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"HERBAL THERAPEUTICS IN ONCOLOGY: UNRAVELLING PHYTOCHEMICAL PATHWAYS AND FUTURE CLINICAL DIRECTIONS"

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ABSTRACT

Cancer remains one of the leading causes of morbidity and mortality worldwide, characterized by uncontrolled cell proliferation, invasion, and metastasis. Despite advancements in chemotherapy, radiotherapy, and targeted therapy, these treatments are often associated with toxicity, resistance, and high cost. Herbal drugs, derived from medicinal plants, have emerged as promising alternatives or complementary approaches in cancer treatment due to their multi-targeted actions and relatively low toxicity. Phytochemicals such as flavonoids, alkaloids, terpenoids, and polyphenols exhibit anticancer activities through mechanisms including apoptosis induction, inhibition of angiogenesis, immune modulation, and suppression of tumor growth.

Recent research highlights that plant-derived compounds interact with multiple molecular pathways involved in carcinogenesis, offering advantages over single-target synthetic drugs. This review provides a comprehensive overview of herbal drugs used in cancer treatment, their phytochemical constituents, mechanisms of action, therapeutic applications, advantages, limitations, and future perspectives.

KEYWORDS: Herbal drugs; Cancer therapy; Phytochemicals; Medicinal plants; Anticancer activity.

1. INTRODUCTION

Cancer is a multifactorial and heterogeneous group of diseases characterized by uncontrolled cell proliferation, evasion of apoptosis, sustained angiogenesis, and the ability to invade and metastasize to distant organs. It remains one of the leading causes of morbidity and mortality worldwide, posing a major challenge to global healthcare systems. According to epidemiological trends, the global burden of cancer continues to rise due to factors such as population aging, environmental exposure, lifestyle changes, and genetic predisposition. (1)(2)Despite significant progress in early detection and therapeutic strategies, cancer treatment remains complex and often associated with limitations such as toxicity, high cost, and therapeutic resistance.

Conventional cancer therapies, including surgery, chemotherapy, radiotherapy, and targeted therapy, have significantly improved survival rates in many cancer types. However, these approaches are frequently associated with severe side effects, including immunosuppression, organ toxicity, and reduced quality of life. Additionally, the emergence of multidrug resistance (MDR) in cancer cells poses a significant obstacle to successful treatment outcomes.(3)(4)These limitations have driven the search for alternative and complementary therapeutic approaches that are more effective, safer, and affordable.

Herbal medicine, also known as phytotherapy, has been utilized for centuries in traditional systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine for the treatment of various diseases, including cancer. (5)(6) These systems rely on the therapeutic properties of medicinal plants and their bioactive constituents to restore physiological balance and promote healing. In recent decades, there has been a resurgence of interest in herbal drugs due to their natural origin, cultural acceptance, and potential therapeutic benefits.

The importance of herbal drugs in modern oncology is underscored by the fact that several widely used anticancer agents are derived from plant sources. For instance, vincristine and vinblastine, obtained from *Catharanthus roseus*, and paclitaxel, derived from *Taxus* species, have become integral components of chemotherapy regimens. (7)(8)(9)These examples highlight the significant contribution of natural products to drug discovery and development.

Herbal drugs are rich in diverse phytochemicals such as flavonoids, alkaloids, terpenoids, and polyphenols, which exhibit a wide range of biological activities. These compounds can modulate multiple molecular pathways involved in carcinogenesis, including cell cycle regulation, apoptosis, angiogenesis, and immune responses.(10)(11) Unlike conventional drugs that often target a single pathway, herbal compounds exhibit multi-targeted actions, which may enhance therapeutic efficacy and reduce the likelihood of resistance.

Furthermore, herbal drugs have shown potential as chemo preventive agents by inhibiting the initiation and progression of cancer. Their antioxidant and anti-inflammatory properties play a crucial role in protecting cells from DNA damage and reducing the risk of tumor development. (12)(13) In

addition, herbal medicines are increasingly being used as adjunct therapies to improve the effectiveness of conventional treatments and reduce their side effects. (14)

Despite these promising attributes, the clinical application of herbal drugs in cancer therapy requires careful evaluation. Issues such as variability in composition, lack of standardization, and limited clinical evidence remain significant challenges.(15)Therefore, scientific validation through rigorous research is essential to establish their safety and efficacy.

In this context, the present review aims to provide a comprehensive overview of the role of herbal drugs in cancer treatment, focusing on their phytochemical composition, mechanisms of action, therapeutic applications, and future prospects.

2. Role of Herbal Drugs in Cancer Therapy

Herbal drugs play a significant role in cancer therapy due to their diverse pharmacological properties and ability to target multiple pathways involved in tumor development and progression. These drugs can be used as primary therapeutic agents, adjunct therapies alongside conventional treatments, or chemopreventive agents that help prevent the onset of cancer. (16)(13) The use of herbal drugs in cancer therapy has gained increasing attention due to their potential to provide effective treatment with fewer side effects compared to conventional therapies.

One of the key advantages of herbal drugs is their ability to modulate multiple molecular targets simultaneously. Cancer is a complex disease involving various signalling pathways, and targeting a single pathway is often insufficient for effective treatment. Herbal compounds, on the other hand, can influence several pathways, including those involved in cell proliferation, apoptosis, angiogenesis, and metastasis.(10)(11) This multi-targeted approach enhances therapeutic efficacy and reduces the likelihood of drug resistance.

In addition to their direct anticancer effects, herbal drugs can also improve the efficacy of conventional treatments. For example, certain phytochemicals can sensitize cancer cells to chemotherapy and radiotherapy, making them more effective. At the same time, these compounds can protect normal cells from the harmful effects of these treatments, thereby reducing side effects and improving patient quality of life.(14)

Herbal drugs also play a crucial role in cancer prevention. Many phytochemicals possess antioxidant and anti-inflammatory properties that help neutralize free radicals and reduce inflammation, both of which are associated with cancer development. By preventing DNA damage and inhibiting the initiation and promotion stages of carcinogenesis, herbal drugs can significantly reduce the risk of cancer. (12)(13)

Furthermore, herbal drugs can enhance the immune system, enabling the body to better recognize and eliminate cancer cells. Immunomodulatory compounds found in medicinal plants stimulate the activity of immune cells such as natural killer cells, macrophages, and lymphocytes, thereby improving the body’s defence mechanisms against cancer.(17)

Despite these benefits, the use of herbal drugs in cancer therapy is not without challenges. Issues such as variability in composition, lack of standardization, and potential herb-drug interactions must be carefully considered. Nevertheless, with continued research and development, herbal drugs have the potential to become an integral part of modern cancer therapy.

3. Phytochemical Constituents of Herbal Anticancer Drugs

Medicinal plants are rich sources of structurally diverse bioactive compounds known as phytochemicals, which are responsible for their therapeutic properties. These phytochemicals include flavonoids, alkaloids, terpenoids, polyphenols, saponins, and glycosides, all of which contribute significantly to anticancer activity. Unlike conventional synthetic drugs that typically act on a single molecular target, phytochemicals exert pleiotropic effects by modulating multiple signalling pathways involved in carcinogenesis, thereby enhancing therapeutic efficacy and reducing the likelihood of resistance development.(10)(11)Flavonoids, one of the most widely distributed groups of phytochemicals, possess strong antioxidant properties and play a crucial role in scavenging reactive oxygen species, thus preventing oxidative DNA damage. They also regulate signalling pathways such as PI3K/Akt and NF-κB, leading to inhibition of cell proliferation and induction of apoptosis.(18)Alkaloids, another important class of compounds, have been extensively studied for their anticancer properties. Compounds such as vincristine and vinblastine disrupt microtubule formation and inhibit mitosis, while camptothecin derivatives inhibit topoisomerase enzymes, resulting in DNA damage and cancer cell death.(19) Terpenoids, including paclitaxel, exert their effects by stabilizing microtubules and preventing cell division, as well as modulating signalling pathways involved in tumor growth and survival.(20) Polyphenols such as resveratrol and epigallocatechin gallate exhibit antioxidant and anti-inflammatory activities, inhibit angiogenesis, and regulate gene expression associated with cancer progression.(21)(22) Saponins and glycosides further contribute to anticancer effects by inducing apoptosis, enhancing immune responses, and disrupting cellular homeostasis in cancer cells.(23) Collectively, these phytochemicals form the basis of the anticancer potential of herbal drugs.

4. Mechanisms of Action of Herbal Drugs in Cancer

Herbal drugs exert their anticancer effects through a variety of interconnected mechanisms that target different stages of cancer development and progression. One of the primary mechanisms is the induction of apoptosis, a programmed cell death process that eliminates abnormal cells. Phytochemicals activate both intrinsic and extrinsic apoptotic pathways by regulating pro-apoptotic and anti-apoptotic proteins and activating caspases, leading to controlled cell death. (24)In addition to apoptosis, herbal compounds inhibit cell proliferation by arresting the cell cycle at specific checkpoints, thereby preventing uncontrolled growth of cancer cells. (3)Another important mechanism is the inhibition of angiogenesis, which is essential for tumor growth and metastasis.

Herbal drugs suppress the expression of pro-angiogenic factors such as vascular endothelial growth factor, thereby limiting blood supply to tumors.(16) Furthermore, phytochemicals exhibit anti-metastatic activity by inhibiting enzymes such as matrix metalloproteinases and blocking processes like epithelial-mesenchymal transition, which are critical for cancer cell migration and invasion.(4)Antioxidant activity also plays a significant role, as herbal compounds neutralize reactive oxygen species and protect cells from oxidative damage that can lead to mutations and cancer development.(12)(15) Additionally, many herbal drugs modulate the immune system by enhancing the activity of immune cells such as natural killer cells and macrophages, thereby improving the body's ability to combat cancer. (17)These multi-targeted mechanisms make herbal drugs highly effective in cancer therapy.

5. Important Herbal Drugs Used in Cancer Treatment

Several medicinal plants have been extensively studied for their anticancer properties and have contributed to the development of modern chemotherapy drugs. *Catharanthus roseus* is one of the most significant plants in this regard, as it produces vincristine and vinblastine, which are widely used in the treatment of leukemia, lymphoma, and other cancers due to their ability to inhibit cell division.(9) Similarly, *Taxus* species are the source of paclitaxel, a potent anticancer agent that stabilizes microtubules and prevents mitosis, making it effective in the treatment of breast, ovarian, and lung cancers.(7)*Curcuma longa*, commonly known as turmeric, contains curcumin, which exhibits strong anti-inflammatory, antioxidant, and anticancer properties by modulating multiple signaling pathways, including NF-κB and STAT3. (17)(25)*Withaniasomnifera*, or Ashwagandha, contains withanolides that induce apoptosis and inhibit cancer cell proliferation while also enhancing immune function. (26)*Camellia sinensis*, the source of green tea, is rich in catechins such as epigallocatechin gallate, which inhibit tumor growth, angiogenesis, and metastasis.(21)*Allium sativum*, commonly known as garlic, contains sulfur compounds like allicin that exhibit anticancer effects by inducing apoptosis and inhibiting tumor progression. (12) In addition to these well-known plants, several others such as *Zingiber officinale*, *Panax ginseng*, and *Aloe vera* have shown promising anticancer activities through their antioxidant and anti-inflammatory properties.

6. Herbal Drugs in Different Cancer Types

Herbal drugs have demonstrated efficacy against a wide range of cancer types through various mechanisms of action. In breast cancer, compounds such as curcumin and resveratrol inhibit tumor growth by modulating estrogen receptor signaling, inducing apoptosis, and suppressing angiogenesis.(17)(18) In lung cancer, phytochemicals such as flavonoids and terpenoids inhibit cell proliferation and induce programmed cell death by targeting key signaling pathways.(20) Colorectal cancer can be effectively targeted by herbal compounds that exhibit antioxidant and anti-inflammatory properties, thereby preventing DNA damage and tumor progression.(27) In prostate

cancer, plant-derived compounds such as green tea catechins and resveratrol inhibit tumor growth by modulating androgen signaling and inducing apoptosis (27) Herbal drugs have also shown potential in the treatment of liver cancer, where compounds such as curcumin and silymarin reduce oxidative stress and inhibit tumor growth. In leukemia, alkaloids such as vincristine and vinblastine are widely used due to their ability to disrupt cell division and induce apoptosis.(9) Additionally, herbal compounds have demonstrated protective effects against skin cancer by preventing UV-induced damage and reducing oxidative stress. The use of herbal drugs in combination with conventional therapies has further enhanced their efficacy and reduced treatment-related toxicity, highlighting their potential as integrative therapeutic agents. (14)

7. Advantages of Herbal Drugs

Herbal drugs offer several advantages that make them attractive alternatives or complements to conventional cancer therapies. One of the most important benefits is their relatively low toxicity, as many herbal compounds selectively target cancer cells while sparing normal cells, thereby reducing adverse effects. (28) In addition, herbal drugs exhibit multi-targeted mechanisms of action, allowing them to modulate multiple pathways involved in cancer development and progression, which reduces the likelihood of drug resistance.(29) They are also cost-effective and widely accessible, particularly in developing countries where access to modern healthcare may be limited. (6)(30)Furthermore, many herbal compounds possess chemopreventive properties, enabling them to prevent or delay the onset of cancer by inhibiting carcinogenesis at various stages. (13)Herbal drugs can also be used in combination with conventional therapies to enhance therapeutic efficacy and reduce side effects, providing a synergistic approach to cancer treatment. (14) Moreover, their immunomodulatory effects help strengthen the immune system, improving the body's ability to fight cancer.(17)These advantages highlight the potential of herbal drugs as valuable tools in cancer management.

8. Limitations and Challenges

Despite their numerous benefits, herbal drugs face several limitations and challenges that hinder their widespread clinical application. One of the primary concerns is the lack of robust clinical evidence supporting their efficacy, as most studies are limited to laboratory and animal models.(15)Additionally, the chemical composition of herbal drugs can vary depending on factors such as plant species, geographical location, and extraction methods, leading to inconsistencies in therapeutic outcomes. (31)The AYUSH-recommended formulations and their components, commonly utilized medicinal plants and formulations by Indians, and additional promising Indian medicinal plants are all reviewed in this message. (32)Poor bioavailability is another major limitation, as many phytochemicals have low solubility and are rapidly metabolized, reducing their effectiveness in vivo. (25) Herb-drug interactions also pose significant risks, as herbal compounds may alter the pharmacokinetics of conventional drugs, leading to reduced efficacy or increased toxicity.

(28)Furthermore, the lack of standardization and quality control in herbal formulations can result in variations in potency and safety. (31)Complex factor interactions are captured by designs like Box-Behnken and central composite, which aid in determining ideal circumstances that boost product reliability, cut waste, and improve performance. (33)Regulatory challenges also exist, as herbal medicines are often not subject to the same stringent standards as pharmaceutical drugs. (34)Addressing these challenges is essential for the successful integration of herbal drugs into modern cancer therapy.This paper evaluates the global impact and difficulties of iodine supplementation programs, looks at the connection between iodine shortage and children's cognitive development, and highlights the crucial iodine requirements during pregnancy and lactation. (35)

9. Recent Advances in Herbal Cancer Therapy

Recent advances in science and technology have significantly improved the potential of herbal drugs in cancer therapy. Nanotechnology-based drug delivery systems have been developed to enhance the bioavailability, stability, and targeted delivery of phytochemicals, thereby improving their therapeutic efficacy. (29) For example, nano formulations of curcumin have shown increased absorption and sustained release, leading to better clinical outcomes. Combination therapy involving herbal drugs and conventional treatments has also gained attention, as it can enhance anticancer effects, reduce drug resistance, and minimize side effects. (14) Advances in analytical techniques have facilitated the identification of novel phytochemicals with potential anticancer activity, providing new opportunities for drug discovery.(36) Efforts to standardize herbal formulations and ensure quality control have further improved their reliability and safety (31) Additionally, the application of molecular biology and bioinformatics has enabled the identification of specific targets for herbal compounds, paving the way for personalized medicine approaches. (37)(38) The International Conference on Harmonization (ICH) is a platform created to synchronize regulatory standards across the United States, Europe, and Japan, and it has been widely discussed. (39)These advancements highlight the growing importance of herbal drugs in modern oncology.With the specific aim of enhancing drug delivery to the brain, numerous types of nanomedicine-based drug delivery devices are presently being researched. (40) Furthermore, the safety and effectiveness of this plant in humans have not been well evaluated. It is anticipated that this review will gather and enhance the current understanding of Kalanchoepinnata's possible application in complementary and alternative medicine. (41)

10. Future Perspectives

The future of herbal drugs in cancer therapy is promising, with numerous opportunities for research and development. There is a need for large-scale clinical trials to validate the safety and efficacy of herbal drugs and establish their role in mainstream medicine. Integration of herbal medicine with conventional therapies, known as integrative oncology, is expected to improve treatment outcomes and enhance patient quality of life. The role of antiviral medications has not yet been determined;

treatment is primarily supportive. Strict infection control procedures in hospitals, such as contact and droplet precautions, and home isolation of suspected cases and patients with mild diseases are all part of prevention. (42)Advances in drug delivery systems, such as nanoparticles and targeted carriers, will further improve the bioavailability and specificity of herbal compounds. Research into synergistic interactions between herbal and conventional drugs may lead to more effective treatment strategies. Additionally, sustainable harvesting and conservation of medicinal plants are essential to ensure their availability for future use. The application of modern technologies such as genomics, proteomics, and metabolomics will provide deeper insights into the mechanisms of action of herbal drugs and facilitate the development of targeted therapies.(37)(38)These developments will play a crucial role in advancing the field of herbal cancer therapy. However, many traditional treatments have not been thoroughly studied scientifically, demonstrating minimal clinical effectiveness.(43) We also look at how nanoparticles might be used in drug delivery systems as nanocarriers. The most recent advancements in quercetin-loaded nanoparticles for cancer treatment can be summed up in this overview. (44)

11. CONCLUSION

Herbal drugs represent a promising and evolving approach in the treatment of cancer, offering significant advantages such as multi-targeted mechanisms of action, reduced toxicity, and cost-effectiveness. The diverse phytochemical composition of medicinal plants enables them to modulate various pathways involved in cancer development, including apoptosis, proliferation, angiogenesis, and immune response. Despite these benefits, challenges such as lack of clinical validation, poor bioavailability, and variability in composition must be addressed to ensure their safe and effective use. Advances in nanotechnology, molecular biology, and pharmacology are expected to overcome these limitations and enhance the therapeutic potential of herbal drugs. The integration of herbal medicine with conventional cancer therapies offers a holistic approach to treatment, improving patient outcomes and quality of life. Continued research and innovation are essential to fully realize the potential of herbal drugs in oncology and to establish them as reliable components of modern cancer therapy.

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