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RESEARCH ARTICLE

THERAPEUTIC EFFICACY OF PLANT-DERIVED ANTI-CANCER AGENTS- A PERSPECTIVE APPRAISAL

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ABSTRACT

Cancer is a major cause of death and the number of new cases as well as the number of individuals living with cancer is expanding continuously. Nature continues to be the most prolific source of biologically active and diverse chemotypes. Although relatively few of the actual isolated compounds advance to become clinically effective drugs in their own right, these unique molecules often serve as models for the preparation of analogues using chemical methodology such as total or combinatorial synthesis, or manipulation of biosynthetic pathways. Plant derived compounds have played an important role in the development of several clinically useful anticancer agents. These include vinca alkaloids, lignans, terpenoids, quinines and phytochemicals such as flavones, flavonoids, flavonol. Various compounds, isolated from different plant sources, are divided into different types for the development of new drug compounds having activity against different types of cancer. Herein, we reviewed some plant derived active compounds having activity against cancerous cells, which are presently being used or would be used in future for the development of effective drug against different types of cancer, without adverse effects.

INTRODUCTION

A group of disease caused by loss of cell cycle control is termed as Cancer. It is associated with abnormal uncontrolled cell growth (Krishnamurthy, 2007). Many factors including external (tobacco, chemicals, radiation and infectious organisms) and internal (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism) are the cause of cancer. It is a substantial universal health problem commonly due to the lack of widespread and comprehensive early detection methods, the associated poor diagnosis of patients in later stages of the disease and its growing incidence on a worldwide scale. Thus, now-a-days the greatest challenge of mankind is to fight against this dreadful disease (Divisi *et al.,* 2006).

Cancer - Indian scenario

Every year about 8, 50, 000 new cancer cases being diagnosed, India resulting about 5, 80, 000 cancer related death every year. India had the highest number of the oral and throat cancer cases in the world. Every third oral cancer patient in the world is from India. In males Oral, Lungs and Stomach cancers was the three most common causes of cancer incidence and death whereas in females Cervical, Breast and Oral cancers were the three main causes of cancer related illnesses and death. Overall cervical cancer was the number one cause of cancer death in India. That was really unfortunate as cervical cancer can be easily prevented and also relatively easy to diagnose and treat at an early stage. Compared to developed countries overall there were less cancer cases in India but that could be due to under diagnosis and under reporting. At the same time regional, ethnic, dietary and socio-economic factors might also results in difference in the cancer susceptibilities and the incidence. Also cancer was mainly a disease of old ages. Worldwide median age at diagnosis was about 60 years. Average life span was about 58 yrs in India compared to 75 yrs in the developed world.

Cancer- Global scenario

Among all the cancer, Lung cancer is the most common worldwide and accounts for major death annually. The following Table 1 shows the global scenario for various types of cancer.

The three leading cancer killers were different than the three most common forms, (i) Lung cancer responsible for 17.8 per cent of all cancer deaths. (ii) Stomach 10.4 per cent and (iii) Liver 8.8 percent. Industrial nations with the highest overall cancer rates include: U.S.A, Italy, Australia, Germany, The Netherlands, Canada and France. Developing countries with the lowest cancer were in Northern Africa. Cancer rates could further increase by 50% to 15 million new cases in the year 2020. However, the report also provides clear evidence that healthy lifestyles, and public health action by governments and health practitioners could stem this trend, thus prevent as many as one third of cancers worldwide.

Plants have been used since ancient times for medicinal purposes in different cultures globally. Plants use as medicinal remedies have been an integral part of the Indian cultural life and this is improbable to change in the future also (Jain & Jain, 2010). Hence, an attempt has been made to screen some medicinal plants used for the prevention and treatment of cancer in India.

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A number of studies have been conducted on herbs evaluating their ethnomedical properties. As for example, data of about 3000 plants having anticancer activities was collected by Hartwell, which were afterwards used as potent anticancer drugs (Cragg & Newman, 2009). Plants produce secondary metabolites which in their natural form or as their semi-synthetic derivatives play an important role in anticancer drug therapy (Pan *et al*., 2010). These include vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, derived from epipodophyllotoxin and paclitaxel (taxol). Several clinical studies are going on the promising new agents such as flavopiridol and combretastin A4 phosphate. These studies are based on their selective activity against cancer related molecular targets. Few agents which failed in earlier clinical studies are stimulating renewed interest. Among the anticancer agents presently in use, about sixty percent are derived in one way or another from natural sources (Cragg *et al*., 2009). Some of the other medicinal plants of anticancer activities are shown in Table. 1.

Complementary and alternative medicine use is common amongst cancer patients. A population-based study conducted by Gansler *et al*. in the United States found that the complementary methods (CM) most frequently reported used by cancer survivors were prayer/spiritual practice (61.4%), relaxation (44.3%), faith/spiritual healing (42.4%), nutritional supplements/vitamins (40.1%), meditation (15%), religious counselling (11.3%), massage (11.2%), and support groups (9.7%)(Dharmani *et al*., 2004). A multinational survey found that 35.9% of cancer patients were either past or present users of complementary and alternative medicine (CAM). Herbal medicines were by far the most commonly used group of treatments, escalating in use from 5.3% before the diagnosis of cancer to 13.9% after the diagnosis of cancer (Sairam *et al*., 2002). Many individuals use certain CAM approaches with expectation or hope for therapeutic effects on the tumour which might improve their survival (Sairam *et al*., 2003). Herbal remedies are believed by the general public to be safe, causeless side-effects and less likely to cause dependency

S. No	Botanical Name	Part used	Family
1	Terminalia arjuna	Bark	Combertacae
2	Androgarphis paniculata	Dried leaves	Acanthacae
3	Catharanthus roseus	Whole plant	Apocynacae
4	Ochrosiael liptica	Trunk Bark	Apocynacae
5	Podophyllum peltatum	Dried Rhizome	Berberidacae
6	Zingiber officinalis	Rhizome	Zingiberacae
7	Curcuma longa	Rhizome	Zingiberacae
8	Vaccinium stamineum	Fruit	Ericaceae
9	Morinda citrifolia	Fruit	Rubiaceae
10	Semecarpus anacardium	Fruit	Anacardiaceae
11	Calotrophis gigantea	Whole plant	Asclepiadaceae
12	Cajanus cajan	Leaves	Fabaceae
13	Butea monosperma	Bark	Fabaceae
14	Bauhinia variegata	Root	Caesalpinaceae
15	Alium cepa	Bulb	Liliaceae
16	Aloe barbadensis	Leaves	Liliaceae
17	Cassia auriculata	Root	Caesalpinaceae
18	Cassia senna	Leaves	Caesalpinaceae
19	Citrus medica	Root	Rutaceae
20	Daucus carota	Root	Apiaceae
21	Jatropha curcas	Leaves, seed, oils	Euphorbiaceae
22	Mimosa pudica	Whole plant	Mimosaceae
23	Nicotiana tabacum	Leaves	Solanaceae
24	Tylopora indica	Root, Leaf	Asclepiadaceae
25	Vitex trifolia	Leaf	Verbanaceae
26	Bacopa monnieri	Whole plant	cropulariaceae
27	Azadirachta indica	Bark	Meliaceae
28	Asparagus racemosus	Root	Liliaceae
29	Aphana mixispolystachya	Bark	Meliaceae
30	Acorus calamus	Rhizome	Araceae
31	Cassia absus	Leaves	aesalpinaceae
32	Catunaregum spinosa	Bark/Fruit	Rubiaceae
33	Citrullus colocynthis	Root	Cucurbitaceae
34	Cissus quadrangularis	Whole plant	Vitaceae
35	Clerodendrum serratum	Root	Verbanaceae
36	Clerodendrum viscosum	Leaves	Verbanaceae
37	Crinum asiaticum	Bulb	maryllidaceae
38	Embelia ribes	Fruit	Myrsinaceae
39	Flacourtia jangomos	Bark/Leaf	Flacourtiaceae
40	Kaempferia galanga	Rhizome	Zingiberaceae
41	Kaempferia rotunda	Tubers	Zingiberaceae
42	Lanata camara	Whole plant	Verbanaceae
43	Lens culinarismedikus	Seed	Fabaceae
44	Limonia acidissima	Fruit	Rutaceae
45	Macrotylom auniflorum	Seed	Fabaceae
46	Operculin aturpethum	Root	Convolvulaceae
47	Rhina canthusnasuta	Whole plant	Acanthaceae
48	Salvadora persica	Bark,Leaf, Shoot, Fruit	Salvadoraceae
49	Symplocus cochinchinensis	Bark	Symplocaceae
50	Vernonia cinerea	Whole plant	Asteraceae
51	Xanthium strumarium	Root	Compositae
52	Zanthoxylum armatum	Bark, Fruit	Rutaceae

(Gupta & tendon, 2004). Relatively, little English language clinical research literature about the use of CAM approaches in cancer has addressed studies of anticancer treatments.

Soybean phytochemicals such as genistein (4', 5, 7-tribydroxy isoflavone) inhibit the growth of transplantable human prostate carcinoma (Ravindranath *et al*., 2004). Epidemiological studies have consistently shown that regular consumption of fruits and vegetables strongly associated with reduced risk of developing chronic diseases such as cancer as the phytochemical extracts from it exhibit strong antioxidant activity (Liu, 2004). Andrographolide the potential cancer therapeutic agent isolated from Andrographis paniculata (Kumar *et al*., 2004). In the screening of Yemeni plants used in folk medicine for the anticancer potential, the methanolic extracts of Dendrosicyos socotrana, Withania aduensis, Withania riebeckii, Dracena Cinnabari and Buxus hildebrandlii exhibited the highest toxicity on all tumor cell lines (Mothana *et al*., 2007). The four varieties of muscadine grape extract had the ability to inhibit the activity of matrix metallo-proteinases implying that those could be good inhibitors of carcinogenesis (God *et al*., 2007). The limonoids isolated from the methanol extract of *Khaya Senegalensis* proved good anticancer activity (Zhang *et al*., 2007). The leaf extract of Ashwagandha selectively killed tumor cells and thus it was a natural source for safe anticancer medicine (Widodo *et al*., 2007). The fruit of deerberry (Vaccinium stamineum) exhibited the anti-cancer capability of human lung and leukemia cancer cells (Wamg *et al*., 2007). Polyphenolic extracts from Vaccinium macrocarpon inhibited the growth and proliferation of breast, colon, prostate, lung, and other tumors as do flavonols, proanthocyanidin, oligomers, and triterpenoids isolated from the fruits of the same (Neto, 2007). Morinda citrifolia showed of cancer preventive effective on both clinical practice and laboratory animal models (Wang *et al*., 2001).

An alcoholic extract of *Biorhythms* sensitivum for antitumor activity could inhibit the solid tumor development on mice induced with Dalton's lymphoma ascites (DLA) cells and increase the life span of mice bearing Ehrlich ascites carcinoma (EAC) tumors (Guruvayoorappan *et al*., 2007). Edible fruits and berries served the source for novel anticancer agents, given that extracts of those foods have demonstrated cytotoxic activity against tumor cell lines (Ferguson *et al*., 2006). Nimbolide, a triterpenoid extract from the flowers of the neem tree was found to have anti-proliferative activity against some cancer celllines oy *et al*., 2007). *Semecarpus anacardium* Linn nut milk extract exerts its anticancer effect through quenching-reactive oxygen species (Arulkumaran *et al*., 2006). The cytotoxic activities of two medicinal herbs *Linum persicum* and *Euphorbia cheradania* that are native to Iran showed cytotoxic activity on tumor cell lines (Amirghofran *et al*., 2006).

The Pomegranate extracts inhibits the growth of breast cancer cells (Jeune *et al*., 2005). Brassinosteroids, steroid plant hormones are promising leads for potential anticancer drugs (Malikovia *et al*., 2007). The *Careya arborea* bark significantly reduced the solid tumor volume induced by DLA cells (Nateson *et al*., 2007). The methanol extract of *Bauhinia racemosa* stem bark exhibited antitumor effect in EAC bearing mice (Gupta *et al*., 2004). The antitumor activity of the ethanol extract of *Indigofera aspalathoides* was established (Mark *et al*., 2005). The extract of 12 Chinese medicinal herbs such as *Anemarrbena asphodeloides* (Root), *Artemisiaargyi* (leaf), C*ommiphora Myrrh* (Resin), *Duchesnea indica* (Aerial Plants), *Gledit siasinessis* (Fruit), *Ligustrum lucidum* (fruit), *Rheum palmatum* (Root and Rhizome), *Rubia cordifolia* (Root), Salvia Chinesis (Aerial parts), *Scutella riabarbata* (Aerial Parts), *Uncaria rhychopylla* (Stem), *Vaccaria segetails* (seed) showed anticancer effects invitro and those effects were markedly greater on cancer cells compared with normal cells (Mark *et al*., 2005).

Phytoconstituents extracted from a large number of plants belonging to the genus Hypericum are known to possess potent anticancer nature (Dongre *et al*., 2008) cytotoxic activity of *Sarris cernuss* extract on human colon and breast carcinoma cultures was proved (Badisa *et al*., 2007). The natural antioxidant gallic acid (GA) isolated from the fruits of an Indonesian medicinal Plant, *Phaleria macrocarpa* was proved to be a potent anticancer compound (Faried *et al*., 2007). The rhizome *Zingiber officinalis*, one of the most widely used species of the ginger family is a common condiment for various foods and beverages. The pungent vallinoids i.e., 6-gingerol and 6-paradol, shogaols and zingerone attribute to the anticancer properties of ginger (Shukla & Singh, 2007).

The antineoplastic activity of methanolic extracts of five medicinal plants that are native to Iran including *Galium mite*, Ferula angulata, Stachy sobtuscrena, Grsium bracteosum, and Echinophora cinerea was investigated and proved to have anti tumor activity (Amirghofran *et al*., 2006). *Panax ginseng* and its extracts have long been used for medical purposes and there increasing interest in developing ginseng products as cancer preventive agents (Wang *et al*., 2007). Purified bioactive compounds derived from medicinal mushrooms were potentially important for new source of anticancer agents (Sullivan *et al*., 2006). The Saponins from the plant of china, *Clematis manshrica* has obvious antitumor effects against various transplanted tumor on mice (Zhao *et al*., 2005). The Embelin derivatives such as 1, 4 – benzoquinone derivative 5-0 ethyl embelin (1) and 5-0 methyl embelin are promising antimitotic and anti-cancermolecules (Xu *et al*., 2005). Sesquiterpenes the class of naturally occurring molecules that are 15-carbonisoprenoid compounds. Those typically found on plants and marine life. They have therapeutic potential in decreasing the progression of cancer (Modzelewska *et al*., 2005). The anticancer activity from Platycodongrandi florum was proved and established (Young lee *et al*., 2004). The methanol extract of stem bark of *Dillenia pentagons* appears to be more active against Dalton'slymphoma (Rosangkenia, *et al*., 2004). Limonium vulgare, Artemisia maritima and *Salicornia europaea* showed antineoplastic activities. The extracts of *Ononis spinosa*, Trifolium fragiferum and *Trifolium repen* showed tumor growth inhibiting activities (Lellau & Liebezeif, 2003). Methanol extract Ledum groelandicum Retzius (Labrador tea) leaf twig extract showed anticancer activity (Dufour *et al*., 2004). The anti-neoplastic activity of guduchi (*Tino sporacordifolia*) on Ehrlich ascities carcinoma was proved (Jagetia & Rao, 2006).

Plant-derived anti-cancer agents in clinical use

The first agents to advance into clinical use were theso-called vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the Madagascar periwinkle, *Catharanthus roseus*G. Don. (Apocynaceae) was used by various cultures for the treatment of diabetes (Gueritte and Fahy, 2005). While

under investigation as a source of potential oral hypoglycemic agents, it was noted that extracts reduced white blood cell counts and caused bone marrow depression in rats, and subsequently they were found to be active against lymphocytic leukemia in mice. This led to the isolation of VLB and VCR as the active agents, so their discovery may be indirectly attributed to the observation of an unrelated medicinal use of the source plant. It is interesting to note that though the plant was originally endemic to Madagascar, the samples used in the discovery of VLB and VCR were collected in Jamaica and the Philippines. More recent semi-synthetic analogs 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, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma.

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" (Lee and Xiao, 2005). The Podophyllum species (Podophyllaceae), Podophyllum peltatum Linnaeus (commonly known as the American mandrake or Mayapple), and Podophyllum emodii Wallich from the Indian subcontinent, have a long history of medicinal use, including the treatment of skin cancers and warts. 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 also isolated, and several of them were introduced into clinical trials, only to be dropped due to lack of efficacy and unacceptable toxicity. Extensive research 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.

A more recent addition to the armamentarium of plant derived chemotherapeutic agents are the taxanes (Kingston, 2005). Paclitaxel (taxol®) initially was isolated from the bark the Pacific Yew, Taxus brevifolia Nutt. (Taxaceae), as part of a random collection program for the NCI by the U.S. Department of Agriculture (USDA). The use of various parts of *Taxus brevifolia* and other *Taxus* species (e.g., *Taxus Canadensis* Marshall, *Taxus baccata* L.) by several Native American tribes for the treatment of some non-cancerous conditions has been reported, while the leaves of *Taxus baccata* are used in the traditional Asiatic Indian (Ayurvedic) medicine system, with one reported use in the treatment of "cancer" (Hartwell, 1982). 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, while docetaxel is primarily used in the treatment of breast cancer and NSCLC. Paclitaxel has also attracted attention in the potential treatment of multiple sclerosis, psoriasis and rheumatoid arthritis. In addition, 23 taxanes are in preclinical development as potential anti-cancer agents.

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 acuminate* Decne (Nyssaceae) (Rahier *et al*., 2005). Camptothecin (as its sodium salt) was advanced to clinical trials by the NCI in the 1970s, but was dropped because of severe bladder toxicity, but extensive research led to the development of more effective derivatives, Topotecan and Irinotecan (CPT-11; Camptosar). Topotecan is used for the treatment of ovarian and small cell lung cancers, while Irinotecan is used for the treatment of colorectal cancers.

Other plant-derived agents in clinical use are homoharringtonine, isolated from the Chinese tree, *Cephalo taxusharringtonia* var. drupacea (Sieb and Zucc.) (Cephalotaxaceae) (Itokawa *et al*., 2005), and elliptinium, a derivative of ellipticine, isolated from species of several genera of the Apocynaceae family, including Bleeke riavitensis 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.

Plant-derived anti-cancer agents in clinical development

Flavopiridol is totally synthetic, but the basis for its novel flavonoid structure is a natural product, rohitukine, isolated as the constituent responsible for anti-inflammatory and immunomodulatory activity from *Dysoxylum binectariferum* Hook. f. (Meliaceae), which is phylogenetically related to the Ayurvedic plant, *Dysoxylum malabaricum* Bedd., used for rheumatoid arthritis. Flavopiridol was one of the over 100 analogs synthesized during structure–activity studies, and was found to possess tyrosine kinase activity and potent growth inhibitory activity against a series of breast and lung carcinoma cell lines (Sausville *et al*., 1999). It also showed broad spectrum in vivo activity against human tumor xenografts in mice, which led to its selection for preclinical and clinical studies by the NCI in collaboration with the company, Hoechst. It is currently in 18 Phase I and Phase II clinical trials, either alone or in combination with other anticancer agents, against a broad range of tumors, including leukemias, lymphomas and solid tumors.

The combretastatins were isolated from the South African "bush willow", Combretum caffrum (Eckl & Zeyh) Kuntze (Combretaceae), collected in southern Africa in the 1970s as part of a random collection program for the NCI by the USDA, working in collaboration with the Botanical Research Institute of South Africa (Pinney *et al*., 2005). Species of the Combretum and Terminalia genera, both of which belong to the Combretaceae family, are used in African and Indian traditional medicine for the treatment of a variety of diseases, including hepatitis and malaria, and several Terminalia species have reportedly been used in the treatment of "cancer".

The combretastatins are a family of stilbenes which act as anti-angiogenic agents, causing vascular shutdown in tumors and resulting in tumor necrosis. A water-soluble analog, combretastatin A4 phosphate (CA4), has shown promise in early clinical trials, and a number of combretastatin (CA4) mimics are being developed. Three are in clinical trials, while are in preclinical development. This chemical class has served as a model for the synthesis of a host of analogs containing the essential trimethoxy aryl moiety linked to substituted aromatic moieties through a variety of two or three atom bridges including heterocyclic rings and sulfonamides, and provides an impressive display of the power of a relatively simple natural product structure to spawn a prolific output of medicinal and combinatorial chemistry (Li and Sham, 2002).

Another synthetic agent based on a natural product model is roscovitine which is derived from olomucine, originally isolated from the cotyledons of the radish, *Raphanus sativus* L. (Brassicaceae) (Meijer and Raymond, 2003). Olomucine was shown to inhibit cyclin-dependent kinases (Cdk), proteins which play a major role in cell cycle progression, and chemical modification resulted in the more potent inhibitor, roscovitine, which currently is in Phase II clinical trials in Europe. Further development of this series, following synthesis of a focused library via combinatorial chemistry techniques, has led to the purvalanols which were even more potent, and are in preclinical development (Chang *et al*., 1999)

CONCLUSION

From the present review, it can be concluded that cancer is the leading cause of death in developing countries like India. As there is an enormous increase in the population day by day, the alternative therapy in the market is getting its glimpse. The cheap herbal drug treatment may highly be recommended to the rural and poor people to treat effectively the cancers of various type is an ideal choice. Based on that the siddha medicines are coming up in combination with metals and other essential supplements to improve the immune status of the cancer patients in India. The above review reveals the role of Indian medicinal plants and the various phytochemicals which may be used for effective treatment for cancer. The available literature finds to be very impressive which may give an indication for the therapeutic usefulness. Only few of the plants listed here and there are hundreds of plants unexplored need much detailed survey. The isolation, identification of active principles and pharmacological studies of the active phytoconstituents may be considered and studied elaborately to treat effectively for various types of cancer.

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