

Traditional Medicine - A Gold Mine in the Treatment of Cancer

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Abstract

The prevalence of non-communicable diseases has been on the rise in the last 2 decades. Amongst which, cancer bags the top spot for being unforgivingly ruthless and is the leading cause of the incessant rise in fatalities globally. The failure of current therapeutic approaches is subject to multiple factors. One of them is their inability to effectively contain or kill cancerous cells that persist. Their unbiased nature, due to which they kill healthy as well as cancerous cells, is one of the biggest drawbacks of the currently available therapeutic options. Recent advances have made targeted therapy a possibility but its high cost renders it an unviable option for a large portion of the affected population. The above mentioned drawbacks of the currently used treatments push our attention towards finding better alternatives to effectively deal with this pestilent disease. Herbal drugs offer tremendous hope and are a potential gold mine that could provide effective treatment options to deal with cancer. In this review, we shed light on a few encouraging herbs like *Withania somnifera*, *Astragalus membranaceus*, *Zingiber officinale*, *Thea sinensis*, *Panax ginseng*, *Hypericum perforatum*, *Allium cepa and Allium sativum* that hold the potential to provide effective alternative therapeutic interventions for the prevention and management of cancer.

Keywords: Astragalus membranaceus, Cancer, Cancerous Cells, Panax ginseng, Thea sinensis, Withania somnifera, Zingiber officinale

1. Introduction

Non-Communicable Diseases (NCDs) are now at the helm of being the most prominent causes of death worldwide. Cancer, which comes under NCDs, is supposed to be hitting the top rank as it is becoming the leading cause of declination in life expectancy of human beings. Cancer is a combination of diseases in which a group of cells exhibit unrestrained growth, infiltration and can also lead to metastasis. The chances of being incurred with cancer are increasing day by day. The most evident causes are mutations caused by chemical carcinogens or ionising radiation, hormone imbalances, immune system failure, genetics and also current lifestyle changes also play a vital role¹. The major types of cancer are classified based on the cell

type that has been damaged or invaded such as: A) Carcinoma: tumours originating from epithelial cells. Example: prostate, breast, lung and colon cancer. B) Sarcomas: these are malignant tumours that develop from connective tissue. C) Lymphoma and leukemia: these are haematological Cancers. D) Germ cell tumour: tumours formed by totipotent cells. Example: ovary, Testicle. E) Blastic tumour (also known as a Blastoma): these tumours are quite common in youngsters. These tumours have the appearance of embryonic or immature tissue¹. In the 21st century, according to the statistical study conducted by the World Health Organization (WHO) in 2015, it was inferred that cancer is the primary or second major cause of death for population who belong to the age category of less

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than 70 in 91 out of 172 countries across the globe and it ranks third or fourth in another 22 nations.

2. Pathophysiology

Enlargement of tumours begins with genetic alteration of cells in which a single cell in a healthy population depicts signs of genetic mutation that enhance its proclivity to proliferate when it should rest. Another sequence of events that occurs is that this changed cell and its progeny look normal, but they start overproducing, a condition known as hyperplasia. After years, one in a million of these genetically altered cells develops another mutation that slackens cell growth restrictions even more. The offspring of these cells are aberrant in form and orientation and undergo abnormal multiplication. This abnormal development is called dysplasia, and the tissue is termed dysplastic. In situ cancer is defined as a tumour that has not yet infiltrated any tissue. This tumour could be controlled forever. On the other hand, a few cells may acquire further mutation and become malignant. These genetically altered tumour cells begin to penetrate the underlying tissue and shed cells into the blood or lymph. The final stage comes when cells with special characteristics called renegade cells come into action. They are prone to forming new tumours (metastases) throughout the body, which might be fatal if a crucial organ is affected².

An oncogene is a gene that is a mutant (changed) version of a normal cell growth gene. Oncogenic mutations in genes can be inherited or produced by exposure to cancer-causing chemicals in the environment. Oncogenedirected metabolic modifications can have wide-ranging effects, and numerous metabolic pathways may be changed at the same time³. Oncogenic mutations in RAS genes (KRAS, NRAS, and HRAS) are found in most cancers, according to the Cancer Genome Atlas (TCGA) and other genome-scale sequencing initiatives^{4,5}. MYC oncogene deregulation is prevalent in human malignancies⁶⁻⁸. The MYC proteins (c-MYC, N-MYC, and L-MYC) are transcription factors that bind to enhancer box (E-box) regions in gene promoters and influence different aspects of cellular transformation and tumour growth9. Another oncogene is the BCR-ABL oncogene, which is also known as a fusion gene. This is because it is formed by the fusion of the BCR and ABLgenes. It is present on the Philadelphia

chromosome, which is formed by human chromosomes 9 and 22¹⁰. The resulting BCR-ABL protein disrupts cell signaling and generates an overabundance of white blood cells, resulting in Chronic Myeloid Leukemia (CML)¹¹. Because the BCR-ABL fusion protein is only found in leukemic cells, it could be used to treat them.

3. Current Scenario

According to many new research, the majority of cancer patients self-medicate with one or more complementary or alternative medicines while on treatment. This complies mostly with herbal or natural products. Nowadays, the most commonly used natural product drug is Paclitaxel, which has been isolated from the bark of the Western yew tree. It attaches to tubulin's beta subunit and creates a stable, non-functioning microtubule bundle, preventing mitosis. Another interesting class of drug used in the current chemotherapy treatment is Vinca alkaloids. It possesses anti-angiogenic and apoptotic properties. It is broken down in the liver. It is given as an infusion. It is most commonly used to treat breast and ovarian cancers. Three alkaloids extracted from the Periwinkle plant (Vinca rosea; Catharanthus rosens) have been found to be effective in the treatment of malignancy: vinblastine, vincristine, and vindesine. Vinorelbine is a semisynthetic derivative of vinca alkaloids. They bind to tubulin and impede the development of the mitotic spindle as a mechanism of action (antimitotic spindle poison). As a result, they induce mitotic cell cycle arrest. Vinca alkaloids exhibit a wide spectrum of cytotoxic activity in terms of pharmacological activities. Despite their near similarities, these two agents have no crossresistance. Orally, vinca alkaloids are poorly absorbed and extremely irritating. Hence, they are given by an IV infusion that runs continuously¹².

Even though today we use a vast quantity of synthetic drugs for the treatment of various diseases, their inability to cure or treat cancer without any serious toxic effects calls for the need for safer and more effective alternatives to the current drug therapy. Many synthetic chemotherapeutic drugs show common side effects of nausea, vomiting, alopecia, etc. But there are many toxic side effects of vinca alkaloids and paclitaxel drug regimens. Vinca alkaloids have been observed to have various adverse effects, such as intestinal obstruction due to severe constipation,

peripheral neuropathy, ataxia, tremors, etc. Similarly, some of the toxic effects of paclitaxel are bone marrow suppression, bradycardia, silent ventricular tachycardia, alopecia, hypersensitivity reactions etc¹². On the other hand, plant-based drug molecules have proven to be much safer with minimal or no serious toxic effects. This, along with its good efficacy against various types of cancer, should push pharmaceutical companies and researchers to conduct intensive studies on various herbs and their extracts, which could prove to be revolutionary in the treatment of breast cancer. In this review, we focus on a few such promising drugs.

4. Herbal Plant Extracts and their Significance in Cancer

4.1 Ashwagandha (Withania somnifera)

This primaeval herb is used extensively in the traditional system of medicine and belongs to the Solanaceae family. It was a household herb in ancient India. This was because of its wide spectrum of therapeutic and biological benefits. Amongst its active constituents are withasomniferin A, withasomniferols A, B and C, withaferin, withanone, withanolides A to Y, etc. Most of these active elements are abundantly present in the roots and leaves of this herb.

Numerous studies focusing on the action of Ashwagandha on different types of cancer have been conducted. An in vitro study on MDA-MB-231 cells revealed that withaferin A suppressed the estrogen receptor - a protein in MCF-7 cells, resulting in a proapoptotic effect¹³. In another study, it was found that WFA inhibited metastasis when used in therapy resistant Triple Negative Breast Cancer (TNBC) cells¹⁴. The mechanism by which WFA executes this anti-cancer action has been studied by various researchers. A study proposed that WFA induces apoptosis in MCF-7 cells by causing aggregation of vimentin filaments¹⁵. Various other studies have revealed that WFA also causes apoptosis by release of Reactive Oxygen Species (ROS)¹⁶⁻¹⁸. A preclinical study on colorectal cell lines showed that WFA led to a decline in function of STAT3 (signal transducer and activator of transcription 3) which arrested the growth of tumour cells¹⁹. Moreover, another in vitro study done on colon cancer cell lines showed that the Notch-1 signaling pathway is inhibited by WFA. This pathway plays a substantial role in the growth of colon cancer^{20,21}.

Various studies have been done to test the effect of WFA on prostate cancer. While studying the mechanism involved in the development of prostate cancer, it was found that the growth of tumour cells is due to the increased activity of AKT signalling, which is subject to inhibition of the tumour suppressor PTEN gene (phosphatase and tensin homologue)22. In a preclinical study performed on mice, it was observed that activation of the AKT pathway was inhibited post-administration of WFA. This activation of Par-4 (prostate apoptosis response-4) induced by FOXO3a (Forkhead box O3a) was also observed in these mice. This activation was responsible for tumour growth suppression^{23,24}. An in silico study revealed that WFA was an ideal agent for targeting Non-Small Cell Lung Cancer (NSCLC). The researchers found that WFA was responsible for apoptosis in EGFR WT as well as NSCLC (mutated)²⁵. Several studies have revealed that WFA has a positive effect in restricting ovarian tumour growth. It is most effective when given in combination with cisplatin²⁶. In an animal-based study conducted on mice having ovarian cancer, it was observed that the combination therapy with cisplatin and WFA resulted in significant reduction in Aldehyde Dehydrogenase Cancer Stem Cells (ALDH+ CSCs). Another study conducted on mice showed that a combination of DOXIL and WFA can be useful in the treatment of relapsed ovarian cancer. This is due to their inhibitory effect on ALDH+ CSCs²⁷.

Data obtained from extensive preclinical studies has shown that Ashwagandha has the potential to treat various forms of cancer. Even though such encouraging results make a strong case for its use in treating patients with different cancers, its use in actual practice is limited. This is largely due to a lack of human-centric evidence. Hence, we believe that large scale clinical studies should be encouraged in order to gather evidence that helps in the adoption of ashwagandha as an alternative therapy for various forms of cancer.

4.2 Astragalus Root (Astragalus membranaceus)

Astragalus root (Fabaceae family) is an adaptogenic herb that holds a strong importance in conventional Chinese herbal medicine²⁸. Active components of astragalus that are responsible for its activity are D- β asparagine, calycosin, cycloastragenol, astragalosides I-VII. Other important substances are pigments like formononetin and astraisoflavan. Amongst these, many constituents

found in astragalus have been shown to possess an extensive ability to scavenge harmful substances like free radicals²⁹. For ages, Traditional Chinese Medicine practitioners have relied on astragalus for the treatment of a condition called "spleen deficiency", and it has also been used extensively for various cardiovascular diseases³⁰.

In a study conducted on humans and animals, astragalus mixed with different herbs in the herbal formula known as Juzentaihoto (Ten Significant Tonic Decoction) was administered and immunity-potentiating effects were observed, such as improved activity of NK cells and increased secretion of interleukins. These components have been shown to enhance the activity of drugs used in chemotherapy, prevent recurrences and decrease toxicity, which is subject to chemotherapy³¹. A study was conducted on human subjects with small cell lung cancer, and 54 patients were given a mixture of astragalus and Chinese herbs along with the conventional drug therapy. The results obtained showed that out of a group of 12 SCLC patients, 10 survived for a time period of 3-17 years with this combinational therapy. A clinical study (randomized) with a sample size of 120 subjects was conducted. In which patients were subject to routine cancer chemo therapy but were prescribed an intravenous astragalus preparation along with that. The results obtained at the end of the study revealed that the group that received the treatment had a lower incidence of disease progression. Along with this, a reduction in the harmful effects of chemo therapy on the white blood cells and platelets was also observed in these patients. Lastly, the treated subjects displayed an improvement in the CD4/ CD8 ratios, IgM, IgG levels, and Karnofsky scores when compared to the group that received a placebo (control group)³². In another experiment involving patients having gastrointestinal cancer, the subjects were prescribed an injection that was a combination formulation containing ginseng and astragalus. At the end of the study, the results stated that the patients that received the herbal drug combination showed a considerable decrease in the suppression of white blood cells³³.

Data obtained from extensive studies carried out to study the effects of astragalus on various types of cancer has shown that astragalus root has immense potential to treat various forms of cancer. Along with this, astragalus is also reported to have anti-bacterial and anti-viral activity. Even though results obtained from astragalus are positive, the data available is limited. Hence, in order to declare

astragalus as an effective therapeutic alternative, it is imperative to dig deeper and conduct further research to study the effects of astragalus on various types of cancer.

4.3 Ginger (Zingiber officinale)

The plant derived components of ginger (*Z. officinale*) include volatile oils, anthocyanins, tannins and pungent phenolic compounds known as gingerols, shogaols, and sesquiterpenes³⁴. There is evidence of many preclinical studies for ginger (*Z. officinale*) which have positive responses in the management and treatment of cancer. Some of these studies are mentioned in the below paragraphs.

An experimental study conducted by a group of researchers proved that Ginger Extract (EG) and 6-gingerol have anti-proliferative, anti-cancer and anti-invasive properties through a variety of pathways, including NFB, STAT3, Rb, MAPK, PI3K, AKT, ERK, cIAP1, cyclin A, cyclin dependent kinase (Cdk), cathepsin D, and caspase3/735. Another experiment was conducted on rats with hepatic carcinoma caused by a choline deficient diet mixed with ethionine and it was discovered that the tumour size was reduced significantly when the rats were treated with ginger extract³⁶. One more study revealed that the effect of 6-gingerol in Human Mammary Carcinoma (MDA-MB 231) has no effect on cell adhesion at concentrations up to 5 units, but showed a 16 percent reduction at 10 units. Furthermore, MDA-MB-231 cells were treated with increasing doses of 6-gingerol, which resulted in a concentration-dependent reduction in cell migration and motility. Furthermore, when MDA-MB231 cells were treated with 6-gingerol, the activities of matrix metalloproteinase (MMP) 2 or MMP9, which have been identified as putative mediators of cancer invasion and metastasis, decreased in a dose-dependent way³⁷. In addition, studies conducted on human colorectal cancer cells by scientists revealed that the anti-cancer effects of 6-gingerol caused a dose-dependent reduction in cell survival in cancer patients. The results also revealed that 6-gingerol causes cell cycle arrest in the G2/M phase and showed no effect in the sub-G1 phase. It also lowers levels of CDK1, cyclin A, and cyclin B138. A study conducted in a population suffering from cervical malignancy gave the brief result that 6-gingerol also increased the cytotoxicity of the standard chemotherapy drug cisplatin. In addition to the above findings, it was also concluded that 6-gingerol could be used alone or in combination with standard

chemotherapeutic agents to manage and cure cervical malignancies³⁹.

Above mentioned pre-clinical studies are showing the anti-cancer activities of ginger, which gives a good in-depth knowledge and insight about the various mechanisms by which 6-gingerol and EG can be effective in the treatment of cancer. So, such evident studies can be taken into consideration for further development of herbal drug molecules in the management and treatment of cancer.

4.4 Green Tea (Thea sinensis)

Green Tea is a commonly used herbal plant which is obtained from the leaf buds of *Thea sinensis* plants (family *Theaceae*). Many of the research says that this plant's extracts have properties that protect humans from oxidative damage by enhancing their total antioxidative status. The extracts have also been found to inhibit oral, esophageal, stomach, skin, lung, liver, prostate, kidney, and other organ cancers in several clinical and in-vitro experiments utilising cancer cell lines and animals. The tea leaves are a rich source of caffeine, theobromine and theophylline⁴⁰.

Scientists have conducted many pre-clinical and clinical studies supporting the fact that extracts of green tea leaves possess anti-cancer activities. In one of the prospective studies conducted in Japan, 1160 females were enrolled with invasive breast cancer and a mean age of 51.5 years. In the study, it was found that with a daily consumption of 3 cups of green tea, the chance of cancer recurrence is reduced (particularly in early-stage cancer)⁴⁰. A study based on a questionnaire in China mentions that increasing the frequency and duration of green tea consumption can lower the risk of ovarian cancer when compared with non-drinkers, and this study was conducted on 254 ovarian cancer patients and 652 controls were taken⁴¹. In patients with prostate cancer, it was found that yearly consumption of 1.5 kg of green tea leaves reduced the risk of incurring prostate cancer. These results were obtained from a study conducted in China on 130 prostatic adeno carcinoma patients and 274 patients were taken as control⁴². In a prospective cohort study conducted in Japan, a total of 8552 people were taken as subjects, and they were made to have 3-10 cups of green tea daily. The results stated that those people who used to drink more than 10 cups of green tea each day had a lower risk of stomach cancer and colorectal cancer⁴³.

The information mentioned above highlights the fact that phytochemical components of green tea are efficacious in the treatment of various types of cancer. So, in upcoming times, this data should be taken into consideration and initiatives should be taken to use the herbal components of green tea in the prevention and management of cancer.

4.5 Ginseng (Panax ginseng)

Ginseng, which means "man-root", is a root that has been used for thousands of years for its medicinal properties by practitioners of conventional Chinese medicine⁴⁴. Ginseng is known as a stress buster due to its potential to improve one's ability to relieve stress. As a result, it is known as an adaptogen. The three widely used species are Asian or Korean ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*), and Siberian ginseng (*Eleutherococcus senticosus*). Ginseng gets its properties from its active constituents called ginsenosides⁴⁵.

In a randomised study, subjects with stomach cancer were prescribed chemotherapy, but instead of giving them chemo therapy alone, they were also given injections of an herbal combination called Shenmai. Shenmai is a formulation that includes ginseng. At the end of the study, it was observed that the subjects treated with the combination of chemotherapy and shenmai had elevated T-cell and NK cell levels. Along with this, an increase in the T-helper/T-suppressor ratio was also reported⁴⁶. In another experimental study, a total of 131 subjects had undergone radiotherapy for nasopharyngeal carcinoma. Out of those, 64 patients were randomly assigned to the experimental group that was prescribed ginseng polysaccharide injections. At the end of the experiment, results stated that there was a significant rise in the activity of various immune cells such as NK, LAK, T3 and T4 cells. An increase in the serum concentration of these cells was also observed. Treatment with ginseng was found to be safe and no major adverse events were reported. In a study involving subjects (sample size 42) with stage 3 gastric cancer, it was observed that taking red ginseng was responsible for having a higher survival rate as compared to patients in the control group 47 .

Experimental studies carried out to study the effects of ginseng on various types of cancer have shown that ginseng has the potential to give positive results in patients with various forms of cancer. It does so by enhancing the activity of various immune cells, such as NK cells and macrophages. It also potentiates the proliferation of lymphocytes and increases antioxidant activity at the cellular level. Even though these promising results make a strong case for the use of ginseng in treating cancer, the evidence present is scarce and there is a dire need for extensive research in this domain.

4.6 Hypericin (*Hypericum perforatum*)

Hypericin also known as St. John's wort, is a flowering plant in the Hypericaceae family and one of the species of the genus Hypericum. This plant is a cross between *H. maculatum* and *H. attenuatum*. Hypericin is a naphthodianthrone, an anthraquinone derivative that is one of Hypericum's main active ingredients, along with hyperforin. Despite breakthroughs in medical and surgical care, the prognosis for cancer remains poor. Many pilot studies have been conducted to study the efficacy of hypericin in the treatment of cancer.

According to recent pre-clinical research, hypericin, a photochemical dye, is activated by green light and creates hazardous radical species in tumours. First and foremost, a pre-clinical study was conducted on mice and it stated that the development of pancreatic cancer cells was significantly reduced both in vitro and in vivo. But it was also found that laser or dye alone had no impact, and intra-tumour hypericin and laser therapy can be effective in patients with unresectable pancreatic cancer⁴⁸. Photodynamic therapy (PDT) is a cancer treatment adjunct that is effective in the ablation of superficial tumours. One of the pilot studies found that laser IPDT with hypericin increased tumour necrosis significantly more than laser alone, suggesting that it could be used as a less invasive adjuvant treatment for recurrent or inoperable human squamous cell malignancies of the head and neck⁴⁹. Hypericin's action on osteoclasts and breast cancer-mediated osteoclastogenesis was linked to NFATc1 signalling pathway suppression and Ca²⁺ oscillation attenuation. Furthermore, studies emphasising hypericin's activity in breast cancer subjects were also done. The results of which stated that hypericin could reduce tumour burden, osteolysis generated by direct inoculation of MDA-MB-231 cells into the tibia's bone marrow cavity, and bone metastasis. It was also found to enhance lifespan in an experimental metastasis model using MDA-MB-231 breast cancer cells injected via the intracardiac route. These findings imply that hypericin

could be an effective option for preventing and treating bone deterioration in patients with breast cancer-related bone metastases⁵⁰.

Taking everything into account we can finally come to a conclusion that hypericin shows anti-cancer activity which can play a significant role in the treatment and management of various types of cancer. But the lack of clinical studies has limited its use. In order to achieve this, more emphasis should be given on conducting more pharmacological research on the herbal extracts of hypericin and their effects on cancer.

4.7 Onion (*Allium cepa*) and Garlic (*Allium sativum*)

Allium is a vast genus of onion- or garlic-scented bulbous amaryllis flowers (Amaryllidaceae). Onion (*Allium cepa*), garlic (*Allium sativum*), chive (*Allium schoenoprasum*) and leek (*Allium porrum*) are all essential food crops, and some are grown as attractive border plants. Allium vegetables include a variety of bioactive chemicals such as flavonoids, oligosaccharides, arginine, and selenium⁵¹. Nevertheless, the majority of studies on allium vegetables focus on their sulfurcontaining components^{51,52}. Many studies have been conducted to study the anti-cancer activity of allium vegetables, some of which are discussed below.

A meta-analysis of 19 case-control and 2 cohort studies found that eating a lot of allium vegetables lowered the risk of stomach cancer in high consumption groups as compared to lower ones⁵³. In another casecontrol study, the intake of onion and garlic was measured independently using a food frequency questionnaire in a network of Italian and Swiss case-control studies with 1037 cases and 2020 controls⁵⁴. In this study, onions and garlic were found to be protective against big bowel tumours by the researchers. Also, it was concluded that the group with the highest intake (>7 servings per week) was linked to having a lower risk of colorectal cancer. This case-control study also reported that consumption of >7 portions of onions per week were protective against esophageal cancer. In addition to the above studies, one more study was conducted which suggested that eating 1-7 servings of onions per week was linked to a lower risk of laryngeal and ovarian cancer compared to people who did not eat onions. Also, eating >2 servings per week compared to 0 was linked to a lower risk of endometrial

cancer. Garlic consumption was also linked to a lower risk of oral cavity/pharyngeal cancer^{54,55}.

At present decent amount of literature is present supporting the claim that onion and garlic could possibly be an effective alternative in the treatment of various types of cancers but still its use has been limited. We believe that further large scale clinical studies would strengthen the case of using onion and garlic in the treatment and management of various forms of cancer.

5. Conclusion

The failure to find an effective alternative to current drug therapy used for cancer management could lead to a 50% rise in the incidence of cancer by the year 2050. These alarming numbers and the drawbacks of current therapeutic options make it imperative for research scholars and pharmaceutical giants to give their undivided focus to finding an effective alternative treatment for cancer management.

We believe that the answer to this lies within the traditional medicinal system. Medicinal herbs used in the traditional system have tremendous potential to cure grave diseases like cancer. This has been backed by multiple preclinical studies conducted to test the effects of various herbs. In this review, we found that the anticancerous effects of herbs such as ashwagandha, atragalus, ginger and others have been extensively studied, but most of these studies are pre-clinical studies. In these studies, the herbs have shown positive effects in treating various kinds of cancers, like colorectal cancer, breast cancer, prostate cancer, ovarian cancer, lung cancer and others. Their use was found to be safe and they showed little or no toxicity. These promising results, along with the nontoxic nature of natural herbs make them a boon for the management of cancer. But their use is limited due to the lack of human-centric studies. Hence, extensive clinical trials should be encouraged to unveil the true potential of these herbs.

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