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Anticancer Drug Development Based on Phytochemicals

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Abstract

Fruits, vegetables and spices form an integral part of daily diet. They have received a great deal of attention from researchers owing to their wide range of disease healing properties. The active components of these natural products contribute to their medicinal properties. Burden of cancer is on the rise and cancer is a major public health concern all over the world. Plant derived compounds or phytochemicals are stud with anti-cancer properties. They are known to be effective in cancer therapy as mechanism of action has been already explored. These plant products are advantageous as they act differentially on cancer cells without affecting the normal cells. There are various modalities of cancer treatment, of which chemotherapeutic drugs is quite popular. However the emerging problem of drug associated toxicity and drug resistance necessitates the development of newer improved anti-cancer drugs. Modifications of chemical structures and computer based modeling might lead to newer drug discovery, but potential of natural products cannot be ignored. Natural plant derived molecules may serve as templates for discovery of new drugs. They may offer a novel and non-toxic way of cancer therapy. A number of plant derived molecules are used as anti-tumor drugs or are undergoing preclinical or clinical trials. Therefore it is time to emphasize on the discovery of anti-tumor drugs based on plant derived molecules.

Keywords: Cancer; Chemotherapy; Drugs; Phytochemicals

Introduction

Plant derived products find many uses in our day to day life. The food that we eat can be made mouth watering by sprinkling a pinch of spices or garnishing with herbs. These are not only gastronomic, but, they are used as medicines as well since ancient times. Ayurveda is an old concept in India which gained its popularity over the ages. Sanskrit words ayur (meaning life) and veda (meaning science or knowledge) has been amalgamated to coin the term ayurveda which means "the science of life". Ayurveda is a branch of medicine which integrates and balances our body, mind, and spirit, which is necessary for contentment and good health [1]. All these are traditional medicines having various philosophies and cultural backgrounds. India is a vast country with a wide range of demographical and climatic variations, owing to which a diversified plants grow, contributing to the name "Botanical garden of the World" [2]. Based on the traditional uses and evidences, ayurveda concept gradually intensified. Usage of alternative medicine for the management of cancer has become a challenging and emerging area. The disease cancer has been defined as inflammatory or non-inflammatory swelling in 'Charaka' and 'Sushruta Samhitas'. The nervous system (Vata or air), the venous system (Pitta or fire) and the arterial system (Kapha or water) are three basics of ayurveda and very important for normal body function. In ayurveda, cancer is an abnormality of these three systems (Tridoshas), leading to tissue damage and finally resulting in abnormal proliferation of cells [3]. These herbal remedies gained popularity in Western world and China as well. Western herbal techniques use herbs that grown in Europe, North America, China and India. This indigenous medicine system based on plants has been well documented for prevention of tumors. Not only cancer, these herbal medicines are used to treat many different health issues. Very often, these medicines are employed as a remedy for anxiety, depression, hay fever, irritable bowel syndrome, menstrual disorders, and skin diseases among many.

Cancer, an ever increasing global problem is not a single process, but involves multitude of mechanisms including initiation, promotion and progression. It is one of the root causes of morbidity and mortality throughout the world. The burden is on a steep rise and epidemic in coming years is likely to occur. Therefore, load on the healthcare system is bound to rise and tackling the disease would become challenging. Prevention is always better than cure and therefore it is the best option to minimise incidence, prevalence and death rate due to cancer. Statistics show that it is a disease of the developed world; however, developing world is now following the footsteps of the western world so far as lifestyle is concerned and is becoming vulnerable to this disease. 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 [4]. The first step in carcinogenesis is the initiation step, where the genetic material DNA is insulted by various agents causing damage and finally mutation. Accumulation of mutation leads to further development of cancer by promotion and progression steps. Targeting each of these steps is the key to chemoprevention. Herbal medicines, botanicals, dietary supplements, and edible plants are instrumental in prevention of the disease. Cancer can be treated by several modalities, depending on the location, type and stage of the tumor. Removal of the offending growth is the best way and that can be accomplished by surgery. Other treatment modalities include chemotherapy, radiation therapy, hormone therapy, targeted therapy and immunotherapy etc. Very often the cancer cells invade the tissues in micro environment or spread to distant sites by metastasis, which is a problem. Main aim of these chemotherapeutic drugs is to stall the

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proliferation and growth of cancer cells. Chemotherapy sometimes may be the sole modality of treating hematological malignancies, such as leukemia and lymphoma. In some cases it may be used as an adjuvant or neoadjuvant therapy. Chemotherapy is also used in the treatment of cancer that has relapsed. Radiations are also very effective in treating certain types of cancer. However, both chemotherapy and radiotherapy may elicit adversities on normal cells, leading to various toxic side effects. Some cancers are hormone dependent and they can be arrested by changing the level of hormones that support the growth of cancer. There are specific genes, proteins or tumor micro environments that are responsible for carcinogenesis. Targeting these factors by drugs may block the growth of cancer cells sparing the normal cells; this is the purpose of targeted therapy. Immunotherapy on the other hand boosts the body's immune system to cope with the disease. In certain cases, such as leukemia, cytotoxicity of the chemotherapeutic drugs is attributable to the fact that they hardly can discriminate between a neoplastic cells and the hematopoietic stem cells within the bone marrow. To overcome the situation stem cell transplants may come to the rescue; they are capable of generating immune response that helps to destroy cancer cells. 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 drugs help to kill the cancer cells by affecting the cell's DNA [5]. Cytostatic drugs on the other hand prevent the growth and multiplication of cancer cells [6]. 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 topoisomerse, 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 [7]. 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 chemopreventive agent.

Herbs are known to possess cancer-preventive properties and they may help to overcome the adverse effects of conventional treatment protocols. Presently, various plants are being explored for their anti-cancer properties. Plants like *Andrographis paniculata, Annona atemoya, Phyllanthus niruri, Piper longum, Podophyllum hexandrum, Tinospora cordifolia, Semecarpus anacardium, Vitis vinifera, Baliospermum montanum, Madhuca indica, Pandanus odoratissimum, Pterospermum acerifolium, Raphanus sativus, Barleria prionitis, Prosopiscineraria, Amorphopallus campanulatus, Oxoxylum indicum, Basella rubra, Flacourtia romantchi, Moringa oleifera, Ficus bengalensis, Curcuma domestica, Allium sativum, Calotropis gigantean, Datura metel, Hygrophila spinosa, Juniperus indica, Moringa oleifera, Nigella sativa, Picrorrhiza kurroa, Rubia cordifolia,* and so on are reported to show anti-tumor potential. Many of the drugs used nowadays are either derived from plants or are altered forms of natural products. 10-hydroxycamptothecin, monocrotaline, d-tetrandrine, lycobetaine, indirubin, colchicinamide, curcumol, curdione, and gossypol are examples of other natural compounds which may be used as cancer curing drugs though intense research is warranted [8,9].

For the development of carcinogenesis, several genes involved in regulation of cell growth and differentiation get altered causing mutation. Cells proliferate with these changes in DNA ultimately culminating in cancer. Bases on Gene expression profiling, certain genes and proteins are found to be aberrantly expressed in cancer. The information so derived often has an impact on occurrence and prognosis of the disease. Various signalling pathways in the process of cancer development have been documented. This has led to the identification of genes responsible for carcinogenesis, which may be targeted for the design of newer anti-cancer drugs.

Figure 1 shows many such markers which when anomalously expressed might lead to malignancy. Penicillin, obtained from the plant *Penicillium notatum* is regarded as a landmark discovery in the history of medicine [10]. Penicillin, apart from being a well known antibiotic, elicited effects at cellular and molecular levels to control proliferation of cancer cells in vitro [11]. Cancer cells divide more rapidly than normal cells. Cancer chemotherapeutics mainly target rapidly dividing cells. They are non-specific, thus they cause significant toxic effects. The process of carcinogenesis involves various changes at the genetic and epigenetic level [12]. Some classes

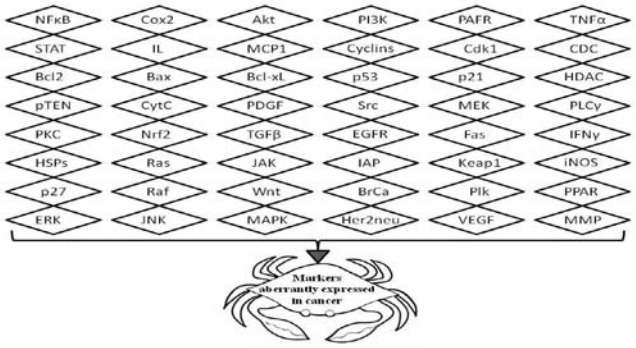

Figure 1: Markers aberrantly expressed in cancer.

of anti-tumor drugs include methyltransferase inhibitors, HDAC inhibitors (HDACI), DNA damaging/pro-oxidant drugs and mitotic disrupters. Inhibitors of hypermethylation may be reversed by gene demethylation. Histone Acetyl Transferases (HAT) and deacetylases (HDAC) regulate acetylation of chromatin. Inhibitors of HDACs reactivate genes in cancer cells that are silenced due to epigenetic modifications and cause cell cycle arrest, eventually leading to apotosis of cancer cells. These effects are mainly mediated by p53 leading to the expression of the endogenous cyclin-dependent kinase inhibitor p21cip1/waf. Other substrates of HDACs like p53, HIF-1α, Rb, β-catenin, HSP90 also contribute to the anti-cancer effects of HDAC inhibitors. Anti-cancer medications that are available also act by inhibiting microtubule dynamics. Drugs that target microtubule inhibit the metaphase anaphase transition through suppression of spindle microtubule dynamics, thereby blocking mitosis and inducing programmed cell death. Microtubule stabilizing agents are drugs that help to stabilize microtubules via binding to tubulin, preventing disassembly. Some of these drugs include taxanes, epothilones, discodermolide, eleutherobin, and monastrol [13].

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 [14].

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, campothecin 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 [15]. 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 [16]. 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 [17]. 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 [13]. Camptothecin a drug derived from *Camptotheca acuminate* selectively inhibits topoisomerase I, thereby hindering DNA replication [18]. 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 [19]. 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 [20]. Compounds like vinblastine, vincristine, etoposide, teniposide, taxol, navelbine, taxotere, topotecan and irinotecan have been recommended and used as antitumor drugs [21]. 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 [22]. 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 [23]. Combrestatin, betulinic acid and silvesterol are some of the other natural cancer fighting agents in clinical or preclinical trials. Combretastatins, isolated from the bark of *Combretum caffrum* (Combretaceae) is effective against cancers of colon, lung and bloodand are potent anti-angiogenic agents [24]. Betulinic acid from *Zizyphus mauritiana, Zizyphus rugosa* and *Zizyphus oenoplia* also possesses anti cancer properties [25]. Silvestrol isolated from the fruits of *Aglaila sylvestre* is effective against lung and breast cancer [26].

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 [27]. 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 [28].

Elliptinium, derived from *Bleekeria vitensis* has well known anti-cancer properties [29]. 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* [30]. 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 [31]. 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 [32]. *Commiphora opobalsamum* may also be used in anti-cancer therapy [33]. Oxindole alkaloids present in *Uncaria tomentosa*, is effective in the treatment of several diseases like ulcers, tumors and infections [34]. *Paris polyphylla*, a Chinese medicinal herb, has been reported to possess anti-carcinogenic properties [35]. *Salvia officinalis*

contain anti-oxidants and are reported to exert anticancer effects [36]. *Lantana camara* is traditionally used as folk medicine owing to its antipyretic, antimicrobial and antimutagenic properties and may be anti-carcinogenic [37]. *Solanum nigrum*, a folk medicine may be used in the treatment of cancer [38]. 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 Gràcies*) , fruit makasar (*Brucca javanica*), Echo China (*Smilax china*), Sunflower (*Helianthus annus*), Leunca (*Solanum nigrum*), Job's Tears (*Coix Lachryma-Jobi*), Bamboo Rope (*Asparagus cochinchinensis*), and so on. Alfalfa, possessing antibacterial and antifungal properties may help in the fight against cancer [39]. The Autumn Crocus, a member of the Lily Family (Liliaceae), is a plant with chemotherapeutic potential [40]. Shikonin, a herbal medicine produced by *Lithospermum erythrorhizon*, has been reported to inhibit tumor growth in mice [41]. 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 [42]. 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 [43]. 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 [44]. Pomiferin a prenylated isoflavonoid from *Maclura pomifera*, possesses anti cancer, anti-oxidant and chemopreventive properties [45]. Isoflavones inhibit production of reactive oxygen species and thus serve as anti-cancer agents [46]. 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 [47]. Actein, the active component of *Actaea racemosa* inhibits the proliferation of human breast cancer and liver cancer cells and thus show antitumor potential [48]. *Allium sativum* contains sulfur compounds which show chemopreventive activity [49]. *Andrographis paniculata* contains andrographolide, which is an anti-cancer compound that inhibits interleukin-6 (IL-6) mediated signaling, and induces programmed cell death [50]. *Ardisia crenata* containing triterpenoid saponins show anti-proliferative and antiproliferative potential, thus serving as anti-cancer agents [51]. 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) signaling [52]. Asiatic acid, a pentacyclic triterpene present in *Centella asiatica* decreases viability of cancer cells by increasing expression of p53 [53]. 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 [54]. *Panax ginseng* contains ginsenosides which are antiproliferative, anti-invasive, and antiangiogenic [55]. Plumbagin, a quinoid obtained from *Plumbago zeylanica* possess anticarcinogenic activity by targeting various proteins involved in the process of carcinogenesis [56]. 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 [57]. 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 [58]. 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 [59]. 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 [60].

Conclusion

Plants have widely been used as medicines since centuries for the treatment of a wide variety of diseases. People over the ages have relied on traditional herbal agents to meet their health care requirements. In spite of presence of conventional drugs, herbal medicines still find a place in treatment owing to their wide range of healing properties. Natural products are a wonderful source for the development of anti-tumor drugs. Secondary metabolites obtained from plants are mainly responsible for their medicinal properties. Intense research is going on for the development of novel anti-cancer drugs. Present day medications show various adverse side effects which may be overcome by using plant derived compounds. The immense potential of plants in cancer therapy still remains unexplored. It is high time to develop newer anti-cancer drugs from plant sources which might pave a way to a non-toxic mode of cancer control. It is of utmost importance to make people aware of the health benefits of plant products and its potent role in cancer prevention and treatment as it might provide a unique means of cancer therapy and management.

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