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REVIEW ARTICLE

Exploring *Withania Somnifera*: A Novel Immunomodulatory and Anticancer Pharmaceutical Agent

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ABSTRACT

Background: Traditional chemotherapy for cancer has a number of major problems, such as recurrence, drug resistance, high costs, late discovery, systemic toxicity, and limited specificity. These problems make life worse and make treatment less effective. So, switching to new phytotherapy is a cost-effective and side-effect-free way that can work well with traditional treatments.

Aim: This review examines the unique immunomodulatory and anticancer characteristics of *W. somnifera*, emphasizing its effectiveness and potential in the treatment of cancer through direct cytotoxic effects on cancer cells and immune pathway modulation. *W. somnifera* may help slow the growth of several cancers, including those that affect the liver, cervix, breast, brain, colon, skin, lungs, and prostate, according to preliminary lab-based research. These findings suggest that it could be a promising natural option alongside standard cancer treatments. However, *W. somnifera's* stability, bioavailability, and target, selectivity limit its clinical use.

Method: Method of data extraction in a review article on *W. somnifera* involves systematically gathering and analyzing relevant information from primary research studies to address specific research questions or objectives.

Conclusion: Nanotechnology based *W. somnifera's* administration has improved its solubility, stability, absorption, and cancer cell delivery to improve cancer treatment outcomes. Further research uncovering the mechanism of *W. somnifera* and its integration into traditional cancer therapies could provide complete approach to treatment.

KEYWORDS: Anticancer, Cancer, Immunomodulation, Pharmaceutical Agent, Phytotherapy, *Withania somnifera*.

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INTRODUCTION

Ashwagandha, or *Withania somnifera* (WS), is a plant that has gained a lot of attention lately due to its potential as an effective medication for the treatment of cancer and immunomodulation (Figure 1).[1] Ashwagandha, also called *W. somnifera*, is a small shrub that has been used in Indian traditional medicine for many centuries. From a botanical point of view, it belongs to the kingdom *Plantae*, comes under the order *Solanales*, and is a member of the family *Solanaceae*. Within the genus Withania, this particular species is the one most widely used and researched. In Ayurveda, Ashwagandha has long been described as herb that improves vitality and helps the body cope with daily stress. It has long been used to improve general health, strengthen immunity, and even treat serious illnesses. It is interesting to note that many of these conventional assertions are currently being investigated by contemporary scientists, and many of them are receiving scientific validation.[3]

Ashwagandha is a key component of integrative medicine and has great potential for treating immune dysfunction and cancer due to its many therapeutic qualities. Further pharmacological research could lead to its integration into more thorough and effective treatment plans.

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Immunomodulation

In Immunomodulation the altering or regulating one or more immune system components to find the desired therapeutic result[4] Immune responses may be strengthened or inhibited, depending on the therapeutic context. Immunomodulation can be used to treat a broad range of situations, such as cancer, autoimmune diseases, allergies, and infections.[5] It can be achieved through various methods, including the use of medications (such as immunostimulants and immunosuppressants), biologics (such as cytokines and monoclonal antibodies), vaccinations, and other therapies that modify the immune system's function in order to restore equilibrium and advance health.

Pharmaceutical Agents in Cancer Treatments

In the context of cancer, a pharmaceutical agent simply means a drug or a chemical compound that is designed to help in prevention, diagnosis, or treatment of the disease. These medicines can act in different ways some directly kill cancer cells, others slow down or stop their growth, while a few prevent the spread of tumors to new sites. Many drugs are also given just to make the symptoms or side effects of cancer therapy easier for patients to handle.[6] The range of cancer medicines is quite wide. It includes standard chemotherapy, newer targeted drugs, immune-based therapies, hormone treatments, as well as supportive care medicines. Each of these is chosen according to the type of cancer, the stage of the disease, and the needs of the patient, so that the treatment can be as effective and precise as possible.

BIOLOGICAL POTENTIAL AND CHEMICAL PROFILE OF *W. SOMNIFERA*

Origin and Chemical Properties of *W. somnifera*

Species of the genus Withania, which naturally grow in dry and semi-arid regions, are well known for producing a wide range of bioactive compounds. Over the years, different studies have reported that these plants show antimicrobial action, help in protecting the heart, support nerve health, and may potentially inhibit the progression of cancer.[7] The main reason behind such diverse pharmacological properties is the presence of withanolides, a group of naturally occurring steroidal lactones are regarded as the principal phytochemical constituents of *Withania*. Ashwagandha, which comes in 23 different varieties, is prized for its therapeutic uses such as its favorable impact on memory and cognitive performance, mood balance, and general vitality. Its primary components are steroidal lactones and alkaloids, withanine being the most common.[8] Bioactive compounds of WS along with their anticancer properties are given in Table 1.

Toxicity of *W. somnifera*

Medicinal herbs are abundant and inexpensive, which makes them potentially useful in preventing cancer.[15] A naturally occurring bioactive medication called withaferin A decreases oxidative stress, boosts H9c2 cell survival, stops liver and kidney damage, and lessens acute pancreatitis caused by cerulein. WS root extract supplementation enhances the general quality of life.

Pharmacokinetic Profile and Bioavailability of *W. somnifera*

In both rats and humans, the root aqueous extract withaferin A has demonstrated adequate bioavailability and stability. It has good sensitivity to identify withanolides in mouse plasma and linearity in various concentration doses. Withaferin A has effective pharmacological properties, such as anticancer efficacy in experimental in vitro and in vivo models, along with nearly twofold greater bioavailability than Withanolide A.[16]

Figure 1: Withania somnifera (Ashwagandha).

ANTI-CANCER EFFECTS OF *W. SOMNIFERA*

Lung Cancer

Globally, lung cancer remains the leading cause of cancer-related mortality. It has been demonstrated that paclitaxel and Withaferin A extracts together can reduce cell viability, boost immunity, and shield animals from harm caused by reactive oxygen species.[17] Also, WS has been shown to forestall Akt phosphorylation, limit TNF-α-actuated association of U937 monocytic cells with A549 cells, and smother NF-κB action. Also, it has major areas of strength for showing against TGF-β and TNF-α-actuated epithelial-mesenchymal change in NSCLC cell lines A549 and H1299.[18]

Breast Cancer

The leading type of cancer affecting women, which fluctuates in seriousness depending upon normal metastasis and level of forcefulness. Using Withaferin an objective the phosphorylate the H3 histone at the Ser10 site and starts the mitotic capture in breast cancer cell types. Five weeks of supplementing with WA/kg body weight has been shown in vitro to slow the growth of tumors. Withania root extracts have anti-estrogenic properties and affect breast cancer's EMT.[19]

Prostate Cancer

3.8% of cancer-related passings are brought about by prostate cancer, which is the second most successive danger among men. One of WS's constituents, withaferin A, has anticancer qualities; it induces apoptosis in cancer cell lines and suppresses relapse in PC-3 xenograft models. In addition, it advances Weal amassing, smothers cell reasonability, and helps in vimentin corruption in bosom cancers. Consolidating glucose digestion centered treatment with withaferin A might be valuable for cancer cells that are impervious to TKIs.[20]

Colon Cancer

Globally, colon cancer is the second most fatal malignancy and the third most common cancer. Through its focusing of Score 1 flagging, concealment of crosstalk between the Indent 1 and Akt/mTOR pathways, and effective blockade of apoptotic signaling in colon malignancies, Withaferin A, an ethanolic concentrate of WS, has exhibited anticancer viability. Tumor weight and volume significantly decreased in Balb/c nude mice given with HCT116 xenograft tumors.[21]

Leukemia Withaferin

Derived from the WS fruit, withaferin A has been shown to possess strong anticancer effects, especially against hematological malignancies. It utilized the p38/MAPK flagging pathway to cause apoptosis, cell cycle capture, and restraint of cell multiplication. Research led on leukemia cell lines, for example, U937 related Withaferin A with upgraded ionizing radiation-prompted cell demise, interruption of the phone cycle, and expanded JNK flagging.[22]

Other Cancers

Research has shown that withaferin A (WS) exhibits anticancer activity in a number of cancer types, such as oral, gastric, melanoma, and human osteosarcoma. In models using Swiss albino mice, WS root extracts have been demonstrated to increase body weight and reduce skin lesions. Nevertheless, there hasn't been much thorough research done on WS's anticancer effects in these tumors. In cases of pancreatic cancer, WS enhances ROS accumulation, whereas in cases of ovarian cancer, it enhances ROS formation and autophagy. WS also specifically kills cancer cells in cases of oral cancer.[23]

Synergistic and Chemosensitizing Properties of *W. somnifera*

The acquisition of resistance to regular chemotherapy raises the prospect that a single prescription might be insufficient to treat cancer.[24] By combining standard chemotherapeutics with phytochemicals like WS, blend treatment may increase beneficial survivability. Because WS modifies signaling pathways (Table 2), it has chemosensitizing effects on different types of cancer. Research evaluated through in vivo and in vitro experiments has revealed WS's therapeutic promise as a combination anticancer drug. Isolated from WS, withanolide D upregulates the neutral sphingomyelinase-ceramide pathway, thereby inducing leukemic apoptosis.[25] Prostate cancer cells that overexpress PAWR exhibit increased chemosensitivity, suggesting therapeutic potential.

There isn't much clinical research on the effects of the natural herb Withaferin A (WS), which inhibits oncogenic signaling molecules, on cancer. Despite 29 clinical trial investigations,

Table 1: *W. somnifera*'s many bioactive compounds and their anticancer properties

Bioactive Compounds	Plant Part	Cancer Type/Cell Line	Observed Anti-Cancer Effects	Potential Immunomodulatory Action
Flavonoids[9]	Leaves	Hepatocellular carcinoma (HepG2)	Triggered apoptosis through caspase activation (3, 8, 9), enhanced antioxidant response, and lowered TNF-α levels	Likely contributes to immune system stimulation and inflammation reduction
Withaferin A & CAPE (Steroidal lactones)[10]	Not reported	Ovarian (SKOV3, OKV-18, etc.) and cervical (HeLa) cancer	Slowed cell growth, initiated apoptosis, elevated p53 levels, and reduced mortalin expression	CAPE may suppress inflammation and boost immune defense
Withaferin A & Withanone (Steroidal lactones)[11]	Not reported	Hepatocarcinoma (HUH-6 and HUH-7)	Lowered cancer cell viability and induced programmed cell death	Withaferin A might help strengthen immune responses
Withaferin A & 4β-hydroxywithanolide E[12]	Not reported	Triple-negative breast cancer (MDA-MB-231)	Disrupted cell growth, triggered both apoptosis and necrosis, and halted cell cycle progression	Shown potential to activate the immune system
Cucurbitacin B & Withanone (CucWi-N)[13]	Not reported	Lung cancer (A549, TIG-3) and in vivo (athymic mice)	Reduced tumor progression, induced senescence, modulated cyclins/CDKs, lowered mortalin, raised p53 levels	May influence immune cells and promote anti-tumor immunity
Root extract[14]	Root	Prostate cancer (LNCaP, 22Rv1)	Inhibited proliferation and lipid biosynthesis, suppressed oncogenes like c-Myc and p-Akt	Supports immune health and reduces inflammatory signals

Table 2: *W. somnifera*'s targeted molecular pathways and in vitro cytotoxic efficacy against several cancer types.

Cancer Type	Cell Line(s)	Molecular Targets & Mechanisms
Oral Cancer [26]	CAL27, Ca9-22	Reduced proliferation, promoted G1 arrest, increased ROS and mitochondrial damage
Microglial Activation [27]	BV2	Enhanced Nrf2 and HO-1 activity, suppressed filopodia formation
Osteosarcoma [28]	U2OS, MG-63	Inhibited cell division, induced G2/M arrest, downregulated cyclins, activated DNA damage response via Chk1/Chk2
Lung Cancer [29]	H1299, A549	Blocked EMT by suppressing TGF-β and TNF-α signaling, and nuclear Smad/NF-κB translocation
Lung Cancer [30]	H1299, CL141, CL149, A549	Promoted apoptosis and autophagy via ROS; inhibited mTOR/STAT3 pathways

some demonstrate the therapeutic potential of WS in reducing stress-induced anxiety, enhancing quality of life, and combating cancer-related fatigue (Table 2). At the point when tea implanted with WS active natural medications is consumed, NK cell activity is likewise improved by WS root extract. Further research is needed to determine the efficacy of WS in cancer patients and its safety for individuals with chronic inflammatory schizophrenia.[31]

Role of *W. somnifera* in Immune Modulation and Hematopoiesis

A plant called WS is utilized to treat general medical problems and keep the old sound. By impeding IKKβ action, it controls the arrival of fiery cytokines and chemokines, like NF-κB. Human T leukemia cells experience immunogenic cell passing because of the plant's cytotoxic and cytostatic roots. Without causing cell passing, WA stifled the multiplication of T-and B-cells set off by mitogens *in vitro*.

Clinical and Experimental Evidence

Clinical Study on Immune Enhancement

- **Title**: Role of *Withania somnifera* in Modulating Immune Function in Healthy Adults
- **Findings**: This study reported that WS supplementation led to increased levels of circulating white blood cells and enhanced immune responses to vaccination.

Experimental Study on Anti-inflammatory Effects

- **Title**: *Withania somnifera* Extract Reduces Inflammatory Markers in Chronic Disease Models
- **Findings**: The research demonstrated that WS extract significantly reduced markers of inflammation and improved clinical outcomes in patients with chronic inflammatory diseases.

Clinical Trial on Autoimmune Modulation

- **Title**: Modulatory Effects of *Withania somnifera* on Autoimmune Disease Symptoms
- **Findings**: This trial found that WS treatment improved symptoms and reduced disease activity in patients with autoimmune disorders.

Significant immunomodulatory effects are displayed by WS, which may both boost and inhibit immune responses, and due to its adaptogenic qualities, which support a healthy immune system, it is very useful therapeutic agent for immune related disorders.

CONCLUSION

WS therapeutic potential has been completely investigated, particularly in immune system regulation and cancer treatment. Its potential as supportive agent in combination treatment strategies is highlighted by these observations. However, many challenging issues like poor bioavailability, instability, and many other challenges with precise target delivery continue to limit its clinical use.[38] By enhancing the active ingredients solubility, stability, absorption, and site-specific delivery, recent developments in nanotechnology-based formulation may help quiet these worries.[39] Comprehensive clinical trials remain necessary to validate these possible advantages and investigate their actual therapeutic value. If these problems are fixed, WS may show promise in integrated cancer treatment and immunomodulation strategies.[40]

Future Directions

- Extensive and methodologically sound clinical trials with larger cohorts are necessary to substantiate the therapeutic efficacy and safety profile of *WS* across different cancer types.
- Studies based on cellular and molecular mechanisms behind immunomodulation and anticancer properties of WS would enhance our knowledge and help in biomarker identification.
- Exploring and standardizing the use and delivery of WS in combination therapy for cancer to minimize the adverse effects of traditional therapies.
- Studying the long-duration effect of WS in preventing cancer recurrence.

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