

Need of an ancient roots to modern medicine in the treatment of cancer- A Review

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Abstract

The already available expensive conventional therapies for cancer like chemotherapy and radiotherapy have a number of side effects such as myelosuppression and neurological, cardiac, pulmonary, and renal toxicity, which pose serious harm to the quality of life. Therefore, there is a need to develop treatment options that include more potent and less toxic anticancer drugs as compared to existing drugs. Studies have shown that regular consumption of fruits and vegetables because of phytochemical compounds extracted from them inhibiting the activity of antioxidant and free radicals which in turn showing anti-cancer activities. More recent semi-synthetic analogues of these agents are vinorelbine (VRLB) and vindesine (VDS). These agents are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers. VLB is used for the treatment of leukaemia, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma, and VCR, in addition to the treatment of lymphomas, also shows efficacy against leukaemia, particularly acute lymphocytic leukaemia in childhood. VRLB has shown activity against non-small-cell lung cancer and advanced breast cancer. Therefore there is need of developing cell cycle-based, mechanism-targeted ancient based modern cancer therapies that emulate the body's natural process in order to stop the growth of cancer cells. This approach can limit the damage to normal cells and the accompanying side effects caused by conventional chemotherapeutic agents. This review focuses on the role of ancient medicine in modern research and anticancer drug development. The current findings and known anticancer agents from natural sources are discussed, and recent therapeutic advances in this field are presented.

Keywords: Photochemical; Cell cycle; Cytotoxic; Cytostatic; Drug resistance

Introduction

Cancer

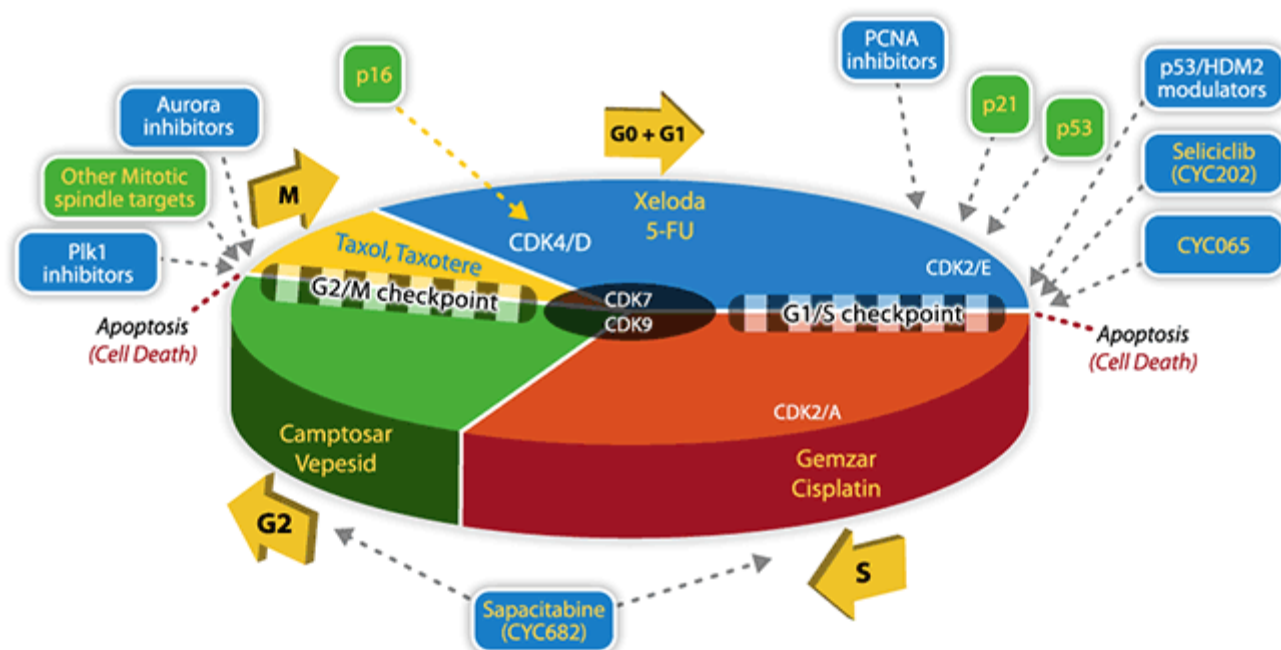
The term "cancer" was used for the first time by Hippocrates, father of western medicine, who applied Greek words "carcinoma" and "Karakinos" to describe tumour. [1] Cancer is uncontrolled growth of abnormal cells in the body. [2] Normally, meiosis and cell death procedure occurs to protect stable condition of tissues in balanced state. [3] Carcinogenesis is a multistage or multi mechanism

procedure. The initial stage of cancer includes irreversible cell changes.

Cell Cycle in Cancer

The cell cycle, the process by which cells progress and divide, lies at the heart of cancer. In normal cells, the cell cycle is controlled by a complex series of signalling pathways by which a cell grows, replicates its DNA and divides. This process also includes mechanisms to ensure errors are corrected, and if not, the cells commit suicide (apoptosis). In cancer, as a result of genetic mutations, this regulatory process malfunctions, resulting in uncontrolled cell proliferation.

Cell Cycle



The cell cycle involves a complex series of molecular and biochemical signalling pathways. As illustrated in the diagram above the cell cycle has four phases:

the G1, or gap, phase, in which the cell grows and prepares to synthesize DNA; the S, or synthesis, phase, in which the cell synthesizes DNA; the G2, or second gap, phase, in which the cell prepares to divide; and the M, or mitosis, phase, in which cell division occurs.

As a cell approaches the end of the G1 phase it is controlled at a vital checkpoint, called G1/S, where the cell determines whether or not to replicate its DNA. At this checkpoint the cell is checked for DNA damage to ensure that it has all the necessary cellular machinery to allow for successful cell division. As a result of this check, which involves the interactions of various proteins, a "molecular switch" is toggled on or off. Cells with intact DNA continue to S phase; cells with damaged DNA that cannot be repaired are arrested and "commit suicide" through apoptosis, or programmed cell death. A second such checkpoint occurs at the G2 phase following the synthesis of DNA in S phase but before cell division in M phase. Cells use a complex set of enzymes called kinases to control various steps in the cell cycle. Cyclin Dependent Kinases, or CDKs, are a specific enzyme family that use signals to switch on cell cycle mechanisms. CDKs themselves are activated by forming complexes with cyclins, another group of regulatory proteins only present for short periods in the cell cycle. When functioning properly, cell cycle regulatory proteins act as the body's own tumour suppressors by controlling cell growth and inducing the death of damaged cells. Genetic mutations cause the malfunction

or absence of one or more of the regulatory proteins at cell cycle checkpoints can result in the "molecular switch" being turned permanently on, permitting uncontrolled multiplication of the cell, leading to carcinogenesis, or tumour development.

More than 100 types of cancer have been recognized. Each cancer is classified according to cell type involved at first. According to National Cancer Institute (NCI) classification, different types of cancer are classified as follows: [4]

- carcinoma
- Leukemia
- lymphoma and myeloma
- central nerve system cancer

Causes of cancer are as follows

Viruses such as *Epstein-Barr-Virus* (EBV), *Hepatitis-B-Virus* (HBV), *Human Papilloma Virus* (HPV).

Environmental and occupational exposure such as ionizing, UV radiation, exposure to chemicals

Including vinyl chloride, benzene and asbestos.

Life style factors such as high-fat, low fiber diets, tobacco, ethanol etc.

Medication such as alkylating agents and immunosuppressant's.

Genetic factors such as inherited mutations, cancer causing genes, defective tumour suppressor genes.



The process of drug discovery and development

For many years, scientists were searching for miracle cures for cancer using chemically synthesized or natural pure compounds. In the last few decades, research has been focused on the use of natural products such as crude plant extracts or a combination of different photochemical for cancer therapy.

The process of drug discovery and development includes three main following research approaches:

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

Traditional medicine and knowledge of Ayurveda help in the discovery of new drug leads with high activity and low toxicity for cancer therapy, initial research focuses on the isolation of bioactive lead compounds, chemical modification and improving other pharmacological profiles [5]

Treatment of Cancer

Cancer chemoprevention, a term coined by Sporn et al is a way to control cancer by administration of synthetic or natural compounds in order to retard, reverse or block the process of carcinogenesis.

Fulfillment of the goal of cancer therapy, i.e. remediation with minimum adverse effects needs to be achieved. Main purpose is to arrest the disease process and to render a good quality life to the patient. Last, but not the least comes palliative care. Be it hospice care or palliative care, the objective is to provide all sort of help and comfort to the patient and their families. The main types of drugs used in cancer therapy may be broadly classified as cytotoxic and cytostatic.

Cytotoxic: These drugs help to kill the cancer cells by affecting the cell's DNA [6].

Cytostatic: These drugs prevent the growth and multiplication of cancer cells [7].

Alkylating agents, anthracyclines, anti-metabolites, anti-tumor antibiotics and monoclonal antibodies are some of the commonly used chemotherapeutic agents. The electron-rich nucleophilic sites on the genetic material are vulnerable to attack by alkylating agents. As a consequence the replicative and transcriptional machinery of the cells get disrupted. These agents also cause strand breaks due to DNA alkylation. Anti-metabolites prevent the incorporation of normal metabolites into DNA, thereby preventing normal cell division. Anthracyclines are a group of drugs which help in inhibition of DNA synthesis by causing DNA strand breaks via formation of free radicals. They also act by inhibiting the enzyme DNA topoisomerase, thus affecting transcription, replication and repair of DNA. Antitumor antibiotics work in the same way as anthracyclines. Monoclonal antibodies work by targeting and inducing an immunological response against the specific cancer

cells. Apart from all these, plant metabolites form an integral part of chemotherapeutic agents [8]. Some of the products of plant origin are presently used clinically as anticancer drugs. Antioxidants present in these plant products render their anticancer activities. The immune-modulatory properties of these products also contribute to cancer fighting ability. Anti-tumor agents may be developed from plants although intense research is needed to assess the standard dose to be administered to patients. Active components may be identified and isolated from plants and their synergistic effects determined to establish their potential in cancer remedy. Thus it is of great significance to exploit novel anticancer drugs from medicinal plants. Exploration of these neutraceuticals has contributed to some extent in this race for the discovery of new anticancer drugs. Phytochemicals not only play a crucial role in the treatment of cancer, but also serve as a chemo preventive agent.

Role of Herbal Medicine in the Treatment of Cancer

Over the past decade, herbal medicine has become a topic of global importance, making an impact on both world health and international trade. Medicinal plants continue to play a central role in the healthcare system of large proportions of the world's population. [9] Among the human diseases treated with medicinal plants is cancer, which is probably the most important genetic disease. Every year, millions of people are diagnosed with cancer, leading to death in a majority of the cases. [10]

According to the American Cancer Society [11], 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 usage. [12]

Plants have been used for treating various diseases of human beings and animals since time immemorial. They maintain the health and vitality of individuals, and also cure diseases, including cancer without causing toxicity. More than 50% of all modern drugs in clinical use are of natural products, many of which have the ability to control cancer cells. [13] According to the estimates of the WHO, more than 80% of people in developing countries depend on traditional medicine for their primary health needs. A recent survey shows that more than 60% of cancer patients use vitamins or herbs as therapy. [14, 15] Over the past decade, herbal medicines have been accepted universally, and they have an impact on both world health and international trade. Hence, medicinal plants continue to play an important role in the healthcare system of a large number of the world's population. Recently the scientific world has experienced an Upsurge of interest in the therapeutic potential of medicinal plants as a source of promising anticancer agents. However, the application of plant-based compounds for the treatment of cancer can be traced back to 1950s. Some of the very first anticancer agents derived from plants are vinca alkaloids, vinblastine, vincristine, and cytotoxic podophyllotoxins.



Statistical data suggest that 16 plant-derived anticancer drugs have been subjected to clinical trials thus far [16]. Landmarks of these clinical trials are flavopiridol, isolated from the Indian tree *Dysoxylum binectariferum*, and meisoindigo, isolated from the Chinese plant *Indigofera tinctoria*, which have been documented to have less toxicity than conventional chemotherapeutic anticancer drugs [17]. These discoveries have propelled the scientific interest of various research groups in the discovery of new anticancer agents from all-natural product sources, inclusive of plant secondary metabolites. The emerging importance of natural anticancer agents demands more research and experimentation in order to develop successful natural therapeutic options for this disease. This review focuses on the phytochemical aspect of some of the potential anticancer medicinal plants with data gathered from the scientific literature of the PubMed database. Thus, the present review aims to assemble information on some of the medicinal plants that possess anticancer properties and thus great potential for cancer treatment.

Medicinal plants as the best choice for cancer treatment

The chemical components of medicinal plants mainly possess antioxidant properties that contribute to their anticancer potential. Flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignans, catechins, and isocatechins are the major classes of bioactive constituents responsible for the antioxidant action [18]. The great potential of plant-based compounds for the treatment and prevention of cancer is attributed to their safety, low cost, and oral bioavailability.

The already available expensive conventional therapies for cancer like chemotherapy and radiotherapy have a number of side effects such as myelosuppression and neurological, cardiac, pulmonary, and renal toxicity, which pose serious harm to the quality of life [19]. Therefore, there is a need to develop treatment options that include more potent and less toxic anticancer drugs as compared to existing drugs. The market statistics mark the availability of approximately 60% plant-based anticancer drugs [20]. Medicinal plants constitute a common alternative to cancer treatment in many countries of the world [21, 22]. Cytotoxic screening of a number of plants has been done to correlate their anticancer activity and further expand their scope for drug development [23]. Owing to potential benefits of plant based drugs for cancer treatment, their use is increasingly growing from 10% to 40% across the globe; specifically, on the Asian continent, it has reached 50% [24, 25]. Anticancer benefits associated with natural plant derivatives demand extensive scientific screening and clinical experimentations for the development of improved drugs.

Natural Products have long been a fertile source of cure for cancer, which is projected to become the major causes of death in this century. However, there is a continuing need for development of new anticancer drugs, drug combinations and chemotherapy strategies, by methodical and scientific exploration of enormous

pool of synthetic, biological and natural products. There are at least 250,000 species of plants out of which more than one thousand plants have been found to possess significant anticancer properties. While many molecules obtained from nature have shown wonders, there are a huge number of molecules that still either remains to be trapped or studied in details by the medicinal chemists. The article reviews many such structures and their related chemistry along with the recent advances in Understanding mechanism of action and structure-function relationships of nature Derived anti-cancer agents at the molecular, cellular and physiological levels.

An alternative to chemotherapy, which is the most common means by which doctors and specialists treat cancer, organically based treatments may not have the severe side effects that radical treatments and chemotherapy has. The harsh side effects of cancer treatments are one motivating factor to finding alternative methods. The use of botanical when treating cancer patients is considered a natural alternative, because some plants may contain properties that naturally have the ability to prevent the spread or risk of developing various forms of cancer. As in all medical testing, careful precautions and considerations are taken when studying the different compounds present in plants that are known to treat cancer.

Modern Therapy VS Herbal Therapy

However, more and more scientific evidences have been obtained from *in vitro* studies and in animal models. The US patents have been issued for herbal compositions which were used in the treatment of cancer and cancer-related health problems in the past years. 69% of anticancer drugs approved were either natural products or developed based on knowledge gained from natural products between the 1980s and 2002, which may indicate that drug development based on the components with lead structures of potent bioactivity isolated from medicinal plants has been a major strategy for developing new anticancer drugs from herbal medicines. [26] Nowadays, the most important approaches including chemotherapy, radiation therapy or surgery used for cancer treatment, could be successful, however, they have fundamental drawbacks. Chemotherapy has severe side effects on cells and can cause damage to healthy cells. Radiation therapy is effective in tumours that their location is specified exactly. Surgery is effective when the tumour location is well known and is not surrounded by sensitive

tissues, such as brain tissue. In the heat hyperthermia approach tissue surrounding cancer cells damaged. In the era of Nanotechnology, nano particles have the ability to selectively bind to cancer cells and these cells are sensitive to light [27]. Herbal medicines include herbs, herbal substances and products, plants or a combination of plants before the discovery of new drugs have being used for more than thousands of years [28]. With the advent of the Industrial revolution and the introduction of new industrial medicine herbs using was forgotten for a long period of time



[28]. However, using new techniques reduced the obstacles in the way of natural compounds and now there is more interest in the use of natural ingredients in the pharmaceutical industry [29,30]. According to World Health Organization (WHO), 80% of people in the world using traditional treatment methods [31]. Sixty percent of the global medicines approved by food and agriculture organization of united nation (FAO), between 1984 to 1994 have been extracted from natural ingredients especially herbs [32]. Among the 121 medicines for treating cancer, 90 medicines have been extracted from medicinal plants. According to a report among the 65 new drugs that have been recorded between 1981 and 2002, 48 of which derived from natural products, including: vinca alkaloid (vincristine-vinblastine-vindesine- vinorelbine), taxans compounds (paclitaxel-docetaxel), podophyllotoxin and compounds derived from it (topotecanirinotecan), antracyclines compounds (doxorubicin-daunorubicin-epirubicin- idarubicin [33,34].

Endemic anti-carcinogenic plants

Plant material is used for the treatment of malignant disease for a few hundred years. Phytochemical examination of plants that have a good history of use in the treatment of cancer in popular culture led to

the isolation of compounds that have anti-cancer properties. Since late 1950, an extensive research on plants, microorganisms and marine animals by the National Cancer Institute (NCI) in the United States of America home began with a screening of the original application. Program was consistent screening for new compounds could be found everywhere in the animal kingdom or plant. Phytochemicals substances such as genistein in soybean help prevent prostate cancer [35]. Studies have shown that regular consumption of fruits and vegetables because of phytochemical compounds extracted from them inhibiting the activity of antioxidant and free radicals which in turn showing anti-cancer activities [36]. In Yemen, the local custom screening of native plants methanol extracted from some species including; *Dendrosicyos socotrana*, *Withania aduensis*, *Withania riebeckii*, *Dracena cinnabari* (dragon's blood tree) used as anti-cancer compounds, and *Buxus hildebrandii* showed cytotoxic effects on tumor cells [37]. Metabolites extracted from plants *Khaya senegalensis* demonstrated anticancer effects [38, 39]. Compounds extracted from the leaves of *Shvagandha* showed anti-cancer effects and this can be used as an anticancer drug [40]. Fruit of *Vaccinium stamineum* has effects against lung cancer and leukemia, respectively [41]. Metabolites derived from *Vaccinia macrocarpon* or blueberries have anti-cancer effects of breast, colon, prostate, lung, respectively [42]. *Morinda citrifolia* or berry Hindi has anticancer effects in both clinical and laboratory [43]. Alcoholic extract derived from *Biorhythms sensitivum* have anti-cancer activity in cancer development induced by Dalton ascites lymphoma cells and prevent the lifespan of mice with cancerous tumors where Ehrlich ascites cells increase [44]. Grains and fruits are a source of anti-cancer drugs [45]. Nymbold as a triterpenoid

extracted from Neem tree showed some anticancer effects on cancer cells [46]. Sap extracted from Baladhuri plants native to India by eliminating oxidative reactions showed its anti-cancer effects [47]. Extracts from two plants *Linum persicum* and *Euphorbia cheradania* that are native to Iran have shown anticancer effects [48]. Pomegranate extract has anti-cancer effect on breast cancer cells [49]. Brassinosteroids has a high potential in the production of anti-cancer drugs containing steroid hormones [50]. *Careya arborea* metabolites extracted from skin reduced cancer for a significant volume which induced by DLA cells [51]. Metabolites extracted from *Tradescantia stem bark* showed anticancer effects in mice [52]. Compounds extracted from *Indigofera aspalathoides* have anticancer effects [53]. Twelve plant species native to China that include *Anemarrhena asphodeloides*, *Artemisia argyi* or

Chinese *Artemisia*, *Commiphora myrrh*, *Duchesnea indica*, *Gleditsia sinensis*, *Ligustrum lucidum*, *Rheum palmatum*, *Rubia cordifolia*, *Salvia chinesis*, *Scutellaria barbata*, *Uncaria rhichopilla*, *Vaccaria segetalis* have anticancer effects [54]. Phytochemical compounds belonging to the hypericum genus has the potential to combat cancer [55]. It has been proven that *Sarris cernuss* has anti-cancer effects on colon and breast cancer [56]. Antioxidant effects of gallic acid extracted from *Phaleria macrocarpa* native to Indonesia has been demonstrated [57]. Ginger is one of the ginger family's plants that are too broad around the world as a seasoning used in foods and beverages. Anti-cancer properties in spicy ginger are attributed to valenoides such as 6- zhyngerol and 6-paradol [58]. Methanol compounds extracted from five plants that are native to Iran has been proven to have anti-cancer properties. These plants include *Galium mite*, *Ferula angulate*, *Stachys obtuscrena*, *Echinophora cinera*, *Circicum bracteosum* [59]. Ginseng plant is used for a long time for drug purposes and currently there are many attentions for extracting anti-cancer metabolites too. [60]. Bioactive compounds that are extracted from fungi have the potential to prevent cancer [61]. Saponins extracted from Chinese clematis have shown significant anti-cancer effects on tumors in mice [62]. Embelin compounds such as 1,4 - benzoquinone derivative 5-0 ethyl embelin(1) and 5-0 methyl embelin are promising antimetabolic and anti- cancer molecules [63]. Sesquiterpenes the class of naturally occurring molecules that are 15-carbon isoprenoid compounds. Those typically found on plants and marine life. They have therapeutic potential in decreasing the progression of cancer [64]. *Platycodon* proven that has anti-cancer properties [65]. The combination methanol extract of *Dillenia pentagons* seems to have anticancer effects against Dalton lymphoma [66]. *Limonium Vulgare*, *Artemisia maritima* and *Salicornia europaea* demonstrated anti-cancer effects.

Drugs discovered from plant for the treatment of cancer



*ETHNOPHARMACOLOGY - Vol. I - *Plants as a Source of Anti-Cancer Agents* - G. M. Cragg and D. J. Newman ©*Encyclopedia of Life Support Systems* (EOLSS)

More recent semi-synthetic analogues of these agents are vinorelbine (VRLB) and vindesine (VDS). These agents are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers. VLB is used for the treatment of leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma, and VCR, in addition to the treatment of lymphomas, also shows efficacy against leukemias, particularly acute lymphocytic leukemia in childhood. VRLB has shown activity against non-small-cell lung cancer and advanced breast cancer. Of over 2069 anti-cancer clinical trials recorded by the NCI as being in progress as of July 2004, over 160 are drug combinations including these agents against a range of cancers. The two clinically-active agents, etoposide (VM 26) and teniposide (VP 16-213), which are semi-synthetic derivatives of the natural product, epipodophyllotoxin (an isomer of podophyllotoxin), may be considered as being more closely linked to a plant originally used for the treatment of "cancer". The *Podophyllum* species (Podophyllaceae), *P. peltatum* Linnaeus (commonly known as the American mandrake or Mayapple), and *P. emodii* Wallich from the Indian subcontinent, have a long history of medicinal use, including the treatment of skin cancers and warts. *P. peltatum* was used by the Penobscot Native Americans of Maine for the treatment of "cancer", and interest was promoted by the observation in the 1940s that venereal warts could be cured by topical application of an alcohol extract of the dried roots (called podophyllin). The major active constituent, podophyllotoxin, was first isolated in 1880, but its correct structure was only reported in the 1950s. Many closely related podophyllotoxin-like lignans were isolated during this period, and several of them were introduced into clinical trials, only to be dropped due to lack of efficacy and unacceptable toxicity. Extensive research at Sandoz Laboratories in Switzerland in the 1960s and 1970s led to the development of etoposide and teniposide as clinically effective agents which are 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. A more recent addition to the armamentarium of plant-derived chemotherapeutic agents is the class of molecules called taxanes. Paclitaxel (taxol®) initially was isolated from the bark of *Taxus brevifolia* Nutt. (Taxaceae), collected in Washington State as part of a random collection program by the U.S. Department of Agriculture (USDA) for the National Cancer Institute (NCI). The use of various parts of *T. brevifolia* and other *Taxus* species (e.g. *T. canadensis* Marshall, *T. baccata* L.) by several Native American tribes for the treatment of some non-cancerous conditions has been reported, while the leaves of *T. baccata* are used in the traditional Asiatic Indian (Ayurvedic) medicine system, with one reported use in the treatment of "cancer". Paclitaxel, along with several key precursors

(the baccatins), occurs in the leaves of various *Taxus* species, and the ready semi-synthetic conversion of the relatively abundant baccatins to paclitaxel, as well as active paclitaxel analogs, such as docetaxel (Taxotere®), has provided a major, renewable natural source of this important class of drugs. Paclitaxel is used in the treatment of breast, ovarian and non-small-cell lung cancer (NSCLC), and has also shown efficacy against Kaposi sarcoma. Paclitaxel has also attracted attention in the potential treatment of multiple sclerosis, psoriasis and rheumatoid arthritis. Docetaxel is primarily used in the treatment of breast cancer and NSCLC. The importance of this class of anti-cancer agents may be judged from the fact that 12 and 23 taxane analogs are in clinical and preclinical development, respectively. In addition, of 2069 cancer clinical trials recorded by the NCI as being in progress as of July 2004, 248 or close to 12% are listed as involving taxane-derived drugs, including 134 with paclitaxel (Taxol®), 105 with docetaxel (Taxotere®), and 10 with miscellaneous taxanes, either as single agents or in combination with other anti-cancer agents. In addition, 23 taxanes are in preclinical development. Another important addition to the anti-cancer drug armamentarium is the class of clinically-active agents derived from camptothecin, which is isolated from the Chinese ornamental tree, *Camptotheca acuminata* Decne (Nyssaceae), known in China as the tree of joy. Camptothecin was discovered from extracts of plants originally collected by the U. S. Department of Agriculture as a possible source of steroidal precursors for the production of cortisone. The extract of *C. acuminata* was the only one of 1000 of these plant extracts tested for anti-tumor activity which showed efficacy, and camptothecin was isolated as the active constituent. Camptothecin (as its sodium salt) was advanced to clinical trials by the NCI in the 1970s, but was dropped because of severe bladder toxicity. However, extensive research was performed by several pharmaceutical companies in a search for more effective camptothecin derivatives, and Topotecan (Hycamtin®), developed by SmithKline Beecham (now Glaxo SmithKline), and Irinotecan (CPT-11; Camptosar®), originally developed by the Japanese company, Yakult Honsha, are now in clinical use. Topotecan is used for the treatment of ovarian and small-cell lung cancers, while Irinotecan is used for the treatment of colorectal cancers. Of the 2069 cancer clinical trials recorded by the NCI as being in progress, as of July 2004, 94 or approximately 4.5% are listed as involving camptothecin-derived drugs, including 64 with irinotecan (CPT-11), 26 with topotecan, and 4 with other miscellaneous analogues, either as single agents or in combination with other anticancer agents. In addition, 15 other camptothecin derivatives are in preclinical development. Other plant-derived agents in clinical use are homoharringtonine, isolated from the Chinese tree, *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.) (Cephalotaxaceae), and elliptinium, a derivative of ellipticine, isolated from species of several genera of the Apocynaceae family, including *Bleekeria vitensis* A. C. Sm., a Fijian medicinal plant with reputed anti-cancer properties. A racemic mixture of harringtonine and homoharringtonine (HHT) has been used successfully in China for the treatment of acute myelogenous



leukemia and chronic myelogenous leukemia. Purified HHT has shown efficacy against various leukemias, including some resistant to standard treatment, and has been reported to produce complete hematologic remission (CHR) in patients with late chronic phase chronic myelogenous leukemia (CML). Elliptinium is marketed in France for the treatment of breast cancer.

Herbal compounds may interact with pharmaceutical drugs when used in conjunction to improve the efficacy and lower the adverse effects of the drug. Several plant derived molecules like curcumin, ginsenosides, piperine, catechins, silymarin, genistein, resveratrol, isothiocyanates etc are reported to increase the effectiveness of conventional therapeutic drugs. They also aid in reduction of drug resistance. P-glycoprotein (P-gp), a multi drug resistance protein is found to be inhibited by various phytochemicals [68].

Various classes of anti-cancer agents derived from plants are currently available for clinical use owing to their diverse mechanism of action. Some of them are vinca alkaloids, podophyllotoxin derivatives, taxanes, camptothecin derivatives and homoharringtonine. Derivatives have been synthesized from the above mentioned class of drugs for clinical use in cancer therapy. Apart from these, a number of plant derived products are currently in pre-clinical and clinical trials to prove their efficacy as potent anti-tumor agents. Vinca alkaloids include two major groups namely vincristine and vinblastine, obtained from the Madagascar periwinkle, *Catharanthus roseus*. They affect the microtubular dynamics during mitotic cell division by binding to tubulin near the GTP-binding site and causing its depolymerization [69]. Other examples in this category include vindesine and vinorelbine. Vinorelbine is used in the treatment of non-small cell lung cancer alone or in conjunction with cisplatin [70]. Podophyllotoxin derivatives like etoposide and teniposide are obtained from the resin of *Podophyllum peltatum* L. (Berberidaceae) and are potent anti cancer drugs. These drugs exert their activity by causing DNA strand breaks by stabilizing the complex between topoisomerase II and DNA, thus inhibiting DNA replication [71]. Taxanes mainly include paclitaxel, obtained from the bark of the Pacific yew tree *Taxus brevifolia* and its derivatives. Paclitaxel acts by binding to polymerized microtubules, stabilizing the microtubule, and inhibiting its disassembly, thereby leading to cell death [67]. Camptothecin a drug derived from *Camptotheca acuminata* selectively inhibits topoisomerase I, thereby hindering DNA replication [72]. Topotecan and irinotecan, semi-synthetic derivatives of camptothecin, are used for the treatment of various types of cancers. Taxanes and camptothecins hold the large share in anticancer market. Homoharringtonine is isolated from the Chinese tree *Cephalotaxus harringtonia*, is another plant derived agent in clinical use. Homoharringtonine is an alkaloid derived from plants which show its anti-cancer properties by preventing protein synthesis. It has been widely used for the treatment of leukemia and myelodysplastic syndrome [73]. Omacetaxine, a semisynthetic form derived from homoharringtonine, has excellent bioavailability and has been approved by FDA of the United States for the treatment of leukemia [74]. Compounds like vinblastine, vincristine,

etoposide, teniposide, taxol, navelbine, taxotere, topotecan and irinotecan have been recommended and used as antitumor drugs [75]. Estramustine is another example of anti-cancer drug that exerts its action by binding to microtubules and is used in the treatment of prostate cancer [76]. Flavopiridol is a flavonoid which shows potent anti-cancer properties and is presently undergoing clinical trials to establish its role in cancer therapy. Some of its anti tumor properties include inhibition of cyclins and Cyclin Dependant Kinases (CDK), induction of apoptosis and inhibition of angiogenesis [77]. Combrestatin, betulinic acid and silvestrol are some of the other natural cancer fighting agents in clinical or preclinical trials. Combretastatins, isolated from the bark of *Combretum cafrum* (Combretaceae) is effective against cancers of colon, lung and blood and are potent anti-angiogenic agents [78]. Betulinic acid from *Zizyphus mauritiana*, *Zizyphus rugosa* and *Zizyphus oenoplia* also possesses anti cancer properties [79]. Silvestrol isolated from the fruits of *Aglaila sylvestre* is effective against lung and breast cancer [80].

Certain compounds like flavopiridol, roscovitine, combretastatin A-4 phosphate, betulinic acid and silvestrol are currently in preclinical or clinical stage of drug development owing to their anti-neoplastic effects. Alvocidib commonly known as Flavopiridol is a anti-tumor drug under clinical development for the treatment of a variety of cancers. It acts by blocking cell division and induction of apoptosis [81]. Certain analogues of epipodophyllotoxin like NK- 611 and Tafluposide 105 are in phase 1 clinical trials. Analogues of paclitaxel like BMS-188797, DHA-paclitaxel and so on are in various stages of experimentation. 9-amino camptothecin, DJ-927, TPI-287 and others are camptothecin analogues undergoing clinical trials. Combretastatin analogues in clinical trials include CA4PO4, AVE- 8064, AVE-8063 [82]. Elliptinium, derived from *Bleekeria vitensis* has well known anti-cancer properties [83]. Active compounds of Terminalia species are reported to effective in cancer therapy. Lapachol and β -lapachone, active components of *Tabebuia impetiginosa*, *Tabebuia rosea* and *Tabebuia serratifolia* have been reported to show anti-tumor activity *in vivo* [84]. Dragon's blood, the red sap of *Croton lechleri* possesses anti-inflammatory, antimicrobial and anticancer properties. Plants like *Colubrina macrocarpa*, *Hemiangium excelsum* and *Acacia pennatula* show cytotoxic activity against human cancer cells [85]. Active compounds in the extracts of *Teucrium polium* and *Pistacia lentiscus*, may be used in the treatment of liver disease, jaundice, diabetes, fertility problems and cancer [86]. *Commiphora opobalsamum* may also be used in anti-cancer therapy [87]. Oxindole alkaloids present in *Uncaria tomentosa*, is effective in the treatment of several diseases like ulcers, tumors and infections [88]. *Paris polyphylla*, a Chinese medicinal herb, has been reported to possess anti-carcinogenic properties [89]. *Salvia officinalis* contain anti-oxidants and are reported to exert anticancer effects [90]. *Lantana camara* is traditionally used as folk medicine owing to its antipyretic, antimicrobial and antimutagenic properties and may be anti-carcinogenic [91]. *Solanum nigrum*, a folk medicine may be used in the treatment of cancer [92]. Other examples of plants

having anti cancer potential Zedoary (*Curcuma zedoaria*), Rodent Tuber (*Typhonium flagelliforme*), God's Crown (*Phaleria macrocarpa*), Artocarpus Integer (*Selaginella corymbosa*), Bamboo Grass (*Loathatreum Gracies*), fruit makasar (*Brucca javanica*), Echo China (*Smilax china*), Sunflower (*Helianthus annus*), Leunca (*Solanum nigrum*), Job's Tears (*Coix Lachryma-Job*), Bamboo Rope (*Asparagus cochinchinensis*), and so on. Alfalfa, possessing antibacterial and antifungal properties may help in the fight against cancer [93]. The Autumn Crocus, a member of the Lily Family (Liliaceae), is a plant with chemotherapeutic potential [94]. Shikonin, a herbal medicine produced by *Lithospermum erythrorhizon*, has been reported to inhibit tumor growth in mice [95]. Phytochemicals like genestein, Indole-3-Carbinol (I3C), 3,3'-diindolemethane, curcumin (-)-epigallocatechin-3-gallate, resveratrol and lycopene are known to prevent growth of malignant cells by modulating various cellular signalling pathways and inducing apoptosis of cancer cells selectively without affecting normal cells [96]. Cruciferous vegetables are an important constituent of diet and are known anti-cancer agents. Isothiocyanates like Sulforaphane (SFN), Phenethyl Isothiocyanate (PEITC), and Benzyl Isothiocyanate (BITC) show chemopreventive activity and help to inhibit the proliferation of cancer cells. They also act as HDAC inhibitors. However further and intense research is required to establish their potential as anti-cancer drugs [97]. The chemopreventive and therapeutic potential of green tea polyphenols catechin, Epigallocatechin-3-Gallate (EGCG) are well documented. They inhibit proliferation of cancer cells, possess anti-oxidant properties, induce apoptosis of cancer cells and affect the epigenome as well [98]. Pomiferin a prenylated isoflavonoid from *Maclura pomifera*, possesses anti cancer, anti-oxidant and chemopreventive properties [99]. Isoflavones inhibit production of reactive oxygen species and thus serve as anti-cancer agents [100]. Thymoquinone, the active component of *Nigella sativa*, targets various signalling pathways involved in the process of carcinogenesis, thus suggesting its possible role in cancer therapy [101]. Actein, the active component of *Actaea racemosa* inhibits the proliferation of human breast cancer and liver cancer cells and thus show antitumor potential [102]. *Allium sativum* contains sulfur compounds which show chemopreventive activity [103]. *Andrographis paniculata* contains andrographolide, which is an anti-cancer compound that inhibits interleukin-6 (IL-6) mediated signaling, and induces programmed cell death [104]. *Ardisia crenata* containing triterpenoid saponins show anti-proliferative and antiproliferative potential, thus serving as anti-cancer agents [105]. Acetyl-11-Keto-B-Boswellic Acid (AKBA), the active ingredient of *Boswellia serrata*, acts as anti-angiogenic agents by inhibiting Vascular Endothelial Growth Factor (VEGF) signalling [106]. Asiatic acid, a pentacyclic triterpene present in *Centella asiatica* decreases viability of cancer cells by increasing expression of p53 [107]. Curcumin, active component obtained from *Curcuma longa* shows a plethora of anti-tumor properties and is effective in prevention of multiple steps involved in the process of development of cancer [108]. *Panax ginseng* contains ginsenosides which are

antiproliferative, anti-invasive, and antiangiogenic [109]. Plumbagin, a quinoid obtained from *Plumbago zeylanica* possess anticarcinogenic activity by targeting various proteins involved in the process of carcinogenesis [110]. Baicalein from *Scutellaria baicalensis* shows anticancer potential by inhibiting 12-lipoxygenase activity. The anticancer property of the plant *Withania somnifera* is attributed to withaferin a [111]. It has been reported to inhibit growth and proliferation of cancer cells. Nitidine, obtained from *Zanthoxylum nitidum* possess anticancer potential. It intercalates into DNA and inhibits topoisomerases I and II, leading to apoptosis in cancer cells [112]. Since there is a requirement for more effective anti-neoplastic agents, it is time to explore the fauna and harness their anti-cancer potential in the development of newer drugs through preclinical and clinical trials.

The drugs that are used are highly toxic as they leave an impact on normal cells also. Therefore it is time to concentrate on fabrication of newer drugs that will act preferentially on cancer cells, leaving the normal counterparts unharmed. Medicinal plants are an important source of new drugs. Drug discovery is therefore an important area which includes isolation of the active compound from plants and other natural resources, determination of the structure, chemical modifications, molecular modeling and finally to assess the effectiveness against the disease process. Vinblastine has been modified to vinflunine, which is a novel fluorinated vinca alkaloid. Vinflunine is more efficacious than the parent drug and is undergoing clinical trial [113]. Exatecan, a novel synthetic camptothecin derivative with a unique hexacyclic structure has been synthesized. Camptothecin shows remarkable anticancer potential, but it has low solubility and adverse affects. The synthetic water soluble derivative exatecan had more potent antitumor activity and less toxicity than other camptothecin [114].

Conclusion

The drugs that are currently used are highly toxic as they leave an impact on normal cells also. Therefore it is time to concentrate on fabrication of newer drugs that will act preferentially on cancer cells, leaving the normal counterparts unharmed. Medicinal plants are an important source of new drugs. Various classes of anti-cancer agents derived from plants are currently available for clinical use owing to their diverse mechanism of action. Some of them are vinca alkaloids, podophyllotoxin derivatives, taxanes, camptothecin derivatives and homoharringtonine. Derivatives have been synthesized from the above mentioned class of drugs for clinical use in cancer therapy. Apart from these, a number of plant derived products are currently in pre-clinical and clinical trials to prove their efficacy as potent anti-tumour agents. Drug discovery is therefore an important area which includes isolation of the active compound from plants and other natural resources, determination of the structure, chemical modifications, molecular modelling and finally to assess the effectiveness against the disease process. Therefore there is need of developing cell cycle-based, mechanism-targeted cancer therapies that emulate the body's natural process in order to



stop the growth of cancer cells. This approach can limit the damage to normal cells and the accompanying side effects caused by conventional chemotherapeutic agents.

Conflict of interest

Authors declare that they have no conflict of interest.

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