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Short Communication
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Herbal Compounds as Potential Anticancer Therapeutics: Current

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Abstract

Cancer is a dreadful disease whose pathological roots lie deep inside the molecular pathways governing different biochemical process. Oncogenic cells divide abnormally in an uncontrolled manner and invade surrounding tissues/organs. Major Treatment strategies for cancer include chemotherapy, radiotherapy and surgery. Anti-cancerous chemical agents used for the treatment often met with serious repercussions. Herbal compounds capable of preventing or inhibiting the process of carcinogenesis represent a better option for obtaining effective anti-cancerous therapeutics. They act at multiple molecular targets involving DNA, enzymes, and cytoskeleton (microtubules) thereby blocking uncontrolled cell division. Taxol, vincristine, vinblastine, topotecan, camptothecin derivatives and etoposide derived from podophyllotoxin are the good examples of such compounds with proven anti-cancerous activity. Numerous natural products such as resveratrol, silvestrol and betulinic acid with promising antineoplastic activities are already in different phases of clinical trials. Over all there is direct medical application of herbal compounds to serve as chemical models or templates for the design, synthesis, and semi-synthesis of novel substances with potential to block cancer development and progression.

Keywords: Oncogenes; Vincristine; Cancer; Clinical trial; Resveratrol

Short Communication

Every year cancer kills 3500 humans per million population throughout the globe [1] thus acting as a big hurdle in the socioeconomic progress of nations. Tumours have the property to grow at a much faster rate and invade surrounding tissues. For this reason they require high supply of energy which they met by forming new blood vessels through the process of angiogenesis [2] Anti-cancer agents whether synthetic or semi-synthetic, destroy cancer cells by stopping their growth or multiplication at some point in their life cycles. These drugs often affect the non targeted cellular pathways, thus disrupting the growth of normal cells as well. Major side-effects of synthetic chemo-preventives include the reduction in WBC count thereby promoting the chances of getting infected by communicable diseases [3]. Also there occurs marked decrease in the RBC count causing anaemia and affecting gaseous transport in the blood circulatory system. This is characterised by decreased capacity of RBCs to carry oxygen to the body cells, making an individual feel tired and breathless. Moreover there is also decline in the blood platelet count. Other harmful effects include loss of appetite, hair loss, skin discoloration, hormonal imbalance, sore throat, constipation, fatigue and general body weakness [4]. The trend for exploring anti-cancerous drugs of plant origin started in 1950's with the discovery of vinca alkaloids including vinblastine, vincristine and the isolation of cytotoxic podophyllotoxins. These scientific advances prompted United States National Cancer Institute (NCI) to initiate an extensive plant collection program during 1960's, which focussed mainly in temperate regions of the world. These efforts lead to the discovery of many novel drugs with potential cytotoxicity activities such as the camptothecins and taxanes [5]. However, the actual development of these drugs into clinically effective therapeutic agents took some 30 years from 1960 to 1990 [6]. Unfortunately, this extensive programme of plant collection was terminated in 1982 but the advent of new screening technologies promoted further exploration of new anticancer herbal agents in 1986. This time the focus of plant exploration was extended to the tropical and sub-tropical regions of the world. Since then many compounds have been isolated from plants, many of which are in different phases of clinical trials and may prove effective drugs in future.

Owing to the detrimental effects of the synthetic anti-tumour drugs, researchers all over the globe are now moving towards herbal approach for treating cancer. Medicinal plants are the biggest

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gift of nature to mankind. They provide wonder drugs with potential anti-cancer activities. Vinca alkaloids represent an important class of such drugs that inhibit cell proliferation by affecting microtubular dynamics during mitotic cell division via induction of tubulin self-association into coiled spiral aggregates [7], thus blocking oncogenic cell proliferation. Some prominent examples of Vinca alkaloids obtained from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (*Apocynaceae*) include Vinblastine (VLB), Vincristine (VCR), Vinorelbine (VRLB) and Vindesine (VDS). Podophyllin is another unique chemotherapeutic compound obtained from the ethanolic extract of *Podophyllum hexandnum Royle*. It acts as a good source for aryltetralin-type lignan podophyllotoxin. Podophyllotoxin and its semi synthetic derivatives like etoposide, teniposide, etoposide Phosphate possess marked cytotoxic potential and are clinically used to cure lung cancer. Etoposide forms a ternary complex with DNA and topoisomerase II thus blocking re-ligation of DNA strands and promoting DNA strands to break. Etoposide is used to treat testicular cancer, and is given in combination with bleomycin and cisplatin [8]. It also shows marked potential against small cell lung carcinoma [9,10]. Etoposide phosphate is an efficient inhibitor of topoisomerase which has an important role in DNA replication. Teniposide, a semi synthetic derivative of podophyllotoxin exerts anticancer activity by inhibiting DNA synthesis via formation of complex with topoisomerase II and DNA molecules. This complex breaks the Double stranded DNA molecules and do not allow DNA repair by topoisomerase II enzyme. Accumulation of such Breaks in DNA prevent cells from entering mitotic (M) phase of cell division, thereby leading to cell death. Taxanes like Taxol (obtained from the bark of Yew tree) and its derivates including Docetaxel exert antitumor activities by enhancing the stability of microtubules thus preventing chromosomal separation during anaphase. Derivatives of camptothecin such as topotecan and irinotecan have shown significant antitumor activity against ovarian cancer and colorectal cancer respectively. These compounds were initially obtained from the bark and wood *of Nyssacea Camptotheca accuminata* and act by inhibiting topoisomerase I. The taxanes and the camptothecins are currently approved for human use in various countries [11]. Catechin compounds like Epigallocatechin gallate represent the most copious entities found in green Tea. Research indicates that such compounds are effective in treating cancers of Prostate, brain, cervix and bladder [12,13]. *Ocimum tenuiflorum* leaf powder also exhibits potent anticancerous properties [14]. Betacyanins present in the beetroot resembles doxorubicin (an anti cancer chemical agent) in its structure [15] Saffron obtained from the flower of *Crocus sativa* is known for its anticancer effects [16]. Ethanolic extract of *Crocus sativa* is being investigated for its effects in modulating colorectal cancer, human lung cancer, skin carcinoma, pancreatic cancer and breast cancer [17]. Extracts of pomegranate exhibits marked activity against cancers like prostate, colon, Breast and skin [18,19]. Indian gooseberry is potent against hepatic cancer, ovarian cancer, and breast cancer [20]. Curry leaves act as an important source of many therapeutic compounds notably gallic acid, naringin, myricetin catechin, epicatechin, rutin, quercetin, ferulic acid, cinnamic acid and vanillic acid, thereby serving as a promising agents for treating cancer especially breast cancer [21]. Three new dimeric indole alkaloids together with five known ones isolated from *Ocimum tenuiflorum*, were found to possess marked anti-cancerous activity [22]. Chloroform extract of *Juglans regia* (walnut) induces cell cycle arrest and is considered a potential source for anticancer agents [23]. *Trigonella foenum graecum* extracts are found to possess cancer preventive properties but the underlying mechanism is yet unknown [24,25].

Many compounds isolated from medicinal plants are under different phases of clinal trials. Betulinic acid (triterpenoid) obtained from *Ziziphus mauritiana* Lam. (Rhamnaceae) has exhibited marked cytotoxicity against brain tumor cells and neuroectodermal cancer [26]. It induces apoptosis via regulation of mitochondrial intrinsic pathway of apoptosis and activation of p38 MAPK and SAP/JNK by initiating ROS [reactive oxygen species] generation [27]. A betulinic acid-containing ointment is currently being tested in Phase I/II clinical trial for the treatment of dysplastic nevi with moderate to severe dysplasia [28]. Silvestrol, obtained from *Aglaia foveolata* pannell exhibited potent cytotoxic activity against several human cancer cell lines and has also shown marked activity both *in vivo* hollow fiber and P-388 lymphocytic leukemia assays [29]. In LNCaP human prostate cancer cells, silvestrol produced a p53-independent cell-cycle arrest at the G2/M check-point, and induced apoptosis by regulating caspases 2, 9 and 10 but not caspases-3 and -7 [30,31]. The compound is also effective against chronic lymphocytic leukemia and acute lymphocytic leukemia models [32]. Currently, silvestrol is going through clinical trials to acts as a potential antileukemic agent [33]. Perillyl alcohol, a monoterpenoid with a monocyclic carbon skeleton present in the essential oils of several plants like cherries (*Prunus aviu)* and lavender (*Lavendula X intermedia)* exhibited a marked cytotoxicity against cancer cell lines derived from pancreatic cancer, lung cancer, breast cancer, prostate cancer, and leukemia. It also showed potent inhibitory effects against DMBA-induced murine melanoma models and UVB-induced skin carcinogenesis under *in vivo* conditions [34,35]. Perillyl alcohol is found to induce cell cycle arrest at the G0/G1 phase, by modulating levels of cyclin-dependent kinases (CDKs) and cyclin dependent kinase inhibitors (CDKIs) [36]. Currently, Perillyl alcohol is undergoing Phase I/II clinical trials in patients with ovarian cancer, breast cancer and glioblastoma multiform [37]. Resveratrol, a phenolic compound is naturally present in several plants such as grapes (*Vitis vinifera)*, white mulberries (*Morus alba*) and peanuts (*Arachis hypogaea*). This compound this compound blocks growth of oncogenic cells by acting at multiple targets such as inhibiting cycloxygenase (COX) and cytochrome P450 enzymes, activating AMP-activated kinase (AMPK) and activating p53 [38,39]. Currently this compound is being tested in Phase I/II clinical trials for treating colon cancer in the United States [40]. Lycopene, distributed widely in vegetables and fruits, especially in tomatoes (*Solanum lycopersicum*) [41] is a well-known red plant pigment and contains the 40-carbon aliphatic chain composed of thirteen trans-double bonds, with eleven of these being conjugated. Besides its anti-inflammatory and anti-oxidant activities, Lycopene also exhibits anti-cancerous activities in both *in vitro* and *in vivo* experimental models [42,43]. Lycopene exerts its anti-cancer activity through the activation of the electrophile/antioxidant response element (EpRE/ARE) transcription system, inducing the expression of phase II detoxifying enzymes, and blocking cell cycle at G0/G1 phase by regulating cyclin D1 and the PI3K/Akt pathway [43]. Currently, Lycopene is being investigated in Phase II clinical trials in the United States for The treatment of prostate cancer [44]. Protopanaxadiol and protopanaxatriol, the two dammarane-type triterpenoids obtained from Asian ginseng *Panax ginseng* and related species [45]. Protopanaxadiol prevents cancer by blocking Wnt/β-catenin signalling pathway, down-regulating AKt activity, and inhibiting the effects of P-glycoprotein (P-gp) [46,47]. Both Protopanaxadiol and protopanaxatriol are reported to possess immunomodulating properties [48]. A mixture of protopanaxadiol

and protopanaxatriol (Pandimex™) has been approved conditionally in mainland China for the treatment of advanced cancers of the breast, colorectum, lung and pancreas; and is ongoing a Phase I clinical trial in the United States for advanced lung, gastric, breast and pancreatic cancers in combination with paclitaxel or alone [49,50].

Synthetic chemotherapeutics besides having serious side effects also pose the threat of drug resistance due to factors like enhancement in drug detoxifying enzymes, increased expression of drug transporters, drug efflux, alteration of drug targets, and modified competence between the drug and the target [51]. This prompts the search for new drugs with significant anti-neoplastic properties and less or no side effects [52]. Medicinal plants represent the best option to obtain such therapeutics. In fact herbal product plays a crucial role in generating leads for treatment of cancer. As per estimates about 47% of total anticancer drugs introduced in Western Europe, North America and Japan during the period of 1940-2006 were either natural products or derived directly from natural products [53]. However, the last decade has witnessed a declining trend in terms of discovering drugs of plant origin [54,55]. One of the major reasons for this decline is the use of rapid high-throughput screening [HTS] technology for drug discovery. This method explores target specific pure compounds directly from chemical libraries using combinatorial chemistry. Although a rapid technology, HTS cannot under-estimate the therapeutic potential of herbal products and there is great demand for large scale screening of anti-neoplastic medicinal plant. From the past research, it is evident that small molecules of plant origin prove to be valuable sources of potential lead compounds in anticancer drug discovery. As per reports, over 85% of higher plants have not been evaluated systematically for the presence of bioactive principles and more than 80% of global population still depends on traditionally used herbal remedies [55,56]. In addition, more than 60 compounds obtained from medicinal herbs are in the pipeline as potential anticancer agents [57,58]. Intense investigations and clinical trials are necessarily required to improve and establish this line of treatment. Innovations in investigation methods may also offer great help in discovering plant-derived anticancer drug. These innovations may include new techniques like enhanced high-throughput biological screening procedures, compound isolation and structural elucidation.

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