PIECUCH, Dawid, SOBOTA, Weronika, ZWOLIŃSKI, Michał, PISKORZ, Przemysław, HAŃCZYK, Edyta, ZEMSTA, Katarzyna and KULESZA, Bartłomiej. Ashwagandha (Withania somnifera) in Cancer Therapy: Anticancer Activities and Their Mechanisms. Quality in Sport. 2024;32:56016. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.32.56016
https://apcz.umk.pl/QS/article/view/56016

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.10.2024. Revised: 13.11.2024. Accepted: 14.11.2024. Published: 15.11.2024.

Ashwagandha (Withania somnifera) in Cancer Therapy: Anticancer Activities and Their Mechanisms

SOBOTA Weronika[1*], PISKORZ Przemysław[2] PIECUCH Dawid[3], HAŃCZYK Edyta[4], ZWOLIŃSKI Michał[5], ZEMSTA Katarzyna[6], Dr KULESZA Bartłomiej[7]

[1*] Faculty of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland
werasobota@gmail.com
https://orcid.org/0009-0000-7778-7030
[2] Faculty of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland
przemekpiskorz95@o2.pl
https://orcid.org/0009-0000-9812-2230
[3] Faculty of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland
dawsid1999@gmail.com
https://orcid.org/0009-0006-8074-0122
[4] Faculty of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland
edyta.hanczyk25@gmail.com
https://orcid.org/0009-0003-2769-943X
[5] Faculty of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland
michzal714586@gmail.com
https://orcid.org/0009-0008-5093-5337

[6] Faculty of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland
k.zemsta99@gmail.com
https://orcid.org/0009-0005-8336-2094
[7] KUL, The John Paul II Catholic University of Lublin; Lublin, Poland
kuleszabartek88@gmail.com
https://orcid.org/0000-0002-9973-9571
***correspondence:** dawsid1999@gmail.com

Keywords: Ashwagandha, cancer, immunomodulation, herbs

Abstract:
Cancers are characterized by rapid development of abnormal cells that multiply uncontrollably, leading to invasive tumors. By 2040, new cancer cases worldwide are expected to reach 30.2 million. In response, research focuses on the anti-cancer properties of ashwagandha (Withania somnifera), used in traditional Indian medicine. Ashwagandha exhibits anti-inflammatory effects by modulating pathways like NF-kB, Nrf2/HO-1, JAK-STAT, MAPK, and NLRP3, reducing cancer-related inflammation. It also has strong antioxidant properties due to compounds like withanolides, increasing antioxidant enzyme activity and reducing oxidative stress, potentially lowering cancer risk. Ashwagandha extract shows cytotoxic effects against cancer cells, inducing apoptosis and arresting cells in the resting phase, leading to DNA damage in cancer cells. It inhibits angiogenesis, the process of forming new blood vessels that supply tumors, through mechanisms such as VEGF inhibition and reduced macrophage infiltration. Additionally, ashwagandha modulates T lymphocytes and cytokine production, enhancing the immune response against cancer, and stimulates NK cell activity, crucial for controlling tumor growth and development. Supplementation with ashwagandha reduces cortisol levels and improves cognitive functions and quality of life in people experiencing stress, potentially lowering cancer risk. Research suggests ashwagandha may be a valuable addition to anti-cancer therapy, acting on various levels of cancer pathogenesis. However, further clinical studies are needed to fully understand its mechanisms of action and to evaluate its efficacy and safety in cancer treatment.

Key points:

1. This article examines various aspects of ashwagandha's potential anticancer effects, highlighting its ability to inhibit tumor growth.
2. Ashwagandha has shown the ability to modulate the immune system by affecting T lymphocytes, NK cells and cytokine production. Stimulation of this system can affect the body's defensive effectiveness against cancer cells.
3. The work highlights the potential effect of ashwagandha on stress reduction, which is important in the context of cancer risk and progression.
4. Ashwagandha shows the ability to regulate the process of apoptosis, which can lead to the elimination of cancer cells. In addition, this plant inhibits the process of angiogenesis, which is crucial in controlling the growth of cancerous tumors.

5. Ashwagandha has strong antioxidant properties, which contributes to the reduction of oxidative stress and potentially reduces the risk of cancer development.

Introduction

Cancer is a term used to describe a variety of diseases that are characterized by the rapid development of abnormal cells that multiply uncontrollably. These abnormal cells usually disturb the balance between cell proliferation and cell death, resulting in benign tumors. These tumors then develop invasive features, which can lead to further progression of the disease. According to the International Agency for Research on Cancer (IARC) report, there will be 30.2 million new cancer cases worldwide by 2040, up from 19.3 million in 2020.[1]

The search for a cancer treatment with high efficacy, minimal side effects, and safety is a subject of extensive research. This is difficult, due to the heterogeneity of cancer cells and their interactions.[2] The researchers noted the existence of many natural methods and plant sources with beneficial anti-cancer properties.

One of these is ashwagandha, also known as Withania somnifera (WS), "Indian winter cherry" or "Indian ginseng".[3] It's a plant in the Solanaceae family and is commonly used in Ayurveda, India's system of traditional medicine.[4] It is naturally native to India, but is also cultivated in other areas.[5] Its history of use in traditional Indian medicine dates back nearly 3,000 years.[6] It has been valued for centuries for its adaptogenic properties, which help the body cope with stress and maintain homeostasis. In addition, the activities shown in Table 1.

The initial experimental evidence in 1967 demonstrated that the root extract of Withania somnifera decreased the incidence of cancer in vivo, focusing the attention and interest of WS and leading researchers to investigate its anticancer activity and therapeutic potential.[7]

This article aims to review the current literature on the effects of Ashwagandha, with a particular focus on its potential anticancer benefits.

Anti-inflammatory capacity

Chronic inflammation triggers uncontrolled immune response and can lead to deoxyribonucleic acid(DNA)-damaging mutations by reactive oxygen species, nitrogen and other free radicals, which initiate cancer formation. In addition, the inflammatory response leads to the spread of cancer, its growth and resistance to drugs.[8]

It is known that anti-inflammatory drugs have a beneficial effect on cancer treatment, but their effect is limited by the side effects they cause.[9]

This is the reason why researchers began to look for other alternatives for treating inflammation that causes tumorigenesis. Withania somnifera has piqued the curiosity of researchers. It has the effect of modulating signaling pathways: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1), Janus Kinase - Signal Transducer and Activator of Transcription (JAK-STAT), mitogen-activated protein kinases (MAPK) and NOD-like Receptor Family, Pyrin Domain-Containing 3 (NLRP3) reducing tumor-associated inflammation.[10]

Heba MA Khalil et al. in a study in rats describe the effects of Ashwagandha on NF-kB and Nrf2/HO-1 pathways.[11] Vanisree Mulabagal et al. examined the modulation of NF-kB and cyclooxygenase pathways.[12]

Ravikumar Aalinkeel et al. described effects on the JAK-STAT pathway, and Abudubari Sikandan et al. on the MAPK and NF-κB pathways.[13]
Yangliu Xia et al. describe that vitapherin A contained in Ashwandhda acts on the NLRP3 pathway.[14] Researchers find Ashwagandha's anti-inflammatory effects in cancer to be an intriguing topic that requires further development and extensive testing in the future.

Antioxidant activity

Ashwagandha has strong antioxidant properties due to the main bioactive molecules[15, 16] contained in withania, namely withanosides, deoxywithastramonolide, withanolide A and withaferin A , that express strong antioxidant activity.[17] The root extract shows stronger antioxidant activity than the leaf extract.[16]
The antioxidant effect was tested on the HepG2 cancer line, there was a statistically significant increase in antioxidative activity, with an increase in the antioxidant enzymes glutathione reductase and glutathione S-transferase.[18]
In the shrimp study, a marked increase in the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase was noted, as well as an increase in the messenger ribonucleic acid (mRNA) expression of the genes responsible for the formation of these enzymes, i.e. cytoplasmic manganese superoxide dismutase (cMN-SOD), catalase (CAT) and glutathione peroxidase (GPx) genes, respectively. At the same time, there was a decrease in malondialdehyde, which is a marker of lipid peroxidation (oxidative stress).[19]
Ashwagandha has also been found to have antioxidant effects in humans.[20] It causes an increase in superoxide dismutase levels with a decrease in malondialdehyde compared to the placebo group. The antioxidant effect is very beneficial because it may reduce the risk of cancer and may have effect of reducing the effects of cellular aging.[21]

Regulation of apoptosis

Withania extract shows a strong cytotoxic effect against HepG2 cells, causing an accumulation of dead tumor cells relative to the control group. There was a significant increase in proapoptotic caspase 3, caspase 8 and caspase 9. In addition, it is suspected that it may arrest the cell in the resting phase by inhibiting cyclin D1, thus expressing an anti-proliferative effect.[18]
In addition, there may be an increase in the proapoptotic protein Bax, with a concomitant decrease in the anti-apoptotic Bcl-2. Eventually, activation of the caspase system leads to activation of caspase 3 and Poly(ADP-ribose) Polymerase (PARP), resulting in DNA damage to the cell.[22, 23] Cytotoxicity against lung and breast cancer cells, and to a lesser extent against gastric adenocarcinoma and colorectal cancer, has also been documented. In contrast, cytotoxicity against healthy cells is minimal.[15]

Inhibition of angiogenesis

Vascular endothelial growth factor (VEGF) is a mediator in the process of angiogenesis which in cancer creates new blood vessels feeding the tumor.[24]
Several mechanisms have been detected by which vitapherin A (WA) stops the process of excessive tumor angiogenesis by inhibiting VEGF function.[25]

One of these is the inhibitory effect of Sp1 (a transcription factor) binding to the VEGF promoter, as described by Prasanna Kumar S. et al.[26]
In addition, an effect on reducing macrophage infiltration and protein tyrosine kinase-2 expression has been demonstrated,[27] as well as WA's ability to bind to VEGF and inhibit its function.[28]
Ran Gao et al. investigated that WA, by directly interacting with the heterogeneous nuclear ribonucleoprotein K (hnRNP) rest domain, disrupts the binding between hnRNP-k and single-stranded DNA (ssDNA). This leads to blockage of hnRNP-k function and inhibition of VEGF expression.[29]
Royce Mohan et al. investigated that Ashwaghanda also has anti-angiogenic effects in vivo.[30]
Anand Setty Balakrishnan et al. described that administration of Withania somnifera extract attenuates the expression of interleukin-8 and cyclooxygenase-2 (COX-2), thereby inhibiting angiogenesis and thus the spread and growth of the tumor in a study.[31]
The use of anticancer therapy focused on blocking angiogenesis results in a reduction in metastasis formation and tumor cell growth.[22]
In light of the anti-angiogenic mechanisms involved in vitapherin A, there is justification for continuing research into its efficacy and considering its potential use in oncological treatment.

Effects of ashwaganda on the immune system
In recent years, there has been increasing interest in researching the effects of ashwaganda on the development and progression of cancer. One of the key aspects is its ability to modulate the immune system.

T-lymphocyte modulation and cytokine production
T lymphocytes play a key role in anti-tumor immunity by recognizing, destroying and controlling cancer cells. Their activation and function are essential for the effective elimination of tumors and the maintenance of immune control of disease progression.[32]
Numerous studies have suggested that ashwagandha may affect the population of T lymphocytes, including cluster of differentiation 4 positive (CD4+) and cluster of differentiation 8 positive (CD8+) T cells, which may contribute to enhancing the immune response against cancer. T lymphocytes play an important role as mediators of cellular cytotoxicity and regulate immune responses through the secretion of cytokines.[33]
Cytokines play a key role in intercellular communication in the immune system. Ashwagandha shows the ability to modulate the production of cytokines such as interferons, interleukins and tumor necrosis factor (TNF). These substances regulate immune responses, and their balance is important in the context of fighting cancer.[34]

NK cell activation and gene expression
Natural killer (NK) cells are an important component of the anti-tumor immune response, acting both by directly destroying tumor cells and by regulating other immune cells. Their activation and function are crucial for the effective control of tumor growth and development.[35] Analyses of scientific studies, conducted mainly on animals by a number of scientific teams in recent years, indicate that the vitamin A contained in ashwaganda

stimulates the activation of NK cells, thereby enhancing the anti-tumor, inhibitory and anti-progression effects of, for example, prostate tumors,[36] breast cancer,[37] and ovarian cancer.[38]
Studies suggest that ashwagandha may regulate the expression of genes related to immune system function. Their modulation may affect various aspects of the immune response in the context of cancer.[39]
From research to date, the potential use of ashwagandha as an adjunctive therapy for cancer treatment by stimulating the immune system and improving the body's response to cancer cells is apparent. However, further research is needed to better understand ashwaganda's mechanisms of action and its effectiveness in cancer therapy.
A summary of ashwagandha's anti-cancer mechanisms is included in Figure 1.

Impact of stress on cancer

Stressful situations have been proven to be significantly associated with a high risk of cancer.[40] Stress affects tumorigenesis through activation of the hypothalamic-pituitary-adrenal (HPA) axis, deregulation of sympathetic nerve signaling (SNS), inflammation and decreased cellular immunity.[41]
The HPA and SNS axis play an important role in all stages of cancer - initiation, growth and progression.[42] Under stressful conditions, the HPA axis is activated, adrenocorticotropic hormone is released, stimulating the adrenal glands to release catecholamines (CAT). The SNS axis stimulates the release of norepinephrine in the bloodstream.[43] Also cortisol is involved in tumor growth and metastasis formation.[41]
Under severe stress, CATs activate β-adrenergic receptors on tumor cells, increasing the expression of matrix metalloproteinases and VEGF in adipose tissue, which is responsible for the formation of new blood vessels.[42] They enhance cancer cell proliferation and prevent apoptosis. They influence the induction of DNA damage and regulation of gene expression by the β-adrenergic receptors/cyclic adenosine monophosphate/protein kinase A (β-ADR/cAMP/PKA) signaling cascade.[44]
Excess CAT inhibits the activity of macrophages, helper T cells and NK cells, which is responsible for the suppression of cellular immunity.[41]
Alex B. Speers and colleagues published a meta-analysis in 2021 on the effects of ashwaganda on stress and neuropsychiatric disorders. Supplementation led to significant reductions of serum cortisol levels, as well as improved scores on questionnaires assessing stress, depression and anxiety.[45]
A team of researchers led by A. Remenapp confirmed that 30 days of Ashwagandha supplementation resulted in improvement in cognitive abilities, reduction in feelings of stress/anxiety, depressive disorders, eating cravings and cortisol levels compared to the placebo group. Moreover, they noted that Central Nervous System (CNS) vital signs such as cognitive flexibility, visual memory, reaction time, psychomotor speed and executive functioning also improved.[46]
Muhammed Majeed et al. in 2023 published the results of their randomized, double-blind, placebo-controlled study, in which they proved that Ashwagandha root extract (ARE-500 mg) standardized to 2.5% vitanolides can effectively reduce stress levels and reduce anxiety in people experiencing mild to moderate stress. This occurs by decreasing cortisol levels and

increasing serotonin levels. The formula also improves cognitive function and the subjects' quality of life.[47]

The results of the presented study suggest that Ashwagangha positively affects CNS function and reduces stress, which is important in the onset and progression of cancer.

Further research into the effects of Ashwagandha on the course of carcinogenesis can undoubtedly contribute to better control of the molecular mechanisms responsible for cancer development. This will possibly contribute to the development of new methods of anticancer prevention and the development of more effective therapies.

Conclusions

Cancer is a huge health challenge worldwide, and future projections suggest an increasing number of cases. In response to the need for effective and safe cancer treatments, researchers have turned their attention to the potential anticancer properties of ashwagandha. Analyzing various aspects of ashwagandha's effects, a number of promising results are visible. The plant exhibits anti-inflammatory effects by modulating inflammation-related signaling pathways, which may be important in fighting cancer. In addition, ashwagandha has strong antioxidant properties, which contributes to the reduction of oxidative stress and may reduce the risk of cancer development.

Studies also indicate ashwagandha's potential to regulate the process of apoptosis, which can lead to the elimination of cancer cells. In addition, the plant has shown the ability to inhibit angiogenesis, which is an important factor in controlling the growth of cancerous tumors and reducing their metastasis. Another important aspect is ashwagandha's effect on the immune system, including modulation of T lymphocytes, activation of NK cells and regulation of cytokine production. Stimulation of the immune system may increase the body's defensive effectiveness against cancer cells. In addition, ashwagandha shows potential in reducing stress, which has been linked to cancer risk and progression. Research indicates that ashwagandha may enhance cognitive function and improve quality of life for individuals experiencing stress. The results of studies to date suggest that ashwagandha may be a valuable addition to the anti-cancer therapy, acting at different levels of cancer pathogenesis. However, further clinical studies are needed to better understand the mechanisms of action of this plant and to evaluate its efficacy and safety in cancer treatment.

Funding:

This Research received no external funding.

Author contributions:

All authors contributed to the article. Conceptualization: WS.; methodology: WS, PP, DP, EH; software: MZ, KZ, WS, PP,; check: EH, DP; formal analysis: BK, KZ; investigation, MZ, KZ,resources: DP, EH; data curation: PP; writing -rough preparation: WS; writing -review and editing: WS, PP, DP, BK; visualization,WS.; supervision: PP; project administration: KZ. All authors have read and agreed with the published version of the manuscript.

Conflict of Interest Statement:

The authors report no conflict of interest.

Financial Disclosure:
The study did not receive any funding.

Institutional Review Board Statement:
Not applicable.

Informed Consent Statement:
Not applicable.

Data Availability Statement:
Not applicable.

References:

1. Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Bhat JA, Akther T, Najar RA, Rasool F, Hamid A. Withania somnifera (L.) Dunal (Ashwagandha); current understanding and future prospect as a potential drug candidate. *Front Pharmacol*. 2022;13:1029123.
3. Paul S, Chakraborty S, Anand U et al. Withania somnifera (L.) Dunal (Ashwagandha): A comprehensive review on ethnopharmacology, pharmacotherapeutics, biomedicinal and toxicological aspects. *Biomed Pharmacother*. 2021;143:112175.
4. Langade D, Kanchi S, Salve J, Debnath K, Ambegaokar D. Efficacy and Safety of Ashwagandha (Withania somnifera) Root Extract in Insomnia and Anxiety: A Double-blind, Randomized, Placebo-controlled Study. *Cureus*. 2019;11(9):e5797.
5. 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.
6. Mikulska P, Malinowska M, Ignacyk M et al. Ashwagandha *(Withania somnifera)*-Current Research on the Health-Promoting Activities: A Narrative Review. *Pharmaceutics*. 2023;15(4):1057.
7. Shohat B, Gitter S, Abraham A, Lavie D. Antitumor activity of withaferin A (NSC-101088). *Cancer Chemother Rep*. 1967;51(5):271-6.
8. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity*. 2019;51(1):27-41.
9. Sostres C, Gargallo CJ, Arroyo MT, Lanas A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Pract Res Clin Gastroenterol*. 2010;24(2):121-132.
10. Kumar P, Sharma R, Garg N. Withania somnifera - a magic plant targeting multiple pathways in cancer related inflammation. *Phytomedicine*. 2022;101:154137.

11. Khalil HMA, Eliwa HA, El-Shiekh RA et al. Ashwagandha (Withania somnifera) root extract attenuates hepatic and cognitive deficits in thioacetamide-induced rat model of hepatic encephalopathy via induction of Nrf2/HO-1 and mitigation of NF-κB/MAPK signaling pathways. *J Ethnopharmacol*. 2021;277:114141.
12. Mulabagal V, Subbaraju GV, Rao CV et al. Withanolide sulfoxide from Aswagandha roots inhibits nuclear transcription factor-kappa-B, cyclooxygenase and tumor cell proliferation. *Phytother Res*. 2009;23(7):987-92.
13. Aalinkeel R, Hu Z, Nair BB et al. Genomic Analysis Highlights the Role of the JAK-STAT Signaling in the Anti-proliferative Effects of Dietary Flavonoid-'Ashwagandha' in Prostate Cancer Cells. *Evid Based Complement Alternat Med*. 2010;7(2):177-87.
14. Xia Y, Wang P, Yan N, Gonzalez FJ, Yan T. Withaferin A alleviates fulminant hepatitis by targeting macrophage and NLRP3. *Cell Death Dis*. 2021;12(2):174.
15. Correia EEM, Figueirinha A, Rodrigues L et al. The Chemical Profile, and Antidermatophytic, Anti-Inflammatory, Antioxidant and Antitumor Activities of Withania chevalieri A.E. Gonç. Ethanolic Extract. *Plants (Basel)*. 2023;12(13):2502.
16. El Moussaoui A, Jawhari FZ, Almehdi AM et al. Antibacterial, antifungal and antioxidant activity of total polyphenols of Withania frutescens.L. *Bioorg Chem*. 2019;93:103337.
17. Nile SH, Nile A, Gansukh E, Baskar V, Kai G. Subcritical water extraction of withanosides and withanolides from ashwagandha (Withania somnifera L) and their biological activities. *Food Chem Toxicol.* 2019;132:110659.
18. Ahmed W, Mofed D, Zekri AR, El-Sayed N, Rahouma M, Sabet S. Antioxidant activity and apoptotic induction as mechanisms of action of Withania somnifera (Ashwagandha) against a hepatocellular carcinoma cell line. *J Int Med Res*. 2018;46(4):1358-1369.
19. Abdel-Tawwab M, Abo Selema TAM, Khalil RH et al. The growth performance, antioxidant and immune responses, and disease resistance of Litopenaeus vannamei fed on diets supplemented with Indian ginseng (Withania somnifera). *Fish Shellfish Immunol*. 2022;128:19-27.
20. Tiwari S, Gupta SK, Pathak AK. A double-blind, randomized, placebo-controlled trial on the effect of Ashwagandha (Withania somnifera dunal.) root extract in improving cardiorespiratory endurance and recovery in healthy athletic adults. *J Ethnopharmacol*. 2021;272:113929.
21. Kuchewar VV, Borkar MA, Nisargandha MA. Evaluation of antioxidant potential of Rasayana drugs in healthy human volunteers. *Ayu*. 2014;35(1):46-9.
22. Lee D, Yu JS, Ha JW et al. Antitumor Potential of Withanolide Glycosides from Ashwagandha (Withania somnifera) on Apoptosis of Human Hepatocellular Carcinoma Cells and Tube Formation in Human Umbilical Vein Endothelial Cells. *Antioxidants (Basel)*. 2022;11(9):1761.
23. Maarouf RE, Azab KS, El Fatih NM, Helal H, Rashed L. Withania *somnifera* Alter BCL2/Bax signaling and trigger apoptosis of MCF-7 and MDA-MB231 breast cancer cells exposed to γ-radiation. *Hum Exp Toxicol*. 2023;42:9603271231180849.

24. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. *Oncology*. 2005;69 Suppl 3:4-10.
25. Xing Z, Su A, Mi L et al. Withaferin A: A Dietary Supplement with Promising Potential as an Anti-Tumor Therapeutic for Cancer Treatment - Pharmacology and Mechanisms. *Drug Des Devel Ther*. 2023;17:2909-2929.
26. Prasanna Kumar S, Shilpa P, Salimath BP. Withaferin A suppresses the expression of vascular endothelial growth factor in Ehrlich ascites tumor cells via Sp1 transcription factor. *Curr. Trends Biotechnol. Pharm*. 2009;3(2):138–148.
27. Wang YX, Ding WB, Dong CW. Withaferin A suppresses liver tumor growth in a nude mouse model by downregulation of cell signaling pathway leading to invasion and angiogenesis. *Tropical Journal of Pharmaceutical Research*. 2015;14(6):1005-1011.
28. Saha S, Islam MK, Shilpi JA, Hasan S. Inhibition of VEGF: a novel mechanism to control angiogenesis by Withania somnifera's key metabolite Withaferin A. *In Silico Pharmacol*. 2013;1:11.
29. Gao R, Shah N, Lee JS et al. Withanone-rich combination of Ashwagandha withanolides restricts metastasis and angiogenesis through hnRNP-K. *Mol Cancer Ther*. 2014;13(12):2930-40.
30. Mohan R, Hammers HJ, Bargagna-Mohan P et al. Withaferin A is a potent inhibitor of angiogenesis. *Angiogenesis*. 2004;7(2):115-22.
31. Setty Balakrishnan A, Nathan AA, Kumar M, Ramamoorthy S, Ramia Mothilal SK. Withania somnifera targets interleukin-8 and cyclooxygenase-2 in human prostate cancer progression. *Prostate Int*. 2017;5(2):75-83.
32. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39(1):1-10.
33. Turrini E, Calcabrini C, Sestili P et al. Withania somnifera Induces Cytotoxic and Cytostatic Effects on Human T Leukemia Cells. *Toxins (Basel)*. 2016;8(5):147.
34. Mazzio EA, Bauer D, Mendonca P, Taka E, Soliman KF. Natural product HTP screening for attenuation of cytokine-induced neutrophil chemo attractants (CINCs) and NO2- in LPS/IFNγ activated glioma cells. *J Neuroimmunol*. 2017;302:10-19.
35. Myers JA, Miller JS. Exploring the NK cell platform for cancer immunotherapy. *Nat Rev Clin Oncol*. 2021;18(2):85-100.
36. Dubey S, Singh M, Nelson A, Karan D. A Perspective on Withania somnifera Modulating Antitumor Immunity in Targeting Prostate Cancer. *J Immunol Res*. 2021;2021:9483433.
37. Singh KB, Hahm ER, Kim SH, Singh SV. Withaferin A Inhibits Fatty Acid Synthesis in Rat Mammary Tumors. *Cancer Prev Res (Phila)*. 2023;16(1):5-16.
38. Barua A, Bradaric MJ, Bitterman P et al. Dietary supplementation of Ashwagandha (Withania somnifera, Dunal) enhances NK cell function in ovarian tumors in the laying hen model of spontaneous ovarian cancer. *Am J Reprod Immunol*. 2013;70(6):538-50.

39. Panossian A, Seo EJ, Efferth T. Effects of anti-inflammatory and adaptogenic herbal extracts on gene expression of eicosanoids signaling pathways in isolated brain cells. *Phytomedicine*. 2019;60:152881.
40. Kruk J, Aboul-Enein BH, Bernstein J, Gronostaj M. Psychological Stress and Cellular Aging in Cancer: A Meta-Analysis. *Oxid Med Cell Longev*. 2019;2019:1270397.
41. Shin KJ, Lee YJ, Yang YR et al. Molecular Mechanisms Underlying Psychological Stress and Cancer. *Curr Pharm Des*. 2016;22(16):2389-402.
42. Chakroborty D, Sarkar C, Basu B, Dasgupta PS, Basu S. Catecholamines regulate tumor angiogenesis. *Cancer Res*. 2009;69(9):3727-30.
43. Bauer ME. Stress, glucocorticoids and ageing of the immune system. *Stress*. 2005;8(1):69-83.
44. Tank AW, Lee Wong D. Peripheral and central effects of circulating catecholamines. *Compr Physiol*. 2015;5(1):1-15.
45. Speers AB, Cabey KA, Soumyanath A, Wright KM. Effects of Withania somnifera (Ashwagandha) on Stress and the Stress- Related Neuropsychiatric Disorders Anxiety, Depression, and Insomnia. *Curr Neuropharmacol*. 2021;19(9):1468-1495.
46. Remenapp A, Coyle K, Orange T et al. Efficacy of Withania somnifera supplementation on adult's cognition and mood. *J Ayurveda Integr Med*. 2022;13(2):100510.
47. Majeed M, Nagabhushanam K, Mundkur L. A standardized Ashwagandha root extract alleviates stress, anxiety, and improves quality of life in healthy adults by modulating stress hormones: Results from a randomized, double-blind, placebo-controlled study. *Medicine (Baltimore)*. 2023;102(41):e35521.