International Journal of Applied Ayurved Research ISSN: 2347- 6362
Published online in: https://ijaar.in

THE ROLE OF *ASHWAGANDHA* (*WITHANIA SOMNIFERA*) IN CANCER TREATMENT: A COMPREHENSIVE REVIEW

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https://doi.org/10.70057/ijaar.2025.70202

ABSTRACT

Ashwagandha (*Withania somnifera*), a prominent herb in Ayurvedic medicine, has been traditionally utilized for its wide range of health benefits, including stress reduction, cognitive enhancement, and anti-inflammatory effects. Recently, its potential in cancer prevention and treatment has garnered significant attention. This review aims to synthesize existing research on *Ashwagandha's* role in cancer therapy, focusing on its anticancer, fatigue-reducing, and immunomodulatory properties. Withaferin A, a bioactive compound in *Ashwagandha*, has demonstrated potent anticancer activity, including apoptosis induction, cell cycle arrest, angiogenesis inhibition, and modulation of critical signalling pathways such as NF-κB, PI3K/Akt, and MAPK. Studies have shown that *Ashwagandha* effectively reduces tumor growth and metastasis in preclinical models, making it a promising candidate for cancer prevention and treatment. Furthermore, *Ashwagandha* has demonstrated significant benefits in mitigating chemotherapy-induced fatigue (CRF), a major debilitating side effect in cancer patients, thereby improving their quality of life (QoL). Clinical studies have reported that *Ashwagandha* supplementation during chemotherapy results in reduced fatigue, better physical and mental well-being, and enhanced survival rates, without compromising the efficacy of conventional treatments. In addition to its anticancer and fatigue-relieving effects, *Ashwagandha* has been shown to have immunomodulatory properties, enhancing immune responses and reducing the oxidative stress caused by chemotherapy agents such as Doxorubicin and Cyclophosphamide. Through its ability to modulate immune functions, *Ashwagandha* helps mitigate the toxic effects of chemotherapy and improve overall immune system efficiency. Despite promising preclinical and clinical findings, the safety, optimal dosage, and long-term effects of *Ashwagandha* in cancer therapy remain to be fully explored. Further clinical trials are necessary to validate its therapeutic benefits and establish standardized treatment protocols. This review highlights the growing evidence supporting *Ashwagandha* as a potential adjunctive therapy in integrative oncology, offering a natural, safe, and effective approach to enhance the treatment outcomes and well-being of cancer patients.

Key words: Ayurveda, *Ashwagandha*, cancer preventive, cancer related fatigue (CRF), quality of life of cancer patient and Ashwagandha, immunomodulatory herbs

INTRODUCTION: Ayurveda, the traditional healing system of India, is globally acknowledged for its deep historical origins and time-tested medical wisdom. It is a plant-based medical system rooted in Indian literature, known for its therapeutic properties—one of the most prominent herbs being *Ashwagandha*.

Ashwagandha (*Withania somnifera*), a member of the *Solanaceae* family, is commonly referred to as Indian ginseng or Indian cherry. It has been traditionally used for over 3000 years due to its numerous health benefits, including stress management, energy enhancement, improved cognitive function, reduction of blood sugar levels, and lowered inflammation, cortisol, anxiety, and depression[1,2,3,4].

Ashwagandha is a perennial evergreen shrub that typically reaches a height of 30 to 60 cm. It flourishes in dry and arid climates, showing a preference for acidic soil conditions[5,6]. *Ashwagandha* (*Withania somnifera*) is a sturdy, grey-toned, and long-living herbaceous plant recognized for its thick, tuber-like roots. It typically features short, stout stems, broad egg-shaped leaves attached by stalks, and small greenish flowers that grow in the leaf axils and possess both male and female reproductive organs. This medicinal plant is native to and widely distributed across regions such as Africa, the Indian subcontinent (including India, Pakistan, and Afghanistan), and has also been introduced to parts of the United States due to its growing popularity in herbal medicine[5].

Metabolomic investigations of crude extracts derived from the leaves and roots of *Withania somnifera* have identified 62 primary and secondary metabolites in the leaves and 48 in the roots[7] . Among these, 29 compounds were found to be common to both plant parts, including various fatty acids, organic acids, amino acids, sugars, flavones, and sterol-related derivatives. Additionally, notable quantitative differences between the metabolic profiles of leaf and root tissues were observed[8,9].

The therapeutic potential of *W. somnifera* is largely attributed to the presence of alkaloids and lactones, particularly withanolides, which are found in varying concentrations across different parts of the plant such as roots, stems, and leaves[5] . Numerous studies have indicated that both the roots and leaves of *Withania somnifera* serve as abundant reservoirs of withanolides and structurally related phytochemicals.

According to Neetu Singh *et al.*, *Ashwagandha* exhibits anticancer properties through mechanisms such as induction of apoptosis, inhibition of cell proliferation, disruption of cell cycle progression, suppression of NF-κB activation (a key regulator of cancer cell survival), interference with signaling pathways, and modulation of protein expression involved in cancer progression[5,10,11].

Hunjie Yang and colleagues demonstrated that Withaferin A, a major biologically active constituent of *Ashwagandha*, exerts anti-cancer effects by acting on the tumor cell proteasome. This action induces programmed cell death (apoptosis) and suppresses the formation of new blood vessels (angiogenesis), thereby contributing to its tumor-inhibiting potential[12].

MATERIAL AND METHODS- All the information and data related to this review article were collected using keywords such as *"Ayurveda, Ashwagandha, cancer preventive, cancer related fatigue (CRF), quality of life (QoL) of cancer patient, and immunomodulatory herbs."* The following sources were searched for data collection: electronic scientific databases such as Google Scholar, Elsevier, PubMed, Taylor & Francis, Science Direct, and Springer. In addition, classical Ayurvedic texts including *Charaka Samhita*, *Sushruta Samhita*, and *Bhavaprakasha Nighantu*, as well as the Ayurvedic Pharmacopoeia of India, were referred for authentic Ayurvedic knowledge on *Ashwagandha*.

Mechanisms of Action and Clinical Study outcome- the article "Metabolic Alteration in Mammary Cancer Prevention by Withaferin A in a clinically relevant Mouse Model" by Hahm et al. investigates the efficiency of Withaferin A (WA), a compound found in the Ayurvedic medicine constituent *Withania Somnifera*, in preventing mammary cancer and its underlying mechanisms. The study utilized a mouse mammary tumor virus neu (MMTV-neu) transgenic model to assess the impact of WA on cancer incidence, tumor burden, and pulmonary metastasis. They found that WA administration led to a significant decrease in mammary tumor size and area, as well as reduced incidence of pulmonary metastasis[13]. Pilliyaguru et al. have found that *Withania Somnifera (WS)* contains compounds with anticancer properties, particularly *Withaferin A (WA).* These compounds can induce cell death, inhibit blood vessel formation in tumors, and modulate various cellular stress responses and further research is needed to confirm its safety and effectiveness in humans[14]. Mehta et al. explored the anti-tumor activities, including apoptosis, inhibiting cell proliferation and invasion, causing cell cycle arrest and targeting multiple oncogenic pathways. It also has anti-inflammatory and immunomodulatory effects, can inhibit angiogenesis, and may sensitize cancer cells to chemotherapy. And further clinical trials are needed to confirm its therapeutic benefits in cancer treatment [15].

Table 1: Preclinical and Clinical Studies on the Anticancer Effects of *Withania somnifera* (*Ashwagandha*)

Study	Design	Cancer Type	Outcome	Reference
Hahm et al.,[13]	Animal model (MIMTV- neu)	Mammary cancer	Reduced tumor size & pulmonary metastasis	Hahm et al.,[13]
Mehta et al.,[15]	Preclinical studies	Various cancer	Apoptosis, cell cycle arrest	Mehta et al.,[15]
Pilliyaguru et al.,[14]	In vitro studies	Breast cancer	Anti-angiogenesis, stress modulation	Pilliyaguru et al.,[14]

Chemotherapy induced fatigue and Quality of life (QoL)

Radiotherapy is employed to eliminate microscopic metastatic cells at the local or regional site, aiming to improve local disease control. Chemotherapy is typically administered using drug combinations to enhance therapeutic effectiveness. However, such combination therapies are frequently linked to adverse effects,

including leucopenia, hair loss, skin discoloration, and episodes of vomiting. Among these, fatigue stands out as one of the most debilitating yet often underreported side effects of chemotherapy[1].Among breast cancer patients undergoing chemotherapy, fatigue is the most commonly reported side effect (84%), followed by pain (75%) and nausea (25%)[17].

In Ayurvedic practice, *Withania somnifera* (WS) is utilized as either the whole plant or its root extract, and it may be prescribed independently or alongside other herbal formulations. A study by Biswal et al., titled *"Effect of Ashwagandha (WS) on the development of chemotherapy-induced fatigue and quality of life in breast cancer,"* evaluated its potential in alleviating treatment-related fatigue and improving patient well-being[16]. reported that patients in the control group had significantly higher fatigue scores compared to the study group, who also experienced a better quality of life. Furthermore, the group receiving *Ashwagandha* exhibited a greater two-year survival rate in comparison to the placebo group, with rates of 72% and 56%, respectively[1].

However, *Ashwagandha* supplementation was not consistently associated with greater improvements in stress levels, blood markers, or general well-being when compared to the placebo group. The authors noted that its stress-reducing effects might vary based on age, sex, BMI, and existing comorbidities. Further clinical studies are needed to confirm its anti-fatigue effects, as fatigue significantly affects both mental and physical health and overall quality of life. *Ashwagandha* was well-tolerated with no significant adverse effects or changes in health markers[18].

In another study, Andrade *et al.*, in their double-blind, placebo-controlled evaluation of the anxiolytic effect of an ethanolic extract of *Withania somnifera*, found that patients treated with WS root extract and chemotherapy experienced significantly less fatigue than the control group (PFSp < 0.003), along with improved quality of life (QoL) ($p = 0.0001$). Although no statistically significant difference was observed in hematological profiles or in the overall 24-month survival rate (75% in the *Withania somnifera* group versus 56% in the control group, $p = 0.174$), a trend suggesting improved survival in the group receiving *W. somnifera* alongside chemotherapy was noted. Supplementation with *Withania somnifera* has demonstrated promise in alleviating fatigue and improving the quality of life (QoL) in breast cancer patients, without compromising the safety or effectiveness of chemotherapy. Nevertheless, larger-scale clinical trials employing standardized methodologies are necessary to substantiate these preliminary outcomes[1].

Immunomodulatory Effects:

Immunity is the body's defence system against harmful invaders such as bacteria and viruses. It comprises:

1. **Innate immunity**, which provides immediate and general defence (e.g., skin, white blood cells), and
2. **Adaptive immunity**, which is a specific defence mechanism that remembers and targets particular pathogens (e.g., antibodies, T-cells).

Together, these systems protect the body from infections and diseases.

Tarique F.R. *et al.*, in their study *"Immunomodulatory Effects of Ashwagandha against Doxorubicin Toxicity,"* explored how *Withania somnifera* (WS) can mitigate the toxic side effects of doxorubicin, a chemotherapy drug. The study demonstrated that WS enhances immune responses and reduces oxidative stress in patients undergoing doxorubicin treatment. These findings suggest that WS could serve as a valuable adjunct therapy to improve patient outcomes and quality of life during chemotherapy[20].

Ramesh A. *et al.*, in their research *"Studies on Immunomodulatory Activity of Withania somnifera (Ashwagandha) Extracts in Experimental Immune Inflammation,"* found that WST (*Withania somnifera* total extract) and WS2 (a specific fraction of *Ashwagandha)* exhibited significant immunomodulatory effects. WS2 showed more pronounced activity than WST, particularly in enhancing immune responses and counteracting cyclophosphamide-induced immunosuppression. Both extracts were found to be beneficial in modulating immune inflammation[21].

Mohammad A. *et al.*, in their study *"Immunomodulatory Effect of Withania somnifera (Ashwagandha) on Cyclophosphamide-Induced Toxicity in Rats,"* reported that *Ashwagandha* significantly improved hematological parameters, boosted immune responses, enhanced macrophage function, and increased antibody production in rats. These results suggest *Ashwagandha's* potential to mitigate cyclophosphamide-induced toxicity and enhance immune function. The authors emphasized the need for further research to understand the underlying mechanisms and to evaluate the clinical applicability of WS in cancer treatment protocols[22].

M. Suresh *et al.* reported that ***Ashwagandha churna*** (a fine powder of WS root) significantly enhanced neutrophil adhesion (a type of white blood cell response) in rats at a dose of 300 mg/kg/day, indicating improved immune activity. Additionally, it increased the Delayed-Type Hypersensitivity (DTH) response at doses of 200 and 300 mg/kg/day, suggesting enhanced cell-mediated immunity[23].

Several studies have consistently shown that root extracts of *Withania somnifera* can elevate white blood cell counts in murine models and enhance the phagocytic activity of macrophages[2,2]. Additionally, the extract promotes the expression of nitric oxide synthase, leading to an increase in nitric oxide (NO) production within macrophages. In a separate investigation, *Withania somnifera* (L.) Dunal exhibited potential in down regulating immunosuppressive markers, thereby improving the response to immunotherapy. The researchers proposed that extracts from *W. somnifera* (L.) Dunal may serve as a potent immunostimulant in the treatment of lung adenocarcinoma, subject to further clinical validation[2].

Limitation and future directions:

Despite the promising anticancer and immunomodulatory effects of *Withania somnifera* (*Ashwagandha*), several limitations must be addressed to advance its clinical application in cancer therapy.

Lack of Standardization in Extracts and Dosages:

The therapeutic efficacy of *Ashwagandha* depends on the type and concentration of its bioactive compounds, such as

withanolides, which vary across plant parts, geographical locations, and extraction methods. There is a need for standardized extracts and defined dosages to ensure consistency and reproducibility in clinical outcomes[1].

Limited Large-Scale Clinical Trials:

Although several preclinical studies and small-scale trials have demonstrated its anticancer properties, there is a paucity of large-scale, randomized controlled trials (RCTs) that confirm its safety, efficacy, and optimal dosage in diverse cancer populations. Future research should focus on multicenter trials to establish its therapeutic role[5,11].

Potential Drug Interactions:

Ashwagandha's immunomodulatory and metabolic effects may interact with conventional cancer therapies, such as chemotherapy and immunotherapy. Comprehensive pharmacokinetic and pharmacodynamic studies are necessary to assess its compatibility and potential contraindications[12,22].

Long-Term Safety Concerns:

The long-term effects of *Ashwagandha* supplementation in cancer patients remain underexplored. Chronic administration might pose risks of immunological overstimulation, hormonal alterations, or other unforeseen side effects. Longitudinal studies are essential to evaluate these aspects[16.]

Understanding Mechanisms of Action:

While significant progress has been made in elucidating *Ashwagandha's* mechanisms, such as apoptosis induction, angiogenesis inhibition, and immune modulation, further molecular studies are required to fully understand its interaction with cancer-specific signaling pathways and cellular environments[13].

Exploration of Synergistic Effects:

The potential of *Ashwagandha* to enhance the efficacy of conventional therapies through synergistic effects remains a promising area of investigation. Future studies should explore its combination with standard treatments like chemotherapy, radiotherapy, and immunotherapy to maximize therapeutic outcomes[21].

Bioavailability and Delivery Mechanisms:

The low bioavailability of withaferin A and other bioactive compounds is a critical limitation. Advances in drug delivery systems, such as nanoparticles and liposomal formulations, may improve their stability, absorption, and therapeutic efficacy[6].

Future research focusing on these areas will help establish *Ashwagandha* as a reliable adjunctive therapy in integrative oncology. Comprehensive investigations and standardization will pave the way for its inclusion in evidence-based cancer care protocols.

DISCUSSION

Ashwagandha (*Withania somnifera*) exhibits promising potential as an adjunctive therapy in cancer treatment. Its key compound, Withaferin A, has demonstrated anticancer effects through apoptosis induction, inhibition of angiogenesis, and modulation of signaling pathways such as NF-κB and PI3K/Akt[15]. Clinical evidence also supports its role in reducing chemotherapy-induced fatigue and improving quality of life in cancer patients [16,21].

Additionally, *Ashwagandha* shows significant immunomodulatory activity by enhancing both innate and adaptive immunity, helping to counteract

chemotherapy-related immunosuppression [1,10]. However, challenges remain, including a lack of standardized extracts, limited large-scale clinical trials, and insufficient long-term safety data[1,5]. Future research is essential to establish its therapeutic role, optimize formulations, and validate safety for integrative oncology use.

CONCLUSION

Ashwagandha (Withania somnifera), a cornerstone of Ayurvedic medicine, has shown promising potential as an adjunct in cancer management due to its multifaceted therapeutic properties. Preclinical and clinical evidence supports its anticancer, immunomodulatory, and anti-fatigue effects, primarily attributed to bioactive compounds such as Withaferin A. *Ashwagandha* has demonstrated the ability to induce apoptosis, inhibit tumor growth and angiogenesis, modulate key signaling pathways, and reduce chemotherapy-induced fatigue, thereby improving the quality of life in cancer patients. Moreover, its immunomodulatory effects help strengthen host defenses and mitigate the toxicities associated with conventional cancer therapies.

Despite these encouraging findings, several gaps remain. The lack of standardized extracts, limited large-scale randomized clinical trials, concerns over long-term safety, and potential drug interactions warrant careful consideration. Future research should prioritize clinical validation through multicenter trials, exploration of synergistic combinations with conventional therapies, and advancements in bioavailability and delivery systems.

In conclusion, Ashwagandha holds considerable promise as a natural, safe, and effective integrative approach in oncology. With further validation, it may play a significant role in enhancing treatment outcomes and improving the overall well-being of cancer patients.

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Source of support: Nil Conflict of interest: None Declared

Cite this Article as :[The Role of Ashwagandha (Withania somnifera) in Cancer Treatment: A Comprehensive Review] *www.ijaar.in : IJAAR VOL VII ISSUE II MAY - JUNE 2025Page No:77-85*