

Analysing of Natural Drugs Plants and Herbal Drugs for Cancer Patients Treatment

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Abstract – Every year, millions of people lose their lives to cancer, making it one of the most common and deadly diseases of our time. In addition to genes, food habits, smoking, nutritional behaviours, radiation, and other environmental factors, there are numerous other factors that contribute to disease. Phytocompounds derived from medicinal herbs and their derivatives are increasingly being recognised as useful complementary cancer treatments. Herbal drugss used in conjunction with conventional therapeutics have been shown in numerous clinical studies to improve cancer patients' survival, immune function, and quality of life (QOL). Only chemotherapy and radiation treatments have proven effective against cancer so far; however, these treatments are often toxic and lethal. Ayurveda knowledge combined with herbal drugs concepts could provide better drug leads for the inhibitory treatment of cancer. Alternative and less toxic medication is desperately needed. Anticancer and antioxidant-rich medicinal plants abound in nature, and many of these can be used to completely eradicate cancer. The search for natural cancer drugs began in the late 1960s and resulted in the discovery of vincristine, vinblastine, camptothecin, and taxol (among other things). This review focuses on herbal drugs derived from natural sources for the discovery of new drug leads for the treatment of cancer.

Key Words – Ayurveda, Cancer, Chemotherapy, Herbal Drugs, Potent Compounds (Secondary Metabolites).

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INTRODUCTION

The knowledge of Ayurveda has led to the promising use of natural products, particularly plants, in the treatment of various diseases in our country for decades. Herbal drugs are a source of new discoveries in developing countries, and each new drug leads to a new set of healthcare issues and formulations. There are many novel therapeutic compounds for preventive and curative drugs in traditional medicines compared to other sources of drug discoveries. Many studies have found antimutagenic and anticancer properties in secondary metabolites like polyphenols, terpenes, and alkaloids. As medicinal plants are antioxidant reservoirs with low toxicity compared to modern drugs, combining Ayurveda with advanced drug discovery may lead to new compounds that address a variety of human sufferings, according to several cancer drug studies and the discovery of new lead molecules towards anticancer activity by using medicinal plants.

CLINICAL USES OF HERBAL DRUGS WITH ANTICANCER EFFECTS

A range of clinical studies have indicated that a spectrum of anticancer activities from various herbal drugss can be detected. In this section, we have organized and classified the clinical use of a number of herbal drugss according to their suppressive effect on specific cancer types (Table 1).

Table 1: Clinical use of herbal drugss exhibiting anticancer activities

Herbal medicine	Suppressive effects on carcinogenesis and cancer metastasis
	For breast cancer
Vitamin A (retinoids)	200 mg/day significantly reduces the recurrence of local breast cancer in premenopausal women.
Vitamin E	Leads to malabsorption or maldigestion in cancer patients; balanced and healthy diet
Isolflavones	To reduce risk of breast cancer
Isolflavones genistein and daidzein	To counter weak estrogenic effects
Alkaloids	Inhibition of cancer cell growth
Coumarins	Inhibition of cancer cell growth
Flavonoids and polyphenols	Antiproliferation
Terpenoids	MCF-7 cell apoptosis
Quinones	To induce G2-M arrest and autophagy by inhibiting the AKT/mammalian target of rapamycin pathway in breast cancer cells
Artemisinin	Decrease the proliferation of human breast cancer cells from expressing a high ERα: ERβ ratio

For prostate cancer	
Vitamin A-D and retinoid	Maintains homeostasis and prevent various metabolic disorders
Vitamin E	Reduce the risk of lethal or advanced prostate cancer relative to nonusers
Epigallocatechin-3-gallate (EGCG)	Arrest LNCaP and DU145 prostate cancer cells at the G0-G1 phase of the cell cycle
Soy isoflavones	Inhibit metalloproteinase in vitro Inhibit 3 α -reductase activity Chemopreventive activities
Scutellaria baicalensis (baicalin)	Inhibit myogenic synthesis of oestrogens Impair the proliferation of androgen-independent PC-3 and DU145 prostate cancer cells in culture
Bicalutamide	Induces cell-cycle arrest at the G0-G1 phase Induces apoptosis of prostate cancer cells at concentrations achievable in humans
Suppression the expression of specific androgen receptor in prostate cancer	
Zinc	Decreases prostate cancer risk Overcomes oxidative damage in lymphocytes Significantly decreases levels of PSA and less oxidative damage
PC-SPEs	Decreases serum testosterone concentrations ($P < 0.05$); decreases serum concentrations of prostate-specific antigen
Hudibia (Hemerocallis)	Antitumor efficacy against cancer cell lines Inhibits the androgen receptor (AR) signaling pathway
For lung cancer	
Platycodon grandiflorum (Campanulaceae)	Anticancer effect in lung cancer patients
Morus alba (Moraceae)	Anticancer effect in lung cancer patients
Prunus armeniaca (Rosaceae)	Anticancer effect in lung cancer patients
Rhus verniciflua (Anacardiaceae)	Anticancer effect in lung cancer patients
Perilla frutescens (Labiatae)	Anticancer effect in lung cancer patients
Stemona japonica (Stemonaceae)	Anticancer effect in lung cancer patients
Tussilago farfara (Compositae)	Anticancer effect in lung cancer patients
Draba nemorosa (Brassicaceae)	Anticancer effect in lung cancer patients
Suppressive effects on carcinogenesis and cancer metastasis	
For liver fibrosis and cancer	
Juchin-ko-to (TJ-10)	
Ti Guan Jue (TJG)	
Ti Guan Jue (TJG)	
Fufang-Zao-Tai-Qing	
Danggui Buaoi Tong (DBT)	
Salicylic acid B	
Cucurbitin	Suppressive effect on hepatic fibrogenesis and carcinogenesis
Oxymentin	
Compound 661	Suppressive effect on hepatic fibrogenesis
Shi cells (S-1)	Reduces/limits the progression of hepatocellular carcinoma
For pancreatic cancer	
GDC-0440, HPI-026, XL-018 and PE-0444911	SMO antagonists; deregulation of sonic hedgehog homology (SHH)
Cyclopamine	Inhibit SHH signaling by directly binding to the 7-beta bundle of the SMO protein; arrest the growth of pancreatic tumors Weakens the recruitment of BMPs to cancer cells and reduce the formation of tumor vasculature The cancerous vascular system becomes unstable after treatment with cyclopamine due to the expression of angiotensin II

1. For Breast Cancer.

Vitamins and selenium have not been proven to play a specific role in the prevention of breast cancer, but in vitro studies have shown some anticancer activities. The vitamin A preparation (Fenretinide) or no treatment was given to 2972 patients with invasive or noninvasive breast carcinoma in one randomised controlled trial. In premenopausal women, the risk of local breast cancer recurrence was significantly reduced 97 months after treatment (HR: 0.65; 95 percent CI: 0.46–0.92). However, there was no discernible difference in terms of metastasis or overall survival [4]. Others have found that taking vitamin E for a long period of time can actually harm breast cancer patients [5, 6]. The current rule appears to cause malabsorption or maldigestion in cancer patients with a concurrent illness, in addition to patients adopting a balanced and healthful diet [4, 7]. Water-soluble isoflavones and lipophilic lignans are the two types of phytoestrogens. In soy beans, isoflavones are abundant, and lignans are found in linseed, wheat, fruit, flaxseed, and vegetables [8, 9]. Linseeds are also rich in lignans. Isoflavone has been linked to a decreased risk of breast cancer in only one of six related clinical trials to date [10]. Women with breast cancer receiving tamoxifen therapy often turn to soy-derived phytoestrogens for relief of postmenopausal symptoms. For example, the isoflavones genistein and daidzein are structurally similar to 17-estradiol and may have weak estrogenic effects [11]. It's not clear

whether phytoestrogens can help treat breast cancer or alleviate menstrual cramps, however [12].

2. For Prostate Cancer.

Because prostate cancer has a long latency period, has a strong dietary influence, and has limited treatment options for advanced disease, many patients turn to complementary and alternative medicines (CAM) in the hope that these medicines represent a viable therapeutic option without negative side effects. An evidence-based study is needed to back up the widespread folkloric belief that this is the case. In order to keep the body in a state of homeostasis and avoid various metabolic disorders, people must consume vitamins, including vitamins A–D and retinoids, which are organic compounds that humans cannot synthesise. Inflammation may play a critical role in the development of prostate cancer, according to new research. Vitamin anti-inflammatory activities on prostate carcinogenesis have been studied in a number of clinical trials. Despite the lack of solid evidence, many men with prostate cancer take vitamin and mineral supplements. These supplements are thought to at the very least not harm in the prevention or treatment of inflammation-associated disease. Compared to nonusers, daily intake of >100 IU of vitamin E decreased prostate cancer risk by 56% in smokers who smoked. SELECT, however, a study examining the effects of selenium and vitamin E supplementation on prostate carcinogenesis, found that taking vitamin E in the form of a supplement increased the risk of prostate cancer in otherwise healthy men. Together, these clinical findings suggest that vitamin E treatment for prostate cancer patients may only target inflammation-related symptoms rather than anticancer activity. Future research is required to resolve this apparent discrepancy between the effects seen in healthy individuals versus cancer patients.

3. For Lung Cancer.

Lung cancer is one of the most deadly cancers, and the lung is a common site of metastasis of tumors from other tissues in the body. Standard chemotherapy regimens often have limited survival benefits due to the severe toxicity of the various anticancer agents, such as gemcitabine, paclitaxel, docetaxel, etoposide, and vinorelbine. Recent reports have suggested that herbal drugs and their phytochemicals which seem to have lower or little toxicity may provide an attractive strategy for lung cancer therapy. Traditionally, herbal plants such as *Platycodon grandiflorum* (Campanulaceae), *Morus alba* (Moraceae), *Prunus armeniaca* (Rosaceae), *Rhus verniciflua* (Anacardiaceae), *Perilla frutescens* (Labiatae), *Stemona japonica* (Stemonaceae), *Tussilago farfara* (Compositae), and *Draba nemorosa* (Brassicaceae) have been used to treat lung cancer. Clinically, the proportion of patients that use herbal drugs as adjuvants alongside conventional (e.g., chemotherapy) treatment for lung

cancer is as high as 77%. Herbs are mainly used in lung cancer to reduce therapy-associated toxicity and cancer related symptoms and sometimes to directly increase anticancer effects [4]. However, it is important to note that some CAM methods or remedies may have adverse effects or reduce the efficacy of conventional treatment, and the primary justification for use of traditional herbal drugs remains empirical evidence, case studies, and hypothetical physiological effects [4].

4. For Liver Fibrosis and Cancer.

Fibrogenesis of the liver is a gradual process of increased extracellular secretion and decreased degradation that can be initiated by activating hepatic stellate cells (HSCs). Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death in the United States. Unfortunately, there are no effective treatments available for HCC patients that are clinically satisfactory. One possible strategy to combat liver fibrosis and HCC is the use of herbal drugs. As far back as ancient China, Japan, and other Asian countries can remember, three medicinal herbs have been used as official drugs. Various chemically induced fibrosis models based on the rat liver system were created in order to test the effectiveness of specific herbal extracts in the treatment of liver fibrosis before clinical trials began. Tested medications include Inchin-ko-to (TJ-135), Yi-Guan Jian (YGJ), and Danggui Buxue Tang (YGJ), as well as Yi-Guan Jian (YGJ) (DBT). Medicinal herbal compounds such as salvianolic acid B (SAB), oxymatrine, and curcumin have been studied for their mechanisms of action in the treatment of hepatic fibrogenesis and carcinogenesis since 2007. It's not known whether or not herbal mixtures such as YGJ, which is traditionally used to treat human liver fibrosis, have any therapeutic or clinical anticancer effects on liver tissue. The discovery of additional active components in these herbal extracts, which are currently unidentified, is critical for their future pharmacological application and improvement. A combination of 10 herbs (named compound 861), including *Salvia miltiorrhiza* (sage), *Astragalus membranaceus*, and *Spatholobus suberectus* known in TCM as the "king herb" components of the formula, that is, the herbs that are pharmacologically active, and seven others (modifiers of toxicity that act synergistically with the king herbs to improve immune function), has been tested in a number of experimental studies for antifibrotic properties. Two uncontrolled open trials of 60 and 22 patients with chronic hepatitis B who were treated with compound 861 reported beneficial effects on liver fibrosis, with the majority of treated patients showing both clinical and histological improvement. Since these clinical studies of compound 861 did not satisfy quality control criteria, clinicians consider that additional well-designed trials are needed for routine and authorized clinical use of compound 861 for the treatment of hepatitis B-induced liver fibrosis.

NATURAL LEAD MOLECULES TOWARDS TREATMENT OF CANCER

In both developed and developing countries, cancer is one of the most deadly diseases because of the irregular cell proliferation it causes. When a healthy cell develops into a cancerous one, every change in the body can be observed. Chemotherapy and modern drugs for treating cancer have more side effects because cancer is still the world's second leading cause of death despite the availability of many treatments. Millions of people are diagnosed with cancer each year, and many of them succumb to it and die. Every year, cancer claims the lives of approximately 3500 million people around the world, or roughly 2-3 percent of all annual deaths. Chemopreventive agents have had some success in the treatment of cancer, but their use is discouraged due to the toxicity they cause. 5,6. Chronic inflammation is caused by factors such as smoking, dietary imbalances, hormones, and infections that last a long time. Because chemotherapy and radiation therapy have such severe side effects, finding more effective and less harmful treatments should happen right away. Anti-cancer measures include healthy eating habits, not smoking, effective treatment of inflammatory diseases, and the use of nutritional supplements that boost the immune system. Unfortunately, chemotherapy, which is currently the only major treatment option for advanced-stage cancers, has a high level of toxicity when administered to healthy tissues. Podophyllotoxin was discovered in the late 1960s, and the search for natural cancer drugs continued with the discovery of vincristine, vinblastine, camptothecin, and taxol. More than a thousand plant species have been found in nature to be anti-cancer. Oncologists have found great success with Taxol in treating cancers like ovarian, breast, and other small cell types. A synthetic modification of this drug's structure led to Etoposide, a drug that has been shown to be effective in treating cancers like lung and testicular small cell types. If medicinally important herbs and their mechanisms of action could be discovered, a new and more effective treatment for cancer prevention would be available. Potent compounds isolated from medicinal plants have been the source of a slew of new drugs for decades. The process of drug discovery and development includes three main following research approaches

- (1) Bioactivity- based on mechanism of specific action-directed isolation and characterization of active compounds,
- (2) Rational drug design - involves modification and synthesis of analog, and
- (3) Mechanism of action studies.

Early research focuses on the isolation of bioactive lead compounds, chemical modification, and improvement of other pharmacological profiles using traditional drugs and Ayurvedic knowledge to find new drug leads with high activity but low toxicity for cancer therapy. The Indian subcontinent continues to use traditional medicines to treat a wide range of ailments, thanks in part to the region's rich botanical diversity. Medical plants have been used as a remedy for a variety of human ailments according to ethnohistorical accounts. This is because medicinal plants contain large amounts of powerful chemical compounds that act as curative drugs with fewer side effects. Natural medicines have become increasingly important in the healthcare system, impacting both global health and international trade. Because most people in developing countries have low incomes and Western drugs are expensive, herbal drugs have been used by a large proportion of the population for a long time. These countries are more open to the use of herbal drugs because of their religious and cultural traditions. Cancer is likely to be the most important genetic disease for which medicinal plants can be used as treatment. See fig. 1.

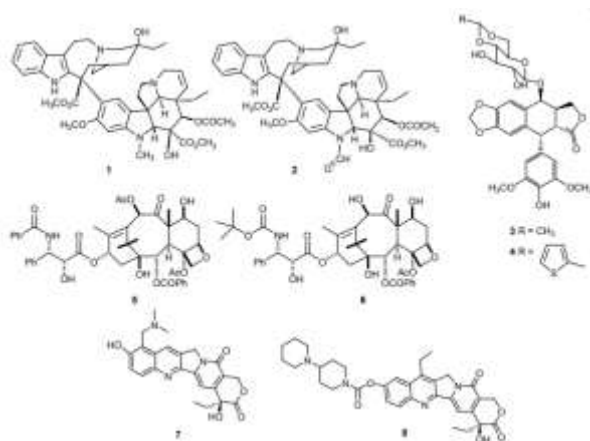


Fig. 1. Plant-derived clinically used anticancer agents: 1. Vinblastine, 2. Vincristine, 3. Etoposide, 4. Teniposide, 5. Taxol, 6. Docetaxel, 7. Topotecan, 8. Irinotecan

Microtubulin assembly into coiled spiral aggregates induced by self-association of tubulin is under the influence and mode of action of Vincristine. Etoposide is a topoisomerase II inhibitor causes DNA breaks, whereas topoisomerase I is inhibited by the action of Docetaxel. Drugs made of synthetic chemistry and use of technological combinatorial chemistry in the synthesis of new leads, still today drugs derived from natural product make an enormous contribution to drug discovery. Nature is an attractive source of new therapeutic candidate compounds as a tremendous chemical diversity is found in millions of species of plants, several plant derived compounds are currently successfully employed in cancer treatment.

PLANTS USED FOR CANCER TREATMENT

Over 3 million people die each year from cancer, according to the American Cancer Society. Research

is ongoing around the world to find effective cancer treatments, including chemotherapy, which uses high doses of chemical drugs and can be toxic in some cases. Some plants may contain properties that naturally have the ability to prevent the spread of cancer or the risk of developing various types of cancer by using the antioxidant, anticancer activities that are known to inhibit or kill carcinogenic cells in medicinal plants. Some examples of plants that may be used for cancer treatment are discussed with their respective advancements are listed in below Table No. 2.

Table 2: List of medicinally important plants towards cancer therapy

Plant name	Species name	Common name	Compound name	Mechanism of action
Azadirachta indica	Celastraceae	Natural Ladder, Indian Neem, and Indian Lilac	Azadirachtin	It is used to treat inflammatory disorders. It is also used for its chemopreventive properties.
Brassica	Brassicaceae	Broccoli	Sulforaphane	Effective in the treatment of prostate cancer patients.
Camptotheca	Camptothecaceae	Witch, Happy Tree	Camptothecin, Topotecan, CPT-11, 9-Azoxacantharidin	It is used as a drug for cancer treatment.
Curcuma	Curcuminaceae	Turmeric	Curcumin	Used in the treatment of breast and lung cancer.
Hypericum	Hypericaceae	St. John's Wort, Hypericum	Hypericin, Hypericidin	Widely used as a drug, commonly known as St. John's Wort. It is used in the treatment of cancer.
Laportea	Laportaceae	Laportea, Pau d'Arco, Tamarillo, and Laportea	Laporticin, Laporticin	It is used in the treatment of cancer.
Mayapple	Podophyllaceae	Devil's Apple, May Apple, Indian Apple, Umbrella Plant, Wild Yam	Podophyllotoxin, Etoposide, Podophyllin, and Teniposide	Treat both lung and testicular cancer.
Podophyllis	Podophyllaceae	Podophyllis Tree	Podophyllotoxin, Etoposide, Podophyllin, and Teniposide	This tree is used to make the anticancer drug etoposide.
Podophyllis	Podophyllaceae	Podophyllis Tree	Podophyllotoxin, Etoposide, Podophyllin, and Teniposide	Treatment of infectious diseases.
Podophyllis	Podophyllaceae	Podophyllis Tree	Podophyllotoxin, Etoposide, Podophyllin, and Teniposide	Unknown, symptoms, breast, lung, pediatric solid cancers and others.

USE OF HERBAL SUPPLEMENTS AS ADJUVANTS IN CONVENTIONAL ANTI-CANCER THERAPIES

Numerous Chinese herbal drugs are being used in combination with chemotherapy or radiotherapy to improve the efficacy of cancer therapy and reduce side effects and complications (Figure 2), although this practice is highly frowned upon by many western physicians. Understanding of the use of specific herbal drugs as adjuvants to conventional therapy, therefore, needs to be increased in consultation and coordination with physicians and other health care providers. This section outlines evidence for use of herbal drugs as adjuvants to conventional drug-based, chemo- or radiotherapy regimes in cancer treatment.

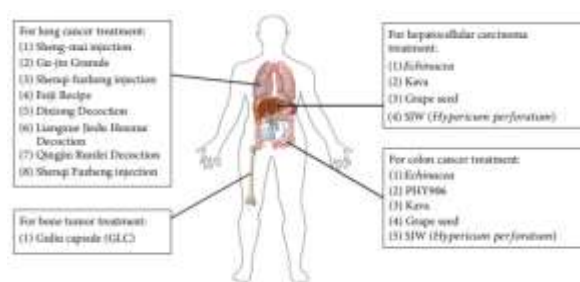


Figure 2: Medicinal herb “extracts” or “formulations” being tested as adjuvant treatments for chemo- or radiotherapies against various cancers.

EFFECT OF HERBAL DRUGS IN RANDOMIZED CONTROLLED TRIALS

Most clinical trials now use randomised controlled trials (RCTs) (also known as randomised comparative trials) as the gold standard to determine the effectiveness of healthcare interventions. As a result, the best estimates of treatment effect are obtained from well-planned and well-executed RCTs, and this information is used to guide clinical decision-making. For example, herbal drug trials may be superior to homoeopathy and acupuncture trials in terms of reporting quality, as noted by Linde et al. Furthermore, the quality of reporting varied greatly across different botanical drugs and continued to improve steadily over the course of several decades, from the 1980s through the 2000s. The controversy over herbal drug trials led an international group of pharmacologists, methodologists and pharmacognosists to convene in June 2004 for the purpose of developing recommendations for the reporting of herbal drug trials in Toronto, Canada. As a result of this meeting, a consensus document was developed. In order to assist researchers in better assessing the internal/external validity and reproducibility of herbal drug trials, an expansion of the CONSORT statement was proposed, allowing for a more accurate assessment of the safety and effectiveness of herbal drugs. One item (item 4 (interventions)) received detailed recommendations, while eight other items (item 1 (title and abstract), item 2 (background), item 3 (participants), item 6 (outcomes), item 15 (baseline data), item 20 (interpretation), item 21 (generalizability), and article 22 [overall evidence] received minor recommendations. Item 4's specific recommendation addressed the herbal drugs intervention's concerns, which still require in-depth elaboration. These suggestions were made to help researchers better report RCT findings. Despite the fact that TCM and other herbal medicines are widely used around the world, their efficacies have only been studied on a sporadic basis, with very few studies that were properly randomised and controlled. Studies by Mok and colleagues and Chan and colleagues, for example, have used high standards of clinical trial methodology. Mok and his colleagues looked into the possibility that Chinese herbal medicines could help reduce the toxicity caused by chemotherapy. In patients with early-stage breast or colon cancer, traditional Chinese herbal medicines appeared to have a significant impact on nausea control, but these herbal medicines did not reduce the hematologic toxicity of chemotherapy. To find out whether or not the test TCMs improved QOL and decreased the side effects of systemic chemotherapy, Chan et al. performed a random, placebo-controlled trial on patients being treated with an established treatment for ovarian cancer. Additionally to standard chemotherapy, ovarian cancer patients were randomised to receive either the experimental TCM formulation or a placebo. Using the Global Health Status (GHS) score and the European Organization for

Cancer Research and Treatment (EORTC) questionnaire, the primary outcome was recorded. Secondary outcomes included other quality-of-life (QOL) items, chemotoxicity levels determined using WHO criteria, and immune system alterations. According to the findings, TCM had effects on immune function maintenance (e.g., lymphocyte count and cytokine activities) rather than quality of life improvement. Even though these randomised trials fell short of their enrollment goals, we may be forced to draw the conclusion that further systematic research with RCTs is needed in order to fully evaluate and demonstrate specific bioactivities and the benefits of different traditional Chinese medicine (TCM) formulations and plant extracts for cancer patients.

CONCLUSION

Herbal properties found in medicinal plants aid in the discovery of new drugs to treat a wide range of disorders and diseases, including cancer, without harming the people being treated. Ayurvedic cancer treatment using natural products and traditional medicines is becoming increasingly important in the field of cancer research. Traditional medicines, medicinal plants in cancer treatment, and anticancer properties of natural products were briefly discussed in this review. The anticancer properties of medicinal plants come from their combination of Immunomodulatory and antioxidant properties. Only a small number of the approximately 1000 species of plants have been studied for biological activity, so additional research into the anticancer activity of the plants that show promising activity must be carried out. A powerful anticancer drug is vinca rosea alkaloids Vinblastine and Vincristine, which come from the plant Vinca rosea. Taxol, a compound derived from the leaves of the Taxus brevifolia plant, has found wide application in the treatment of cancer. According to the findings of this review, cancer is the leading killer in developing nations like India. For rural and poor people, herbal drug treatment may be a highly recommended option for treating cancers of various types effectively.

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