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Role of *Withania somnifera* in Prevention and Treatment of Cancer: An Overview

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ABSTRACT
Cancer is hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Millions of people die every year with different types of cancer such as lung cancer and mesothelioma from inhaling asbestos fibers and tobacco smoke, or leukemia from exposure to benzene at their workplaces. In the last century, great advances were made in modern medical system in cure and prevent of this disease. However, success rates are very low. Withania somnifera (WS) has been used as traditional medicine for decades for the treatment of various ailments. The various parts of WS and its constituents 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, pancreatic cancer. We are conducting clinical studies to prove the efficacy of WS in prevention and treatment of different forms of cancer including prostate and lung cancers, especially in last stages, and this wonder medicinal herb is found to be beneficial in many patients. We have some cases of lung cancer that were refused modern therapy and recovered clinically and radiologically with our therapy of Ashwagandha. Clinical studies suggest its use as anti-tumor and immunomodulatory agent in sarcoma, brain cancer, uterine tumor, fibroids and other tumors including endodermal carcinoma**.** Therefore, this medicinal herb WS alone can be used as alternative medicine in the treatment of cancer patients or it can also be used as adjunct/ complimentary medicine along with chemotherapy or radiotherapy to patients. As the causative factors in formation and development of cancerous conditions can be multifactorial eg. stress- physical, chemical, biological and emotional, viral infection like Herpes cause several time more cancer of bladder, low immune syndrome plays major role in spread and causation of cancer, environmental chemical toxins, allopathic drugs, pesticide infected food with heavy metals and some not properly developed metallic preparation of Ayurvedic or other Folk Medicine can be a causative factor, leave aside genetic processes of the Individual for the development of the risk of cancer. If we look in the properties of WS like adaptogen/ anti-stress agent, immunomodulator, antioxidant (reducing free radical damage, anabolic effect, improving resistance of body, reducing fatigue and detoxificant effects, we are inclined to suggests that WS works through all above mechanisms in controlling the dreaded cancer, rather than its effect on stopping the cell division. As during radio and chemotherapy body's natural normal cells are also killed and low immunity develops, WS helps prevent these adverse effects of both and helps patients better recovery and life styles. However, multicentric long term clinical studies by oncologists, although deviated from their routine, must be carried out on WS to prove our contentions.

Keywords: *Withania somnifera*, withaferin A, colon cancer, lung cancer, blood cancer, skin cancer, breast cancer, renal cancer, fibrosarcoma, prostate cancer, pancreatic cancer.

INTRODUCTION

Cancer is hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. [1] 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. [2] In the last century, great advances were made in modern medical system in cure and prevention of this disease, but failure of treatment is common. To find out Novel and safe therapies, some scientists are exploring from traditional medicine for their anti cancerous effects. A

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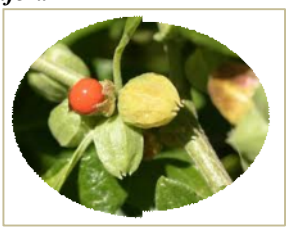
popular ayurvedic herb Ashwagandha is commonly known as "Indian Winter cherry" or "Indian Ginseng". The root smells like horse ("*ashwa*"), that is why it is called Ashwagandha (on consuming it gives the power of a horse). The species name *somnifera* means "sleep-inducing" in Latin, indicating its sedating properties. Some herbalists refer to ashwagandha as Indian ginseng, since it is used in ayurvedic medicine in a way similar to that *Panax ginseng* used in traditional Chinese medicine. This herb is commonly used in herbal formulation for its wide range of health benefits. Withaferin A (WFA), a withanolide derived from this medicinal plant, has been reported for its anti-tumorigenic activity against various cancer cells. [3] *Withania somnifera* (WS) flowers are small and green, while the ripe fruit is orange-red and has milk-coagulating properties. [4] The roots of WS are mainly used for medicinal purposes. It is cultivated in many of the drier regions of India such as Manasa, Neemuch, and Jawad tehsils of the Mandsaur District of Madhya Pradesh, Punjab, Sind, and Rajasthan. [4] The active ingredients of WS are alkaloids (isopelletierine, anaferine, cuscohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins. [5] Sitoindosides and acylsterylglucosides 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. [6] Many of its constituents support immunomodulatory actions. [7] The aerial parts of WS yielded 5-dehydroxy withanolide-R and withasomniferin-A. [8] This review presents the scientific and clinical studies conducted to evaluate the efficacy of WS in prevention and treatment of various kinds of cancer.

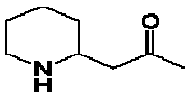
Classification of *Withania somnifera*

Kingdom	:	Plantae
Division	:	Angiosperms
Class	:	Dicotiledoneae
Order	:	Tubiflorae
Family	:	Solanaceae
Genus	:	*Withania*
Species	:	*somnifera*

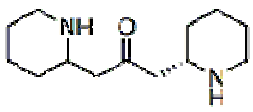


Chemical Constituents

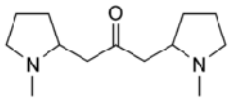
The chemical structures of some important constituents present in *Withania somnifera* (Ashwagandha) are given as under



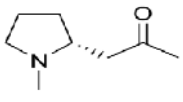
isopelletierine



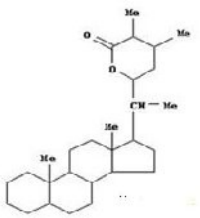
anaferine



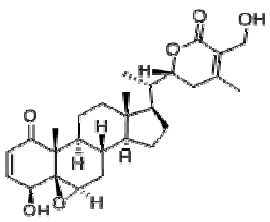
cuscohygrine



Hygrine



withanolide



Withaferin

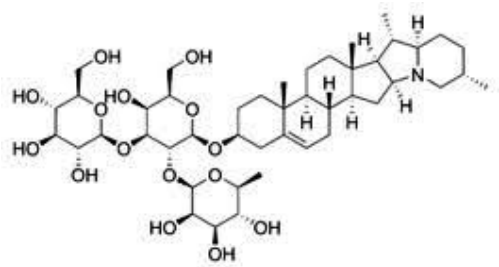


Fig. 1: Chemical Structure and active ingredients of *Withania somnifera* (Ashwagandha)

Anti- cancer activities of WS

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

Colon Cancer

Muralikrishnan *et al* (2010) observed that *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. The results of this study revealed that azoxymethane induced colon cancer and immune dysfunction was controlled by *W. somnifera*. [9] In another study, Muralikrishnan *et al* (2010) 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. [10] Koduru *et al* (2010) observed that the anticancer activity of Withaferin-A (WA), which exhibits potential for further development for targeted chemotherapy and/or chemoprevention strategies in the context of colon cancer. [11] Further, studies were conducted to isolate twelve withanolides such as withaferin A , sitoindoside IX, 4-(1-hydroxy-2, 2-dimethylcyclpropanone)-2, 3-dihydrowithaferin A, 2, 3-dihydrowithaferin A, 24, 25-dihydro-27-desoxywithaferin A, physagulin D (1-->6)-beta-D-glucopyranosyl- (1-->4)-beta-D-glucopyranoside, 27-O-beta-D-glucopyranosylphysagulin D, physagulin D, withanoside IV, and 27-O-beta-D-glucopyranosylviscosalactone B, 4, 16-dihydroxy-5beta, 6beta-epoxyphysagulin D , viscosalactone B (12) from the leaves of this species. Compounds 1-12 and diacetylwithaferin A were tested for their antiproliferative activity on NCI-H460 (Lung), HCT-116 (Colon) and SF-268 (Central Nervous System; CNS and MCF-7 (Breast) human tumor cell lines The inhibitory concentration to afford 50% cell viability (IC_{50}) for these compounds was determined by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. Withaferin A and its derivatives exhibited inhibitory concentrations (50%) ranging from 0.24 ± 0.01 to 11.6 ± 1.9µg/ml. Viscosalactone B (12) showed the 50% inhibition at concentrations ranging from 0.32 ± 0.05 to 0.47 ± 0.15µg/ml whereas its 27-O-glucoside derivative (10) exhibited IC_{50} between 7.9 ± 2.9 and 17.3 ± 3.9µg/ml. However, Physagulin D type withanolides showed either weak or no activity at 30µg/ml. Therefore, incorporation of withanolides in the diet may prevent or decrease the growth of tumors in human. [12] The study conducted to evaluate *in vitro* cytotoxicity in 50% ethanol extract of root, stem and leaves of WS against five human cancer cell lines of four different tissues i.e. PC-3, DU-145 (prostrate), HCT-15 (colon), A-549 (lung) and IMR-32 (neuroblastoma)

demonstrated that Root, stem and leaves extracts showed cytotoxicity activity ranging 0-98% depending on the cell lines but maximum activity was found in 50% ethanol extract of leaves of WS. Ethanol extract of leaves obtained from treatments T2, T3, T4 and T5 showed strong activity against PC-3 and HCT-15 with 80-98% growth inhibition, while the 50% ethanol extract of leaves from T1 treatment showed a minimum of 39% and T3 treatment showed a maximum of 98% growth inhibition against HCT-15. [13]

Lung Cancer

In vitro studies have shown that root extracts of WS exhibited cytotoxic properties against lung, colon, central nervous system, and breast cancer cell lines. [12] WS Dunal has been shown to posses tumor preventing activity against urethane induced lung- adenomas in adult male albino mice by inducing a state of nonspecific increased in resistance (Adaptogen) and immunostimulant properties. [14] Pharmacokinetic studies in mice revealed that WFA reaches peak concentrations up to 2 μM in plasma with a half-life of 1.36 h following a single 4 mg/kg dose. In a breast cancer metastasis mouse model, WFA showed dose-dependent inhibition of metastatic lung nodules and induced vimentin ser 56 phosphorylation, with minimal toxicity to lung tissue. [15] Recent studies showed that ashwagandha extract inhibited the growth of human breast, lung, and colon cancer cell lines in the laboratory. This inhibition was comparable to that achieved with the common cancer chemotherapy drug doxorubicin (Caelyx®, Myocet®). In fact, researchers reported that withaferin A, a specific compound extracted from ashwagandha, was more effective than doxorubicin in inhibiting breast and colon cancer cell growth. [12,16] In another study, the combination of paclitaxel with W. somnifera could effectively treat the benzo(a)pyrene-induced lung cancer in mice by offering protection from reactive oxygen species damage and also by suppressing cell proliferation. [17] In another study and Based on the data, the carcinogen as well as the paclitaxel , affects the immune system, the deleterious effects on the immune system is more reversible and more controllable by *W. somnifera* (L.) Dunal. These results show the immunomodulatory activity of *W. somnifera* (L.) Dunal extract, which is a known immunomodulator in indigenous medicine. [18] WS has been found to be beneficial in lung cancer. [13, 19]

Blood Cancer

Malik *et al* [20] observed that withaferin A major chemical constituents of WS, primarily induces oxidative stress in human leukemia HL-60 cells and in several other cancer cell lines and the results of these studies demonstrate that withaferinA induced early ROS generation and mitochondrial dysfunction in cancer cells trigger events responsible for mitochondrial -dependent and -independent apoptosis pathways. Another study demonstrated that Withanolide D (C4β-C5β,C6β-epoxy-1-oxo-,20β, dihydroxy-20S,22R-witha-2,24-dienolide; WithaD), a pure herbal compound isolated from WS has capability to induce apoptosis in a dose and time dependant manner both in myeloid (K562) and lymphoid (MOLT-4) cells being nontoxic to normal lymphocytes and control proliferative cells and One of the Withanolides, WithaD enhances the ceramide accumulation by activating N-SMase 2, modulate phosphorylation of the JNK and p38MAPK and induced apoptosis in both myeloid and lymphoid cells along with primary cells derived from leukemia patients. Taken together, this pure herbal compound (WithaD) may be considered as a potential alternative tool with additive effects in conjunction with traditional chemotherapeutic treatment, thereby accelerate the process of conventional drug development. [21] Oza *et al* [22] studied anticancer properties of highly purified L-asparaginase from *Withania somnifera* L. against acute lymphoblastic leukemia and observed that *W. somnifera* L. proved to be an effective and a novel source of L-asparaginase.

Skin Cancer

Scientific studies conducted in mice revealed that the roots of WS have capability to inhibit Forestomach and skin carcinogenasis in mice. [23] Mathur *et al* [24] observed that 1-oxo-5beta; 6beta-epoxy-witha-2-enolide a chemical constituent isolated from the root of WS has the potential for acting as an effective agent to prevent the incidence of skin carcinoma induced by ultra violet radiation. The chemopreventive effect of WS hydroalcoholic root extract (WSRE) on 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin cancer was investigated in Swiss albino mice and the results of the study revealed a significant decrease in incidence and average number of skin lesions in mice compared with DMBA alone at the end of Week 24. Further, a significant impairment was also noticed in the levels of reduced glutathione, malondialdehyde, superoxide dismutase, catalase, glutathione peroxidase, and glutathione S-transferase in skin lesions of DMBA-treated control mice compared with vehicle-treated mice. These parameters returned to near normal in WSRE to DMBA-treated mice. The present study reflects that WRSE possesses potential chemopreventive activity in this experimental model of cancer and the chemopreventive activity may be linked to the antioxidant/free radical-scavenging constituents of the extract. [25] Davis and Kuttan (2001) observed that administration of an extract of WS reduced two stage skin carcinogenesis induced by DMBA (dimethyl benzanthracene) and croton oil. Enzyme analysis of skin and liver showed significant enhancement in antioxidant enzymes such as GSH, GST, Glutathione peroxides and Catalases in WS treated group when compared with the control. The elevated level of lipid peroxide in the control group was significantly inhibited by WS administration. These studies indicate that WS could reduce the papilloma induced alterations by its antioxidant defense systems. [26]

Breast Cancer

Leaf extract of WS has been shown to produce antiproliferative activity on MCF-7 (breast) human tumor cell lines. [13] Different Withanolides isolated from leaves of WS namely withaferin A , sitoindoside IX , 4-(1-hydroxy-2, 2-dimethylcyclpropanone)-2, 3-dihydrowithaferin A, 2, 3-dihydrowithaferin A, 24, 25-dihydro-27-desoxywithaferin A, physagulin D (1-->6)-beta-D-glucopyranosyl- (1-->4)-beta-D-glucopyranoside , 27-O-beta-D-glucopyranosylphysagulin D, physagulin D, withanoside IV, and 27-O-beta-D-glucopyranosylviscosalactone B, 4, 16-dihydroxy-5beta, 6beta-epoxyphysagulin D, viscosalactone B from the leaves of this species. Compounds 1-12 and diacetylwithaferin A and diacetylwithaferin A were shown to produce antiproliferative activity on MCF-7 (Breast) human tumor cell lines. [12] Withaferin A (WFA), a vimentin cytoskeleton inhibitor, has been found to be a potent breast cancer anti-metastatic agent and the anti-metastatic activity of WFA is, at least in part, mediated through its effects on vimentin and

vimentin ser56 phosphorylation. [15] Withaferin A (WA), a promising anticancer constituent of Ayurvedic medicine plant WS, has been found to inhibit growth of MCF-7 and MDA-MB-231 human breast cancer cells in culture and MDA-MB-231 xenografts in vivo by causing apoptosis. In addition these studies indicate that WA functions as an anti-estrogen, and the proapoptotic effect of this promising natural product is partially attenuated by p53 knockdown and E2-ER-α. [27] WS has been found to inhibit constitutive as well as interleukin-6 (IL-6)-inducible activation of signal transducer and activator of transcription 3 (STAT3), which is an oncogenic transcription factor activated in many human malignancies including breast cancer. The IL-6-stimulated activation of STAT3 conferred a modest protection against WA-mediated suppression of MDA-MB-231 cell invasion. The results of the study indicate that WA can trigger apoptosis and largely inhibit cell migration/invasion of breast cancer cells even after IL-6-induced activation of STAT3, which should be viewed as a therapeutic advantage for this agent. [28] A novel bioactive compound withanolide sulfoxide obtained from methanol extract of WS roots has been shown to suppress human tumor cell proliferation and its IC_{50} value against human breast (MCF-7) cancer cell lines in the range of 0.74-3.63µm. In addition, S-containing dimeric withanolides were also found to completely suppress TNF-induced NF-κB activation when tested at 100µm. [29]

Renal Cancer

Yang *et al* reported that the chemical constituent Withaferin A enhanced radiation-induced apoptosis in human renal cancer cells (Caki) cells through ROS generation, down-regulation of Bcl-2 and Akt dephosphorylation. [30] In another study, treatment of Caki cells with withaferin A induced a number of signature ER stress markers, including phosphorylation of eukaryotic initiation factor-2α (eIF-2 α), ER stress-specific XBP1 splicing, and up-regulation of glucose-regulated protein (GRP)-78. In addition, withaferin A caused up-regulation of CAAT/enhancer-binding protein-homologous protein (CHOP), suggesting the induction of ER stress. Pretreatment with N-acetyl cysteine (NAC) significantly inhibited withaferin A-mediated ER stress proteins and cell death, suggesting that reactive oxygen species (ROS) mediate withaferin A-induced ER stress. Furthermore, CHOP siRNA or inhibition of caspase-4 activity attenuated withaferin A-induced apoptosis. Taken together, the present study provides strong evidence supporting an important role of the ER stress response in mediating withaferin A-induced apoptosis. [31]

Fibrosarcoma

The studies conducted on organic extracts of selected plant species, used by Palestinian traditional healers to treat different illnesses and diseases, revealed that the extract from WS presented an IC_{50} value at 24 h of 150 and 60 microg/ml, on L929sA and MCF7 cells, respectively, while the extract from *Psidium guajava* L. (Myrtaceae) presented an IC_{50} value at 24 h of 55µg/ml on MCF7 cells. Other extracts examined, like *Laurus nobilis* L. (Lauraceae) and *Salvia fruticosa* M. (Labiatae), also displayed a remarkable activity. WS extract also exhibited the strongest NFκB-inhibitory activity. [32] The chemopreventive studies of a hydro-alcoholic extract of WS roots, against 20-methylcholanthrene induced fibrosarcoma tumours in Swiss albino mice revealed that WS extract (one week before injecting 20-methylcholanthrene and continued until 15 weeks thereafter) significantly reduced the tumour incidence, tumour volume and enhanced the survival of the mice, compared with 20-methylcholanthrene injected mice. The tumour incidence was also delayed in the treatment group when compared with 20-methylcholanthrene injected mice. A significant modulation of reduced glutathione, lipid peroxides, glutathione-S-transferase, catalase and superoxide dismutase in extract treated mice compared with 20-methylcholanthrene injected mice was also recorded. These studies indicate that chemopreventive activity of WS extract may be due to its antioxidant and detoxifying properties. [33] In another study, administration of an extract from the root of the plant *Withania somnifera* (20mg/dose/animal i.p) was found to inhibit the 20-methylcholanthrene induced sarcoma development in mice and increase the life span of tumour bearing animals and inhibit the lipid peroxide formation (152 nanomoles/mg protein) ($P<0.01$) compared with control (198 nanomoles/mg protein). [34]

Prostate cancer

The study conducted to evaluate *in vitro* cytotoxicity in 50% ethanol extract of root, stem and leaves of WS against five human cancer cell lines of four different tissues i.e. PC-3, DU-145 (prostrate), HCT-15 (colon), A-549 (lung) and IMR-32 (neuroblastoma). Revealed that root, stem and leaves extracts showed cytotoxicity activity against ranging 0-98% depending on the cell lines but maximum activity was found in 50% ethanol extract of leaves of WS. Further, ethanol extract of leaves obtained from treatments T2, T3, T4 and T5 showed strong activity against PC-3 and HCT-15 with 80-98% growth inhibition, while the 50% ethanol extract of leaves from T1 treatment showed a minimum of 39% and T3 treatment showed a maximum of 98% growth inhibition against HCT-15. [35]

Pancreatic Cancer

The study conducted to investigate the efficacy and the mechanism of Hsp90 inhibition of Withaferin A (WA), a steroidal lactone occurring in WS, in pancreatic *cancer in vitro* and *in vivo* revealed that Withaferin A acts as a potent antiproliferative activity against pancreatic cancer cells in vitro (with IC_{50} of 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. [36]

DISCUSSION

Cancer is one of the major threats of modern life and is considered as the second cause of death after myocardial infarction. [37] Millions of people every year die with different types of cancer despite tremendous efforts to find methods of control and cure. Although great advances were made in modern medical science to control disease but many diseases like cancer are not yet curable fully. The underlying mechanism leading up to cancer are still unknown and cancer remains a mystery disease. Some oncologists themselves claim that cancer is not a disease, the anaerobic cell growths are meant to absorb the toxins which kill the patients. However, by surgery, chemotherapy and radiotherapy we destroy the protective mechanism and metastasis from one organ to other organ is common. Here, Andreas Moritz, 2008 in his book "CANCER IS NOT A DISEASE" has quoted

experienced oncologist Professor, Dr. Jones who says "My studies have proven conclusively that cancer patient who refuse chemotherapy and radiation actually live up to four times longer than treated cases, including untreated breast cancer cases". [38] To find out newer, safe and effective therapeutics, scientists are evaluating some medicinal plants and herbs which are a rich source of a variety of chemicals with nutritive and therapeutic properties. World-over the pharmaceutical companies and research organizations are focusing on the vast untapped potential of herbals as potent drugs.

WS is one of the most important herbs of Ayurveda (the traditional system of medicine in India) used for millennia as a Rasayana for its wide ranging health benefits. It is known as "Sattvic Kapha Rasayana" Herb. [39] It is an ingredient in many formulations prescribed for a variety of musculo-skeletal conditions (e.g., arthritis, rheumatism), and as a general tonic to increase energy, improve overall health and longevity, and prevent disease in athletes, the elderly, and during pregnancy. [40-41] WS is well known for its other biological activities like adaptogenic/anti-stress [42-44], immunomodulatory [45-46], anti-ageing [42-44, 47-48], anti-fatigue [42-44, 49], antioxidant [47, 50], anti-parkinsonism [51-52], anti-ulcerogenic [43-44], anti-tumors/adenomas [14, 35, 53], support healthy thyroid function [54]. The results of the studies described above demonstrate that WS 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. At the International Institute of Herbal Medicine (IIHM), Lucknow also we are conducting clinical studies to prove the efficacy of WS in prevention and treatment of different forms of cancer including prostate, dermatofibrosarcoma, breast cancer, fibroids of uterus, squamous cell carcinoma of penis etc. especially in last stages, and this wonder medicinal herb is found to be beneficial in many patients. [55] We have some cases of lung cancer who have been refused modern therapy and recovered clinically and radiologically with our therapy of Ashwagandha. [56] Our clinical studies suggest its use as anti-tumor and immunomodulator agent in sarcoma, brain cancer, uterine tumor, fibroids and other tumors including endodermal carcinoma. [55] Besides having an anticancer activity, it may also reduce the side effects of anticancer agents which invariable make the patient's life miserable and reduce immunity.

The extensive clinical studies conducted by us have shown that WS has capability to produce beneficial effects in variety of cancer patients. We hypothesize that this medicinal herb has capability to prevent the proliferation of cancer cells or delay the progression of cancer due to its combined multi factorial properties as described above. It may have potential to eliminate various kinds of toxins causing proliferation of cancerous cells and acts as strong detoxifying agent. Considering these beneficial actions of WS, we are giving this herb in the treatment of cancer patients in IIHM clinic. Therefore, this medicinal herb WS alone can be used as alternative medicine in the treatment of cancer patients or it can also be used as adjunct/ complimentary medicine along with chemotherapy or radiotherapy to patients. As the causative factors in formation and development of cancerous conditions can be multifactorial e.g. stress- physical, chemical, biological and emotional, viral infection like Herpes cause several time more cancer of bladder, low immune syndrome plays major role in spread and causation of cancer, environmental chemical toxins, allopathic drugs, pesticide infected food with heavy metals and some not properly developed metallic preparation of Ayurvedic or other Folk Medicine can be a causative factor, leave aside genetic processes of the Individual for the development of the risk of cancer.

If we look in the properties of WS like adaptogen/ anti-stress agent, immunomodulator, antioxidant (reducing free radical damage, anabolic effect, improving resistance of body, reducing fatigue and detoxificant effects, we are inclined to suggests that WS works through all above mechanisms in controlling the dreaded cancer, rather than its effect on stopping the cell division. As during radio and chemotherapy body's natural normal cells are also killed and low immunity develops, WS helps prevent these adverse effects of both and helps patients better recovery and life styles. However, multicentric long term clinical studies by oncologists, although deviated from their routine, must be carried out on WS to prove our contentions.

REFERENCE

1. Aggarwal BB, Ichikawa H, Garodia P, Weerasinghe P, Sethi G, Bhatt ID, Pandey MK, Shishodia S, Nair MG. From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer. Expert Opin Ther Targets 2006; 10(1): 87-118.
2. World Health Organization (2007-04-27). "WHO calls for prevention of cancer through healthy workplaces" Press release. Retrieved 2007-10-13.
3. Mayola E, Gallerne C, Esposti DD, Martel C, Pervaiz S, Larue L, Debuire B, Lemoine A, Brenner C, Lemaire C. Withaferin A induces apoptosis in human melanoma cells through generation of reactive oxygen species and down-regulation of Bcl-2. Apoptosis 2011; 16(10):1014-1027.
4. Mirjalili MH, Moyano E, Bonfill M, Cusido RM, Palazón J. Steroidal lactones from *Withania somnifera*, an ancient plant for novel medicine. Molecules. 2009; 14 (7): 2373–93.
5. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera*. (Ashwagandha): A review. Alternative Medicine Reviews 2000; 5: 334-46.
6. Bhattacharya SK, Goel RK, Kaur R., Ghosal S. Anti - stress activity of Sitoindosides VII and VIII, New Acylsterylglucosides from *Withania somnifera*. Phytother. Res. 1987; 1: 32-37.
7. Ghosal S, Srivastava RS, Bhattacharya SK, Upadhyay SN, Jaiswal AK, Chattopadhyay U. Immunomodulatory and CNS effects of sitoindosides IX and X, two new glycowithanolides form *Withania somnifera*. Phytother. Res. 1989; 2: 201–206.
8. Rahman A, Abbas S, Shahwar D, Jamal SA, Choudhary MI, Abbas S. New withanolides from Withania spp. Journal of Natural Products 1991; 56: 1000–1006.
9. Muralikrishnan G, Dinda AK, Shakeel F. Immunomodulatory effects of *Withania somnifera* on azoxymethane induced experimental colon cancer in mice. Immunol Invest. 2010; 39(7):688-98.
10. Muralikrishnan G, Amanullah S, Basha MI, Dinda AK, Shakeel F. Modulating effect of *Withania somnifera* on TCA cycle enzymes and electron transport chain in azoxymethane-inducedcolon cancer in mice. Immunopharmacol Immunotoxicol. 2010; 32(3):523-527.
11. Koduru S, Kumar R, Srinivasan S, Evers MB, Damodaran C. Notch-1 inhibition by Withaferin-A: a therapeutic target against colon carcinogenesis. Mol Cancer Ther. 2010 Jan; 9(1):202-10.
12. Jayaprakasam B, Zhang Y, Seeram NP, Nair MG. Growth inhibition of human tumor cell lines by withanolides from *Withania somnifera* leaves. Life Sci. 2003; 74(1):125-32.
13. Yadav B, Bajaj A, Saxena M, Saxena AK. *In Vitro* Anticancer Activity of the Root, Stem and Leaves of *Withania Somnifera* against Various Human Cancer Cell Lines. Indian J Pharm Sci. 2010; 72(5): 659-663.
14. Singh N, Singh SP, Nath R, Singh DR, Gupta ML, Kohli RP, Bhargava KP. Prevention of urethane induced Lung adenomas by *Withania somnifera* (L) Dunal in albino mice. Int J of Crude Research 1986; 24(2):90-100.

15. Thaiparambil JT, Bender L, Ganesh T, Kline E, Patel P, Liu Y, Tighiouart M, Vertino PM, Harvey RD, Garcia A, Marcus AI. Withaferin A inhibits breast cancer invasion and metastasis at sub-cytotoxic doses by inducing vimentin disassembly and serine56 phosphorylation. Int J Cancer 2011.
16. Anon Monograph. *Withania somnifera*. Altern Med Rev. 2004; 9(2):211-214.
17. Senthilnathan P, Padmavathi R, Magesh V, Sakthisekaran D. Chemotherapeutic efficacy of paclitaxel in combination with *Withania somnifera* on benzo(a)pyrene-induced experimental lung cancer. Cancer Sci. 2006; 97(7):658-64.
18. Senthilnathan P, Padmavathi R, Banu SM, Sakthisekaran D. Enhancement of antitumor effect of paclitaxel in combination with immunomodulatory *Withania somnifera* on benzo(a)pyrene induced experimental lung cancer. Chem Biol Interact. 2006; 159(3):180-185.
19. He QP, Ma L, Luo JY, He FY, Lou LG, Hu LH. Cytotoxic withanolides from *Physalis angulata* L. Chem Biodivers. 2007; 4(3):443-9.
20. Malik F, Kumar A, Bhushan S, Khan S, Bhatia A, Suri KA, Qazi GN, Singh J. Reactive oxygen species generation and mitochondrial dysfunction in the apoptotic cell death of human myeloid leukemia HL-60 cells by a dietary compound withaferin A with concomitant protection by N-acetyl cysteine. Apoptosis 2007; 12(11):2115-2133.
21. Mondal S, Mandal C, Sangwan R, Chandra S, Mandal C. Withanolide D induces apoptosis in leukemia by targeting the activation of neutral sphingomyelinase-ceramide cascade mediated by synergistic activation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinase. Mol Cancer. 2010; 9:239.
22. Oza VP, Parmar PP, Kumar S, Subramanian RB. Anticancer properties of highly purified L-asparaginase from *Withania somnifera* L. against acute lymphoblastic leukemia. Appl Biochem Biotechnol. 2010; 160(6):1833-1840.
23. Padmavathi B, Rath PC, Rao AR, Singh RP. Roots of *Withania somnifera* Inhibit Forestomach and Skin Carcinogenesis in Mice. Evid Based Complement Alternat Med. 2005; 2(1):99-105.
24. Mathur S, Kaur P, Sharma M, Katyal A, Singh B, Tiwari M, Chandra R. The treatment of skin carcinoma, induced by UV B radiation, using 1-oxo-5beta, 6beta-epoxy-witha-2-enolide, isolated from the roots of *Withania somnifera*, in a rat model. Phytomedicine. 2004; 11(5):452-460.
25. Prakash J, Gupta SK, Dinda AK. *Withania somnifera* root extract prevents DMBA-induced squamous cell carcinoma of skin in Swiss albino mice. Nutr Cancer. 2002; 42(1):91-7.
26. Davis L, Kuttan G. Effect of *Withania somnifera* on DMBA induced carcinogenesis. J Ethnopharmacol. 2001; 75(2-3):165-168.
27. Hahm ER, Lee J, Huang Y, Singh SV. Withaferin a suppresses estrogen receptor-α expression in human breast cancer cells. Mol Carcinog. 2011; 50(8):614-624.
28. Lee J, Hahm ER, Singh SV. Withaferin A inhibits activation of signal transducer and activator of transcription 3 in human breast cancer cells. Carcinogenesis 2010; 31(11):1991-1998.
29. Mulabagal V, Subbaraju GV, Rao CV, Sivaramakrishna C, Dewitt DL, Holmes D, Sung B,Aggarwal BB, Tsay HS, Nair MG. Withanolide sulfoxide from Aswagandha roots inhibits nuclear transcription factor-kappa-B, cyclooxygenase and tumor cell proliferation. Phytother Res. 23(7):987-992.
30. Yang ES, Choi MJ, Kim JH, Choi KS, Kwon TK. Withaferin A enhances radiation-induced apoptosis in Caki cells through induction of reactive oxygen species, Bcl-2 downregulation and Akt inhibition. Chem Biol Interact. 2011; 190(1):9-15.
31. Choi MJ, Park EJ, Min KJ, Park JW, Kwon TK. Endoplasmic reticulum stress mediates withaferin A-induced apoptosis in human renal carcinoma cells. Toxicol *In Vitro*. 2011; 25(3):692-698.
32. Kaileh M, Vanden Berghe W, Boone E, Essawi T, Haegeman G. Screening of indigenous Palestinian medicinal plants for potential anti-inflammatory and cytotoxic activity. J Ethnopharmacol. 2007; 113(3):510-516.
33. Prakash J, Gupta SK, Kochupillai V, Singh N, Gupta YK, Joshi S. Chemopreventive activity of *Withania somnifera* in experimentally induced fibrosarcoma tumours in Swiss albino mice. Phytother Res. 2001; 15(3):240-244.
34. Davis L, Kuttan G. Effect of *Withania somnifera* on 20-methylcholanthrene induced fibrosarcoma. J Exp Clin Cancer Res. 2000 Jun; 19(2):165-167.
35. Yadav B, Bajaj A, Saxena M, Saxena AK. *In Vitro* Anticancer Activity of the Root, Stem and Leaves of *Withania Somnifera* against Various Human Cancer Cell Lines. Indian J Pharm Sci. 2010; 72(5):659-663.
36. Yu Y, Hamza A, Zhang T, Gu M, Zou P, Newman B, Li Y, Gunatilaka AA, Zhan CG, Sun D. Withaferin A targets heat shock protein 90 in pancreatic cancer cells. Biochem Pharmacol. 2010; 79(4):542-551.
37. Kathy C, Bedker D, Roussel P. "Myocardial Infarction: Review of Clinical Trials and Treatment Strategies." Critical Care Nurse. 1998; 18(2):39–51.
38. Moritz A. Cancer is not a disease. 2nded. USA: Ener-Chi Wellness Press, 2008. pp. 21-23.
39. Sharma CG. Ashwagandharishta – Rastantra Sar Evam Sidhyaproyog Sangrah-Krishna- Gopal Ayurveda Bhawan (Dharmarth Trust), Nagpur, 1938, pp. 743-744.
40. Chatterjee A, Pakrashi SC. The Treatise on Indian Medicinal Plants 1995; 4:208-212.
41. Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Monographs for the Western Herbal Practitioner. Australia. Phytotherapy Press. 1996; 137-141.
42. Singh N, Agarwal AK, Lata A, Kohli RP. Evaluation of Adaptogenic properties of *Withania somnifera*. Proc Ind Pharmacol Soc. 1976, pp. 21.
43. Singh N, Agarwal AK, Lata A, Kohli RP. Experimental evaluation of 'adaptogenic' properties of *Withania somnifera*. In the Proceeding of the XIIth Scientific Seminar on Indian Medicine, Institute of Medical Sciences. Varanasi. 1977, pp. 4.
44. Singh N, Singh SP, Sinha JN, Shanker K, Kohli RP. *Withania somnifera* (Ashwagandha) A rejuvenator herbal drug which enhances survival during stress (An adaptogen). Int. J. Crude Res. 1982; 3: 29-35.
45. Singh N. A pharmacoclinical evaluation of some ayurvedic crude plant drugs as antistress agents and their usefulness in some stress diseases of man. Ann Nat Acad Ind Med. 1986; 2(1): 14-26.
46. Davis L, Kuttan G. Effect of *Withania somnifera* on cell mediated immune responses in mice. J Exp Clin Cancer Res. 2002; 21(4): 585-590.
47. Bhattacharya A, Ghosal S, Bhattacharya SK. Antioxidant effect of *Withania somnifera* glycowithanolides in chronic foodshok stress induced perturbation of oxidative free radical scavenging enzymes and lipid peroxidation in rat frontal cortex and striatum. J Ethanopharmacol. 2001; 74(1): 1-6.
48. Bhattacharya S, Satyan KS, Ghosal S. Antioxidant activity of glycowithanolides from *Withania somnifera*. Ind J Exp Biol. 1997; 35(3):236-239.
49. Singh B, Saxena AK, Chandan BK, Gupta DK, Bhutani KK, Anand KK. Adaptogenic activity of a novel withanolide-free aqueous fraction from the roots of *Withania somnifera*. Dun Phytother Res. 2001; 15(4): 311-318.
50. Kaur K, Rani G, Widodo N, Nagpal A, Taira K, Kaul SC, Wadhva R. Evaluation of the anti proliferative and antioxidative activity of leaf extract from *in vivo* and *in vitro* raised Ashwagandha. Food Chem Toxicol. 2004; 42 (12): 2015-2020.
51. Nagashayana N, Sankarankutty P, Nampoothiri MR, Mohan PK, Mohan Kumar KP. Association of M Dopa with recovery following Ayurveda medication in Parkinson Disease. J Neurol Sci. 2000; 176 (2):124-127.
52. Ahmad M, Saleem S, Ahmad AS, Ansari MA, Yusuf S, Hoda MM, Islam F. Neuroprotective effect of *Withania somnifera* on 6-hydroxydopamine indused Parkinsonism in rat. Hum Exp Toxicol, 2005; 24(3):137-147.
53. Singh SP, Singh DR, Gupta ML, Singh N, Kohli RP, An experimental Evaluation of Anti Tumor activity of *Withania somnifera* (Ashwagandha) and "Geriforte" Proc. XI Annual Conf of Ind Pharmacol Sos. 1979; 11(1):65.
54. Panda S, Kar A. *Withania somnifera* and *Bauhinia pupurea* in the regulation circulating thyroid hormone concentration in female mice. J Ethanopharmacol. 1999; 67: 233-239.
55. Singh N, Gilca M. Herbal Medicine – Science embraces tradition – a new insight into the ancient Ayurveda. Lambert Academic Publishing (Germany), 2010, pp. 51-67.
56. Singh N, Bhalla M, Jager P, Gilca M. An Overview on Ashwagandha: A Rasayana (Rejuvenator) of Ayurveda. Afr J Tradit Complement Altern Med. 2011; 8(S):208-213.