Ancient Medicine, Modern Use: *Withania somnifera* and its Potential Role in Integrative Oncology

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Abstract

Withania somnifera **Dunal, commonly known as ashwagandha, has been used for centuries in Ayurvedic medicine to increase longevity and vitality. Western research supports its polypharmaceutical use, confirming antioxidant, anti-inflammatory, immune-modulating, and antistress properties in the whole plant extract and several separate constituents. This article reviews the literature pertaining to** ***Withania somnifera*** **and its botanical constituents as antitumor agents and in conjunction with radiation and chemotherapy treatment. Following a search of MEDLINE and EBSCO databases, it can be concluded that** ***Withania somnifera*** **reduces tumor cell proliferation while increasing overall animal survival time. Furthermore, it has been shown to enhance the effectiveness of radiation therapy while potentially mitigating undesirable side effects.** ***Withania somnifera*** **also reduces the side effects of chemotherapeutic agents cyclophosphamide and paclitaxel without interfering with the tumor-reducing actions of the drugs. These effects have been demonstrated** ***in vitro*** **on human cancer cell lines, and** ***in vivo*** **on animal subjects, but there have been no human trials to date. Given its broad spectrum of cytotoxic and tumor-sensitizing actions,** ***Withania somnifera*** **presents itself as a novel complementary therapy for integrative oncology care.** ***(Altern Med Rev*** **2006;11(4):269-277)**

Introduction

Withania somnifera Dunal (WS), commonly known as ashwagandha, has been used for centuries in Ayurvedic medicine to increase longevity and vitality.[1] Western research supports its polypharmaceutical use, confirming antioxidant, anti-inflammatory, immune-modulating, and antistress properties in the whole plant extract and several separate constituents.[2] As an antioxidant, WS and active constituents sitoindosides VII-X and withaferin A (WA) have been proven to increase levels of endogenous superoxide dismutase, catalase, and ascorbic acid, while decreasing lipid peroxidation.[3-6] WS acts as an anti-inflammatory agent through inhibition of complement, lymphocyte proliferation, and delayed-type hypersensitivity.[7] The actions of WS on the immune system are subtler than simply suppressing the immune/inflammatory response. WS modulates the immune response, increasing the expression of T-helper 1 (Th1) cytokines, as well as CD4 and CD8 counts, and natural killer (NK) cell activity.[8-10] Several studies also support Withania's ability to increase circulating cortisol, decrease fatigue, increase physical performance, and decrease refractory depression in animals subjected to stress.[11,12]

Withania somnifera, however, is often underutilized in the oncology arena, despite the fact that it shows direct antitumor and cancer preventive activity. Furthermore, WS has the potential to increase tumor sensitization to radiation and chemotherapy while reducing some of the most common side effects of these conventional therapies.[13] This article evaluates

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ashwagandha's antitumor activity, explores potential mechanisms behind this action, and outlines the effects of treatment with WS and concomitant radiation and chemotherapy.

Methods

The literature review was limited to books and articles published in English and indexed on the MEDLINE and EBSCO medical databases. Keywords used in the search included: *Withania somnifera*, Dunal, ashwagandha (including alternate spellings ashwaghanda, ashwaganda, aswaganda, aswagandha), winter cherry, Indian ginseng, withanolide, glycowithanolide, withaferin, and rasayana. The results of the database search were reviewed to identify relevant articles.

Results

A total of 218 articles about *Withania somnifera* Dunal were identified using the search method outlined. Fifty-five articles pertain directly to the antineoplastic actions of the herb and confirm WS's antitumor activity or explore the effects of the herb when administered concomitantly with radiation and/or chemotherapy.

Antineoplastic Effects

Both *in vivo* and *in vitro* research attest to the cytotoxic and antitumor potential of WS. *In vitro* research has been conducted primarily using powdered WS leaf extract. In a study by Kaur et al,[14] osteogenic sarcoma and breast carcinoma cell lines were treated with 3-24 μg/mL aqueous leaf powder extract of WS. Cells treated with WS showed reduced proliferation compared to controls and assumed morphology more closely related to senescent cells. Osteogenic sarcoma and breast carcinoma cells exposed to high oxidative stress via a high-glucose medium or exposure to H_2O_2 were actually more susceptible to the effects of oxidative damage after treatment with the WS extract. This suggests WS has an antiproliferative effect, but not an antioxidant effect, on human tumor cells.

Jayaprakasam et al[15] tested 13 different constituents of WS for their antiproliferative capabilities on lung, colon, central nervous system (CNS), and breast tumor lines. A dose-dependent anti-proliferative effect was observed for 11 of 13 constituents, with lung cells showing the greatest sensitivity and colon cell lines showing the greatest resistance to treatment. WA demonstrated the greatest antiproliferative effects, with an IC_{50} of 0.24, 0.36, 0.28, and 0.27 μg/mL for lung, colon, CNS, and breast cancer cell lines, respectively. WA demonstrated more potent inhibition of colon and breast cancer lines than adriamycin, which had an IC_{50} of 0.97 and 0.36 μg/mL for colon and breast cancer, respectively. The only withanolides without antiproliferative effects were two separate physagulin D type constituents.

In vivo research on WS as an antitumor agent confirms its usefulness in slowing tumor growth and increasing survival time. Christina et al[16] inoculated Swiss albino mice with Dalton's ascitic leukemia, followed by an intraperitoneal (IP) dose of 20 mg/kg of powdered aqueous root extract of WS. Animals given WS demonstrated a cancer cell number of 0.92±0.12 x 10^6 cells, compared to 1.35±0.08 x 10^6 cells in the control group. The WS extract also significantly reduced packed cell volume and tumor weight, while increasing lifespan by 27.5 percent.

In another experiment, Prakash et al[17] induced fibrosarcoma via a subcutaneous injection of 200 μg 20-methylcholanthrene/0.01 DMSO (MCA). A hydro-alcoholic extract of WS root was administered to an experimental group of mice at a maximum dose tolerance of 400 mg/kg per oral (PO) daily, beginning one week before MCA administration and continuing 15 weeks. The WS-treated mice showed delayed onset of fibrosarcoma compared to controls, as well as significantly decreased overall incidence. Overall fibrosarcoma incidence in the control group reached 96 percent by week 15 compared to 60 percent in the WS-treated group; 88 percent of the WS-treated mice survived the experiment compared to 56 percent of the MCA-only group. Tumor volume was also significantly reduced in the WS-treated group. Prakash postulates the antineoplastic effect seen in the WS-treated mice is due to the antioxidant activity of WS. The antioxidants reduced glutathione (GSH), superoxide dismutase (SOD), catalase, and glutathione S-transferase (GST) present in the liver of WS treated mice were 1.25-, 1.52-, 1.56-, and 1.67-fold higher, respectively, than in the untreated mice.

Davis et al[18] treated Swiss albino mice with 20 mg/animal/day IP powdered WS root extract for

five days prior to and 10 weeks following inoculation with 7,12-dimethylbenzanthracene (DMBA; 470 nM in 200 μL acetone). The number of animals that developed papillomatous growth in the WS-treatment group was reduced by 50 percent, and the mean number of papillomas per animal was six in the treatment group compared to 11 in the control group. This study examined the effect of WS on antioxidants. Levels of GSH, GST, glutathione peroxidase (GPx), and catalase were significantly elevated in the liver and skin of WS-treated animals compared to the control group, while levels of lipid peroxide in the liver and skin of treated animals were significantly lower than in controls.

In a similar study, Padmavathi et al[19] also showed that Swiss albino mice treated with DMBA-induced forestomach and skin papilloma showed decreased tumor incidence and number when treated with WS powdered root extract. These results were achieved via PO doses of either 2.5- or 5.0-percent WS extracted root powder daily for two weeks prior and two weeks following DMBA inoculation.

Leyon et al[20] studied the effect of WS root powder extract and one of its constituents, withanolide D, on B16F-10 melanoma. C57BL mice were injected with melanoma cells and either pretreated or simultaneously treated with 20 mg/dose/animal/24 hours of powdered WS root extract IP or 500 μg/dose/animal/24 hours IP of withanolide D for 10 days. Simultaneous treatment with WS or withanolide D resulted in a significant reduction in tumor growth, with 122±10 and 126±9 tumors, respectively, compared to 250 in the control group; these mice also showed an increase in lifespan of 72.58 percent and 68.40 percent, respectively. Interestingly, pretreatment with WS or withanolide D did not reduce tumor number and only modestly increased overall survival time.

In vivo research has been conducted on another constituent of WS, 1-oxo-5ß,6β-epoxy-with a-2-enolide. Mathur et al[21] induced skin carcinoma in Wistar rats via one hour of ultraviolet (UV) B irradiation/day for 20 days. Animals administered 20 mg/kg IP of 1-oxo-5β,6β-epoxy-with a-2-enolide for five days prior and 12 weeks after irradiation showed no evidence of malignancy after 12 weeks, with normal epithelium and no signs of necrosis. Animals exposed only to UV B radiation demonstrated malignant cells with necrotic areas surrounded by necrotic neutrophils, lymphocytes, and histiocytes.

Antitumor Mechanisms

Withania's antitumor mechanisms are most likely multifactorial. WS exhibits both antioxidant and pro-oxidant activity. Tumor-bearing animals treated with both IP and PO doses of WS showed increased GSH, SOD, GPx, and catalase in the liver and skin.[18,19] These effects could clearly repair oxidative damage caused by tumor growth and inflammation, thus reducing the likelihood of disease progression. This antioxidant activity is enhanced by the potential of WS to up-regulate phase II liver enzymes. Padmavathi et al[19] demonstrated that Swiss albino mice fed a 2.5- and 5.0-percent Withania root extract diet showed 1.67- and 1.26-fold up-regulation of DT-diaphorase (DTD) and GST, respectively. Both are phase II liver enzymes that conjugate metabolites of cytochrome p450, which aids in liver detoxification of toxic phase I byproducts. In this study, WS did not up- or down-regulate phase I or p450 enzymes. This feature makes WS compatible with other medications, since it is not likely to affect the half-life of pharmaceutical drugs.

WS may also mitigate unregulated cell growth via the potent tumor suppressor gene p53, which regulates cell cycle proliferation. In research by Mathur et al,[21] cells from Wistar rats exposed to UV B radiation demonstrated clusters of mutated p53 proteins, a precursor to carcinogenesis. Pretreatment of an extracted constituent of WS, 1-oxo-5β,6β-epoxy-with a-2-enolide, at 20 mg/kg body weight IP for five days prior to irradiation and 12 weeks following, resulted in no mutant p53 foci. These animals showed normal dermis and skin tissue, without evidence of necrosis or carcinogenesis, suggesting a possible role for WS in conjunction with radiation.

Kaur et al[14] noted that, *in vitro*, tumor cells exposed to WS in a highly oxidized environment showed more sensitivity to oxidative stress than untreated cells, resulting in apoptosis and providing a possible mechanism of cytotoxic activity for WS. Tumors are often surrounded by increased inflammatory cells and subject to higher levels of oxidative stress. Thus, WS could act directly on these cells to decrease tumor size.

WS also appears to regulate the cell cycle in a number of ways. Singh et al[22] showed that methanol extracts of WS root at a dose of 65 μg/mL or 265 μg/mL were able to down-regulate the expression of p34cdc2, a cell-cycle regulatory protein. This protein is expressed during cellular proliferation, and down-regulation arrests the cell cycle in the G2/M transition phase. Interestingly, the extract utilized in this experiment did not contain WA, the WS constituent most often identified as having the most potent anti-neoplastic activity.

WS has also been investigated as an inhibitor of angiogenesis. Mathur et al[23] demonstrated the antiangiogenic actions of WS, inoculating leghorn chicken eggs with either vascular endothelial growth factor (VEGF) or a combination of VEGF and 10 ng of fractionated WS root powder extract. Neovascularization was significantly reduced in eggs inoculated with both VEGF and WS compared with eggs inoculated with VEGF alone. VEGF neovascularization was also significantly reduced in Swiss albino mice treated with 100 ng WS root extract in conjunction with 100 ng VEGF, administered subcutaneously. Mohan et al[24] demonstrated that WS inhibited angiogenesis *in vitro* in human umbilical vein epithelial cells (HUVEC) and *in vivo* in C57BL/6J mice treated with FGF-2 Matrigel plugs, at levels as low as 2 μg/mL. This antiangiogenic activity correlated with a reduction in nuclear factor kappaB (NF-κB) binding to the HUVEC DNA. NF-κB is a transcription factor, allowing genetic expression of inflammatory mediators. WA was identified via mass spectrometry as the most potent constituent of WS to inhibit tumor necrosis factor-alpha- (TNF-α) induced NF-κB activation, inhibiting angiogenesis at a dose of 7 μg/kg/day.

NF-κB may play a key role in the antitumor action of WS since it is activated by carcinogens, tumor promoters, and inflammatory agents. It can then proceed to impact gene expression, tumor promotion and invasion, and angiogenesis. Suppression of apoptosis can also be impacted by NF-κB. Ichikawa et al[25] investigated the varied impacts that WS's suppressive effect on NF-κB has on tumor cells. Human chronic myeloid leukemia, embryonic kidney carcinoma, breast adenocarcinoma, and murine monocyte cells were incubated with 5μmol/L of withanolide, an acetyl derivative of WA. Withanolide completely suppressed the NF-κB activation pathway in all cell lines. Withanolide, in combination with TNF-α, suppressed TNF-α-induced NF-κB activation at 5 μmol/L. This NF-κB suppression went on to block expression of pro-inflammatory cyclo-oxygenase-2 (COX2) and to enhance cytotoxicity by TNF-α and taxol. In fact, TNF-α cytotoxicity was increased from two percent to 22 percent. Furthermore, when WS was incubated with H1299 cells and TNF-α in a Matrigel invasion chamber for 24 hours, cell invasion was also suppressed. This implicates NF-κB suppression as one mechanism by which WS could decrease inflammation, enhance cytotoxicity and apoptosis of tumor cells, and decrease metastasis.

WS also exerts a beneficial effect on the immune system, which may explain some of its antitumor activity. Davis and Kuttan[26] demonstrated that 20 mg/kg body weight IP WS root powder extract for five days to balb/c mice increased the total white blood cell (WBC) count more than two-fold over controls. Even more telling was the increase in macrophage count, which increased to 76.5/200 cells compared to 31.5/200 cells in the untreated control group. Dhuley[27] went further, showing that mice treated with the tumor-inducing and macrophage-suppressing ochratoxin A (OTA), as well as WS powdered root extract at 100 mg/kg/day PO for 17 weeks, actually showed more macrophage chemotaxis than control mice not exposed to OTA at all. This immune-enhancing effect has also been demonstrated in tumor-bearing animals. Davis and Kuttan[10] observed significantly enhanced NK-cell activity in tumor-bearing mice. The peak NK-cell activity in tumor-bearing mice treated with WS was observed even earlier than in the control group. The strong immune-stimulating effect WS elicits from macrophages and NK cells can increase tumor cell surveillance and control.

Table 1 summarizes the antitumor mechanisms of Withania.

Radiation Therapy Interactions

P. Uma Devi pioneered research concerning *Withania somnifera* and radiation therapy. He showed that tumor-bearing balb/c mice given 500 mg/kg body weight IP WS for 10 days in conjunction with radiation therapy showed increased tumor regression, tumor growth delay, and increased

Table 1. Antitumor Mechanisms of Withania

Mechanism	Author	Study type	WS preparation	Cancer type	Effect
Antioxidant	Davis et al[18]	in vivo	WS root extract, 20 mg/kg/ animal, IP	DMBA-induced skin papilloma	↑GSH liver & skin ↑GST liver & skin ↑GPx liver ↑catalase liver
Antioxidant	Padmavathi et al[19]	in vivo	WS root extract, 2.5-5.0% of diet, PO	B(a)-P-induced forestomach carcinoma; DMBA-induced skin papilloma	↑SOD ↑catalase ↑GSH ↓LDH
Up-regulation of phase II liver enzymes	Padmavathi et al[19]	in vivo	WS root extract, 2.5-5.0% of diet, PO	B(a)-P-induced forestomach carcinoma; DMBA-induced skin papilloma	↑GST ↑DTD
Regulation of cell cycle proliferation	Mathur et al[21]	in vivo	1-oxo-5β, 6β-epoxy-with a-2-enolide, 20 mg/kg/body weight	UV B-induced skin carcinoma	↓p53+ foci
Regulation of cell cycle proliferation	Singh et al[22]	in vitro	WS root extract, 65-265 mcg/mL		↓concentration of p34cdc2
Increased tumor apoptosis	Kaur et al[14]	in vitro	WS leaf extract, 3-24 mcg/mL	Osteogenic sarcoma; breast carcinoma	↑sensitivity of tumor cells to H_2O_2 ↑glucose
Inhibition of angiogenesis	Mathur et al[23]	in ovo, in vivo	WS root extract 2.5-10 ng; WS root extract 100 ng		↓vascularization in presence of VEGF
Inhibition of angiogenesis	Mohan et al[24]	in vitro, in vivo	200 nM withaferin A; WS root extract and withaferin A		↓blood vessel sprouting ↓NF-κB
NF-κB suppression	Ichikawa et al[25]	in vitro	5μM/L withanolide	Chronic myeloid leukemia; embryonic kidney carcinoma; breast adenocarcinoma	↓NF-κB activation ↓COX2 expression ↑TNF-α cytotoxicity ↑taxol cytotoxicity
Enhanced immune system	Davis et al[26]	in vivo	WS root powder, 20 mg/kg/body weight, IP		↑total WBC count ↑macrophage count ↑bone marrow cellularity ↑antibody titer
Enhanced immune system	Dhuley[27]	in vivo	WS root extract, 100 mg/kg/body weight, PO		↑macrophage chemotaxis
Enhanced immune system	Davis et al[10]	in vivo	WS root powder, 20 mg/kg/body weight, IP		↑NK cell activity ↑lymphocytes ↑bone marrow cellularity

survival time compared to mice receiving radiation alone.[28] Interestingly, mice exposed to WS showed significantly decreased levels of GSH within the tumor; these levels did not stabilize up to three hours post-treatment. This echoes Kaur's[14] findings that WS enhances cytotoxicity in conditions of increased oxidative stress, possibly leading to increased cancer cell death in conjunction with targeted radiation. Similar effects were seen when Sharada et al[29] tested IP doses of WA on Swiss albino mice with Erlich ascites carcinoma. Treatment with an extract of WA combined with radiation therapy showed the most tumor growth inhibition and the longest survival for up to 120 days. The best effect was after two WA doses of 30 mg/kg body weight IP. Similar results were seen when treating B16F1 mouse melanoma with a combination of 10-60 mg/kg body weight WA given IP followed by radiation.[30] WA was most effective at delaying tumor growth and doubling time when administered one hour prior to irradiation. This was also shown to be the case with fibrosarcoma, when treated with WA, radiation, and hyperthermia.[31]

Further research by Devi et al[32] on *in vitro* V79 hamster cells demonstrated that WA at a concentration of 2.1 μM one hour before radiation increases tumor cell death in conjunction with radiation. A 10.5 μM concentration of WA resulted in maximum cell death, halting cells in the G2/M transition phase of the cell cycle four hours post-treatment. This could be related to the observation by Singh et al[22] that treatment with WS resulted in an accumulation of tumor cells halted in the G2/M phase. However, it is worth noting that Singh used a Withania extract without WA.

In addition to enhancing the effect of radiation on tumor size, WS also exhibited the capacity to mitigate some side effects of the therapy itself. Balb/c mice treated with a methanol extract of WS in conjunction with radiation therapy showed a 143.6-percent increase in bone marrow cellularity compared to mice being treated with radiation therapy alone. Animals treated with WS and radiation also maintained levels of normochromic and polychromic erythrocytes similar to those in the control group.[33]

One study by Ganasoundari et al[34] demonstrated that whole body irradiation in conjunction with WA had the unwanted effect of enhancing bone marrow sensitivity to radiation. In this study, nucleated bone marrow cells were injected into the bloodstream of Swiss albino mice, followed by whole body irradiation coupled with either 30 mg/kg^{-1} WA or 45 mg/kg^{-1} cyclophosphamide (CTX). Animals in the control group produced 11.66±0.52 spleen cell colonies compared to 4.85±0.26 cells in animals treated with irradiation alone, and 2.04±0.29 cells in animals receiving a combination of radiation and WA. This was comparable to levels seen with radiation coupled with CTX. The discrepancy in bone marrow cellularity in these two studies could possibly be explained by increased cytotoxicity of the isolated constituent WA or the fact that bone marrow cells were circulating in the bloodstream of the animals in Ganasoundari's study. Further research is needed to elucidate the effect of *Withania somnifera* and withaferin A on bone marrow cellularity.

Chemotherapy Interactions

Davis and Kuttan have extensively studied *Withania somnifera* in conjunction with chemotherapeutic treatment with cyclophosphamide. Swiss albino mice treated with both 25 mg/kg body weight CTX and an extract of powdered WS root at a dose of 20 mg IP experienced less leucopenia than those treated with CTX alone. Initially, both groups experienced a decrease in WBC count, but the group receiving treatment with both CTX and WS saw a rebound and normalization of WBC count by day 15. By day 30, total WBC in the CTX and WS group reached 6,120 cells/mm^3 compared to 3,270 cells/mm^3 in the CTX-only group. Combination therapy with CTX and WS also resulted in a greater than two-fold increase in bone marrow cellularity. Average bone marrow cellularity in CTX-treated mice was 5.6 x 10^6 cells on day 11, while animals treated with both CTX and WS had an average of 13.1 x 10^6 cells. Body weight was increased in animals treated with CTX and WS compared to weight loss observed in the CTX-only group, which is partially due to increase in size of the spleen and thymus in animals treated with CTX/WS. Enhanced digestive function may also be a factor, since animals treated with CTX alone demonstrated blunted and necrotic intestinal villi, while animals treated with CTX/WS maintained completely normal villous architecture.[35]

Davis et al[36] demonstrated that WS at 20 mg/day IP for five days combined with CTX mitigated CTX-induced urotoxicity in mice. The bladders of animals treated with CTX alone demonstrated severe inflammation, discoloration, and areas of necrosis, while animals treated with WS in combination with CTX maintained normal bladder architecture. Blood urea nitrogen (BUN) was elevated in the CTX group (136.78 mg/100 mL), while those treated with WS and CTX demonstrated average BUN levels of 52.08 mg/100 mL. Animals treated with WS and CTX also showed an elevation in kidney and liver glutathione levels.

Withania increased cytokine production in combination with CTX. Interferon gamma (IFN-γ), interleukin-2 (IL-2), and granulocyte macrophage-colony stimulating factor (GM-CSF) are often suppressed with CTX treatment; WS administered with CTX reversed these declines. Balb/c mice treated with a combination of CTX and WS had IFN-γ, IL-2, and GM-CSF levels of 74 pg/mL, 7.5 pg/mL, and 35.47 pg/mL, respectively, compared to 30 pg/mL, 4.5 pg/mL, and 19.12 pg/mL, respectively, in mice administered CTX alone. Meanwhile, mice treated with WS had significantly lower levels of TNF-α than mice treated with CTX,[37] which correlates with the potential for Withania to block NF-κB.

Most importantly, the immuno-stimulatory and myelo-protective effects of WS have not been shown to interfere with antitumor activity of CTX. An oral dose of WS showed marked immuno-stimulation and myelo-protection, without altering the effect of CTX on tumor size. In an experiment by Diwanay et al[38] balb/c mice treated with CTX showed lowered platelets, total WBCs, and hemagglutinating (HA)- and hemolytic (HL)-antibody titers. Treatment with a polar, alkaloid-free extract of WS increased WBCs and HA- and HL-antibody titers, while exerting an anti-inflammatory effect via lowered polymorphic lymphocyte numbers. Administration of WS did not alter the impact CTX treatment had on tumor size.

Table 2. Herbal Formula for Reducing Cardiotoxicity of Doxorubicin

Botanical	Plant Part Used	Amount/Dosage
Withania somnifera	Root extract	25 mg
Terminalia arjuna	Bark extract	25 mg
Emblica officinalis	Fruit extract	25 mg
Ocimum sanctum	Leaf extract	12.5 mg
Boerhaavia diffusa	Root extract	12.5 mg

Research has also been conducted on the combination of WS and paclitaxel. An oral dose of 200 mg/kg of an aqueous WS extract reduced the suppressive effects of paclitaxel on neutrophil and total WBC count. When WS was administered four days prior to and 12 days after treatment with 1 mg/kg IV paclitaxel, neutrophil counts were significantly normalized.[39] Senthilnathan et al[40] followed up this research using paclitaxel in conjunction with an oral dose of 400 mg/kg body weight WS root powder extract for four weeks to Swiss albino mice. The combination therapy resulted in lowered tumor markers, including aryl hydrocarbon chydroxylase, γ-glutamyl transpeptidase, 5'nucleotidase, and lactate dehydrogenase compared to controls. These enzymes are each associated with progressive lung damage due to lung cancer, while decreasing levels are associated with a positive response to therapy. Body and lung weights were brought within the normal range after combination therapy with WS and paclitaxel. WS in conjunction with paclitaxel also normalized mitochondrial enzymes and tricarboxylic acid cycle enzymes in the liver and lungs.[41]

Finally, there is limited research exploring the possibility of mitigating doxorubicin (DXR) cardiotoxicity through utilization of an herbal formula (CardiPro) that includes 25 mg WS root extract (Table 2). Mohan et al[42] treated mice with 4 mg/kg body weight of DXR in conjunction with oral CardiPro 150 mg/kg body weight twice daily for seven weeks. Animals receiving combination therapy demonstrated less ascites and a halving of mortality rate. Moreover, the cardiotoxicity of DXR was also mitigated, with

animals receiving the herbal formula showing higher GST and SOD in the myocardium, as well as lower levels of lipid peroxidation. Research is warranted to establish whether WS alone could act as a cardioprotective therapy in conjunction with DXR.

Conclusion

As modern medicine continues to expand, so do the uses of botanical medicines. *Withania somnifera* shows great potential as a safe and effective antineoplastic agent. More research is needed to determine if *Withania somnifera* can duplicate this activity in humans, and to determine an optimal dosage range for achieving these effects. The potential beneficial effects of Withania in conjunction with radiation and chemotherapy treatment speak to its potential role in integrative oncology care. Experienced natural medicine practitioners, working hand-in-hand with oncologists, could increase effectiveness and decrease side effects of conventional treatments with the use of *Withania somnifera*.

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