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Anticancer Agents: A Review of Relevant Information on Important Herbal Drugs

Review Article

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Abstract

Cancer has almost created havoc amongst the human society as the number of mortalities is increasing day-by-day and year after year. Numerous studies have been done to find out the cure for cancer but to no avail. Herbals have been considered as efficient anticancer agents and their importance in the treatment and management of cancer cannot be overlooked. Present review is a sincere attempt to compile the most promising anticancer agents from plant origin and list their major cancer curative potentials.

Keywords: Anticancer; Herbal Drugs.

Introduction

The uses of plants as medicine are as old as human civilization. About 60% of the anticancer drugs are derived from plant sources, e.g., taxol from *Taxus brevifolia*, camptothecin from *Camptotheca acuminata* etc. It is noted that the management of cancer is still lagging behind and there is an urgent need to search new drugs for the prevention and treatment of cancer. In this context, the plants still hold the hope for the management of cancer [1].

In recent years, the morbidity and mortality of cancer has reached a high plateau and is a major public health problem worldwide. Searching for new compounds for the treatment of cancer is the aim of numerous studies, and many works are focused on plant-derived compounds that have curative potential and have been used widely in traditional medicines [2].

Cancer is a class of diseases in which a group of cells display the traits of uncontrolled growth, invasion and sometimes metastasis. These three malignant properties of cancer differentiate them from benign tumors, which are self-limited, do not invade or metastasize. Most cancers form a tumor but some, like leukemia, do not.

Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Cancer causes about 13% of all deaths. According to the American Cancer Society, 7.6 million people died from cancer in the world during 2007. Cancers can affect other animals besides humans, and plants, too.

Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may be randomly acquired through errors in DNA replication, or are inherited, and thus present in all cells from birth. Complex interactions between carcinogens and the host genome may explain why only some develop cancer after exposure to a known carcinogen. New aspects of the genetics of cancer pathogenesis, such as DNA methylation, and microRNAs are increasingly being recognized as important.

Genetic abnormalities found in cancer typically affect two general classes of genes. Cancer-promoting oncogenes are often activated in cancer cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments. Tumor suppressor genes are often inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.

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Cancer is usually classified according to the tissue from which the cancerous cells originate, the primary tumor, as well as the normal cell type they most resemble. These are location and histology, respectively. A definitive diagnosis usually requires the histologic examination of a tissue biopsy specimen by a pathologist, although the initial indication of malignancy can be symptoms or radiographic imaging abnormalities. Most cancers can be treated and some cured, depending on the specific type, location, and stage. Once diagnosed, cancer is usually treated with a combination of surgery, chemotherapy and radiotherapy. As research develops, treatments are becoming more specific for different varieties of cancer. There has been significant progress in the development of targeted therapy drugs that act specifically on detectable molecular abnormalities in certain tumors, and which minimize damage to normal cells. The prognosis of cancer patients is most influenced by the type of cancer, as well as the stage, or extent of the disease. In addition, histologic grading and the presence of specific molecular markers can also be useful in establishing prognosis, as well as in determining individual treatments.

Research on Cancer

Around 1980, cancer was first attributed to malfunctioning genes and subsequently, cancer research has become a major area of scientific research supporting the foundations of modern biology to a great extent. To unravel the human genome sequence was one of those extra ordinary tasks, which has largely been fuelled by cancer research and many of the fascinating insights into the genetic circuits that regulate developmental processes have also emerged from research on cancer. Diverse biological disciplines such as cytogenetics, virology, cell biology, classical and molecular genetics, epidemiology, biochemistry together with the clinical sciences have close links in their research to find remedies to stop the abnormal growth, which is characteristic of cancerous cells.

Role of Plant Based Drugs

Plant derived compounds have been of great significance to cancer therapy. The medicinal value of plants has been recognized by almost every society on this planet. In the nineteenth and earlier centuries, natural product extracts, particularly those derived from botanical species, provided the main source of folk medicines. In industrialized nations at the present times, some fifty percent of all prescribed drugs are derived or synthesized from natural products, the widely available sources for which are plants and microorganisms. It is considered that because of the structural and biological diversity of their constituents, terrestrial plants offer a unique and renewable resource for the discovery of potential new drugs and biological entities.

The goals of using plants as sources of therapeutic agents:

1. To produce bioactive compounds of novel or known structures as lead compounds for semisynthesis to produce patentable entities of higher activity and/or lower toxicity, e.g., metformin, nabilone, oxycodon (and other narcotic analgesics), which are based, respectively, on morphine, taxol, podophyllotoxin, etc.
2. To use agents as pharmacologic tools, e.g., lysergic acid diethylamide.
3. To use the whole plant or part of it as a herbal remedy, e.g., cranberry, garlic, ginkgo, etc.
4. To isolate bioactive compounds for direct use as drugs, e.g., digoxin, morphine, reserpine, vinblastine, vincristine, etc.

Development of Anticancer Drugs from Plants

It is estimated that there are roughly 500,000 higher flowering plant species occupying terrestrial habitats. A large number of species have only been very superficially examined for their pharmacological and medical application. Less than 1% of these species has been thoroughly investigated for their potential use as novel therapeutic agents.

Traditionally, cancer drugs were discovered through large-scale screening of synthetic chemicals against animal tumor systems, primarily murine leukemia's. The agents discovered in the first two decades of cancer chemotherapy (1950-1970) largely interacted with the DNA or its precursors, inhibiting the synthesis of new genetic material or causing irreparable damage to DNA itself. In the area of cancer treatment, many claims have been made for the beneficial effects of plants [3].

Drug discovery from medicinal plants has played an important role in the treatment of cancer. Of all available anticancer drugs between 1940 and 2002, 40% were natural products per se or natural product-derived with another 8% considered natural product mimics [4].

Epipodophyllotoxins

In the development of the anticancer drugs, etoposide, and teniposide, as semi synthetic derivatives of epipodophyllotoxins were isolated from *Podophyllum peltatum* L. and *Podophyllum emodi*. [5]. *Podophyllum peltatum* is most commonly known as the mayapple, but in various regions it is also known as Devil's apple, hog apple, Indian apple, umbrella plant, wild lemon, and American mandrake. Podophyllotoxin, extracted from the mandrake plant (may-apple; *Podophyllum peltatum* L.) was used as a folk remedy by the American Indians and early colonists for its emetic, cathartic and anthelmintic effects. The mayapple is a perennial plant in the barberry family (Berberidaceae), which is found in woodlands in Canada and the Eastern U.S. The two-leaved plants normally produce a single, small white flower (usually in May, thus the name) from the fork in the stem. The flower develops into a pulpy, lemon yellow berry, which ripens in late summer and is the only part of the plant that isn't poisonous. The plant's long, thin rhizome (a horizontal underground stem from which the roots grow) is the most poisonous part, but also the most useful because it contains high concentrations of the compounds podophyllotoxin and alpha and beta peltatin, all of which have anticancer properties. Podophyllotoxin (podofilox) and its derivatives, etoposide and teniposide, are all cytostatic (antimitotic) glucosides. Podofilox, an extract of the mayapple generally acts as a cell poison, to which cells undergoing mitosis (division) are particularly vulnerable. Podophyllotoxin binds to tubulin at a site distinct from that for interaction with the vinca alkaloids. Etoposide and teniposide have no effect on microtubular structure or function at usual concentrations [6, 7].

Currently, extracts of the plant are used in topical medications for genital warts that are caused by the human papilloma virus (HPV), and some skin cancers. The purgative action of mayapple

rhizome powder is very strong, and the compounds in it are too toxic to attempt self-medication with this plant. The FDA rates the use of this plant as "unsafe."

Paclitaxel

Taxus baccata and *Taxus brevifolia* are members of the yew family (Taxaceae). *T. baccata* is commonly known as the English yew. *T. brevifolia* is most commonly known as the Pacific Yew, but it may also be referred to as the Western or American yew. The FDA designated it the only approved source of paclitaxel (Taxol), an anticancer drug that has gained a lot of attention. The bright red fruits of yews are called arils and each cups a single seed. The arils, which are moderately sweet, are the only parts of the plant that do not contain poisonous alkaloids called taxines.

Paclitaxel's anticancer properties were first discovered in the 1960s as a result of a huge plant-screening program initiated by the National Cancer Institute (NCI). Researchers further identified its specific functions (it keeps fiber-like cell structures called microtubules from breaking down) in 1979, and clinical trials to test its safety started in 1983. The compound has been identified in lesser quantities in other yew species such as the American yew and *T. cuspidata*, the Japanese Yew. The English yew contains a similar compound called docetaxel, which is marketed under the name Taxotere. The development of paclitaxel firstly isolated from the bark of western yew tree in 1971 has proved an effective drug for the treatment of breast and ovarian cancers [8].

Paclitaxel, which is sold as Taxol by Bristol-Myers Squibb, binds to microtubules and inhibits their depolymerization (molecular disassembly) into tubulin [9, 10]. This means that paclitaxel blocks a cell's ability to break down the mitotic spindle during mitosis (cell division). With the spindle still in place the cell can't divide into daughter cells (this is in contrast to drugs like colchicine and the Vinca alkaloids, which block mitosis by keeping the spindle from being formed in the first place). Paclitaxel is given intravenously (it irritates skin and mucous membranes on contact), and is most effective against ovarian carcinomas and advanced breast carcinomas.

Docetaxel

Rhone-Poulenc Rorer has trademarked Docetaxel as Taxotere. Like paclitaxel, it prevents the mitotic spindle from being broken down by stabilizing the microtubule bundles, but clinical trials indicate that it is about twice as effective as paclitaxel in doing so. Docetaxel, which is also given intravenously, is being tested on carcinomas of the bladder, cervix, lung, and ovaries, on malignant melanoma and on non-Hodgkin's lymphoma.

Beta-lapachone and Lapachol

A quinone is derived from lapachol (a naphthoquinone), which can be isolated from the lapacho tree (*Tabebuia avellanedae*), a member of the catalpa family (Bignoniaceae). Like camptothecin and topotecan, ß-lapachone inhibits DNA topoisomerase I.

Researchers have found that this compound has promising anticancer and antiviral properties. Topoisomerase inhibitors, including beta-lapachone, seem to be effective against several types of cancer, including lung, breast, colon and prostate cancers and malignant melanoma. The use of beta-lapachone in humans has been limited due to its toxicity. However, 3-allyl-beta-lapachone has been found to have lower toxicity in cell culture tests, and therefore may prove to be more useful than beta-lapachone.

Beta-lapachone works by disrupting DNA replication. Topoisomerase I is an enzyme that unwinds the DNA that makes up the chromosomes. The chromosomes must be unwound in order for the cell to use the genetic information to synthesize proteins. Beta-lapachone keeps the chromosomes wound tight, and so the cell can't make proteins. As a result, the cell stops growing. Because cancer cells grow and reproduce at a much faster rate than normal cells, they are more vulnerable to topoisomerase inhibition than are normal cells. Beta-lapachone also interferes with the replication of HIV-1, thereby slowing the advancement of the disease.

Colchicine

It is a water-soluble alkaloid found in the autumn crocus that blocks or suppresses cell division by inhibiting mitosis. Specifically, it inhibits the development of spindles as the nuclei are dividing. Normally, the cell would use its spindle fibers to line up its chromosomes, make a copy of them, and divide into two new cells with each daughter cell having a single set of chromosomes. With colchicine present, the spindle fibers don't form, and so the cell can't move its chromosomes around. The cell may end up copying some or all of the chromosomes anyway, but can't parcel them out into new cells, and so it never divides. Because cancer cells divide much more rapidly than normal cells, cancers are more susceptible to being poisoned by mitotic inhibitors such as colchicine, paclitaxel, and the Vinca alkaloids, vincristine and vinblastine.

Vincristine and Vinblastine

Vinca alkaloids are obtained from the Madagascar periwinkle plant. They are naturally occurring or semi synthetic nitrogenous bases extracted from the pink periwinkle plant *Catharanthus roseus* G. Don. There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine and vindesine (VDS), but only VCR, VBL and VRL are approved for use in the United States.

The main mechanisms of vinca alkaloid cytotoxicity is due to their interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, directly causing metaphase arrest. However, they can do many other biochemical activities that may or may not be related to their effects on microtubules. Many of the effects that do not include microtubule interruption happen only after treatment of cells with clinically irrelevant doses of the vinca alkaloids. Nevertheless, the vinca alkaloids and other antimicrotubule agents also have an effect on both nonmalignant and malignant cells in the nonmitotic cell cycle, because microtubules are involved in many nonmitotic functions.

The vinca alkaloids connect to binding sites on tubulin that they are separate from those of the taxanes, colchicine, podophyllotoxin and guanosine 5' triphosphate. Binding occurs rapidly and can reverse too. Existing evidence maintains the existence of two

vinca alkaloid binding sites per mole of tubulin dimer [11].

Developments Towards Newer Anticancer Agents

In the early development of modern medicine, biologically active compounds from higher plants have played a vital role in providing medicines to combat pain and diseases. For example, the organic monographs of British Pharmacopoeia of 1932 had more than 70% plant-derived products. However, with the advent of synthetic medicinal chemistry, the role of plant derived therapeutic agents significantly declined (mostly) in the economically developed nations. The synthetic drugs are more toxic to animal body. Besides curing cancer, they harm the normal cells of the body and are producing severe side effects that are not only long living but may pose threat to patient's life.

Ganoderma lucidum, commonly referred to as Lingzhi in Japan or Reishi in China, has been used in Asia for health promotion for centuries. It is considered to be a natural medicine that promotes longevity and maintains the vitality of human beings. Its beneficial clinical effects in patients with hepatitis, hyperglycemia, chronic bronchitis, cancer, muscular dystrophy, arteriosclerosis, hypertension, hypercholesterolemia, and leukopenia have been confirmed in pharmacologic studies in recent years. The fruiting bodies, mycelia, and spores have recently received more and more attention not only as home remedies but also as new drug sources [12, 13]. The anti-cancer effects of *G. lucidum* have been demonstrated in both *in vitro* [14] and *in vivo* studies. In addition, the observed anti-cancer activities of Ganoderma have prompted its usage by cancer patients alongside chemotherapy [15]. The usefulness of Ganoderma in benign prostatic hyperplasia has already been reported in rat models [16].

Sphaeranthus indicus (Compositae) is an herb found mostly in southern India. It is bitter stomachic, stimulant, alterative, pectoral, demulcent, and external emollient. The herb is an ingredient of certain proprietary marketed preparations in India, namely, "Prostabliss" used for the management of benign prostatic hyperplasia. Nahata et al., (2013) screened *S. indicus*, *Ganoderma lucidum* and *Urtica dioica* for their cytotoxicity against human cancer cell lines and found *S. indicus* to be the most effective in inhibiting the proliferation of prostate cancer cell lines, that is, PC-3 and DU-145. The petroleum ether, ethanol and aqueous extracts of the test drugs were screened for their *in vitro* cytotoxicity. *S. indicus* proved to be the best in these studies and its petroleum ether extract exhibited inhibitory activity against most of the human cancer cell lines, namely, lung (A549), prostate (PC-3 andDU-145), colon (Colo-205), neuroblastoma (IMR-32), and breast cancer (MCF-7). It was concluded that *S. indicus* induces apoptosis through mitochondrial-dependent pathway in HL-60 Cells and exerts cytotoxic potential on several human cancer cell lines [14]. *Sphaeranthus indicus* and *Urtica dioica* have already been reported for their usefulness in benign prostatic hyperplasia [17, 18].

The Chinese herbal medicine *Radix sophorae* is widely applied as an anti-carcinogenic/anti-metastatic agent against liver cancer. Cheung et al., (2007) showed that Leachianone A, isolated from *Radix sophorae*, possessed a profound cytotoxic activity against human hepatoma cell line HepG2 *in vitro*, with an IC_{50} value of 3.4 mg/ml post-48-h treatment. Its mechanism of action involved both extrinsic and intrinsic pathways of apoptosis. Its anti-tumor effect was further demonstrated *in vivo* by 17–54% reduction of tumor size in HepG2-bearing nude mice, in which no toxicity to the heart and liver tissues was observed. In conclusion, this is the first report describing the isolation of Leachianone A from *Radix sophorae* and the molecular mechanism of its anti-proliferative effect on HepG2 cells [19].

The pomegranate tree, *Punica granatum*, especially its fruit, possesses a vast ethnomedical history and represents a phytochemical reservoir of heuristic medicinal value. The tree/fruit can be divided into several anatomical compartments: seed, juice, peel, leaf, flower, bark and roots, each of which has interesting pharmacologic activity. Juice and peels, for example, possess potent antioxidant properties, while juice, peel and oil are all weakly estrogenic and heuristically of interest for the treatment of menopausal symptoms and sequelae. The use of juice, peel and oil has also been shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis [20].

Betulinic acid, a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from Betula species (Betulaceae). Pisha et al., (1995) extracted *Ziziphus mauritiana* Lam. (Rhamnaceae) collected in Zimbabwe. The ethyl acetate-soluble extract displayed selective cytotoxicity against human melanoma cells (MEL-2). Betulinic acid was then found to be active *in vivo* using athymic mice carrying human melanomas, with little toxicity. Further biological studies indicated that betulinic acid works by induction of apoptosis [21]. Pre-clinical development towards a topical formulation is also ongoing.

Turmeric has been shown to possess variety of pharmacological properties such as anti-inflammatory, anti-carcinogenic and anti-oxidant by different workers. Yasmin et al., (1998) have reported that turmeric also activates the lymphocytes and induces apoptosis of tumor cells [22]. Spectrofluorimetric determination can now be carried out for curcumin in any formulation or drug mixtures [23].

The antitumor activity of the methanolic extract of *Glinus lotoides* has been evaluated against Dalton's ascitic lymphoma (DAL) in Swiss albino mice. A significant enhancement of mean survival time of tumor bearing mice and peritoneal cell count in normal mice was observed with respect to the control group [24].

Andrographolide, the major diterpenoid of the *Andrographis paniculata* extract has shown cytotoxic activity against KB (human epidermoid carcinoma) and P-388 (lymphocytic leukemia) cells. The methanol extract of aerial parts of *Andrographis paniculata* and some of the isolated compounds showed growth inhibitory and differentiating activity on M1 (mouse myeloid leukemia) cells [25].

β-hydroxyisovalerylshikonin (HIVS), which was isolated from the plant *Lithospermum radix* (roots of *Lithospermum erythrorhizon*) induces apoptosis in various cell lines of human tumor cells. Suppression of the activity of PLK-1 (polo-like kinase 1) via inhibition of tyrosine kinase activity by β- HIVS might play an important role in the induction of apoptosis [26].

Bioassay directed fractionation of *Saussurea lappa* led to the isolation of a novel lappadilactone and seven sesquiterpene lactones as cytotoxic principles against selected human cancer cell lines. Lap-

padilactone, dehydrocostus lactone, and costunolide exhibited the most potent cytotoxicity against Hep-G2, OVCAR-3 and HeLa cell lines [27].

Litchi fruit pericarp (LFP) extract contains significant amounts of polyphenolic compounds and exhibits powerful antioxidative activity against fat oxidation *in vitro*. This study confirmed the anticancer activity of LFP extract on human breast cancer *in vitro* and *in vivo*, and elucidated the mechanism of its activity [28].

An isolate "CD lignan mixture" comprising lignans from stem wood of *Cedrus deodara* consisting of (-)-wikstromol (75 - 79 %), (-)-matairesinol (9 - 13 %) and benzyl butyrolactol (7 - 11 %) was studied for its *in vitro* cytotoxicity against human cancer cell lines. The *in vivo* anticancer activity of CD lignan mixture was studied using Ehrlich ascites carcinoma and colon carcinoma (CA-51) models in mice [29]. The tumor regression observed with Ehrlich ascites carcinoma and CA-51 was 53 % and 54 %, respectively, when CD lignan mixture was given at 300 mg/kg, i.p. for nine days in the Ehrlich ascites carcinoma bearing mice and 400 mg/kg, i.p. for the same period in the CA-51 model. It was comparable with 5-fluorouracil at 22 mg/kg and 20 mg/kg, respectively.

Pine needles (*Pinus densiflora* Siebold et Zuccarini) have long been used as a traditional health-promoting medicinal food in Korea. To investigate their potential anticancer effects, antioxidant, antimutagenic, and antitumor activities were assessed *in vitro* and/or *in vivo* by Kwak et al., (2006). PNE exposure effectively inhibited the growth of cancer cells (MCF-7, SNU-638, and HL-60) compared with normal cell (HDF) in 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide assay. In *in-vivo* antitumor studies, freeze-dried pine needle powder supplemented (5%, wt/wt) diet was fed to mice inoculated with Sarcoma-180 cells or rats treated with mammary carcinogen, 7, 12-dimethylbenz [a] anthracene (DMBA, 50 mg/kg body weight). Tumorigenesis was suppressed by pine needle supplementation in the two model systems. Moreover, blood urea nitrogen and aspartate aminotransferase levels were significantly lower in pine needle-supplemented rats in the DMBA-induced mammary tumor model. These results demonstrated that pine needles exhibit strong antioxidant, antimutagenic, and antiproliferative effects on cancer cells and also antitumor effects *in vivo* and point to their potential usefulness in cancer prevention [30].

Polyalthia longifolia is a lofty evergreen tree found in India and Sri Lanka. We are reporting first time the anticancer potential of *P. longifolia* leaves extract (A001) and its chloroform fraction (F002). Both inhibited cell proliferation of various human cancer cell lines in which colon cancer cells SW-620 showed maximum inhibition with IC_{50} value 6.1 µg/ml. Furthermore, F002 induce apoptosis in human leukemia HL-60 cells as measured by several biological end points. F002 induce apoptotic bodies formation, DNA ladder, enhanced annexin-V-FITC binding of the cells, increased sub-G^0 DNA fraction, loss of mitochondrial membrane potential ($\Delta\Psi_{mt}$), release of cytochrome c, activation of caspase-9, caspase-3, and cleavage of poly ADP ribose polymerase (PARP) in HL-60 cells. All the above parameters revealed that F002-induced apoptosis through the mitochondrial-dependent pathway in HL-60 cells [1].

Ashwagandha is regarded as a wonder shrub of India and is commonly used in Ayurvedic medicine and health tonics that claim its variety of health-promoting effects. Surprisingly, these claims are not well supported by adequate studies, and the molecular mechanisms of its action remain largely unexplored to date. Widodo et al., (2007), undertook a study to identify and characterize the antitumor activity of the leaf extract of ashwagandha. Selective tumor-inhibitory activity of the leaf extract (i-Extract) was identified by *in vivo* tumor formation assays in nude mice and by *in vitro* growth assays of normal and human transformed cells [31].

Conclusion

In recent years, considerable attention has been focused on identifying naturally occurring substances capable of inhibiting, retarding, or reversing the process of multistage carcinogenesis [32]. Anticancer drug having low side effects, inducing apoptosis and target specific cytotoxicity to the cancer cells are drugs of choice.

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