and finally crystallized from aqueous alcohol. The yield of this compound from the South-African plants is reported to be as high as 0.86 percent. The curative properties of the leaves and roots are attributed to Withaferin A [12].

### 2.7. Traditional use

Traditionally it is commonly used in emaciation of children (when given with milk, it is the best tonic for children), hindrance from old age, rheumatism, vitiated conditions of vata, leucoderma, constipation, insomnia, nervous breakdown, goiter etc.. The paste formed when roots are crushed with water is applied 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 scorpion-sting. It also helps in leucorrhoea, boils, pimples, flatulent colic, worms and piles. The Nagori Ashwagandha is the supreme among all Ashwagandha varieties. Maximum benefit appears when fresh Ashwagandha powder is used [8].

### 2.8. Pharmacological activity

*Withania* (Ashwagandha) benefits all parts of the body and can be used as a tonic or in oral form. Several studies have shown that Ashwagandha is useful in addressing the following health problems:

The herb may help protect against inflammation and cartilage damage associated with osteoarthritis. Ashwagandha had an anti-anxiety effect similar to that of lorazepam (a medication used to treat anxiety disorders). The herb also appeared to ease depression. It may help normalize high blood sugar and improve insulin receptors and signaling mechanisms sensitivity. Ashwagandhaused as an anti-oxidant, as studies have shown that it can eliminate free radicals from the immune system. Free radicals are the agents that cause the breakdown of body's tissue, alternatively known as aging. Studies show that supplementing with ashwagandha can provide the energy needed to get through long workouts while also allowing for maximum recovery and cell re-growth. Ashwagandha is a tonic, which increases sperm count and sexual potency. In the rural areas vegetable made out of this plant is given to tuberculosis patients. It also increases the iron content in the blood. It could also be used in anxiety and depression, parkinson'sandalzheimer's disease, cancer, immunostimulatory effect, rejuvenativeand reproductive action, and GABA-mimeticactivityhavinganxiolytic effect [9]. WS used for treatment of many cancers such as Colon Cancer,Lung Cancer, Skin Cancer, Blood Cancer, Breast Cancer, Renal Cancer, Prostate cancer, Pancreatic Cancer and Fibrosarcoma [10].

#### *2.8.1. Immune system effects*

Withanolides inhibit murine spleen cell proliferation, and an extract of *W. somnifera* reversed ochratoxin's suppressive effect on murine macrophage chemotaxis. Withanolide glycosides activated murine macrophages and phagocytosis, and increased lysosomal enzymatic activity secreted by the macrophages, while also displaying antistress activity and positive effects on learning and memory in rats. Alpha-2 macroglobulin synthesis stimulated by inflammation was reduced by W. somnifera extract. Similarly, the extract prevented myelosuppression caused by cyclophosphamide, azathioprine, or prednisolone in mice. In a clinical study, ashwagandha 6 mL root extract administered twice daily for 4 days resulted in increases in CD4 expression, as well as activation of natural killer cells. Additional effects on cytokines and the complement system, lymphocyte proliferation, and humoral and cell-mediated responses have been discussed [10].

#### *2.8.2. Immunomodulatory Activity*

Immune protective mechanisms include the elaboration of potent inflammatory molecules, antibodies, andkiller cell activation - which together not only destroy invading microorganisms, pathogenic autoreactiveIf cells, and tumors, but also may mortally injure normal cells. Accordingly, the immune response is tightly regulated by immuno-regulatory cells, cytokines and external influences.Understanding the immuno-modulatory mechanisms of Ashwangandha can provide insight into immune function and regulation that could further help in immunoregulatory procedures. Chemical investigation with the extract of roots and leaves of *Withainia somnifera* (WS) has yielded bioactive withanolides, which inhibit cyclooxygenase enzymes, lipid peroxidation, and the proliferation of tumor cells. It has been reported that WS extract preferentially reduces inflammatory processes by inactivating nuclear factor-kappaB (NF-kB) activation, by inducing cellular death by apoptosis, inhibiting inflammation and abolishing osteoclastogenes is through suppression of NF-kB activation and NF-kB-regulated gene expression [11].

Similar studies show that the leaf extract of WS, as well as its major constituent withaferin A (WA), potently inhibits NF-kB activation by preventing the tumor necrosis factor-induced activation of I-kappaB kinase beta. Studies indicated that pure WA or WA-enriched WS extracts can be considered as a novel class of NF-kB inhibitors, which hold promise as novel anti-inflammatory agents for the treatment of various inflammatory disorders andlor cancer. It has been proposed that the antiproliferative, proapoptotic, anti-invasive, antiosteoclastogenic, antiangiogenic, antimetastatic, radiosensitizing, antiarthritic, and cardioprotective effects assigned to withanolide may be mediated in part through the suppression of NF-kB and NF-kB-regulated gene products [12].

Recently, withaferin A (made from the crushed air-dried leaves of *Withania somnifera* Dun.) was used to induce apoptosis in parasitic protozoa *Lesihmania donovani*, which acts as a novel protein kinase inhibitor and it is facilitated by apoptotic topoisomerase I-DNA complex [9].The anti-microbial effect of WS was also shown in a prophylactic administration of WS extract, which increases host resistance in Listeria monocytogenes- infected mice [10]. Moreover, the therapeutic role of *Withania* has potential usage in inflammation and the patho-physiology of immune regulation [13].

Asgand showed a significant modulation of immune reactivity in animal models. Administration of Asgand was found to prevent myelo-suppression in mice treated with three immunosuppressive drugs viz. cyclophosphamide,

azathioprin, and prednisolone. Treatment with Asgand was found to significantly increase Hb concentration, RBC count, platelet count, and body weight in mice. Administration of Asgand extract was found to significantly reduce leucopenia induced by cyclophosphamide (CTX) treatment. Administration of Asgand extract increased the number of alpha-esterase positive cells in the bone marrow of CTX treated animals, compared to the CTX alone treated group. Administration of Asgand extract was found to significantly reduce leucopenia induced by sub-lethal dose of gamma radiation. Withaferin A and Withanolide E exhibited specific immunosuppressive effect on human B and T lymphocytes and on mice thymocytes. Withanolide E had specific effect on T lymphocytes whereas Withaferin A affected both B and T lymphocytes [14].

Cyclophosphamide is used alone for the treatment of several types of cancers but often in combination with other drugs to treat breast cancer, leukemia and ovarian cancer or tumor but cyclophosphamide reduces the production of blood cells from the bone marrow. Aqueous extract of immunomodulator plant like Ashwagandha was studied against toxicity of cyclophosphamide. After administration of cyclophosphamide at 250 mg/kg b.w. orally by gastric intubation method to rats marked reduction in total count of WBC, RBC and platelets were observed on day 4. When Ashwagandha (300 mg/kg b.w.) was administered five days prior to cyclophosphamide administration and continued for ten days then significant increase in total count of WBC, RBC and platelets were observed after treatment. Thus, findings showed that therapeutic potency of Ashwagandha ameliorate the toxicity produced during cancer chemotherapy by mitigating the bone marrow depression [15].

Immunomodulatory effect was assessed in If IgE-mediated anaphylaxis as reduction of ovalbumin-induced paw edema, in animals treated with WS2 at doses of 150 and 300 mg/kg, and the results were compared with the standard drug disodium chromoglycate. In the DTH model, the modulatory effect was assessed as potentiation or suppression of the reaction, revealing an increase or decrease in mean foot pad thickness, respectively. Potentiation of the DTH reaction was observed in animals treated with cyclophosphamide at a dose of 20 mg/kg, WST at a dose of 1000 mg/kg and WS2 at a dose of 300 mg/kg. On the other hand, cyclophosphamide-induced potentiation of DTH reaction was suppressed in animals treated with WST and WS2. A significant increase in white blood cell counts and platelet counts was observed in animals treated with WST. A protective effect in cyclophosphamide-induced myelosuppression was observed in animals treated with WST and WS2, revealing a significant increase in white blood cell counts and platelet counts. Cyclophosphamide-induced immunosuppression was counteracted by treatment with WS2, revealing significant increase in hemagglutinating antibody responses and hemolytic antibody responses towards sheep red blood cells [16].

*2.8.3. Anti-cancer activities*

Cancer is hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Cancer is one of the major threats of modern life and is considered as the second cause of death after myocardial infarction. Millions of people suffer from various kinds of cancer and die every year with cancers such as lung cancer and mesothelioma from inhaling asbestos fibers and tobacco smoke or leukemia from exposure to benzene at their workplaces are increasing day by day. The two main components of Ashwagandha Withaferin A and Withanolide E inhibit the growth of tumor showing a strong immune suppressive effect by stopping cancerous cells division. It is evident that foods rich in anti-oxidants play an important role in the prevention of cancer, cardiovascular and neurogenerative diseases [17].

It was reported that the ASH-WEX is cytotoxic to cancer cells selectively, and causes tumor suppression *invivo*. Its active anticancer component was identified as triethylene glycol (TEG). Molecular analysis revealed activation of tumor suppressor proteins p53 and pRB by ASH-WEX and TEG in cancer cells. In contrast to the hypophosphorylation of pRB, decrease in cyclin B1 and increase in cyclin D1 in ASH-WEX and TEG-treated cancer cells (undergoing growth arrest), normal cells showed increase in pRB phosphorylation and cyclin B1, and decrease in cyclin D1 (signifying their cell cycle progression). We also found that the MMP-3 and MMP-9 that regulate metastasis were down regulated in ASH-WEX and TEG-treated cancer cells; normal cells remained unaffected [18].

Several studies have been conducted to evaluate the effectiveness of WS in prevention and treatment of different kinds of cancer which are highlighted below.

*W. somnifera* significantly altered the level of leucocytes, lymphocytes, neutrophils, immune complexes and immunoglobulins (Ig) A, G and M in experimental colon cancer in mice induced by azoxymethane [19].

In another study, it was observed that WS decreased the activities of TCA cycle key enzymes such as isocitrate dehydrogenase (ICDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH), and alpha-keto glutarate dehydrogenase (alpha-KGDH) in colon cancer bearing animals [20]. In vitro studies have shown that root extracts of

WS exhibited cytotoxic properties against lung cancer. Scientific studies conducted in mice revealed that the roots of *Withania somnifera* have capability to inhibit Forestomach and skin carcinogenasis in mice. Leaf extract of WS has been shown to produce antiproliferative activity on breast human tumor cell lines [19].

Withaferin A acts as a potent antiproliferative activity against pancreatic cancer cells in vitro (with IC50of 1.24, 2.93 and 2.78μ) in pancreatic cancer cell lines Panc-1, MiaPaCa2 and BxPc3, respectively.The results of the study demonstrate that Withaferin A binds Hsp90, inhibits Hsp90 chaperone activity through an ATP-independent mechanism, results in Hsp90 client protein degradation, and exhibits in vivo anticancer activity against pancreatic cancer.

### 2.9. Biosynthesis of Withanolides

Chemically, withanolides are 30-carbon compounds called triterpenoids. Triterpenoid backbone, like other terpenoid compounds is biosynthesized by metabolic pathway requiring isoprene units (isopentenylnpyrophosphate; IPP and dimethyl allyl pyrophosphate; DMAPP) as precursors. Therefore, isoprenogenesis could be one of the key upstream metabolic processes governing flux of isoprene units for synthesis of metabolic intermediate(s) of triterpenoid pathway committed to withanolide biosynthesis [21].

Dual autonomous pathways for the isoprenoid precursor biosynthesis co-exist in plant cell including the classical cytosolic mevalonic acid (MVA) pathway and the alternative route, plastidial methyl erythritol phosphate (MEP) pathway [22].

Plastidial MEP pathway synthesizes IPP and DMAPP required for production of photosynthesis associated isoprenoids (carotenoids and side chains of chlorophylls, plastoquinones, and phylloquinones) and hormones (gibberellins and abscisic acid). In plants, MVA-derived isoprenoid end products comprise of sterols (modulators of membrane architecture and plant growth and developmental processes), brassinosteroids (steroid hormones), dolichol (involved in protein glycosylation), and the prenyl groups necessary for protein prenylation and cytokinin biosynthesis [23]. However, now there is growing evidence that a considerable cross-talk between the two pathways of isoprenogenesis exists and exchange of isoprene units may occur at different sub-cellular locations [24].

## 3. Conclusion

The herb *Withania somnifera* holds an important place among various anticancer medicinal plants. It is very essential to further screen and to investigate different formulations for anticancer therapy *in vitro* as well as *in vivo* in combination with established chemotherapy.

*W. somnifera* has enjoyed a long and important history in traditional medicine system wherein withanolides are attributed with significant remedying properties. Nevertheless, withanolide biosynthesis is still in its infancy with regard to being understood in entirety that enormously hampers the exploitation of its full biotechnological potential. Though, investigations at molecular and *in vitro* levels have begun, but we are still a long way from understanding how diverse withanolides are synthesized and regulated in *W. somnifera*. However, the gene elucidation data, omics resource and *in vitro* study inferences generated so far offers significant promise for enormous increase in truthful annotation, functional characterization of enzymes and for comprehending the assorted interactions amongst sophisticated biosynthetic and regulatory mechanisms crucial for successful implementation of withanolide metabolic engineering strategies. Furthermore, advancing metabolic engineering technologies for transgenics, precursor feeding, gene over-expression and inhibition and mutant selection in *W. somnifera* still awaits investigation. There is much to be learned about the chemical ecology of withanolides to answer an important question about their evolution in the form of sophisticated and diverse structures and types. Though, anticipation about withanolides acting as growth regulators owing to their partial coinciding biosynthetic route with brassino steroids do exist, but it further demands in-depth examination to build a framework for elaborate pathway modulation strategies.

'Recent studies invitro also provided evidence for Ashwagandha extracts and their bioactive constituents to offer neuro-protective effects and modulate neurite outgrowth. Additional interest is the ability for Ashwagandha to offer anxiolytic and nootropic activity.

Various parts of *Withania somnifera* especially the roots with its unique contents are proved promises effective against different kinds of cancers. The most active components withanolides and withaferins along with a few other metabolites including withanone and withanosides have been reported effective against different types of cancer cell lines. *Withania*

*somnifera*could be known to allocate substantial resources toward developing chemical solutions to enhance survival strategies in the form of varied natural products. These natural products could be carefully used as pharmaceuticals.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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