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Review Article

PLANT DERIVED ANTICANCER AGENTS AND THEIR STRUCTURE: A REVIEW

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ABSTRACT

It is well known fact that natural products exhibit large number of benefits to the society such as nutritional, medicinal and other useful products. It is also considered that medicinal properties of natural product possess socio-economic importance. Thus, investigators are exploring natural sources for novel agents which have medicinal and pharmaceutical importance. Still today, large numbers of natural products are being used as pharmaceutical compound which have been analyzed by required clinical trials and used as drugs. Plants are one of the important sources of natural products and these compounds are also called as phytochemicals. Phytochemicals exhibit structural and functional diversity. These phytochemicals are reported for large number of medicinal properties such as antimicrobial activity, anti-inflammatory activity, anti-obesity activity, anti-HIV activity and anticancer activity etc. These phytochemicals also serve as skeleton compounds for further improvement of their therapeutic potential by slight alteration in structure. In this review, we have analyzed the anticancer potential and mode of action of some reported phytochemicals.

Keywords: Natural products; Nature; phytochemicals; medicinal compounds; anticancer compounds

INTRODUCTION

Cancer has become great threat to human beings throughout the world. Today cancer does not need any introduction and this disease is playing leading role in morbidity and mortality of people throughout the globe. By effecting lives of millions of people per year, cancer is considered one of the top ten diseases to be main cause of death on our planet[1]. Cancer is being supposed to takes death toll of approximately 8.8 million lives in 2015 and expecting one in six deaths. It was also assumed that about 70% deaths are caused by cancer in low and middle income countries[2]. It is assumed that by 2020 world's population is supposed to be 7.5 billion and approximately 17 million new cancer cases. Including this, it was also suggested that age distribution and population size will also influence the number of cancer cases[3]. It is also assumed that cancer occupies second position after cardio vascular disease and responsible for the 70% of death in poor country.

CANCER, IT'S CAUSES AND CONTROL

Main causes of the cancer

Cancer disease is mainly caused by deregulation of cell cycle control, due to malfunctioning of proto-oncogene (promote cell division in regulated manner) or tumor suppresser gene (prevent cell division). Gain in function is caused by mutational change in the cellular proto-oncogene into oncogene that functions in unregulated manner and change the normal cells into malignant cells. It is also suggested that mutation in one allele of cellular proto-oncogene is sufficient to cause cancer while in case of tumor suppresser gene mutation of both alleles are necessary for malignancy of normal cells[4]. Including this, a third class of genes involving in DNA repair also found to be associated with cancer induction. Thus, proto oncogene, tumor suppressor, and DNA repair gene are considered as driver of cancer. Like this, some mutation is also recognized as driver mutation that instantly cause cancer and other is known as passenger mutation that accumulate in gene to play indirect role in causing malignancy[5]. It is suggested that every cancer is raised by single abnormal cell (Figure 1) and this abnormality is caused by malfunctioning in proteins which are associated with cell growth, cell division, and cell death cause development of cancer (Figure 2). These proteins are involved in repair of DNA, signaling, regulation of cell growth and cell cycle, apoptosis and tissue architecture are found associated with cancer[4].

Factors associated with cancer

There are various factors which directly or indirectly are associated with development of cancer. Among the various factors such as alcohol use, less physical activities, diet lack in fruits and vegetable and the use of tobacco are considered as the prominent risk factor for cancer and contribute 22% of death due to cancer[6]. In India, there are 28 cancer registry programs that collect the population-based data on cancer throughout the country. In our country males are usually suffer from cancer of mouth, esophagus, lungs, stomach and intestinal while cancer of cervix, breast, mouth and esophagus are prominent cancer of women. Moreover, women in metro cities are prone to breast cancer while rest is susceptible to cancer cervix. According to an assumption, all type's cancer case will get up in upcoming years not only in India but throughout the world. This would increase the huge burden on medicine facility. Further, cancer cells also have ability to develop resistant against drugs used to treat them.

Resistance in cancer cells against drugs

The cancer cells develop resistance against the drugs by the mechanisms such as; drugs inactivation, alteration of drugs

targets, efflux of drugs and failure of apoptosis system. The drugs to be activated require many alterations before acting on target site. Such as, Cytarabine (AraC) drug use in treatment of acute myelogenous leukemia gets activated by multiple phosphorylation and converts into AraC-triphosphate[7]. Therefore, the mutation that causes the down regulation of this phosphorylation process result into inactivation of AraC[8,9]. In case of alternation of drugs, target site mutation changes the binding affinity of the target site towards the drugs. Thus, drugs become insensitive to target site and become useless. This type of resistance is reported for drugs that inhibit the topoisomerase activities[10]. Like prokaryotic efflux pump, cancer cells are also reported to harbor efflux pumps known as drugs pump that efflux the hydrophobic drugs. It has been reported that efflux phenomenon is associated with over expressing of the multi drugs resistance associated protein (MRP) in SW-1573 cells. The over expression of MRP protein increases the efflux of certain drugs by active transport system that result in less accumulation of drugs inside the cells[11]. Considering the problem of drugs resistant in cancer cells, we need to explore other alternative ways to find out novel drugs.

PLANT DERIVED PRODUCTS AGAINST CANCER

Phytochemicals as bioactive agents

Plants are considered to be good source of various bioactive agents and these agents are being used for preparation of homemade remedies for the treatment of various mild illnesses. Till date many bioactive compounds have been isolated from plants and screened for their bioactive potential. Further, these isolated bioactive compounds have been approved as drugs by regulatory bodies after evaluation of systematic side effects and clearance of prescribed clinical trials. Bioactive compounds which act as drugs in native form and their efficacy can be enhanced by biological or chemical modification. Further, plants secondary metabolites which are skeleton prototypes for drugs proved to be boon for chemical analyst in development of drugs. Thus, these molecules act as skeleton precursor for synthesis of new chemical agents by slight alteration in original structure to enhance the efficacy for their targets[12]. Generally, it is not economically feasible to synthesize the active compounds having more chiral centers in laboratory by chemical synthesis, but these compounds are frequently reported in plant metabolites. Thus, semi-synthetic method reduces the cost of chemical synthesis and also reduces the problem of low yield of bioactive agents from the plants.

There are hundreds of plants derived drugs that are currently in use and many are under the process of isolation and characterization. The isolation of these bioactive agents involves the tedious process of fractionation, isolation, in-vitro, and in-vivo screening[13]. Till date, large number of plants, mentioned in ancient medical literature, have been screened by the chemical analysts for their bioactive potential and many antibacterial, antifungal, anti-malarial and anti-cancerous compounds have been isolated[14]. Some plant derived bioactive agents that are used as medicine to cure diseases such as: bacterial infection, fungal infection, malaria, cancer, HIV and many more. Many of such plant derived drugs are still on clinically trial. It might be said that phytochemicals are not the substances in absence of which, humans are not able to survive but their intake improved their health[15].

Plants derived compounds are important source of anticancer drugs. Large numbers of anticancer drugs have been isolated by plants are being investigated against many types of the cancers. These agents have different mode of actions and control cell cycle at different check points (Figure 3). Out of anticancer products isolated and reported from plants some are mentioned below;

Vinca alkaloids

Vinca alkaloids, vinblastine and vincristine from *Catharanthus roseus* were the first agents to use clinically. Earlier, *Catharanthus roseus* was used as hypoglycemic agent among folk people. Canadian scientists, Robert Noble and Charles Beer were the first who got success in 1950 for isolation of vinca alkaloids[16]. Recently, Vinca alkaloids are beings used to treat cancer. Various derivatives of vinca alkaloids such as vinblastine, vinorelbine, vincristine, vindesine and vinflunine have been clinically used[17]. Vinca alkaloids and their derivatives acts on microtubules and causes metaphase arrest that result into cells death[18].

Epipodophyllotoxin

Epipodophyllotoxin was extracted from *Podophyllum peltatum* and *Podophyllum emodi* a North America and Indian species respectively. Etoposide (Figure 4) and teniposide semi derivative of epipodophyllotoxin (Figure 5) are being used for the treatment of cancer. Epipodophyllotoxin and it's both derivatives teniposide and etoposide not only interfere with micro spindle at S and G_2 phase of cell cycle but also inhibit the topoisomerase II activity[19]. Etoposide has been used as potent agent for the treatment of verities of cancer.

Camptothecin

Alkaloid camptothecin was isolated by a group of researchers from bark of *Camptotheca acuminate* [20]. *Camptotheca acuminate* has been reported for treatment of cancer in traditional Chinese medicine[21]. Camptothecin (Figure 6) is reported to inhibit the topoisomerase- I activity at ligation step that result into single strand break in DNA and this activates apoptosis signaling resulting cells death[22]. Moreover, two derivatives of camptothecin (CPT) namely topotecan (TPT) and irinotecan (CPT-11) are reported as potent anticancerous agents[23]. Topotecan is mainly used for the treatment of small cell lung cancer but currently it is also recommended for epithelial ovarian cancer[24]. Likewise, irinotecan along with fluorouracil is used to treat colon cancer[25] and in case of lung cancer it is used with cisplatin.

Taxol

Taxol from plant *Taxus brevifilia* is an anticancer agent. In clinical trials, it is being used for treatment of advanced ovarian carcinoma and melanoma (Figure 7). Taxol is known to cause halt in cell cycle progression at G2/M phase or prevent the cell cycle entering into S phase by stabilizing microtubule bundle[26]. Similarly, docetaxel, semisynthetic molecule from the inactive taxoid precursor arising out of taxane family is used for the treatment of various cancers such as breast cancer, intestinal cancer, lung cancer, and melanoma. Docetaxel acts via inhibiting the process of depolymerization of microtubules. Thus, being a mitotic spindle poison docetaxel leads to mitotic block in proliferating cells and proved to be a good anticancerous agents.

Ingenol mebutate

Ingenol mebutate derived from *Euphorbia peplus* has been used as herbal remedy against various dermatological lesions[27]. Currently, it is used as a potent agent against actinic keratosis and superficial basal cell carcinoma[28]. Ingenol mebutate (Figure 8) is reported to cause swelling of mitochondria of epithelial cancerous

cells and induce cell death via primary necrosis and it also increase the infiltration of macrophage at the site of application[29]. For the treatment of actinic keratosis, gel form of drug (Ingenol mebutate) has been approved by Food and Drug Administration (FAD) and European Medicine Agency (EMA).

Plumbagin

Plumbagin, (naphthoquinone derivative, Figure 9) isolated from the roots of *Plumbago zeylanica* had been reported for anticancer activity[30]. This product has been reported as growth inhibitor of hormone refractory prostate cancer[31]. It was found that plumbagin inhibited the invasion of Prostate cancer cells and induced cell death in these cancer cells by selective manner, but it was not found effective in immortalized non-tumorigenic prostate epithelial RWPE-1 cells[31].

Honokiol

Honokiol is a natural biphenolic compound extracted from magnolia tree bark (Figure 10). This is reported for antiinflammatory, antiangiogenic, and antitumor activities without significant toxicity. Researchers have reported the role of honokiol in human cancer cells by suppression of survival signals mediated by ras dependent phospholipase D activity[32]. Including this, necrosis mediated cell death via transition pore formation in mitochondrial membrane by honokiol is also reported[33,34].

Resveratrol

Resveratrol is a polyphenolic compound founds in majority of plant species and also found in red wine (Figure 11). Resveratrol is documented to reduce the risk of cardiovascular diseases[35]. Recently resveratrol has drawn the attention of researcher for its potential as anticancer agent against human cancer cells[36]. In a similar way, another group of researchers explained the mode of action of resveratrol to act via signaling pathways[37]. It has been found that resveratrol effect on ovarian cancer cells via inhibiting STAT3 signaling[38]. Investigators have found out the role of resveratrol for induction of apoptosis via up regulation Bax/Bcl-2 and p53 in HepG2 cells[39]. Researchers also have investigated the synergetic effect of resveratrol along with other drugs against neck squamous cell carcinomas[40].

Curcumin

Curcumin from *Curcuma longa* is documented for its anti-oxidant, analgesic, anti-inflammatory and antiseptic activity in Ayurveda[41]. Including this, curcumin (Figure 12) is also reported for immunomodulatory, cytokines release, mediator of radio resistance and chemo-resistance, enhancing of the apoptosis, and anti-angiogenic activities[42]. It is hydrophobic polyphenol which is also called as diferuloyl methane. It was reported that curcumin causes down regulation of cell division cyclin 20 (Cdc20) and was reported associated with cell death in pancreatic cancer cells[43]. Moreover, curcumin also has been reported as chemo protective compound for cervical neoplasia, pancreatic cancer, colon cancer and Barrets metaplasia activities[42]. It has been suggested that antitumor property of curcumin is due to down-regulation of transcription factors AP-1, NF-kappa B, and Egr-1; suppressed proliferation of variety of cancer cells, down-regulation of the expression of MMP-9, uPA, NOS, TNF, LOX, chemokines, COX2, cell surface adhesion molecules and cyclin D1; down-regulation of growth factor receptors and inhibition of the activity of protein tyrosine kinases, c-Jun N-terminal kinase, and protein serine/threonine kinases. It also has been suggested that curcumin can reduce cancer initiation, cancer promotion and metastasis[44].

Colchicine

Colchicine is an alkaloid and isolated from *Colchicum autumnale* and *Gloriosa superba* L. Structure of colchicines (Figure 13) contains a seven-member ring, trimethoxyphenyl ring (A ring), with acetamide at seventh positions (B ring) and a tropolonic ring (C ring). Colchicine exhibited cytotoxic activity due to inhibition of formation of spindle fiber by binding with microtubules and inhibit mitotic assembly which further induces apoptosis[45,46]. Colchicine is used to treatment of cancer, acute gout attack, Bechet's disease, familial Mediterranean fever etc.

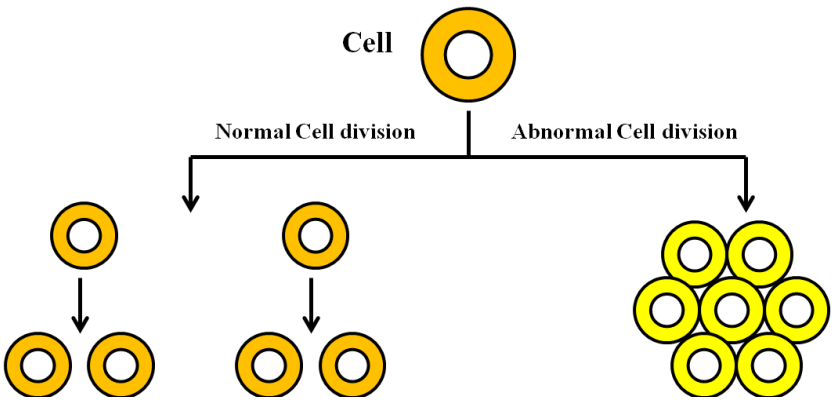

Figure 1: Diagrammatic representation of normal and abnormal cell division

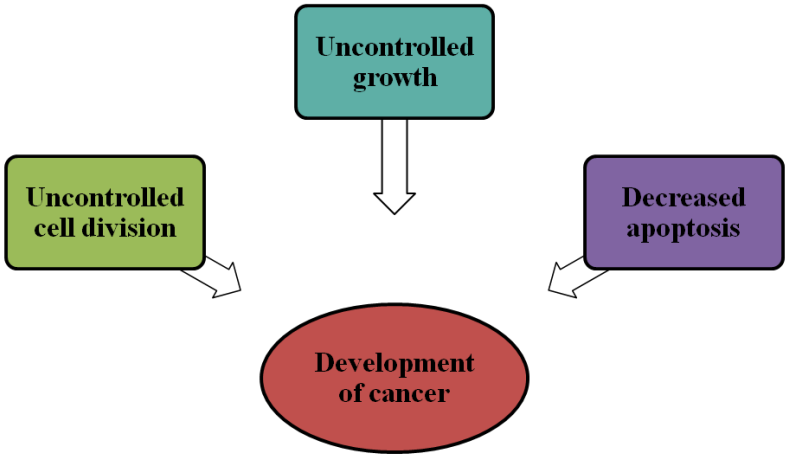

Figure 2: Diagrammatic representation of major changes that leads to development of cancer

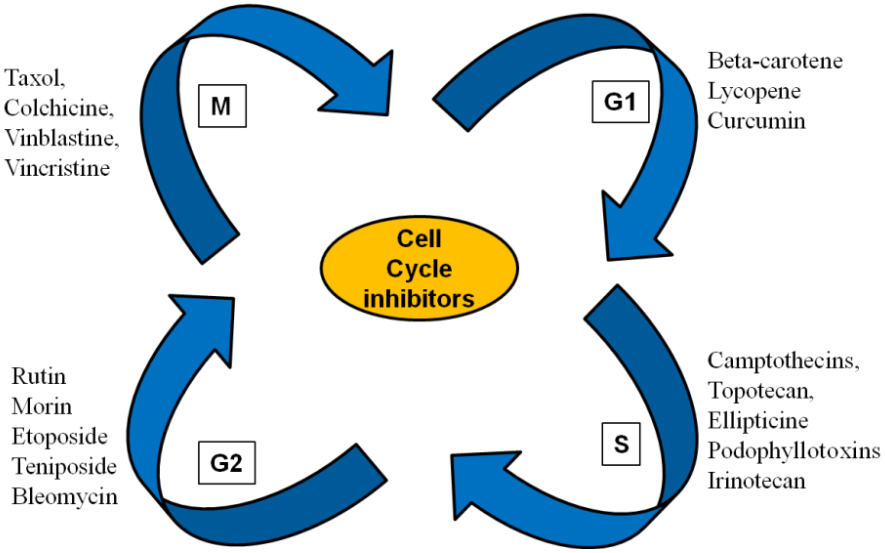

Figure 3: Cell cycle inhibitors isolated from plants which are anti-cancer in nature

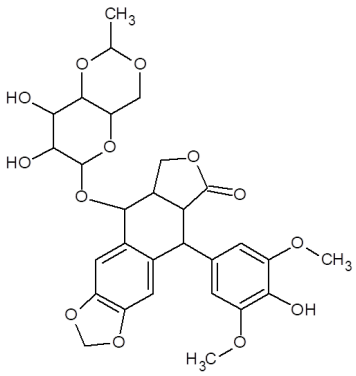

Figure 4: Structure of Etoposide

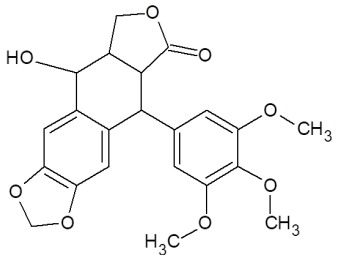

Figure 5: Structure of Epipodophyllotoxin

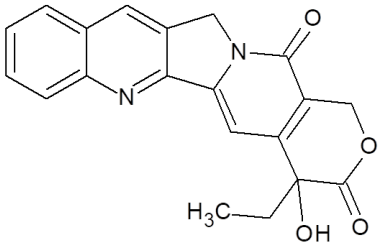

Figure 6: Structure of Camptothecin

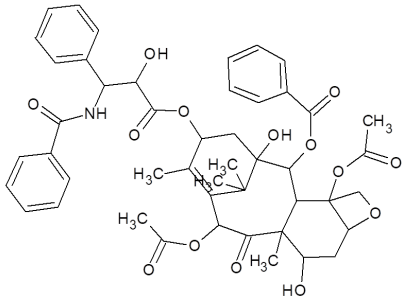

Figure 7: Structure of taxol

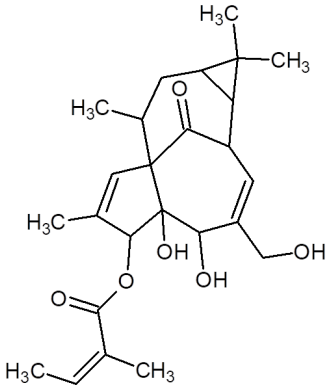

Figure 8: Structure of Ingenol mebutate

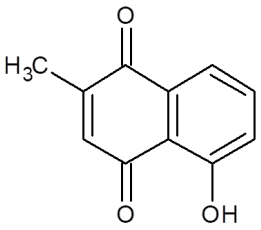

Figure 9: Structure of plumbagin

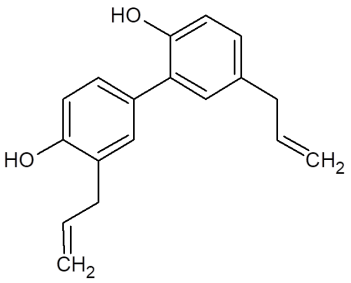

Figure 10: Structure of honokiol

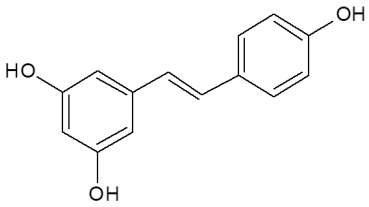

Figure 11: Structure of reservatrol

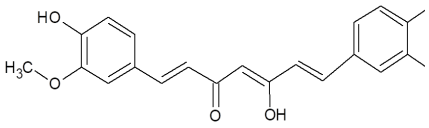

Figure 12: Structure of curcumin

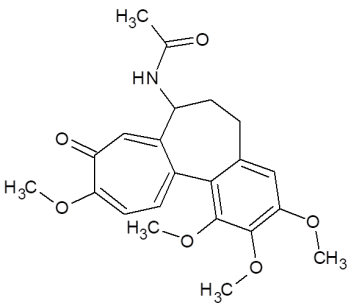

Figure 13: Structure of colchicine

FUTURE PERSPECTIVES

It is our primary attempt to understand the role of different phytochemicals as anticancer agents. Further study requires analysis of the scientific literature in more detail to understand the mechanism of action of plant derived anticancer agents at molecular level. Including this, efficacy of derivatives of these anticancer agents may be studied in order to develop more potent and less toxic anticancer drug which can be developed into anticancer medicine.

CONCLUSION

Plants are nature's largest laboratory which synthesizes phytochemicals with enormous structural and functional diversity. These phytochemicals exhibit large number of medicinal activities. These phytochemicals also exhibit pharmaceutical importance as many of these are being used in drugs as key ingredient. It is found that, large numbers of phytochemicals possess anticancer properties which control growth and development of cancer cells. Some reported plant derived agents possessing anticancer activity are vinca alkaloids, taxol, plumbagin, etoposide, honokiol, resveratrol, curcumins and colchicines etc. It is also important that, these agents exhibit anticancer activity by different mechanisms. Furthermore, structure of these compounds may be used as skeleton to develop novel and potent anticancer drugs which are less toxic and economic.

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