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THE THERAPEUTIC ROLE OF *WITHANIA SOMNIFERA* IN CANCER MANAGEMENT: A META-ANALYTICAL PERSPECTIVE

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ABSTRACT

Withania somnifera (WS), also known as Ashwagandha, is an herb that has been utilized in traditional Indian medicine since the time of Ayurveda. According to studies on WS and its chemical components which include Withaferin A, Withanolide D and others, is useful in both the prevention and treatment of various cancers, including those of the colon, blood, lung, skin, breast, renal, fibrosarcoma, prostate, pancreatic, and other types by inhibiting the growth and spread of cancer cells, regulating cell cycle markers, and modifying haematological, biochemical, and physiological variables, malignant melanoma, and biochemical variables, cell cycle marker regulation, etc. Since low immunity and the body's original normal cells are both destroyed during radiotherapy and chemotherapy thus patients can use this medicinal herb WS as an alternative treatment for cancer or in conjunction with chemotherapy or radiation therapy as an adjunctive or complementary treatment. WS aids in preventing these negative effects and promotes better healing and lifestyles for patients.

KEYWORDS: *Withania somnifera*, Ayurveda, Cancer, Withaferin A, Withanolide D.

INTRODUCTION

Cancer is a deadly disease which is characterized by apoptosis dysregulation, invasion, transformation and metastasis **Shah et al., (2018)**. Cancer results in significant suffering and financial loss on a global scale. Despite significant advancements in cancer treatment, the incidence and mortality rates for the majority of cancer types continue to be high **Jayaprakasam et al., (2003).** Cancer is caused by Multiple changes by a direct interaction

between hazardous substances and DNA and chromosomal mutations. Different cancer types exhibit altered oncogene and tumour suppressor gene expression. As a result, the tumour cells themselves emit growth signals that cause unchecked proliferation, resistance to antigrowth signals and apoptosis suppression **Turrini et al., (2016).** Surgery, radiation, chemotherapy, and targeted therapy are some of the therapeutic techniques that are available for cancer. Radiotherapy and chemotherapy have negative side effects on nearby healthy cells and affect the patient's quality of life **Shah et al., (2018)**. Despite advancements in the field of anticancer research, the current standard therapeutic regimen is still based on conventional cytotoxic chemotherapy. This is distinguished by a higher inherent toxicity, primarily because of its low cancer cell selectivity. Additionally, the capacity of cancer cells to acquire medication resistance represents a significant issue in cancer treatment **Rivera et al., (2010).**

Ayurveda is an ancient medical system in which different diseases are treated with the help of natural ingredients **Garodia et al., (2007).** Ayurveda is a medical system that deals not only with the body but with the mind and spirit as well. According to ayurveda, most diseases are connected with the psychophysiologic and pathologic changes in the body which are caused by imbalance in three different dosha (ie, vata, pitta, and kapha) **Chopra et al., (2002).** According to ayurveda, cancer develops by lifestyle choices that contribute to vata imbalances, such as eating unhealthily, maintaining poor cleanliness, or acting badly which damages the inner layer of the dermis, which is the skin's sixth layer, and the development of blood vessel branches that are aberrant. **Garodia et al., (2007).** When compared to synthetic pharmaceuticals, plants have an advantage due to their greater molecular diversity, which is important given the necessity to provide novel medications to the market and the modifications in cellular function that follow are more complex. The biodiversity and plant resources are frequently the foundation for the creation of synthetic medications that exhibit a variety of characteristics, chemical structures and undiscovered physicochemical processes properties **Rai et al., (2016).**

WS is an ancient medicinal plant, also known as Ashwagandha, Indian ginseng and Indian winter cherry **Singh et al., (2011).** WS is a small herb seen throughout India, has been recommended for the treatment of aphrodisiac, liver tonic, antiinflammatory agent, astringent, and more recently to treat bronchitis, asthma, ulcers, emaciation, insomnia, and senile dementia etc. Ashwaganda's chemopreventive properties make it a potentially useful adjunct for the cancer patients undergoing radiation and chemotherapy **Verma et al., (2011).**

WS is a green shrub from the Solanaceae family that can be found in all of the drier regions of India, Balochistan, Pakistan, Afghanistan, Sri Lanka, the Congo, South Africa, Egypt, Morocco, and Jordan. It is commonly cultivated in the Indian provinces of Madhya Pradesh, Uttar Pradesh, the plains of Punjab, and the country's northwest, including Gujarat and Rajasthan **Kulkarni et al., (2008**). It is a tiny woody shrub that grows up to two feet. **Gupta et al., (2007).** The fruit of this plant has a vivid red colour and is picked in the late autumn, and the seeds are dried for spring sowing. It is a rather simple plant to grow and needs a warm, protected spot in full sun as well as well-drained. It has a distinctive smell, tastes bitter, and is acrid. The entire plant, including the leaves, roots, stem, green berries, fruits, seeds, and bark, is used for therapeutic purposes, however roots are the most frequently employed component **John et al., (2014).** The powdered root of the WS plant, known as Ashwagandha churna, is frequently used to treat a range of illnesses **Palliyaguru et al., (2016).**

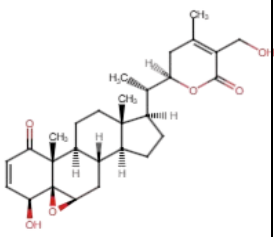
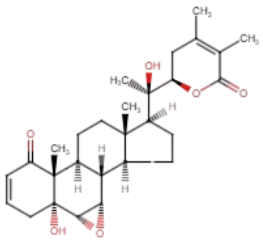
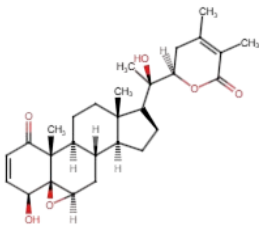
The existence of alkaloids and lactones in WS at various levels is accountable for the plant's pharmacological diversity and is associated with the variety of therapeutic uses for it. **Garodia et al., (2007).** Ashwagandha has been shown in numerous studies to have antioxidant, anticancer, antistress, anti-inflammatory, immunomodulatory, hematopoietic, anti-ageing, anxiolytic, and antidepressive rejuvenating qualities **Sharma et al., (2011)**. One of WS's main chemical components, withaferin A, has anti-arthritic, antibacterial, antimitotic, and viricide properties **Madhuri et al., (2009).** A clear picture of plant *Withania somnifera* can be seen in fig.1.

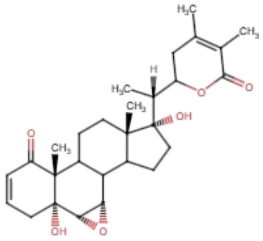
Fig. 1: Picture of *Withania somnifera* plant.

Phytochemistry of *Withania somnifera*

The plant WS is rich in various biological compounds that are distributed across different parts of the plant. The most prominent of these compounds are C-28 steroidal lactones, triterpenoids, which are also known as withanolides. The most common are withanoid A, withanoid D. The structure of withanoids is composed of an ergostane backbone, which is characterized by a lactone ring to C-8 or C-9 side chain. Other bioactive compounds such as alkaloids, flavonoids, steroids, withanamides, withanosides, withanolide, glycosides and steroids are also found in different parts of plants Withanolides and alkaloids make up the majority of WS phytoconstituents **John et al., (2014).** In addition to these chemical components, plants also contain a significant amount of iron, withaniol, acyl steryl glucosides, starch, reducing sugar, hentriacontane, and dulcitol. They also contain a variety of amino acids, such as aspartic acid, proline, tyrosine, alanine, glycine, glutamic acid, and tryptophan **Gupta et al., (2007).** In fig. 2. Various phytochemicals and forms of cancer are shown. Withaferin-A (WA) is a powerful angiogenesis inhibitor and also seen to cause apoptosis **Kumari et al., (2015).** Important Active ingredients, their molecular formulae and their location in plant can be seen in table no. 1

Table 1: important Active ingredient, their molecular formulae and location in plant.

Sr. No.	Active Ingredient	Molecular formulae	Structure	Location	Reference
1	Withaferin A	C28H4OO6		Roots	Subramanian et al.,(1969)
2	Withanolide A	C28H38O6		Roots	Jayaprakasam et al. 2003
3	Withanolide D	C28H38O6		Roots and leaves	Palliyaguru et al.,(2016)

4	**Withanone**	**C28H38O6**		**Roots**	**Palliyaguru et al.,(2016)**

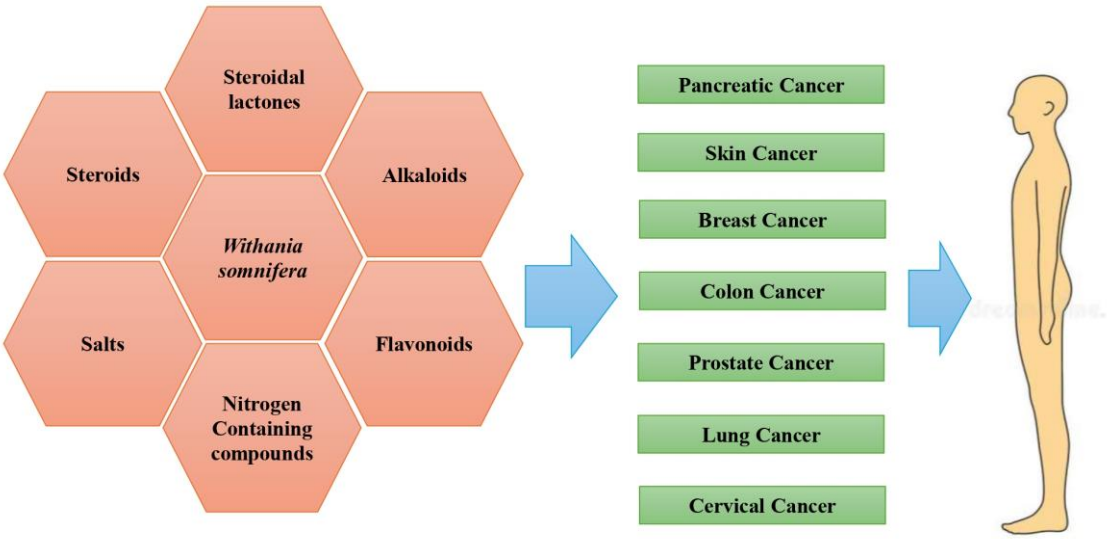


Fig. 2: Various phytochemicals and forms of cancer.

Activity of *Withania somnifera* against cancer

Numerous research has been carried out to assess the efficiency of WS in the prevention and treatment of various cancer types.

Pancreatic Cancer

One of the deadliest diseases in humans, pancreatic cancer is a significant unresolved health issue at the beginning of the twenty-first century. Prior to the disease progressing to an advanced stage, the majority of people with pancreatic cancer experience no symptoms. **Kamisawa et al., (2016).** According to research conducted both in vitro and in vivo, Withaferin A has strong antiproliferative action against pancreatic cancer cells in vitro (IC50 values of 1.24, 2.93, and 2.78µ) in the cell lines Panc-1, MiaPaCa2, and BxPc3, respectively. The study's findings show that Withaferin A binds to Hsp90, degrades Hsp90 client proteins, suppresses Hsp90 chaperone activity via an ATP-independent mechanism, and has anticancer properties against pancreatic cancer in vivo **Yo et al., (2010).** WS have steroidal lactones which show strong anti-proliferative effects in MIAPaCa2 cells. **Sarkar et al., (2014)**. In human pancreatic cancer cells, WA, greatly enhanced autophagosomes while preventing the

degradation of autophagic cargo by preventing SNARE-mediated fusion of autophagosomes and lysosomes. Apoptosis caused by ER stress was selectively enhanced by WA, which also encouraged the accumulation of ubiquitinated proteins and proteasome inhibition. Meanwhile, early-stage defective autophagy brought on by WA was probably brought on by ER stress. **Li et al., (2016).** When the synergistic effects of oxaliplatin and withaferin A (WA), on human PC both in vitro and in vivo. Through a mechanism involving mitochondrial malfunction and PI3K/AKT pathway inactivation, we discovered that WA significantly increased oxaliplatin-induced growth suppression and death in PC cells (Panc-1, MIAPaCa-2, SW1990) When compared to single drugs, combined therapy demonstrated the best anti-tumor efficacy in vivo with no discernible extra harm. These findings lend credence to the idea that oxaliplatin and WA combined therapy may help create a successful PC treatment plan**. Li et al., (2015)**. A cell-based assay method that targets GLI1-mediated transcription was used to assess the suppression of Hh signal. Six compounds were isolated from the *Withania somnifera* MeOH extract using activity-guided isolation: WA(1) and its derivatives (2–6). Hh/GLI1-mediated transcriptional activity was strongly inhibited by compounds 1 and 2m, with IC50 values of 0.5 and 0.6 lM, respectively. Human breast (MCF7), prostate (DU145), and pancreatic (PANC-1) cancer cells were all susceptible to the cytotoxic effects of compounds 1, 2, 3, and 6. **Yoneyama et al., (2015).**

Breast Cancer

Breast cancer refers to the erratic growth and proliferation of cells that originate in the breast tissue **Khuwaja et al., (2004)**. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Early diagnosis of breast cancer is one of the best approaches to prevent this disease. **Sun et al., (2017).** Approximately 6%-10% of patients have metastatic disease at the time of diagnosis and approximately 30% of patients initially diagnosed with earlier-stage breast cancer will eventually develop recurrent advanced or metastatic disease **Shaughnessy et al., (2015), Bertucci et al., (2019).** Purified from the plant *Withania somnifera*, withaferin A (WA) inhibits the vimentin cytoskeleton. The findings demonstrated that WA maintained strong anti-invasive effect at low concentrations while exhibiting mild cytotoxic and apoptotic activity at concentrations less than or equivalent to 500 nm. Vimentin depolymerization occurs quickly after perinuclear vimentin buildup. Parallel to vimentin breakdown, there was an observed rise of vimentin ser56 phosphorylation. These relationships demonstrated that the anticipated vimentin-binding region of WA is required for both the anti-invasive effect of

the compound and to cause vimentin ser56 phosphorylation. With no harm to lung tissue, WA demonstrated dose-dependent suppression of metastatic lung nodules and increased vimentin ser56 phosphorylation It infers that WFA is a strong anti-metastatic drug for breast cancer and that its effects on vimentin and vimentin ser56 phosphorylation, at least in part, mediate its anti-metastatic activity. **Thaiparambil et al., (2011).** In a concentration-dependent way, the WA treatment reduced the viability of human breast cancer cells MCF-7, which is estrogen-responsive, and MDA-MB-231, which is estrogen-independent. There was a correlation between the induction of apoptosis, which is characterized by DNA condensation and cytoplasmic fragmentation of histone-associated DNA and poly-(ADP-ribose)-polymerase cleavage. The production of Bim-s and Bim-L isoforms in MCF-7 cells and the induction of Bim-s and Bim-EL isoforms in MDA-MB-231 cells occurred concurrently with the WA-mediated apoptosis. A significant defence against WA-mediated increase of Bim expression was provided by FOXO3a knockdown. When compared to the tumors from control mice, the tumors from WA-treated mice showed higher apoptosis and decreased cell proliferation **Stan et al., (2008).** The anti-breast cancer cytotoxic evaluation with the help of WS extract was carried out using the MCF-7 cell line, and the results showed significant cytotoxic effects in a dose-dependent manner **Prasad et at., (2021).**

Three fractions A4, A5, and A6 and two extracts (WS and WS-chloroform) adversely impacted Hep2 and these were further studied pharmacologically. Cell cycle disruption and a build-up of hypoploid (sub G1) cells were identified A chickchorio-allantoic membrane (CAM) was used to examine their anti-angiogenic capability. The results showed a significant decrease of vascular endothelial growth factor (VEGF) These results imply that *Withania somnifera 's* roots have anti-angiogenic and cell cycle disruption properties, which may be a key mechanism behind their anti-cancer properties. **Mathur et al., (2004).** Desoxywithaferin A (Twelve withanolides, including with aferin A (1), sitoindoside IX (2), 4-(1-hydroxy-2, 2-dimethylcyclpropanone)-2, 3-dihydrowithaferin A (3), 2, 3, and 4, have been identified. Physagulin D (1!6), 24, 25-dihydro-27-), and dihydrowithaferin A (5)-h-D-glucopyranosyl- (1!4)From the leaves of this plant, researchers have isolated 27-O-h-D-glucopyranosylphysagulin D (7), physagulin D (8), withanoside IV (9), 27-O-h-D-glucopyranosylviscosalactone B (10), 4, 16-dihydroxy-5h, 6h-epoxyphysagulin D (11) and viscosalactone B (12). The antiproliferative effects of compounds 1 through 12 and diacetyl withaferin A (13), on the human tumour cell lines MCF-7 (Breast) were seen **Jayaprakasan et al., (2003).**

WS root extract concentrations prevent cancer spread by inhibiting EMT. Additionally, dosages of WS root extract exhibit little toxicity in typical mouse organs, indicating the possibility of therapeutic application for orally taken *Withania somnifera* root extract(WRE) capsules. **Yang et al., (2013)**. When the effects of a methanolic extract of WS leaves were studied against MCF-7, HCT116, and HepH2 cell lines, all cell lines were sensitive to the extract's potent antiproliferative effects Results from flow cytometry revealed that the extract stopped the cell cycle at the S phase and increased the caspase The extract may be able to cause cell death through a caspase-mediated route **Dar et al., (2019).**

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. **Lee et al., (2010)**

Prostate Cancer

Prostate cancer is the most frequently diagnosed malignancy in males. Prostate cancer is still the leading cause of cancer-related death in males, despite frequently taking an indolent course. **Litwin et al., (2017).** Three factors are known to increase the risk of prostate cancer Key fatty acid metabolism enzymes such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FASN), and carnitine palmitoyltransferase 1A (CPT1A) showed statistically significant decreases in protein levels in WRE-treated cells when compared to solvent control, according to Western blotting and confocal microscopy. Additionally, WRE-treated cells had lower levels of the mRNAs for ACLY, ACC1, FASN, and CPT1A than control cells. In comparison to solvent control, WRE-treated cells exhibited statistically significant reductions in protein levels of key fatty acid metabolism enzymes, including ATP citrate lyase (ACLY), acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FASN), and carnitine palmitoyltransferase 1A (CPT1A), as demonstrated by Western blotting and confocal microscopy. Furthermore, compared to control cells, WRE-treated cells exhibited reduced levels of the mRNAs for ACLY, ACC1, FASN, and CPT1A **Kim et al., (2020).**

There have been reports of WS equally significant anticancer effectiveness against prostate cancers, when its application led to metabolic. The potential of W. somnifera as a regulator of the phase G2/M cell cycle of tumor cells and its efficacy against prostate cancers are evident from the inactivation of Cdc2 catastrophe followed by cell death **Roy et al., (2013). Siddique et al., (2014)** identified a novel withanolide 5,6-de-epoxy-5-en-7-one-17-hydroxy withaferin A from W. somnifera roots and leaves. It has turned out to be more effective against breast, liver cancer, prostate and colon cancer. Five human cancer cell lines from four distinct tissues—PC-3, DU-145 (prostrate), HCT-15 (colon), A-549 (lung), and IMR 32 (neuroblastoma)—were tested for in vitro cytotoxicity in a 50% ethanol extract of WS's roots, stem, and leaves. demonstrated that the cytotoxic activity of root, stem, and leaf extracts ranged from 0 to 98%, depending on the cell lines **Yadav et al., (2010)** When combined with other anti-androgens, WA caused regressions of PC-3 xenografts in naked mice and promoted prostate apoptosis response-4 (Par-4) dependent apoptosis in prostate cancer cells. **Srinivasan et al., (2007).** We found that the half-maximal inhibitory concentration (IC50) was 10 mg/mL, which significantly reduced the viability of the cells. Although PC3 cells and prostate tissue samples had primarily high levels of IL-8 and COX-2 expression, the lowest dose of W. somnifera dramatically reduced the increased expression of these two proteins in PC3 cells throughout a 24-hour period. Furthermore, the rapid accumulation of PC3 cells demonstrated that W. somnifera extract (10 mg/mL) irreversibly stopped the cell cycle in the G2/M phase. **Balakrishnan et al., (2017).** Proinflammatory cytokines IL-6, IL-1b, chemokine IL-8, HSP70, and STAT-2 were dramatically downregulated by ashwagandha administration, whereas p38 MAPK and STAT-2 were upregulated in the opposite direction.Caspase 6, Cyclin D, PI3K, and c-myc. Additionally, the use of Ashwagandha considerably manipulated the JAK-STAT pathway, which controls both apoptosis and the signalling by MAP kinases. **Aalinkeel et al., (2010).** WA does not cause the production of ROS in normal fibroblasts, but it did in PC-3 and DU-145. WA damaged the vimentin cytoskeleton, according to immunocytochemistry and immuno-electron microscopy. **Nishikawa et al., (2015).**

Cervical cancer

One of the most frequent malignancies in women worldwide is cervical cancer. Cervical cancer is an increasing worldwide burden for both developing and developed countries. According to the World Health Organisation (WHO), high risk areas include Melanesia, Eastern, Southern, and Middle Africa. Africa in particular Cervical cancer is the primary

reason for cancer-related mortality in women in North and Central America. **Vu et al., (2018).** High-risk subtypes of the human papillomavirus (HPV) cause almost all cervix cancers and HPV screening and vaccination programmes are effective strategies in disease prevention The most typical cancers are carcinoma and adenocarcinoma., the number of histological subtypes, which is about 70% and 25%, respectively, of all cervical cancers **Cohen et al., (2019).** Apoptosis induction is regarded as a crucial stage in the biology of cancer. When ethanolic extracts of Ocimum sanctum and Azadirachta indica leaves and *Withania somnifera* roots were applied to a squamous cervical cancer cell line, SiHa, at IC50 values for 48 hours, it was found that internucleosomal DNA fragments. Following treatment with these plant extracts, the development of apoptotic bodies was also demonstrated by the examination of morphological alterations. The MTT test **Jha et al., (2012).** By suppressing HPV oncogenes and upregulating tumor suppressor proteins, WA has an effect on p53-dependent apoptosis in human cervical cancer cells. When tested against different cervical cell lines, including CaSki, HeLa, SiHa, and C33a, WA exhibits dose-dependent anticancer activity. According to the study's findings, withaferin treatment causes p53 to accumulate and downregulates the HPV E6 and E7 oncoprotein, which in turn activates a number of apoptotic markers, including Bcl2, Bax, caspase-3, and cleaved PARP.The elevated level of p34 cdc2, cyclin B1, and PCNA is linked to the G2/M cell cycle arrest, which is brought on by the The relationship between p21 cip1/waf1 and proliferating cell nuclear antigen (PCNA). Additionally, WA therapy lowers the amount of The phosphorylation of STAT3 to Tyr 705 and Ser 727 **Munagala et al., (2011).**

Colon Cancer

According to scientific research on nutrition, exercise, and cancer prevention, colorectal cancer is mostly avoidable with the right diet and other risk factors. The evidence showing that consumption of red meat, processed meat, large amounts of alcohol body fatness, abdominal fatness, and factors that increase adult height or its effects all contribute to the development of colorectal cancer. smoking, prolonged use of NSAIDs and aspirin, as well as a few colorectal disorders, genetic predispositions, and the metabolic syndrome, are recognised non-dietary risk factors for colon cancer **Labianca et al., (2010**). Wnt signalling appears to be dysregulated in a wide range of different cancers, which results in a shortened protein, in beta-catenin at critical phosphorylation sites, or, in very rare circumstances, in the axin gene. By blocking its breakdown in the absence of a Wnt signal, each of them causes beta-catenin to accumulate. The movement of beta-catenin from the nucleus to the cytoplasm,

chromosomal segregation, and mitosis have all been linked to the APC protein. The shortened protein loses these roles in colon cancers with mutant APC, which causes nuclear beta-catenin accumulation and aneuploidy **Oving et al., (2002).** In colorectal cancer cell lines HCT116 and SW480 it is demonstrated that WA inhibits the Spindle Assembly Checkpoint's (SAC) ability to initiate mitosis. WA causes apoptosis and Mad2 and Cdc20, a crucial component of the Spindle Checkpoint Complex, are degraded by proteasomes. By restoring correct anaphase initiation and maintaining a greater number of viable cells, further overexpression of Mad2 partially reverses the harmful effect of WA. According to our theory, WA kills cancer cells by delaying mitosis and then causing chromosomal instability **Das et al., (2014).** In three colon cancer cell lines HCT-116, SW-480, and SW-620, withaferin-A suppresses Notch-1 signalling and downregulates prosurvival pathways including Akt/NF-B/Bcl-2. In colon cancer cells, WA triggered c-Jun-NH2-kinase-mediated apoptosis and downregulated the levels of pS6K and p4E-BP1, two mammalian targets of rapamycin signalling subunits **Koduru et al., (2010).** Key TCA cycle enzymes such ICDH, SDH, MDH, and -KGDH were shown to have decreased activity in colon cancer-bearing mice. When W. somnifera was given to experimental mice that had been exposed to azoxymethane, these enzymes levels returned to normal. According to these findings, WS is a potential chemotherapeutic drug for the treatment of colon cancer **Muralikrishna et al., (2010).**

Lung Cancer

One of the most frequent cancer diagnoses is lung cancer. It is furthermore one of the most avoidable Smoking is the main risk factor for lung cancer. Smoking is thought to be the cause of 75–80% of lung cancer-related fatalities **Cersosimo et al., (2002**) However, very few patients with no history of smoking develop this cancer **Couraud et al., (2012**). The most common cancers are large-cell the least prevalent type, accounting for 10% to 15% of lung cancer cases. These tumours typically develop in peripheral regions at a rate similar to squamous-cell malignancies. The majority of small-cell carcinomas are 20–25% of lung cancer cases. They usually start in centralised areas and expand quickly; the increase It has been roughly 29 days.12 A Most individuals with small cell carcinomas already have metastatic illness when they are diagnosed **Zheng et al., (2016).** After using WS orally daily in a model, the haematological alterations were discovered to be fully reversible as shown by noticeably higher total leucocyte counts and lymphocyte percentages Singh **et al., (1986).** When *Withania somnifera* extract was administered to cancer-causing benzo(a)pyrene-

induced animal models. This changed the numbers of immunocompetent cells, immune complexes, and immunoglobulins. It was seen that both paclitaxel and a carcinogen have hazardous side effects that have an impact on the immune system. is more controlled and reversible thanks to *Withania somnifera* **Liu et al., (2017).** withaferin A Inhibits the development and having lethal effects on the human lung cancer cell line (NCI-H460), all three substances **Choudhary et al., (2010).** According to research, ashwagandha root extracts in ethanolic form have promising superoxide radical scavenger properties and may be cytotoxic to the A549 lung cancer cell line both the generation of ROS in cancer cells and the dose-dependent triggering of apoptosis **Nile et al., (2022).** A549 and H1299 cells' invasion, adhesion, and migration were observed to be inhibited when cells were pre-treated with WA; for both cell lines, the WA reduced TGFβ1 and TNFα-induced EMT, as well as the nuclear translocation and phosphorylation of NF-κB and Smad2/3 in H1299 and A549 cells, according to qRT-PCR, immunofluorescence, and western blot examination **Aquil et al., (2018).** WA is an effective anti-lung cancer agent and anti-lung cancer stem-like cell (CSC). The study's findings demonstrated that WA can prevent the emergence of Lung CSCs inhibit mTOR/STAT3 signaling, which lowers side population cells and prevents the formation of spheroid cells in lung cancer. Furthermore, the synergistic activity of WA and chemotherapy is crucial because it increases the lethality of cisplatin on CSC by inhibiting the viability of EGFR wild-type lung cancer cells in particular **Hyu et al., (2019).** Furthermore, Swiss albino mice were given benzo(a)pyrene to cause lung cancer, and WS root extracts reversed the levels of immune cells, inhibited cell division, and demonstrated antioxidant activity, shielding the mice from harm caused by reactive oxygen species (ROS) following the administration of paclitaxel and WS (400 mg/kg body weight) extracts together **Senthilnathan et al., (2006).**

Lung (10.6%), mouth (8.4%), prostate (6.1%), tongue (5.9%), and stomach (4.8%) were the anticipated top five cancer locations in men. The cervix (10.6%), ovary (6.2%), corpus uteri (3.7%), lung (3.7%), and breast (28.8%) were the anticipated top five cancer sites in females. While thyroid (3.6%) and gallbladder (2.7%) cancers were in the top ten among females but not among males, liver cancer (3.9%) was in the top ten malignancies in males but not in females. **Sathishkumar et al.,(2025).** Different mode of action of *Withania somnifera* on different cancer cell line can be seen in table no.2

Table 2: Tables show different mode of action of *Withania somnifera* on different cancer types.

Cancer type	Cell line	Mechanism of action
Pancreatic Cancer	Panc-1 MiaPaCa2 and BxPc3 MIAPaCa2 Panc-1, SW1990, MIAPaCa-2, AsPC-1 and BxPc-3 Panc-1, MIAPaCa-2, SW1990 PANC-1	Hsp 90 degradation anti-proliferative effects enhanced autophagosomes by preventing SNARE-mediated fusion of autophagosomes and lysosomes oxaliplatin-induced growth suppression and death in PC cells. Inhibition of Hedgehog (Hh) signaling system
Breast Cancer	MCF-10A MCF-7 Hep2 MCF- MDA-MB-231, MCF-7 and T47D MCF-7, HCT116, and HepH2 MDA-MB-231	Inhibits the vimentin cytoskeleton Induction of Bim-s and Bim-EL isoforms Cytotoxic effect Decreased vascular endothelial growth factor (VEGF) Antiproliferative effects Inhibiting EMT Cell cycle inhibition Inhibit the activator of transcription 3 (STAT3)
Prostate Cancer	PC-3 PC-3 and DU-145 PC-3 and DU-145	Par-4-dependent apoptosis G2/M arrest cytotoxicity activity
Cervical Cancer	CaSki, HeLa, SiHa, and C33a, SiHa	decreased pro-caspase 3/Bcl2 and p53 expression apoptosis
Colon Cancer	HCT116 and SW480 HCT-116, SW-480, and SW-620,	apoptosis and Mad2 and Cdc20, suppresses Notch-1 signalling and downregulates prosurvival pathways including Akt/NF-B/Bcl-2.
Lung Cancer	A549 A549 and H1299 CSC	generation of ROS in cancer cells and the dose-dependent triggering of apoptosis reduced TGFβ1 and TNFα-induced EMT, inhibit mTOR/STAT3 signaling

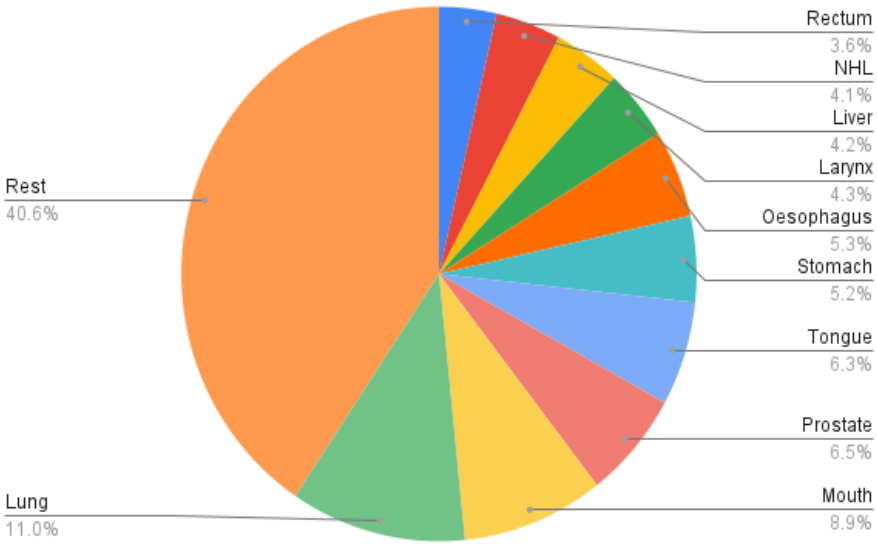


Fig. 3: Estimated percentage of India's top 10 cancer locations by sex, males, 2024.

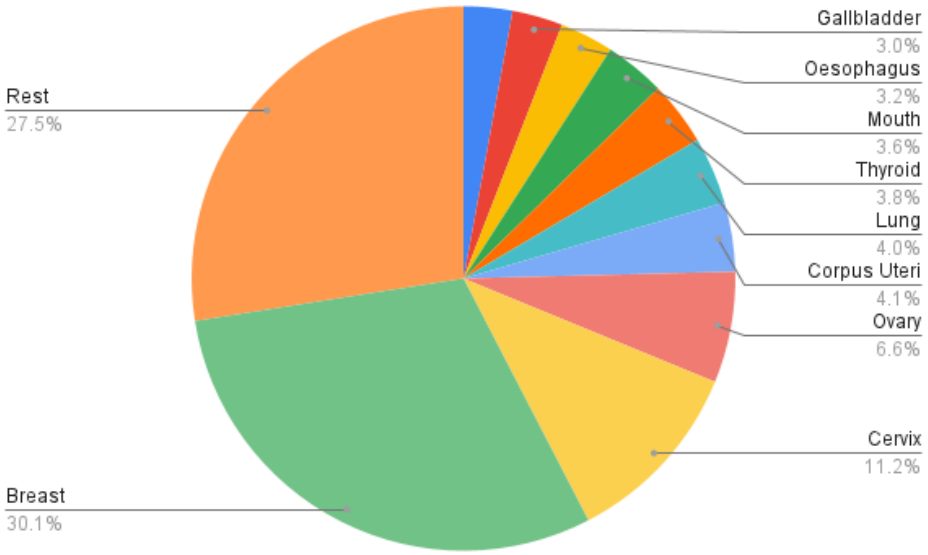


Fig. 4: Estimated percentage of India's top 10 cancer locations by sex, females, 2024.

CONCLUSION

In conclusion, cancer is a devastating disease characterized by dysregulation of apoptosis, invasion, transformation, and metastasis. It causes significant suffering and financial loss worldwide, and despite advancements in treatment, incidence and mortality rates remain high for most cancer types. Current therapeutic techniques such as surgery, radiation, chemotherapy, and targeted therapy are available, but they often have negative side effects and impact the patient's quality of life. Conventional cytotoxic chemotherapy, despite being the standard treatment, has limitations due to its toxicity and the development of drug

resistance by cancer cells. Ayurveda, an ancient medical system, treats various diseases using natural ingredients and considers the mind, body, and spirit in its approach. *Withania somnifera* has been used in Ayurveda for various purposes and has shown therapeutic potential in clinical trials and animal research for anxiety, cognitive and neurological disorders, inflammation, and even as an adjunct for patients undergoing radiation and chemotherapy. Derivative of this plant, has demonstrated anti-tumorigenic activity like Par-4-dependent apoptosis, Cell cycle arrest, cytotoxicity, ROS generation, Anti - proliferative properties etc against different cancer cells Overall, the integration of traditional medical systems like Ayurveda and the exploration of natural compounds from plants like *Withania somnifera* hold promise for advancing cancer treatment and addressing its associated challenges. However, multicentric long-term clinical studies by oncologists on WS are required to support our claims.

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