

International Journal of Drug Research and Technology

Available online at <http://www.ijdrct.com/>

Review Article

A REVIEW ON MEDICINAL PLANTS USED AS A SOURCE OF ANTICANCER AGENTS

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ABSTRACT

In this review we describe and discuss several approaches to selecting higher plants as candidates for drug development with the greatest possibility of success. We emphasize the role of information derived from various systems of traditional medicine (ethnomedicine) and its utility for drug discovery purposes. Cancer is a major public health burden in both developed and developing countries. An attempt has been made to review some medicinal plants used for the prevention and treatment of cancer. Medicinal herbs have been on the forefront whenever we talk about anticancer remedies, Herbal medicines have a vital role in the prevention and treatment of cancer. With advanced knowledge of molecular science and refinement in isolation and structure elucidation techniques, various anticancer herbs has been identified, which execute their therapeutic effect by inhibiting cancer-activating enzymes and hormones. Several anticancer agents including taxol, vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, and etoposide derived from epipodophyllotoxin are in clinical use all over the world. A number of promising agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid and silvestrol are in clinical or preclinical development.

Keywords: Anticancer, Medicinal plants, Herbal medicine, Taxol, Cancer treatment.

INTRODUCTION

Natural Products, especially plants, have been used for the treatment of various diseases for Thousands of years. Terrestrial plants have been used as medicines in Egypt, China, India and Greece from ancient time and an impressive number of modern drugs have been developed from them. The first written records on the medicinal uses of plants appeared in about 2600 BC from the Sumerians and Akkaidians.¹ According to World Health Organization, 80 % of the people living in rural areas depend on medicinal herbs as primary healthcare system. A great deal of pharmaceutical research done in technologically advanced countries like USA,

Germany, France, Japan and China has considerably improved quality of the herbal medicines used in the treatment of cancer. Some herbs protect the body from cancer by enhancing detoxification functions of the body. Some herbs reduce the toxic side effects of chemotherapy and radiotherapy. Scientists all over the world are concentrating on the herbal medicines to boost immune cells of the body against cancer. By understanding the complex synergistic interaction of various constituents of anticancer herbs, the herbal formulations can be designed to attack the cancerous cells without harming normal cells of the body.^{2,3} Cancer is a major public health burden in both developed and developing countries. It was estimated that there

were 10.9 million new cases, 6.7 million deaths, and 24.6 million per-sons living with cancer around the world in 2002 (Parkin *et al.*, 2005). Cancer, after cardiovascular disease, is the second leading cause of death^{4, 5} in the United States (Hoyert *et al.*, 2005), where one in four deaths is due to cancer. The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity (Shoeb, 2005). Of the 92 anticancer drugs commercially available prior to 1983 in the US and among worldwide approved anticancer drugs between 1983 and 1994, 60% are of natural origin (Cragg *et al.*, 1997). Documentation of the Ayurvedic system recorded in Sushruta and Charaka dates from about 1000 BC.⁶ The Greeks also contributed substantially to the rational development of the herbal drugs. Dioscorides, the Greek physician (100 A.D.), described in his work “*De Materia Medica*” more than 600 medicinal plants. Phytochemicals have been proposed to offer protection against a variety of chronic ailments including cardiovascular diseases, obesity, diabetes, and cancer. As for cancer protection, it has been estimated that diets rich in phytochemicals can reduce cancer. The old saying “Prevention is always better than cure” is particularly true in the case of cancer where a cure, if at all possible, is associated with high cytotoxic loads and/or invasive procedures. With our growing understanding of the molecular etiology of cancer, it has become apparent that strategies which limit DNA damage and/or increase the probability of DNA repair by inhibiting aberrant proliferation will decrease cancer incidence.⁷

Cancer and its Classification

Cancer is a general term applied of series of malignant diseases that may affect different parts of body. These diseases are characterized by a rapid and uncontrolled formation of abnormal cells, which may mass together to form a growth or tumor, or proliferate throughout the body, initiating abnormal growth at other sites. If the

process is not arrested, it may progress until it causes the death of the organism. The main forms of treatment for cancer in humans are surgery, radiation and drugs (cancer chemotherapeutic agents). Cancer chemotherapeutic agents can often provide temporary relief of symptoms, prolongation of life, and occasionally cures. In recent years, a lot of effort has been applied to the synthesis of potential anticancer drugs. Many hundreds of chemical variants of known class of cancer chemotherapeutic agents have been synthesized but have a more side effects. A successful anticancer drug should kill or incapacitate cancer cells without causing excessive damage to normal cells. This ideal is difficult, or perhaps impossible, to attain and is why cancer patients frequently suffer unpleasant side effects when under-going treatment. However, a waste amount of synthetic work has given relatively small improvements over the prototype drugs. There is a continued need for new prototype-new templates to use in the design of potential chemotherapeutic agents: natural products are providing such templates. Recent studies of tumor-inhibiting compound of plant origin have yielded an impressive array of novel structures.⁸

Types of Cancers⁹

1) Cancers of Blood and Lymphatic Systems

- a) Hodgkin's disease, b) Leukemias,
- c) Lymphomas, d) Multiple myeloma, e) Waldenstrom's disease

2) Skin Cancers

- a) Malignant Melanoma

3) Cancers of Digestive Systems

- a) esophageal cancer, b) Stomach cancer, c) Cancer of pancreas, d) Liver cancer, e) Colon and Rectal cancer, f) Anal cancer

4) Cancers of Urinary system

- a) Kidney cancer, b) Bladder cancer, c) Testis cancer, d) Prostate cancer

5) Cancers in women

a) Breast cancer, b) Ovarian cancer, c) Gynecological cancer, d) Choriocarcinoma

6) Miscellaneous cancers

a) Brain cancer, b) Bone cancer, c) Carcinoid cancer, d) Nasopharyngeal cancer, e) Retroperitoneal sarcomas f) Soft tissue cancer, g) Thyroid cancer

Breast cancer is the most common form cancer in worldwide.^{10,11} Amongst south African women, breast cancer is likely to develop in one out of every 31 women in the country. breast cancer in India is the second most common cancer in women after the cancer of uterine cervix. The BRCA2 gene is implicated in approximately 30-45% familial breast cancer. The absence of any significant BRCA2 mutation in the level expression of the gene indicates that the BRCA2 gene may not be playing an important role in the sporadic breast as well as familial breast carcinogenesis in Indian women.¹² Human papilloma virus is sexually transmitted and casually related to cervical cancer. Almost of all cervical cancer and high grade cancer precursor caused by specific high risk types of human papilloma virus.¹³

Causes of Cancer

The main cause of cancer is mutation; changes in DNA that reduce or eliminate the normal controls over cellular growth, maturation, and programmed cell death. These changes are more likely to occur in people with certain genetic backgrounds (as illustrated by the finding of genes associated with some cases of cancer and familial prevalence of certain cancers) and in persons infected by chronic viruses (e.g., viral hepatitis may lead to liver cancer; HIV may lead to lymphoma). The ultimate cause, regardless of genetic propensity or viruses that may influence the risk of the cancer, is often exposure to carcinogenic chemicals (including those found in nature) and/or to radiation (including natural cosmic and earthly radiation), coupled with a failure of the immune system to eliminate the cancer cells at an early stage in their

multiplication. The immunological weakness might arise years after the exposure to chemicals or radiation. Other factors such as tobacco smoking, alcohol consumption, excess use of caffeine and other drugs, sunshine, infections from such oncogenic virus like cervical papillomaviruses, adenoviruses Kaposi sarcoma (HSV) or exposure to asbestos. A Cancer cell also has the character of immortality even in vitro whereas normal cells stop dividing after 50-70 generations and undergoes a programmed cell death (Apoptosis). Cancer cells continue to grow invading nearby tissues and metastasizing to distant parts of the body. Metastasis is the most lethal aspect of carcinogenesis.¹⁴

The Mechanism on Cancer Therapy¹⁵

- Inhibiting cancer cell proliferation directly by stimulating macrophage phagocytosis, enhancing natural killer cell activity.
- Promoting apoptosis of cancer cells by increasing production of interferon-I, interleukin-2, immunoglobulin and complement in blood serum.
- Enforcing the necrosis of tumor and inhibiting its translocation and spread by blocking the blood source of tumor tissue.
- Enhancing the number of leukocytes and platelets by stimulating the haemopoietic function.
- Promoting the reverse transformation from tumor cells into normal cells.
- Promoting metabolism and preventing carcinogenesis of normal cells.
- Stimulating appetite, improving quality of sleep, relieving pain, thus benefiting patients health.

Plants Used as Anticancer Agents

The first agents to advance into clinical use were the isolation of the vinca alkaloids, vinblastine and vincristine from the Madagascar periwinkle, *Catharanthus roseus* (Apo-cynaceae) introduced a new era of the use of plant material as anticancer agents. They were the first agents to advance into clinical use for the treatment of cancer. Vinblastine and vincristine are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma. The discovery of paclitaxel from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae), is another evidence of the success in natural product drug discovery. Various parts of *Taxus brevifolia* and other *Taxus* species (e.g., *Taxus Canadensis*, *Taxus baccata*) have been used by several Native American Tribes for the treatment of some noncancerous cases.¹⁶ *Taxus baccata* was reported to use in the Indian Ayurvedic medicine for the treatment of cancer. Paclitaxel is significantly active against ovarian cancer, advanced breast cancer, small and non-small cell lung cancer. Camptothecin, isolated from the Chinese ornamental tree *Camptotheca acuminata* (Nyssaceae), was advanced to clinical trials by NCI in the 1970s but was dropped because of severe bladder toxicity. Topotecan and irinotecan are semi-synthetic derivatives of camptothecin and are used for the treatment of ovarian and small cell lung cancers, and colorectal cancers, respectively.^{17,18} Epipodophyllotoxin is an isomer of podophyllotoxin which was isolated as the active antitumor agent from the roots of *Podophyllum* species, *Podophyllum peltatum* and *Podophyllum emodi* (Berberidaceae). Etoposide and teniposide are two semi-synthetic derivatives of epipodophyllotoxin and are used in the treatment of lymphomas and bronchial and testicular cancers.¹⁹ Homoharringtonine isolated from the Chinese tree *Cephalotaxus harringtonia* (Cephalotaxaceae), is another plant-derived agent in clinical use.²⁰ Combretastatins were isolated

from the bark of the South African tree *Combretum caffrum* (Combretaceae). Combretastatin is active against colon, lung and leukemia cancers and it is expected that this molecule is the most cytotoxic phyto-molecule isolated so far.^{21,22}

Ayurvedic Medicine for the Treatment of Cancer

The structure of paclitaxel was elucidated in 1971 and was clinically introduced to the US market in the early 1990s (Wani *et al.*, 1971; Rowinsky *et al.*, 1992). Paclitaxel is significantly active against ovarian cancer, advanced breast cancer, small and non-small cell lung cancer (Rowinsky *et al.*, 1992). Camptothecin²³, isolated from the Chinese ornamental tree *Camptotheca acuminata* Decne (Nyssaceae), was advanced to clinical trials by NCI in the 1970s but was dropped because of severe bladder toxicity (Potmeisel, 1995). Topotecan and irinotecan are semi-synthetic derivatives of camptothecin and are used for the treatment of ovarian and small cell lung cancers, and colorectal cancers, respectively (Creemers *et al.*, 1996; Bertino, 1997). Epipodophyllotoxin is an isomer of podophyllotoxin which was isolated as the active anti-tumor agent from the roots of *Podophyllum* species, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich (Berberidaceae) (Stahelin, 1973). Etoposide and teniposide are two semi-synthetic derivatives of epipodophyllotoxin and are used in the treatment of lymphomas and bronchial and testicular cancers (Cragg and Newman, 2005; Harvey, 1997). Homoharringtonine isolated from the Chinese tree *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.) (Cephalotaxaceae), is another plant-derived agent in clinical use (Itokawa *et al.*, 2005; Powell *et al.*, 1970). A racemic mixture of harringtonine and homoharringtonine has been used successfully in China for the treatment of acute myelogenous leukemia and chronic myelogenous leukemia (Cragg and Newman, 2005; Kantarjian *et al.*, 1996). Elliptinium²⁴ a derivative of ellipticine, isolated from a

Fijian medicinal plant *Bleekeria vitensis* A.C. Sm., is marketed in France for the treatment of breast cancer (Cragg and Newman, 2005).

Herbs with Anticancer Activity

Allium sativum contains more than 100 biologically useful secondary metabolites, which include alliin, alliinase, allicin, S-allyl-cysteine (SAC), diallyldisulphide (DADS), diallyltrisulphide (DATS) and methylallyltrisulphide.²⁵ *Aloe vera* contains aloemodin, which activates the macrophages to fight cancer. *Aloe vera* also contains acemannan, which enhances activity of the immune cells against cancer. *Aloe vera* is found to inhibit metastases.²⁶ *Annona species* contain acetogenins, which possess significant cytotoxic activity against leukemia and sarcoma. Acetogenins are found to be effective in the treatment of nasopharyngeal carcinoma.²⁷ *Arctium lappa* contains potent anticancer factors that prevent mutations in the oncogenes. It has been used in the treatment of malignant melanoma, lymphoma and cancers of the pancreas, breast, ovary, oesophagus, bladder, bile duct and the bone. A study revealed that it reduces the size of tumour, relieves the pain and prolongs the survival period.²⁸ *Betula utilis* contains betulin that can be easily converted into betulinic acid. Studies have revealed that betulinic acid inhibits growth of malignant melanoma and cancers of the liver and the lung.²⁹ *Gossypium barbadense* contains gossypol. Recent studies have revealed that gossypol possesses selective toxicity towards cancerous cells.³⁰ *Gyrophora esculenta* is a mushroom that inhibits growth of cancer by enhancing activity of the natural killer cells. A study revealed that it inhibits carcinogenesis and metastases.³¹

Plant-derived anticancer agents for future development

Numerous types of bioactive compounds have been isolated from plant sources. Several of them are currently in clinical trials or preclinical

trials or undergoing further investigation. Flavopirido is a synthetic flavone, derived from the plant alkaloid rohitukine, which was isolated from *Dysoxylum binectariferum* Hook. f. (Meliaceae) (Kellard *et al.*, 2000). It is currently in phase I and phase II clinical trials against a broad range of tumors, including leukemia, lymphomas and solid tumors (Christian *et al.*, 1997). Synthetic agent roscovitine (which is derived from natural product olomucine, originally isolated from *Raphanus sativus* L. (Brassicaceae), is in Phase II clinical trials in Europe (Cragg and Newman, 2005; Meijer *et al.*, 2003). Combretastatins were isolated from the bark of the South African tree *Combretum caffrum* (Eckl. & Zeyh.) Kuntze (Combretaceae) (Pettit *et al.*, 1987). Combretastatin A-4 is active against colon, lung and leukemia cancers and it is expected that this molecule is the most cytotoxic phyto-molecule isolated so far (Ohsumi *et al.*, 1998; Pettit *et al.*, 1995). Bangladesh. Betulinic acid a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from *Betula* species (Betulaceae) (Cichewitz *et al.*, 2004). Pervilleine-A was isolated from the roots of *Erythroxylum pervillei* Baill. (Erythroxylaceae) (Silva *et al.*, 2001). Pervilleine A was selectively cytotoxic against a multidrug resistant (MDR) oral epidermoid cancer cell line (KB-V1) in the presence of the anticancer agent vinblastine (Mi *et al.*, 2001). Pervilleine A is currently in preclinical development (Mi *et al.* 2003). Silvestrol was first isolated from the fruits of *Aglaila sylvestre* (M. Roemer) Merrill (Meliaceae) (Hwang *et al.*, 2004). Silvestrol exhibited cytotoxicity against lung and breast cancer cell lines (Cragg and Newman, 2005). Biological studies are ongoing to determine the mechanism(s) of action for silvestrol. Two novel alkaloids, schischkinnin and montamine have been isolated from the seeds of *Centaurea schischkinii* and *Centaurea montana* (Shoeb *et al.*, 2005; 2006). Both of the alkaloids exhibited significant cytotoxicity against human colon cancer cell lines. The unique structural features

of schischkinnin and montamine can be exploited as a template for generating compounds with enhanced anticancer activity. However, further investigations are necessary for their use as anticancer agents.

CONCLUSION

Medicinal plants have contributed a rich health to human beings. Plant extracts and their bioactive compounds present in them which are responsible for anticancer activity have to be screened for their valuable information. This review had given some of the plants possessing anticancer activity for various types of cancer. This review can help others to explore herbs to further extent and its use in various other disease and toxicity studies along with clinical trials.

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