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Chapter- 2

A comprehensive analysis of ethnopharmacological and pharmacotherapeutics of *Withania somnifera* (L.) Dunal (Ashwagandha)

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Keywords: *Withania somnifera*, Ethno-botanical, Phytochemicals, Ayurveda, Therapeutics.

Abstract:

Ashwagandha [*Withania somnifera* (L.) Dunal] has been used as an Indian traditional medicine for a long time. Traditional uses of this plant include a plethora of medical conditions like hypertension, diabetes, stress, asthma, cancer, bronchitis, ulcers, conjunctivitis, epilepsy, insomnia, senile dementia, Parkinson's disease, nervous disorders, arthritis, intestinal infections, impotency etc. Different parts of this plant, specifically the roots, have been used as a traditional Rasayana herb to treat various ailments. The plant also possesses sedative, diuretic, anti-inflammatory properties and demonstrates strong immunostimulatory activity. According to Ayurveda, Ashwagandha is considered one of the most important medicinal herbs with varied functions. The multipurpose uses of Ashwagandha have numerous other beneficial health effects that are relevant in light of pharmaceutical perspectives. In this chapter, we present a comprehensive sketch of geographical distribution, description, phytochemistry and pharmacological activities of *W. somnifera* along with its active constituents. A brief description of the uses of *W. somnifera* against various cancer and its relevant signaling pathways are also descried. Preclinical studies with the extracts of various parts of Ashwagandha are also elucidated in this chapter. However, more detailed studies are required on the clinical use of Ashwagandha (*W. somnifera*) against human diseases.

Introduction:

Plants are great sources of food, medicine, oxygen, aromas, flavours and many essential ingredients that are widely used in our daily life (Maiti et al., 2010; Maiti et al., 2013; Kar et al.,

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2022). In ancient India, treatment was based upon plant derivatives. Ayurveda, Unani, Siddha, Chinese all these are traditional treatment methods relied upon plant extracts or phytochemicals (Sarkar et al., 2016; Sarkar, 2017; Sanyal et al., 2018; Bhattacharjee, 2021). The father of medicine, Hippocrates (440 BC), stated that "Let food be thy medicine and medicine be thy food". At present, multiple lifesaving drugs derived from plants are used widely (Bhandari et al., 2012; Banerjee et al., 2014; Acharya, 2016; Acharya et al., 2021). According to World Health Organization (WHO), 80% of people in new-age countries use conventional plant-based treatments. India houses about 47000 plant species among which 7500 plants have known medicinal importance. Many more are still to be discovered (Gahlawat et al., 2014; Sarkar, 2016; Sanyal et al., 2016).

Study of the inter-relationship between people and plants, the practical uses of these plants or their various parts through the traditional knowledge of local culture and people is known as ethnobotany (Erfani, 2021). Ethno-botanical knowledge can conduct the discovery of many new bioactive compounds (Gahlawat et al., 2014; Chakraborty et al., 2019; Kundu, 2022). Indian subcontinent is known as "the botanical garden of the world" and it consists of four major biodiversity hotspots. India has a large expansion of plants with novel phytochemicals and with ethnobotanical importance. Among these phyto-chemicals multiple has demonstrated promising medicinal outcomes. The classical texts of Ayurveda, Sushruta Samhita and Charaka Samhita, Ayurvedic Materia Medica demonstrated medicinal plants along with their therapeutic potential. *Withania somnifera* (Ashwagandha), a well-known medicinal plant in India, is also known as Indian ginseng or Indian Winter Cherry. It is an important ancient plant and its roots are used in traditional Indian medicine Ayurveda and Unani.

Withania somnifera (L.) Dunal (*W. somnifera*) belongs to the Solanaceae family and is commonly named as Ashwagandha. It's an evergreen shrub or woody herb distributed almost all over the Indian subcontinent. Ashwagandha has both ecological and economic importance. The roots of *Withania* have been used for over 3000 years in various clinical treatments of different ailments. The roots of these plants are the major ingredient of more than 200 formulations used in Indian folk medicine. It can be used in stress release, increasing vitality, blood sugar regulation, cognitive health improvement etc. It can also treat anxiety and depression (Afewerky et al., 2021). Additionally, reports have also demonstrated the use of root extract to treat asthma, inflammation, insomnia, psoriasis, constipation, fatigue, weakness, ulcers etc. (Pandian et al., 2020).

Distribution of Ashwagandha in India:

Ashwagandha or *Withania somnifera* is an Indian native plant species commonly distributed in a different states of India, including Rajasthan, Uttar Pradesh, Punjab, Maharashtra, Haryana, Kerala, West Bengal, Gujarat, Madhya Pradesh etc. It is also found in other tropical and subtropical areas (Gill et al., 2019). This plant species generally grows well in dry condition. They are highly cultivated in sandy loam, black, light red soil at suitable pH 7.5 to 8.0 (Devi et al., 2020; Gill et al., 2019).

Description of the plant:

Withania somnifera is an evergreen shrub about 2 feet long and covered with woolly pubescence. It consists of a short stem, long roots and simple green leaves. Root of this plant is whitish brown, fleshy and stout with strong medicinal values. Leaves are very simple, opposite and ovate type. Flowers are yellowish or greenish with orange-red berries and yellow seeds. The ripe fruit is orange-red and has milk-coagulating properties. Fruits are harvested in the late fall. Seeds are dried and stored for further plantation in the following Spring (Gupta et al., 2007).

Parts of plant with therapeutic values:

Roots are the most important parts of this plant with strong therapeutic properties. Leaves, fruits, stems, green berries, bark and seeds are also used for the same (Gupta et al., 2007). Till date 29 common metabolites are extracted from the plant leaves and roots. These are found to have anti-oxidant, anti-inflammatory, anti-arthritic, anti-cancer, anti-diabetic, anti-epileptic, anti-pyretic and anti-coagulant properties along with efficacies of regenerating, rejuvenating, analgesic and growth-promoting attributes (Dutta et al., 2019).

Bioactive compounds extracted from Withania are abundant with macro and micro-nutrients like copper, iron, zinc, phosphorous and magnesium. Different parts of Ashwagandha are being widely used for different treatments strategies like, severe cuts and wounds and the extracts of fruits, leaves, root can be applied to reduce anxiety, stress, in regulating cardiac issues, swelling, maintaining cholesterol, diabetes, asthma, cancer, bronchitis, ulcers, conjunctivitis, epilepsy, insomnia, senile dementia and preventing hair loss. It can also act as a potent antioxidant (Afewerky et al., 2021). Among all parts of *W. somnifera*, roots are the most potent one to exert pharmaceutical properties. *W. somnifera* may also demonstrate some adverse side effects like abdominal irritation and loose motion in few cases (Afewerky et al., 2021).

Biochemical compositions:

Roots of *W. somnifera* consist of various valuable phytochemicals like alkaloids, steroidal lactones, withanoloides and saponins. The leaves of this plant are mainly composed of withanolides, a steroidal lactone compound having C28 steroidal nucleus. According to study reports 35 withanolides, 12 alkaloids and many sitoindosides chemical constituents are isolated from this herbal plant species. It is an important source of iron. Withaferin A, Withanolide D are the two most common pharmacologically active withanolides used to treatvarious diseases (Narinderpal et al., 2013). *W. somnifera* also contains various amino acids including aspartic acid, glycine, glutamic acid, proline, cysteine, tyrosine, alanine and tryptophan. This plant exhibits three chemotypes till date having the same chemical nature but with different withanolide contents (Gupta et al., 2007).

List of major bioactive compounds of Ashwagandha (*W. somnifera*) that are isolated from different parts of the plant is summarized in Table 1 (Narinderpal et al., 2013; Dar et al., 2016; Gupta et al., 2007).

Table 1.List of major bioactive compounds extracted from Ashwagandha (*W. somnifera*)

Groups	Name of bioactive compound
Steroidal lactones	Withaferin A, Withanolide A to Y, Withasomniferols A to C, Ashwagandhanolide, Withasomniferin, Withanone, Asomnidienone, Withasomidienon.
Alkaloids	Somniferinine, Somniferin, Somnine, tropine, Withanine, Anaferine, Pseudo-withanine, Isopelletierine, Ashwagandhine, Cuscohygrine, Anahygrine and Tropine.
Other chemical compounds	Glycosides, Scopoletin, Chlorogenic acid, Dulcitol, Saponins, Acylsteryl glucosides, Withaniol, starch, hantreacotane, reducing sugars and amino acids.

Pharmaceutical properties of *Withania somnifera* (Ashwagandha):

Anti-oxidant properties:

Our brain and nerves are lipid and iron-rich portions and are prone to oxidative damage. This damage may lead to ageing and neural diseases like schizophrenia, Alzheimer's, Parkinson's, epilepsy and other diseases. It is experimentally established that, Withaferin A is a steroidal lactone, derived from *W. somnifera* can increase the concentration of superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT) and ascorbic acid and can decrease lipid peroxidation in rat and mice models (Singh et al., 2019). In vivo experiments in a rat model showed that *W. Somnifera* has antioxidant effect on the brain and a protective effect on neuronal tissues. It also exhibited the prevention of lipid peroxidation in mice and rabbit models (Gupta et al., 2007). Root extract (aqueous) of W. somnifera prevented the increase of stress-induced lipid peroxidation in mice and rabbits following certain bacterial infections (Gupta et al., 2007).

Anti-inflammatory properties:

NF-κB activation plays a major role in inflammation. Evidence suggests that withanolides can suppress the activation of NF-κB and also the NF-κB regulated gene expressions and promote apoptosis (Gupta et al., 2007). Reports demonstrated that Withaferin A can also inhibit the binding of NF-κB and exert anti-inflammatory capacity both *in vitro* as well as *in vivo* (Heyninck et al., 2014). Leaf extract of *W. somnifera* can inhibit microglial activation and may have the potency to suppress neuro-inflammation (Gupta et al., 2016). Mitochondrial oxidative stress release is one of the important roles of withanolides (Wei et al., 2020). The root extract of Ashwagandha, with a few other herb's mineral-based formulation is an effective anti-inflammatory agent and can be used as a complementary and alternative treatment (Trivedi et al., 2017). Withaferin A also showed promising antibacterial, antitumoral, immune-modulating and anti-inflammatory properties in animal models (Singh et al., 2011). Root extract of *W. somnifera* showed an anti-inflammatory role in different rheumatologic conditions. Inhibition of cyclooxygenase (COX) may be involved in such mechanism of action (Gupta et al., 2007).

Ashwagandha extract produced significant analgesic activity in the rat model. The involvement of pain mediators, namely prostaglandin and 5-hydroxytryptamine, in the analgesic activity of Ashwagandha was studied thoroughly. The analgesic activity of Ashwagandha was potentiated significantly by cyproheptadine, suggesting the involvement of serotonin but not prostaglandins in the analgesic activity of Ashwagandha (Singh et al., 2011).

Anti-stress and analgesic effects:

Ashwagandha has been known to reduce stress in humans and other animals. Researchers investigated that *W. somnifera* can reduce the frequency of stress-induced ulcers, induce male sexual behaviour and reduce chronic stress (Jana et al., 2018). Experimentally it has been established that, Withania can increase pain threshold time and act as an analgesic agent (Krutika et al., 2016).

It is reported that root extract powder of *W. somnifera* prevented stress-induced neuronal degeneration in the hippocampal Cornu Ammonis-2 (CA2) and CA3 areas compared to control or non-stressed animals. It has been further documented to provide significant protection against stress-induced gastric ulcers and other stress-related disorders in animal models. Experimental studies revealed that the root extract reduced stress significantly without any side effects in adults (Paul et al., 2021). Experimentally, *Withania* can increase pain threshold time and act as a potent analgesic agent (Krutika et al., 2016).

Anti-anxiety and anti-depressive properties:

Ashwagandha is known to have anti-anxiety properties. Experimental studies showed that *W. somnifera* bears GABA-like activity and delivers anti-anxiety and calming effects. GABA inhibits excess neuronal activities and gives sedative effects, reducing anxiety and mood regulation. It can also reduce depression (Jana et al., 2018).

Glycowithanolides have potent anxiolytic effects compared with many prominent anti-anxiety drugs and can effectively reduce rat brain levels of tribulin, a marker of clinical anxiety. It has also exhibited an antidepressant effect. Root extract of *Withania* may act as a mood stabilizer in the rat model's clinical conditions of anxiety and depression (Bhattacharya et al., 2000).

Anti-microbial Activity:

Anti-microbial properties of Ashwagandha are well known in the literatures. It’s a potent anti-fungal agent and can act against fungal species namely *Radicis lycopersici* and *Fusarium oxysporum* (Nefzi et al., 2016). *W. somnifera* can inhibit *E. coli* population and is reported as a potent anti-herpetic drug (Vinod et al., 2021). It can reduce the growth of different acid-fast, gram positive bacteria, and aerobic bacilli. Ranikhet virus, vaccinia virus and *Entamoeba histolytic* are inhibited by *W. somnifera* plants extracts. The antibiotic property of Withaferin A relies upon the presence of unsaturated lactone ring (Jana et al., 2017). Aqueous and alcoholic extracts of Ashwagandha (both root and leaves) were found to exhibit anti-bacterial property

against various kinds of bacterial species. Synergistic increase in the antibacterial effect of these extracts along with other antibiotics, are also reported in the literature (Gupta et al., 2007).

Anti-diabetic Activity:

Jonathan et al. (2015) reported that among all withanolides, withaferin A is more efficient in glucose uptake by skeletal myotubes. On the other hand, it was also proved that leaf extract is more efficient than root extract in glucose uptake. The study revealed the potent anti-diabetic nature of withaferin extracts (Jonathan et al., 2015; Vinod et al., 2021). Root powder of *W. somnifera* showed excellent results in diabetic patients with associated metabolic disturbances. These extracts are also effective and safe herbal therapeutic alternatives against diabetes-associated hyperlipidemia. It is well tolerated without any severe adverse effects and the bioactive metabolites of the plant showed anti-hyperlipidemic and Hb1Ac level suppressing effects. All these data established *W. somnifera* as an anti-diabetic plant. It's extracts could eventually lead to novel therapeutics and strategies are needed for preventing and curing diabetes with this plant (Kumar et al., 2017).

Immuno-modulation and hematopoiesis by *Withaferin*:

The role of the root extract of *W. somnifera* as an immune-modulator has been extensively studied. The root extract has been reported to enhance white blood cell count and increase phagocytic activity of macrophages in mice (Davis et al., 2000). Increased cytotoxic effect and enhanced phagocytic activity of macrophages exposed to *Withaferin* extracts have also been reported. These results confirmed the immunomodulatory activity of *Withaferin* extract in indigenous medicine. The report displayed that immunosuppressive effect of root powder could be a potential candidate for developing an immunosuppressive drug for inflammatory diseases (Gupta et al., 2007). Ashwagandha treatment can also enhance body weight increase RBC number and platelet number and haemoglobin concentration. Cyclophosphamide (CTX) treated patients with leucopenia have shown low pathological effects after administration of Ashwagandha. Withaferin A and withaferin E have an immune-suppressive effect on human B and T lymphocytes. Withanolide E is specified for T lymphocytes and withaferin A is specified for both B and T lymphocytes (Narinderpal et al., 2013).

Anti-ageing activity:

Ashwagandha is known for its anti-ageing properties. It has shown excellent results in the improvement of haemoglobin and RBC cell count, calcium retention and decrease in serum cholesterol by withaferin treatment have been shown by in-vivo experiments (Narinderpal et al., 2013).

Effects on sexual behaviour and reproduction:

Withaferin extract preparation, including ghee, sugar and honey, is used in ayurvedic treatment to improve semen quantity, quality and sperm motility. It can treat erectile dysfunction and early ejaculation and induce libido (Umadevi et al., 2012). Ashwagandha root powder with

boiled milk can cure female sterility. Traditional use of Ashwagandha roots to induce vigour, vitality, youth and physical strength is very well-known (Pandian et al., 2020).

Ashwagandha can treat spermatopathia, impotence and seminal depletion and increase vigour and vitality in men. Root extract with boiled milk can cure sterility in women (Singh et al., 2019). Ashwagandha has been known to reduce stress in humans and other animals. Researchers investigated that *W. somnifera* can reduce the frequency of stress-induced ulcers, induce male sexual behaviour and reduce chronic stress (Jana et al., 2018).

Act as an antivenom:

In India, snake charmers' ethnomedicinal practice in rural locations is still present. Snake bite victims can be treated with plant extracts externally as an antidote. Cobra (*Naja naja*) and viper (*Daboia russelii*) venoms having hyaluronidase, destroy extra-cellular matrix integrity and help rapidly spread the venom. Withaferin extracts bear hyaluronidase inhibitors and can somewhat inhibit venom spreading (Gupta et al., 2007).

Hypoglycemic, hypocholesterolemic and hypolipidemic effects:

A formulation with Ashwagandha extracts and other ingredients was administrated into streptozocin (STZ)-induced hyperglycaemic rats (Narinderpal et al., 2013). In this model, pathogenicity was caused by decreased superoxide dismutase (SOD) activity in pancreatic islet cells. This incident leads to the aggregation of reactive oxygen species (ROS). After the treatment hyperglycaemia was found to be decreased. This anti-hyperglycaemic effect might be exerted by pancreatic islets' free radicle scavenging activities (Narinderpal et al., 2013).

Ashwagandha is commonly used as an ayurvedic herb for weight loss. Hypolipidemic effect of withaferin is practised to reduce body fats. Withaferin root powder can reduce total lipids, triglycerides and cholesterol in hyper-cholesteremic animals. But it increases plasma HDL-cholesterol, neutral sterol and bile acid content in liver. Significant decreases in lipid-peroxidation rate and lipid profile are also important effects of Ashwagandha root extracts. Ashwagandha fruits also show similar properties. In humans, withaferin roots exhibit hypo-glycemic, diuretic and hypocholesterolemic effects. It can increase urine volume and urine sodium level and reduce serum cholesterol, LDL, VLDL and triglycerides level (Narinderpal et al., 2013).

Neural improvement and cognitive effect:

Sitoindosides VII to X and withaferin were isolated from aqueous methanolic extract of Ashwagandha roots and were studied upon brain glutamatergic, cholinergic and GABAergic receptors of rats. This treatment was reported to modulate basal forebrain and cortical cholinergic-signal transduction cascade. Withaferin extracts can enhance cognitive behaviour and improve memory in humans and other animals. In an experimental study, it was reported that withanolides could inhibit neuronal damage and increase neurite outgrowth. Withanosides can also exert positive effectsin Alzheimer’s patients with neuronal dysfunction. Ashwagandha

exhibit a nootropic effect in naïve and amnesic mice (Narinderpal et al., 2013). Figure 1 presents the pharmaceutical properties of Ashwagandha (*Withania somnifera*).

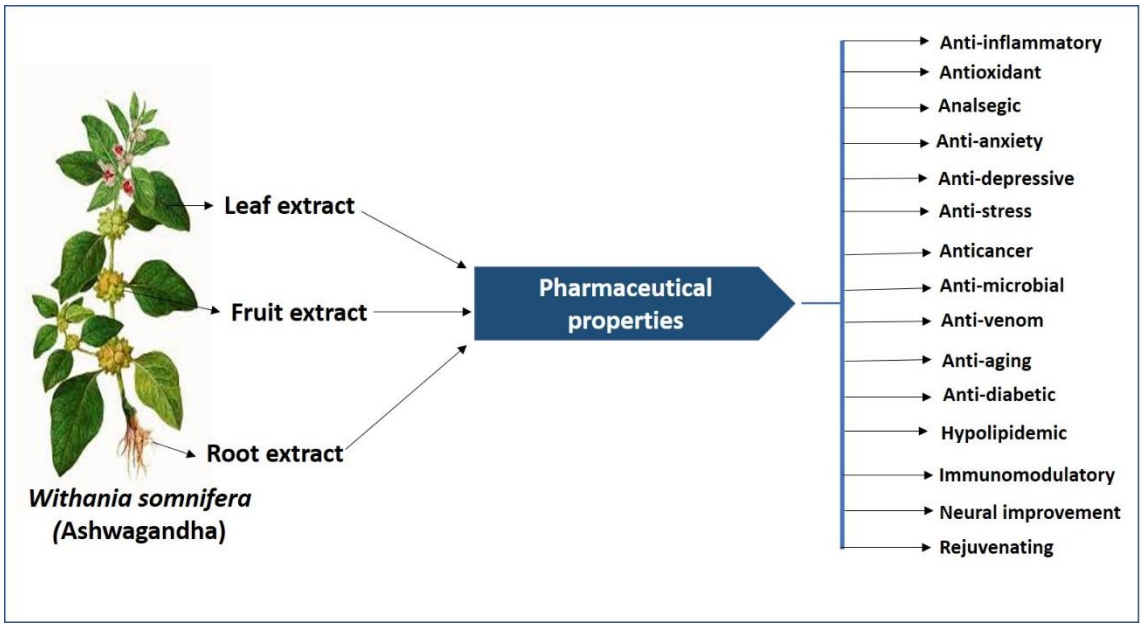

Figure 1. Pharmaceutical properties of different parts of *Withania somnifera* (Ashwagandha)(The Plant figure has been taken from Botanistry.com)

Pharmacological importance of Withania somnifera (Ashwagandha) against few diseases:

Cancer:

W. somnifera (Ashwagandha) and its bioactive secondary metabolites exhibitedanti-cancer properties in various ways such as inducing DNA damage, increasing ROS production, regulating cancer progression pathways etc. (**Figure 2**). Dysregulation of tumor suppressor genes with significant upregulation of oncogenes are commonly found in many cancers (Saggama et al., 2020). Leaf extract of Ashwagandha potentially activated the function of tumor suppressor gene p53 which acts as a growth suppressor by blocking unregulated cell cycle and inhibiting tumour cell growth (Saggama et al., 2020). Withaferin A (WA) is one of the strong bioactive phytochemicals that significantly increase the function of PP2A (protein phosphatase 2A) and reduce cancer cell proliferation. PP2A is a tumour suppressor that can decrease phosphatase activity in several cancers (Saggama et al., 2020). Beside the excessive proliferation capacity, cancer cells also have an ability to avoid apoptosis by inhibiting apoptotic signalling with increasing expression of several anti-apoptotic factors like Bcl-2 (B-cell lymphoma 2) (Kim et al., 2017). Ashwagandha and its other phytochemicals can upregulate extrinsic (via death receptor) and intrinsic (via mitochondrial caspase) apoptosis signalling. WA enhances PARP (poly adenosine diphosphate-ribose polymerase) cleavage and increases pro-apoptotic factors Par4 (protease-activated receptor 4), and caspase expression (Saggama et al., 2020). Additionally, WA also interferes with replicative immortality by suppressing the Alternative Lengthening of the Telomeres process (ALT) and its associated factors. High amounts of nutrition & O2 requirements are essential for tumor expansion. Tumor microenvironment creates

a hypoxic condition to induce angiogenesis by upregulation of various angiogenic factors like vascular endothelial growth factor (VEGF) (Saggama et al., 2020). Angiogenesis is the procedure of establishing a new vascular network around the tumor that fulfils the necessary environment for tumor growth. WA has also been shown to effectively suppress factors involved in angiogenesis. Additionally, phytochemicals of Ashwagandha also act as anti-metastatic agent by downregulating metastasis responsible molecules including MMPs (matrix metallop-roteinases), vimentin, pro-inflammatory cytokine (IL-8), chemokineetc. WA attenuates the expression of metastasis inducible signalling pathways like NF-kβ (nuclear receptor kappa β), cox-2 (cyclooxygenase-2), STATs in many cancer cells (Saggama et al., 2020). The mechanical action of *W. somnifera* and its phytochemicals in different cancer are listed in **table 2**.

Table 2. Anticancer effect of *W. Somnifera* (Ashwagandha) by targeting multiple signaling pathways in various cancer.

Sl No.	Types of Cancer	Molecular mechanism of action by *W. somnifera*	Reference
1.	Breast	Upregulates p53, PP2A function, inhibit cell growth and enhance cytotoxicity by ROS production in breast cancer cell line. Downregulates Bcl-2 and Survivin expression.	Saggama et al., 2020; Dutta et al., 2019.
2.	Cervical	Upregulates caspase-3, PARP cleavage and p53 function. Downregulates E6/E7 oncogenes expressed by human papilloma virus (HPV).	Dutta et al., 2019
3.	Colorectal	Increases caspase-mediated apoptosis of cancer cells Decrease proliferation, metastasis in colorectal cancer cell line. Inhibits STAT3, Notch, NF-kβ, mTOR signalling. Supress pro-inflammatory cytokines expression TNF-α, IL-6.	Dutta et al., 2019
4.	Glioblastoma	Block cell cycle (G2-M phase), suppress the expression of Heat shock protein (Hsp) 70, VEGF and matrixmetallo proteinases (MMPs). Increase expression of NCAM (neuronal cell adhesion molecules).	Halder et al., 2017; Lee et al., 2016.
5.	Lung	Enhances Bax, caspase activity and ROS production. Reducesepithelial mesenchymal transition (EMT) and lung cancer cell migration. Downregulates PI3/Akt signalling.	Dutta et al., 2019

6.	Lymphoma	Downregulates Hsp 90, Bcl-2, MAPKs expression and inhibits cell proliferation. Upregulates caspase-3 mediated cell death with significantly increased PARP cleavage.	Halder et al., 2017.
7.	Melanoma	Improves mitochondrial translocation, upregulates the apoptosis pathway by increasing the activity of both caspases 9 and caspase 3, promotes tumor regression.	Bungau et al., 2021; Saggama et al.,2020
8.	Ovarian	Reduces the number of ALDH-positive ovarian cancer stem cells (CSCs), and inhibits cancer progression.	Dutta et al., 2019
9.	Prostate	Downregulates Chk1 and Chk2 in prostate cancer cells line. Upregulates the expression of apoptosis-associated factors Bax, caspase-3 and increase p27 function.	Halder et al., 2017; Saggama et al., 2020
10.	Pancreatic	Upregulating apoptosis pathway by significantly inhibiting the activity of PI3K/AKT signalling activity. Block cell cycle mediated cancer cell proliferation in the different pancreatic cancer cell lines.	Halder et al., 2017

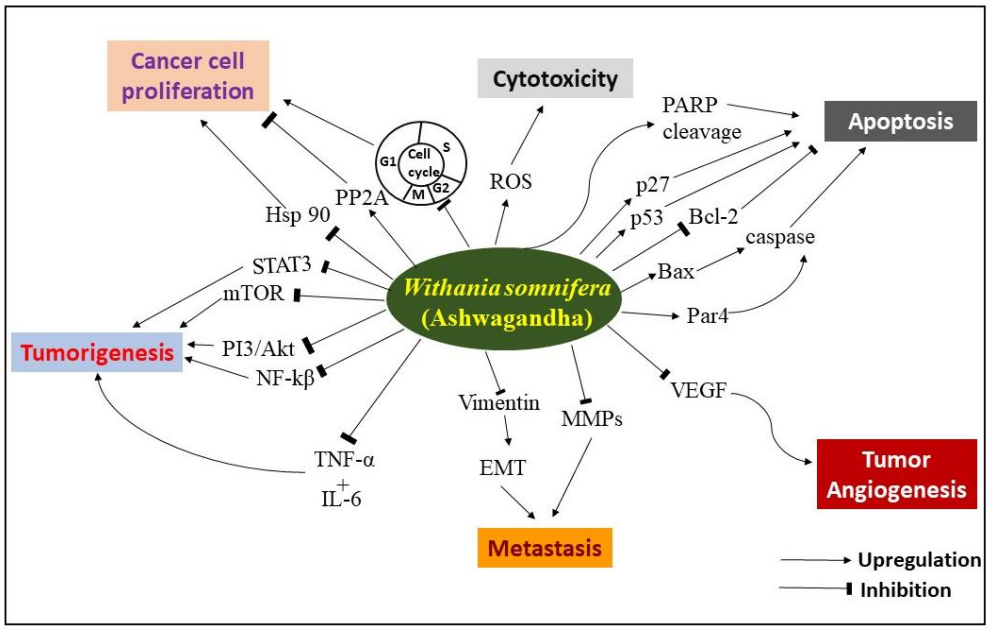

Figure 2. The major signaling pathway(s) regulated by *W. somnifera* (Ashwagandha) in the pathogenicity of cancer.

Cardiovascular disorder:

W. somnifera (WS) is largely used as herbal medicine (mostly in Ayurveda and Unani) to treat various cardiovascular disorders. It is a cardio-protector that reduces myocardial infarction and ischaemia-reperfusion injury in cardiac system (Afewerky et al., 2021). *W. somnifera*

significantly reduces cardiac damage caused by doxorubicin in *in-vivo* system. It elevates the expression of detoxification genes by enhancing the activity of nuclear factor-erythroid-2 (Nrf−2) in cardiomyocytes (Paul et al., 2021). Withaferin A has been emphasized as cardio-protector in cardiorespiratory damage caused by corona virus infection (COVID-19). Root extract of Ashwagandha has been reported to reduce hypertension via lowering the systolic blood pressure considerably (Afewerky et al., 2021). Histopathological studies exhibited that *W. somnifera* minimize cardiac cell death (apoptosis) and improves overall cardiac function due to its antioxidant and anti-lipoperoxidation properties (Afewerky et al., 2021). The extracts of *W. somnifera* showed a strong cardio-protective effect against isoprenaline-induced myonecrosis in rat models (Narinderpal et al., 2013).

Neurodegenerative diseases:

Several clinical reports suggest that different phytochemicals derived from *W. somnifera* act as neuro-protector. The toxic effects of scopolamine (atoxic agent) in neurons and glial cell can bereversed by Withanone, a leaf-extracted phytochemical of *W. Somnifera* (Paul et al., 2021). It also reduces the harmful toxic effects of lead in glial cells by maintaining the normal expression of different proteins, including Heat shock protein 70, GFAP (Glial fibrillary acidic protein), mortalin and NCAM (neural cell adhesion molecule). Glycowithanolides is another phytochemical of *W. somnifera*, exhibited strong antioxidant effect by downregulating the oxidative stress markers and significantly upregulated the expression of a different antioxidant enzyme such as SOD, glutathione peroxidase etc. (Paul et al., 2021). Root extraction of *W. somnifera* exhibited its neuroprotector properties by regulating the activity of Bcl-2/Bax axis and can maintain the balance between apoptosis and anti-apoptosis pathway (Prakash et al., 2014).

Since the last few decades, the occurrence of neurodegenerative disorders have increased day by day. Parkinson's, Alzheimer's, a Huntington's are the most harmful, complicated, irreversible neurodegenerative diseases. Till now, no specific effective treatments are available for neurodegenerative diseases (Afewerky et al., 2021). Pharmacological investigations suggested that intake of antioxidant rich *W. Somnifera* may lead the way-out of several brain disorders such as bipolar disorder, loss of memory and locomotor disability etc. Additionally, in neuron-like cells, the Amyloid-beta (Aβ)-triggered ROS production, which is relatively alleviated by the root-extracted compounds of *W. somnifera*. This root extract also increased the neuron integrity and maintained the unimpaired neuronal transmission in Alzheimer animal model after the treatment with the extract (Afewerky et al., 2021). Reports also exhibited that *W. somnifera* has been used to treat Parkinson's disease by enhancing dopamine levels and restoring normal coordinated movements (Afewerky et al., 2021). In addition, it can alleviate the NO level by reducing the iNOS activity. Furthermore, in Parkinson's disease-affected brain, this herbal plant extract modulates the expression of Glial fibrillary acidic protein (Paul et al., 2021). *W. somnifera* is also documented for treating Huntington's disease by protecting the basal ganglia from the damage caused by huntingtin protein (in animal model)(Afewerky et al., 2021). GABAergic signalling and the level of different antioxidant molecules in Huntington's disease-

affected brain, could be restored significantly by *W. somnifera* extract. The plant extract also improved mental apprehension and locomotor coordination (Afewerky et al., 2021).

Arthritis:

Ashwagandha is an anti-inflammatory and analgesic used to reduce many inflammatory diseases and their related symptoms. Among the inflammatory diseases, arthritis is a common inflammatory disorder characterized by excessive pain and swelling around the joint area. Few reports suggested that Ashwagandha (root) is an effective treatment in arthritis as it can significantly reduce the arthritis-related pain and recover joint flexibility in animal models (Khan et al., 2015; Elgaret al., 2021). It has been found that root extract of *W. somnifera* can decrease the ROS level and decrease the biomarker of rheumatoid arthritis, such as rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (Khan et al., 2015). Withaferin A is a potent analgesic phytochemical compound which can regulate COX pathway down and also deliver relief from prostaglandin-induced pain (Elgar et al., 2021).

Thyroid disorder:

Several clinical studies reported that *W. somnifera* could significantly increase the thyroxine hormone level and reverse the thyroid's dysregulation by regulating (hypothalamus−pituitary−thyroid) HPT axis activity. Additionally, it also interacts with metabolism of thyroid hormone. *W. somnifera* is a beneficial therapeutic effect against hypothyroidism (Elgar et al., 2021).

Conclusion:

Withania somnifera or Ashwagandha is a natural medicinal herb used in various disease treatments. It greatly contributes to Indian ayurvedic practices because of its renowned pharmaceutical activities. Phytochemical composition may vary in terms of geographical distribution. Roots, leaves and fruits are the main parts to extract phytochemicals, including alkaloids, steroids and other bioactive compounds. Various scientists have reported anticancer, anti-oxidant, antibiotic, anti-ageing, anti-stress, anti-inflammatory and other important activities with Ashwagandha's extracts. This evergreen herb also regulates rejuvenation, sexual behaviour and Alzheimer, Parkinson, Huntington disease treatment. A wide variety of this plant’s secondary metabolites have been isolated to date. Many more are waiting to be explored. Recognition and cultivation of these ethnomedicinal plants are growing day to day. *Withania somnifera* should be studied more extensively, and clinical trials are in demand to uncover its other pharmaceutical properties.

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Conflict of interest:

The authors declare no conflict of interest.

References:

Acharya, C. K. (2016). Ethnicity and Scientific validation of West Bengal Amla (*Phyllanthus emblica* L.) with special reference to GC-MS screening. *International Journal of Experimental Research and Review*. 3: 51- 59.doi: https://doi.org/10.52756/ijerr.2016.v03.006

Acharya, C. K., Khan, N.S., & Madhu, N. R. (2021). Medicinal uses of amla, *Phyllanthus emblica* L. (Gaertn.): a prospective review**.** *Mukt Shabd Journal***.** X (X): 296-310.

Afewerky, H. K., Ayodeji, A. E., Tiamiyu, B. B., Orege, J. I., Okeke, E. S., Oyejobi, A. O., Bate, P. N. N., & Adeyem, S. B. (2021). Critical review of the *Withania somnifera* (L.) Dunal: ethnobotany, pharmacological efficacy, and commercialization signifcance in Africa. *Bulletin of the National Research Centre.* 45: 176.doi:https://doi.org/10.1186/s42269-021-00635-6

Banerjee, J., Biswas, S., Madhu, N. R., Karmakar, S. Re., & Biswas, S. J. (2014). A better understanding of pharmacological activities and uses of phytochemicals of Lycopodium clavatum: A review. *Journal of Pharmacognosy and Phytochemistry*. 3 (1): 207-210.

Bhandari, P. R. (2012). Curry leaf (Murrayakoenigii) or cure leaf: review of its curative properties. *Journal of Medical Nutrition and Nutraceuticals.* 1(2): 92-97.doi: 10.4103/2278-019X.101295

Bhattacharjee, P. (2021). Some medicinal plants with anti-fertility potential used by the tribal people of the District Cooch Behar, West Bengal, India. *International Journal of Experimental Research and Review*. 24: 30-39.doi: https://doi.org/10.52756/ijerr.2016.v03.006

Bhattacharya, S. K., Bhattacharya, A., Sairam, K., & Ghosal, S. (2000). Anxiolytic-antidepressant activity of *Withania somnifera*glycowithanolides: an experimental study. *Phytomedicine.* 7(6): 463-469.

Bungau, S., Vesa, C. M., Abid, A., Behl, T., Tit, D. M., Purza, A. L., Pasca, B., Todan, L. M., & Endres, L. (2021). Withaferin A-a promising phytochemical compound with multiple results in dermatological diseases. *Molecules.* 26: 2407.

Chakraborty, D., Das, D., Samal, A. C., & Santra, S. C. (2019). Prevalence and Ecotoxicological significance of heavy metals in sediments of lower stretches of the Hooghly estuary, India. *International Journal of Experimental Research and Review*. 19: 1-17. doi: https://doi.org/10.52756/ijerr.2019.v19.001

Dar, P. A., Singh, L. R., Kamal, M. A., & Dar, T. A. (2016). Unique medicinal properties of *withania somnifera*: phytochemical constituents and protein component. *Current Pharmaceutical Design.* 22(5):535-540.doi: 10.2174/1381612822666151125001751.

Davis, L. & Kuttan, G. (20000. Immunomodulatory activity of *Withania somnifera. Journal of Ethnopharmacology.*71(1–2):193-200.

Devi, G. (2020). Medicinal Plant: Ashwagandha. *International Journal of Current Research.* 12(06): 12073-12074. doi:https://doi.org/10.24941/ijcr.39031.06.2020.

Dutta, R., Khali, R., Green, R., Mohapatra, S. S., & Mohapatra, S. (2019). Withania Somnifera (Ashwagandha) and Withaferin A: potential in integrative oncology. *International Journal of Molecular Sciences.* 20: 5310. doi:10.3390/ijms20215310.

Erfani, H. (2021). The practical and potential importance of herbs such as ginger in Chemical Environmental Science. *International Journal of Experimental Research and Review*. 24:24-29. doi: https://doi.org/10.52756/ijerr.2021.v24.003

Elgar, K. (2021). Ashwagandha: a review of clinical use and efficacy. *Nutritional Medicine Journal*. 1(1): 68-78.

Gahlawat, D. K., Jakhar, S., & Dahiya, P. (2014). Murrayakoenigii (L.) Spreng: an ethnobotanical, phytochemical and pharmacological review. *Journal of pharmacognosy and Phytochemistry*. 3(3): 109-119.

Gill, M. K., Kumar, S., Sharma, M., Singh, T. P., Kumar, K., & Kaur, R. (2019). Role of ashwagandha incorporated functional foods for betterment of human health: a review. *Journal of Agricultural Engineering and Food Technology*. 6: 161-165.

Gupta, G. L., & Rana, A. C. (2007). Withania somnifera (Ashwagandha): a review. *Pharmacognosy Reviews*. 1(1): 128-136.

Gupta, M., & Kaur, G. (2016). Aqueous extract from the Withania somnifera leaves as a potential anti-neuroinflammatory agent: a mechanistic study. *Journal of Neuroinflammation.* 13(1):193.

Heyninck, K., Lahtela, K. M., Veken P, V., Haegeman, G., & Berghe W., V. (2014). Withaferin A inhibits NF-kappaB activation by targeting cysteine 179 in IKKβ. *Biochemical Pharmacology*. 91(4): 501-509.doi.org/10.1016/j.bcp.2014.08.004.

Halder, B., & Thakur, S. S. (2017). *Withania somnifera*has potential to treat cancer. *Science of Ashwagandha: Preventive and Therapeutic Potentials.* Springer, Cham.Pp. 213-226. doi:10.1007/978-3-319-59192-6_10.

Jana, S. N., &Charan, S. M. (2018). Health benefits and medicinal potency of Withania somnifera: A Review. *International Journal of Pharmaceutical Sciences Review and Research.* 48(1): 22-29.

Jonathan, G., Rivka, R., Avinoam, S., Lumír, H., &Nirit, B. (2015). Hypoglycemic activity of withanolides and elicitated Withania somnifera. *Phytochemistry.* 116(1): 283–289. https://doi.org/10.1016/j. phytochem.2015.02.029.

Kar, D., Ghosh, P., Suresh, P., Chandra, S., & Paul, D. (2022). Review on Phyto-chemistry & pharmacological activity of Melia azedarach. *International Journal of Experimental Research and Review*. 28: 38-46. https://doi.org/10.52756/ijerr.2022.v28.006

Khan, M. A., Subramaneyaan, M., Arora, V. K., Banerjee, B. D. & Ahmed, R. S. (2015). Effect of Withania somnifera (Ashwagandha) rootextract on amelioration of oxidative stress and autoantibodies production in collagen-induced arthritic rats. *Journal of Complementary and Integrative Medicine.* 12(2): 117–125.

Kim, G., Kim, T. H., Hwang, E. H., Chang, K. T., Jung, J. H. & Park, J. H. (2017). Withaferin A inhibits the proliferation of gastric cancer cells by inducing G2/M cell cycle and apoptosis. *Oncology Letters.* 14: 416-422.

Krutika, J., Tavhare, S., Panara, K., Kumar, P. & Karra, N. (2016). Studies of Ashwagandha (Withania somnifera Dunal). *International Journal of Pharmaceutical & Biological Archives.* 7(1): 1-11.

Kundu, K. (2022). Management of root-knot nematodes, Meloidogyne incognita in Okra using wheat flour as bionematocides. *International Journal of Experimental Research and Review*. 28: 8-14. doi: https://doi.org/10.52756/ijerr.2022.v28.002

Kumar, V., Dey, A., & Chatterjee, S. S. (2017). Phytopharmacology of Ashwagandha as an anti-diabetic herb. *Science of Ashwagandha: Preventive and Therapeutic Potentials*. Springer International Publishing AG 2017. Pp. 37–68. doi:10.1007/978-3-319-59192-6_2.

Lee, I. C., & Choi, B. Y. (2016). Withaferin-A—a natural anticancer agent with pleitropic mechanisms of action. *International Journal of Molecular Sciences.* 17: 290. doi:10.3390/ijms17030290

Maiti, A., Madhu, N.R., & Manna, C. K. (2010). Ethnomedicine used by the tribal people of the district Purulia, W. B., India in controlling fertility : and experimental study. Pharmacologyonline. 1: 783-802.

Maiti, A., Madhu, N. R., & Manna, C. K. (2013). Natural products traditionally used by the tribal people of the Purulia district, West Bengal, India for the abortifacient purpose. *International Journal of Traditional Medicine* (TANG). 3(2): e14. doi: http://dx.doi.org/10.5667/tang.2012.0045

Narinderpall, K., Junaid, N., & Raman, B. (2013). A Review on Pharmacological Profile of Withania somnifera (Ashwagandha). *Research and Reviews: Journal of Botanical Sciences.* 2(4): 6-14.

Nefzi, A., & Ben Abdallah, R. A. (2016). Antifungal activity of aqueous and organic extracts from *Withania somnifera L.* against *Fusariumoxysporum* f. sp. radicis-lycopersici. *Journal of Microbial & Biochemical Technology*. 8(3): 144–150. https://doi.org/10.4172/1948- 5948.1000277.

Pandian, A., Ashokkumar, K., Sekar, S., Sivakumar, P., Vijai, K. S., Karthik, S. M., & Hariprasath, L. (2020). Botany and ethnopharmacological potential of ashwagandha. *Journal of Current Opinion in Crop Science.* 1(1): 35-40.

Paul, S., Chakraborty, S., Anand, U., Dey, S., Nandy, S., Ghorai, M., Saha, S. C., Patil, M. T., Kandimalla, R., Proćków, J., &Dey, A. (2021). Withania somnifera (L.) Dunal (Ashwagandha): A comprehensive review on ethnopharmacology, pharmacotherapeutics, biomedicinal and toxicological aspects. *Biomedicine & Pharmacotherapy.* 143: 112-175.doi: https://doi.org/10.1016/j.biopha.2021.112175.

Prakash, J., Chouhan, S., Yadav, S. K., Westfall, S., Rai, S. N., & Singh, S. P. (2014). *Withania somnifera* alleviates parkinsonian phenotypes by inhibiting apoptotic pathways in dopaminergic neurons. *Neurochemical Research.* 39(12): 2527-2536. doi: 10.1007/s11064-014-1443-7.

Sanyal, R., Bala, S., & Mazumdar, A. (2016). Indigenous knowledge of Ethnic community on usage of Satavari (*Asparagus racemosus* Willd) and its preliminary screening. *International Journal of Experimental Research and Review*. 7: 62-68.

Sanyal, R., Mallick, S., & Mazumder, A. (2018). Indigenous Knowledge of Ethnic Community on Usage of Kripa (*Lumnitzera racemosa*) and its preliminary screening. *International Journal of Experimental Research and Review*. 15: 44-50. doi: https://doi.org/10.52756/ijerr.2018.v15.007

Sarkar, B. (2016). Ethnic practices and human welfare in India: An attempt for controlling fertility. *International Journal of Experimental Research and Review*. 2: 28-31. doi: https://doi.org/10.52756/ijerr.2016.v2.006

Sarkar, B., Jana, S. K., Kasem, S. K., & Behera, B. K. (2016). Therapeutic potential of some Medicinal plants on wound healing. *International Journal of Experimental Research and Review*. 2: 1-4. doi: https://doi.org/10.52756/ijerr.2016.v2.001

Sarkar, B. (2017). Traditional use of medicinal plants and its biodiversity in India. *International Journal of Experimental Research and Review*. 10: 23-26.

Saggama, A., Tillua, G., Dixitb, S., Chavan-Gautama, P., Borsea, S., Joshic, K., & Patwardhan, B. (2020). Withania somnifera (L.) Dunal: A potential therapeutic adjuvant in cancer. *Journal of Ethnopharmacology*. 255: 112759. https://doi.org/10.1016/j.jep.2020.112759.

Singh, N. Bhalla, M., de Jager, P., & Gilca, M. (2011). An overview on Ashwagandha: A rasayana (rejuvenator) of ayurveda. *African Journal of Traditional Complementary and Alternative Medicine*. 8(5): 208-213. doi: 10.4314/ajtcam.v8i5S.9.

Singh, N., & Singh, A. R. J. (2019). Biochemical and therapeutic properties of Withania Somnifera in traditional medicinal system. *International Journal of Trend in Scientific Research and Development (IJTSRD)*. 3(3): 550-556.

Trivedi, M. K., Mondal, S. C., Gangwar, M., & Jana, S. (2017). Effect of a novel ashwagandha-based herbomineral formulation on pro-inflammatory cytokines expression in mouse splenocyte cells: A potential immunomodulator. *Phermacognosy Magazine*. 13(49): 90-94.

Umadevi, M., Rajeswari, R., Rahale, C. S., Selvavenkadesh, S., Pushpa, R., Kumar, K. P. S., &Bhowmik, D. (2012). Traditional and medicinal uses of Withania Somnifera. *The Pharma Innovation*. 1(9): 102-110.

Vinod, S., &Senthil, K. (2021). Withaferin A – a natural multifaceted therapeutic compound. *Current Botany*. 12: 36-52. doi: 10.25081/cb.2021.v12.6867.

Wei, Z., Li, T., Su, H., Wang, Q., &Kuang, H. (2020). Pharmacological effects of withanolides. *Biomedical Journal of Scientific and Technical Research*. 25(3): 19243-19248. doi: 10.26717/BJSTR.2020.25.004218.

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