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Review on Anticancer Activity of Medicinal Plants

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Abstract: This article has been prepared to review some medicinal plants used for the treating cancer disease. The plant sources of India are likely to provide effective anticancer agents. Herbs have a vital role in the prevention and treatment of cancer. Examples are provided in this review of promising bioactive compounds obtained from various plants with medicinal and other therapeutic uses. The photochemical exploration of these herbs has contributed to some extent in this race for the discovery of new anticancer drugs. In recent years owing to the fear of side effects people prefer to use natural plant products for cancer treatment. This review also helps to summarize the diverse methodologies and various ways to evaluate the potential natural compounds having anticancer activity. Although drug discovery from medicinal plants continues to provide an important source of new drug leads, numerous challenges are encountered including the procurement of plant materials and their selection.

Keywords: Medicinal Plants, Anticancer Agents, Bioactive Compounds.

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 times 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 Acadians1. Among the human diseases, cancer is one, probably the most important genetic disease which can be treated with medicinal plants. Every year, millions of people are diagnosed with cancer, leading to death in a majority of the cases. Cancer is the abnormal growth of cells in our bodies that can lead to death. Cancer cells usually invade and destroy normal cells. These cells are born due to an imbalance in the body and by correcting this imbalance, cancer may be treated. Billions of dollars have been spent on cancer research and yet we do not understand exactly what cancer is2. Every year, millions of people are diagnosed with cancer, leading to death. According to the American Cancer Society deaths arising from cancer constitute 2–3% of the annual deaths recorded worldwide. Thus cancer kills about 3500 million people annually all over the world. Several chemopreventive agents are used to treat cancer, but they cause toxicity that prevents their usage3. The increasing costs of conventional treatments (chemotherapy and radiation) and the lack of effective drugs to cure solid tumors encouraged people in different countries to depend more on folk medicine which is rooted in medicinal plants use. Such plants have an almost unlimited capacity to produce substances that attract researchers in the quest for new and novel chemotherapeutics. Of over 2069 anti-cancer clinical trials recorded by the National Cancer Institute as being in progress as of July 2004, over 160 are drug combinations including these agents against a range of cancers.

Types of Cancers

1**) Cancers of Blood and Lymphatic Systems**:

a) Hodgkin's disease, b) Leukemia's, 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 the 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) Characinoid cancer d) Nasopharyngeal cancer

Plant Derived Anti-Cancer Drugs

1. ***Vinca Alkaloids***

The first agents introduced in clinical use were vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the Catharanthusroseus. (Apocynaceae).These drugs were discovered during an investigation by oral hypoglycemic agents. While research investigators could not confirm this activity, it was noted that plant extracts reduced significantly white blood cell counts and also caused bone marrow depression in rats13. Plant extract also prolongs the life of mice bearing a transplantable lymphocytic leukemia. The plant was originally endemic to Madagascar, but the samples used in the discovery of vincristine and vinblastin were collected in Philippines and Jamaica. Recently semi-synthetic analogues of vinca alkaloids are vinorelbine (VRLB) and vindesine (VDS). These are primarily using alone or in combination with other chemotherapeutic drugs to combat a variety of cancers. VLB is using for the treatment of lymphomas, leukemias, breast cancer, testicular cancer, lung cancers, and Kaposi's sarcoma. VCR had also shown efficacy against leukemia, particularly acute lymphocytic leukemia in childhood [1].

Vinca alkaloids include vincristine, vinblastine, and vinorelbine. Peripheral neuropathy (PN) is one of the commonest side effects of these agents. Patients with decreased level of serum folate and vitamin B 12 are more prone to develop peripheral neuropathy. Underlying hepatic impairment and concurrent drugs which decrease Vinca alkaloids hepatic metabolism also increase the susceptibility to neuropathy. Peripheral neuropathy can be troublesome for a significant number of patients. There is no specific therapy for this complication, however; symptoms improve with the use of pyridoxine, pregabalin, and NSAIDs in some cases. The aim of this case study was to review the characteristics and outcomes of patients who suffered from peripheral neuropathy due to vincristine or vinblastine. Keywords: vinca alkaloids, peripheral neuropathy, cycles of chemotherapy, serum folate level, dose reduction. [2]

Vinca alkaloids are a subset of drugs obtained from the Madagascar periwinkle plant. They are naturally extracted from the pink periwinkle plant, Catharanthusroseus G. Don and have hypoglycemic as well as cytotoxic effects. They have been used to treat diabetes, high blood pressure and have been used as disinfectants. The vinca alkaloids are also important for being cancer fighters. There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). VCR, VBL, and VRL have been approved for use in the United States. Vinflunine is also a new synthetic vinca alkaloid, which has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium is being developed for other malignancies. Vinca alkaloids are the second-most-used class of cancer drugs and will stay among the original cancer therapies. Different researches and studies for new vinca alkaloid applications will be carried out in this regard. [3]

2. P*odophyllotoxin derivatives*

The species of Podophyllaceae family such as Podophyllumpeltatum Linn., Podophyllumemodii have been reported with a long history of therapeutical use, including the treatment of skin cancers and warts. Podophyllumpeltatum has been used by the Native Americans for the treatment of "cancer" [2]. The interest was promoted by the observation in the 1940s that an alcohol extract of the dried roots (called podophyllin) cures venereal warts by topical application. The chief cytotoxic therapeutic constituents were identified as podophyllotoxins and have been first isolated in 1880, but its correct structure could only be elucidated in the 1950s with the advancement in spectroscopic techniques. Other closely related podophyllotoxins like lignans were also isolated during this period and became introduced into clinical trials, but they were dropped due to lack of efficacy and unacceptable toxicity. Extensive research studies at Sandoz Laboratories in Switzerland in the 1960s and 1970s led to the development of etoposide and teniposide as clinical agents which are being used in the treatment of lymphomas and bronchial and testicular cancers. Of 2069 anti-cancer clinical trials recorded by the NCI as being in progress as of July 2004, over 150 are drug combinations including etoposide against a range of cancers[4]

Podophyllotoxin (PPT) is a naturally occurring antimitotic agent and an interesting lead in the development of anticancer agents. Its optimization led to the development of etoposide and teniposide used in combination chemotherapy with other anticancer drugs; unlike PPT these drugs act by inhibiting topoisomerases. Clinical success and toxicity issues at later stages of etoposide usage

inclined researchers to develop structurally modified PPT derivatives. Some of the compounds obtained are under clinical investigations and are anticipated to reach the market. Areas covered: The present review summarizes the attempts made by researchers across the globe to find out newer anticancer agents based on the PPT structure. It brings out the outline of the inventions filed in the form of patents during the years 2012 - 2014. Expert opinion: After the successful development of etoposide and teniposide there has been considerable interest in the PPT skeleton to develop newer chemotherapeutic agents. In this regard, several PPT derivatives such as TOP53, GL331, NK611, F11782, and so on, have been developed and are undergoing clinical trials. However, its low natural abundance is a major problem in carrying out research on PPT skeleton. This issue is expected to be addressed with the development of newer synthetic strategies to access structurally modified PPTs. [5]

3. ***Allium sativum*** (Allicin)

Allium sativum (garlic, lasun) is used to treat a wide variety of diseases in India. Allicin is a major component of raw garlic and ajoene is a product of the rearrangement of allicin. Its cytotoxic effect has been tested using human primary fibroblasts, a permanent, nontumorigenic cell line derived from baby hamster kidney cells and a tumorigenic lymphoid cell line derived from a Burkitt lymphoma. The cytotoxic action was in the range 2-50 µg/ml17. Some organosulfur compounds from garlic, like S-allyl cysteine, are reported to retard the growth of chemically induced and transplantable tumors in several animal models [4]. Administration of garlic (250 mg/kg, p.o., thrice a week) in male wistar rats, has been significantly suppressed 4-nitro quinoline-1-oxide induced tongue carcinogenesis as revealed by the absence by the carcinomas in the initiation phase and their reduced incidence in the post-initiation phase [6]. Thus the consumption of garlic may beneficial providing some kind of protection from cancer[7]

Throughout history, many different cultures have recognized the potential use of garlic for prevention and treatment of different diseases. Recent studies support the effects of garlic and its extracts in a wide range of applications. These studies raised the possibility of revival of garlic therapeutic values in different diseases. Different compounds in garlic are thought to reduce the risk for cardiovascular diseases, have anti-tumor and anti-microbial effects, and show benefit on high blood glucose concentration. However, the exact mechanism of all ingredients and their long-term effects are not fully understood. Further studies are needed to elucidate the pathophysiological mechanisms of action of garlic as well as its efficacy and safety in the treatment of various diseases.[8]

4. ***Andrographis Paniculate***

Phytochemical investigation of the ethanol extract of the aerial parts of Andographispaniculata has been reported the isolation of 14 compounds; a majority of them are flavonoids and labdane diterpenoids. The cytotoxic activities of these compounds have been evaluated against various cell lines and found that these isolates have a potent tumour inhibitory activity against all investigated cell lines [9]. The methanol extract of Andrographispaniculata was fractionated, dichloromethane fraction reported to possess three active constituents which were further tested and exhibited cytotoxic activity and also potent immunostimulating activity [10]. However, there were also its adverse side effects were also reported which may include gastric upset, headache, bitter taste and fatigue. High doses of Andographispaniculata may have affected the normal functions of liver [11].

Plants have been effectively used in traditional medicines for centuries. The present review aims at compiling vast pharmacological applications to comprehend and synthesize the potential image of Andrographispaniculata as a multipurpose medicinal agent. The aerial part of the plant contains a large number of chemical constituents, mainly lactones, diterpenoids, diterpene glycosides, flavonoids and flavonoid glycosides. It has multiple pharmacological properties such as antibacterial, hepatoprotective activity, anticancer, antitumor, hypoglycemic, immunomodulatory and hypotensive activities. The plant is widely cultivated and its importance as a medicinal plant is growing up with stronger reports in support of its multifarious therapeutic uses. Taking great concern of the useful benefits of the plant, it can be advocated as a safe, highly important medicinal plant for mankind. Stronger reports in support of its multifarious therapeutic uses. Taking great concern of the useful benefits of the plant, it can be advocated as a safe, highly important medicinal plant for mankind.[12]

5. ***Annona muricata***

Graviola is known by its scientific name, Annonamuricata. The important class of medicinal components found in graviola is acetogenins. Acetogenins was found in the fruit, seeds, leaves, and bark of the graviola plant. Preliminary research showed that acetogenins block production of adenosine triphosphate, which inhibits the pump that removes cancer drugs from the cell, allowing chemotherapy to be more effective. Furthermore, research suggested that acetogenin may have chemotherapeutic potential, especially against cancer that resistant to multiple drugs [10] Parkinson like symptoms can occur on oral ingestion of graviola [13]. Some specific acetogenins have been reportedly identified to be toxic for various cancer cell lines like lung solid human breast cancer, tumor carcinoma, pancreatic carcinoma, prostatic adenocarcinoma, colonic adenocarcinoma, human lymphoma, liver cancer, and multiple-drug-resistant human breast adenoca. [13]

Annona muricata is a member of the Annonaceae family and is a fruit tree with a long history of traditional use. A. muricata, also known as soursop, graviola and guanabana, is an evergreen plant that is mostly distributed in tropical and subtropical regions of the world. The fruits of A. muricata are extensively used to prepare syrups, candies, beverages, ice creams, and shakes. A wide array of ethnomedicinal activities is contributed to different parts of A. muricata, and indigenous communities in Africa and South America extensively use this plant in their folk medicine. Numerous investigations have substantiated these activities, including anticancer, anticonvulsant, anti-arthritic, antiparasitic, antimalarial, hepatoprotective and antidiabetic activities. Phytochemical studies reveal that annonaceous acetogenins are the major constituents of A. muricata. More than 100 annonaceous acetogenins have been isolated from

leaves, barks, seeds, roots and fruits of A. muricata. In view of the immense studies on A. muricata, this review strives to unite available information regarding its phytochemistry, traditional uses, and biological activities.[14]

Natural products with a lengthy recorded indigenous use. It had also been found to be a promising new anti-tumor agent in numerous in vitro studies. The present investigation concerns chemopreventive effects in a two-stage model of skin papilloma genesis. Chemopreventive effects of an ethanolic extract of A. muricata leaves (AMLE) was evaluated in 6-7 week old ICR mice given a single topical application of 7,12-dimethylbenza(α)anthracene (DMBA 100ug/100ul acetone) and promotion by repeated application of croton oil (1% in acetone/ twice a week) for 10 weeks. Morphological tumor incidence, burden, and volume were measured, with histological evaluation of skin tissue. Topical application of AMLE at 30, 100 and 300mg/kg significantly reduced DMBA/croton oil-induced mice skin papilloma genesis in (i) peri-initiation protocol (AMLE from 7 days prior to 7 days after DMBA), (ii) promotion protocol (AMLE 30 minutes after croton oil), or (iii) both peri-initiation and promotion protocol
l(AMLE 7 days prior to 7 days after DMBA and AMLE 30 minutes after croton oil throughout the experimental period), in a dose-dependent manner

6. ***Apis mellifera***

Apismellifera is the scientific name of the honey bee, from which honey is produced. Honey is used to hasten to healing skin wounds, ulcerations, and burns in Indian system of medicine. A protein of the honeybee Apismellifera has been reported to enhance proliferation of primary cultured rat hepatocytes and also suppresses apoptosis [13]. It has also shown cytotoxicity in normal human lymphocytes and HL-60 cells. Hamzaoglu et al. (2000) implanted cancer cell into neck wounds of mice, then divided mice into two groups. A significant decrease in wound cancer tumors was observed in the groups of mice that were treated with surgical wounds coated with honey pre and postoperatively. This finding may have some application in human surgery. [15]

7. *Gossypium hirsutum*

Gossypium hirustum or Gossypium herbaceumalso called as Gossypol or cottonseed oil and used as a male contraceptive, in the treatment of metastatic carcinoma of endometrium or ovary and also used in HIV. Some in vivo and in vitro studies revealed the antitumor properties of gossypol on many cytosolic and mitochondrial enzyme systems that are fundamental to tumor cell growth, including melanoma, endometrial, colon, lung, prostate, breast, brain, and adrenocortical cancer31. However, no typical dose is yet suggested for the treatment of cancer and self-medication with gossypol is not safe because of its potential toxicity [16]

8. *Zingiber officinale*

Zingiber officinale ethanol extract was investigated to find out its antitumor effects in skin tumorigenesis model. Pre-application of Zingiber officinale ethanol extract onto the skin of mice resulted in significant inhibition of 12-0-tetradecanoylphorbol-13-acetate (TPA)-caused induction of epidermal ODC, cyclooxygenase, and lipoxygenase activities and ODC mRNA expression in a dose-dependent manner. Preapplication of Zingiber official ethanol extract to mouse skin also resulted in a significant inhibition of TPA caused epidermal edema and hyperplasia. In prolonged time studies, topical application of Zingiber officinale ethanol extract thirty minutes prior to that of each TPA application to 7, 12-dimethylbenz (a)anthracene initiated mice caused a marked protection against skin tumor incidence its multiplicity[17]. Ginger's natural bio-actives, specifically ginger extract and 6-gigerol have also been investigated for their in vitro inhibition of two key aspects of colon cancer biology, cancer cell proliferation and angiogenic potential of endothelial cell tubule formation. These active ginger constituents linked to a direct effect on cancer cells. Among other compounds, 6-gingerol was found more effective even at lower doses resulted in inhibition of endothelial cell tube formation40.The suggested mechanism of action of Ginger extract on colon cancer cells may be its suppression and arresting the G0/G1-phase, reducing DNA synthesis and inducing apoptosis [18].

Ginger is a medicinal plant that has been widely used in Chinese, Ayurvedic and Tibb-Unani herbal medicines all over the world and has a long history of use in traditional systems of medicine. The primary pungent agents are due to the presence of phenyl alkyl ketones or vanillyl ketones. Gingerol and who gaol are two most active constituents of ginger based preparations. They are reported to demonstrate antiemetic, antipyretic, analgesic, antiarthritic, and anti-inflammatory activities. Ginger, the rhizome of Zingiber officinale, is one of the most widely used species of the ginger family (Zingiberaceae) and is a common condiment for various foods and beverages. Ginger has a long history of medicinal use dating back 2,500 years in China and India for conditions such as headaches, nausea, rheumatism, and colds. Characterized in traditional Chinese medicine as spicy and hot, ginger is claimed to warm the body and treat cold extremities, improve a weak and tardy pulse, address a pale complexion, and strengthen the body after blood loss. The review article focuses on experimental advances in the pharmacology of gingerol and its analogues. Keywords: Ginger, phenyl alkyl ketones, pharmacology, gingerol[19]

CONCLUSION

Medicinal plants keep the health and vitality of individual and also cure various diseases including cancer without causing toxicity. Natural products discovered from medicinal plants have played an important role in the treatment of cancer. In this review, some anti-cancer plants have been presented. These plants possess good immunomodulatory and antioxidant properties leading to anticancer activity. In conclusion, this article provides the knowledge about anticancer medicinal plants of foreign origin, which are used by people all over the world. Also, it is of significance to exploit novel anticancer drugs from medicinal plants. Without this early warning system, the problem of overcoming development of chemoresistance is quite considerable. In an ideal situation, therapy would

be tailored to suit the individual at the outset; this is unlikely at least for the very near future, despite rapid progress in pharmacogenomics. In the meantime, a better understanding of the mechanisms of resistance will at least allow the physician to modulate the therapy on a need to do basis. 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.

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