



Medicinal Plants of Asian Origin Having Anticancer Potential: Short Review

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Article Details

Received:

19th June 2012

Received in revised form:

27 July 2012

Accepted:

15th Aug 2012

Available online

22nd Aug 2012



Online ISSN 2249-622X
<http://www.jbiopharm.com>

ABSTRACT

Cancer is a major public health burden in both developed and developing countries. It is the second largest common disease spread world-wide. Traditional medicines or herbal formulations can serve as the source of potential new drugs, so that initial research focuses on the active constituent of the plants. The development of novel plant derived natural products and their analogs for anticancer activity are going day by day. A number of promising agents of medicinal plants are used in clinical and preclinical development. Several anticancer agents including taxol, vinblastine, vincristine, camptothecin derivatives, topotecan and irinotecan, etoposide etc. derived from plants are in clinical use all over world.

KEYWORDS: Cancer, vinblastine, camptothecin derivatives, anticancer, *Allium sativum*

1. INTRODUCTION

Plants have been used for the treatment of various diseases for thousands of years. Terrestrial plants have been used as medicines in Egypt, China, India and Greece. Now, an impressive number of modern drugs have been developed from the plants. Plant secondary metabolites have proved to be an excellent reservoir of new medical compounds. Coronary disease and cancer together are responsible for over 80% of all deaths in industrialized countries. Eight out of ten people dies due to coronary heart diseases and cancer. The second-largest common disease is cancer-malignant tumors. Incidences of cancer keep increasing on a global scale. There is only one plausible explanation for this conventional medicine does not know the causes for cancer nor how this disease spreads. Because of this there is no effective cancer therapy available and the disease can keep expanding on a global scale. [1] Cancer is a major public health burden in both developed and developing countries. It was estimated that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons living with cancer around the world in 2012. [8-10]

Cancer is a group of diseases characterized by unregulated division and spread of cells. Cancer is a complex genetic disease that is caused primarily by environmental factors. The cancer-causing agents (carcinogens) can be present in food and water, in the air, and in chemicals and sunlight that people are exposed to. Since epithelial cells cover the skin, line the respiratory and alimentary tracts, and metabolize ingested carcinogens, it is not surprising that over 90% of cancers occur in epithelia. More significantly, a globalization of unhealthy lifestyles, particularly cigarette smoking and the adoption of many features of the modern Western diet (high fat, low fibre content) will increase cancer incidence. Tobacco use and diet each account for about 30% of new cancer cases, with infection associated with a further 15%; thus, much of cancer is preventable. [2-3]

CLASSIFICATION AND NOMENCLATURE OF CANCER:

In terms of behaviour, tumours are either 'benign' or 'malignant'. Benign tumours are generally slow-growing expansive masses that compress rather than invade

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surrounding tissue. Malignant tumours are usually rapidly growing, invading surrounding tissue and, most significantly, colonizing distant organs. The ability of tumour cells to detach from the original mass (the primary tumour) and set up a metastasis (secondary tumour) discontinuous with the primary is unequivocal proof of malignancy. The suffix 'oma' usually denotes a benign tumour, and tumours of glandular epithelia are called 'adenomas' (e.g. colonic adenoma). Tumours of surface epithelia are called 'papillomas' (e.g. skin papilloma). However, carcinoma and sarcoma refer to malignant tumours of epithelia and connective tissue respectively, qualified by the tissue of origin (e.g. prostatic carcinoma). The cancerous cells may occur in liquids, as in leukemia. Most, however, occur in solid tumors that originally appear in various tissues in various parts of the body. By their original locations they are classified into various types of cancer, such as lung, colon, breast, or prostate cancer.

SURVIVAL AND CANCER THERAPY:

Cancer treatment is usually a combination of a number of different modalities. If the tumour is amenable to surgery, then surgery is the single most effective tool in the anticancer armamentarium. Targeted radiotherapy is another option, as are combinations of anticancer drugs. Most conventional anticancer drugs have been designed with deoxyribonucleic acid (DNA) synthesis as their target. Therein lies the problem, in that tumour cells are not the only proliferating cells in the body; cells that line the alimentary tract, bone marrow cells that generate red blood cells and cells to fight infection, and epidermal cells including those that generate hair are all highly proliferative. Thus, patients with cancer receiving chemotherapy commonly suffer unwanted (hair loss) and sometimes potentially life-threatening (anaemia and proneness to infections) side effects that limit treatment. Localized tumors can be removed by surgery or irradiation with high survival rates. As cancer progresses, however, it metastasizes- invading the surrounding tissues, entering the blood stream, spreading and establishing colonies in distant parts of the body. Only a third of patients with metastasized cancer survive more than five years. High death rate associated with cancer and serious side effects of chemotherapy and radiation therapy, so, many cancer patients seek alternative and/or complementary methods of treatment. [4-5, 29-30]

HERBAL MEDICINAL PLANTS:

Herbal cancer therapy comprises a number of alternative treatments in the fight against cancer. As early as more than 3,000 years ago, Chinese doctors had used herbs in treatment of cancer patients. Ayurveda is an

ancient Indian herbal medicine system and is followed till date for anticancer treatment. This medicinal system is also proven to be at par with traditional Chinese Medicinal System. Currently, there are numerous herbal databases that provide information on herbal anticancer compounds. [6] Here to review some medicinal plants used for the prevention and treatment of cancer.

The World Health Organization estimates that approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care. [7] The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity. [11] From this screening two or three most important anti cancer compounds available today, namely taxol and camptothecin. [12-15] Various types of anti-cancer plant are zedoary (*Curcuma zedoaria*), marijuana (*Cannabis sativa*), indian trumpet (*Oroxylum indicum*), celandine (*Chelidonium majus*), yew (*Taxus baccata*), turmeric (*Curcuma longa*), rodent tuber (*Typhonium flagelliforme*), god's crown (*Phaleria macrocarpa*), madagascar periwinkle (*Catharanthus roseus*), artocarpus integer (*Selaginella corymbosa*), bamboo grass (*Loathatreum gracies*), handsome (*Taraxacum mongolicum*), fruit makasar (*Brucca javanica*), garlic (*Allium sativum*), echo china (*Smilax china*), sunflower (*Helianthus annus*), leunca (*Solanum nigrum*), job's tears (*Coix Lachryma-Jobi*), bamboo rope (*Asparagus cochinchinensis*), acanthopanax root bark (*Acanthopanax gracilistylus*), licorice (*Glycyrrhiza glabra*) etc. A brief description of medicinal plants in Asian origin used for the prevention and treatment of cancer is given below. The review gives information on the active anticancer components of the plants.

***Acanthopanax gracilistylus*:**

Acanthopanax gracilistylus, belonging to family Araliaceae and its extract (AGE), markedly suppressed the proliferative responses of human peripheral blood lymphocytes stimulated with mitogens concanavalin A (Con A) and *Staphylococcus aureus* Cowan I (SAC) on human lymphocytes *in vitro*. Both T cell and B cell activities- production of interferon-gamma and immunoglobulin- were suppressed by AGE. The mechanism of AGE-induced suppression of lymphocytes is to arrest the cell cycle at the G₀/G₁ stage without a direct cytotoxic effect. AGE also suppressed the alloantigen-specific cytotoxic T lymphocyte response. However, natural killer cell activity was less sensitive to the suppressive activity of AGE. In contrast, AGE markedly enhanced monocyte function to produce cytokines. These activities of AGE were associated with a 60-kD protein which was sensitive to treatment with pronase E, but not with NaIO₄. These suggested that AGE has an

immunomodulating activity on human lymphocytes and its properties could be clinically applied in the treatment of several diseases such as autoimmune and allergic diseases. [16-17]

Allium sativum:

Allium sativum is a member of family liliaceae, contains plentiful of chemical compounds that are helpful in prevention and treatment of different types of cancer. Allicin- a compound possessing antioxidant and anticancer activities isolated from *Allium sativum*. Allicin can penetrate very rapidly into different compartments of the cell and is completely metabolized in the liver. Experimental studies provide evidence that garlic and its organic allyl sulfur components are effective inhibitors of the tumor growth. [18]

Glycyrrhiza glabra:

Glycyrrhiza glabra belonging to family fabaceae, *in-vitro* cytotoxic screening of standard glycyrrhetic acid was carried using three different extracts (chloroform, methanol and water) of the drug through MTT method. Cell viability of previously identified glycyrrhetic acid in three different extracts of *Glycyrrhiza glabra* was determined by two fold trypan blue method using two different cell lines MCF7-cancerous and Vero-normal cell line. The percentage viability of two different cell lines was 45.71% for Vero-normal cell line and 78.78% for MCF7-cancerous cell line. The result of the study showed glycyrrhetic acid is a potential source of natural anticancer component and the percentage of which was found higher in the chloroform extract. [19-20]

Cannabis sativa:

The antiproliferative properties of cannabis compounds were first reported almost 30 years ago. Cannabis compound inhibits lung-adenocarcinoma cell growth *in vitro* and after oral administration in mice. *Cannabis sativa* (belonging to family Cannabaceae) found effective against lung carcinoma *in vivo* (mouse) study. It decreased tumour size and during *in vitro* study inhibits the cell-growth. [21] Other reported examples of cannabinoid selectivity towards tumour cells include thyroid epithelioma and skin carcinoma cells. In addition, though perhaps mechanistically unrelated, cannabinoids protect neurons from death in various models of toxic damage, whereas neuroblastoma cells are sensitive to cannabinoid-induced death. [22-23]

Oroxylum indicum:

Oroxylum indicum vent is a member of family Bignoniaceae and it is widely used by the Indians for the

treatment of various ailments. It is effectively used in treating cancer. The decoction of the bark is taken for curing gastric ulcer and the paste of the bark is applied to mouth for cancer, scabies, tonsil pain and other diseases. [24]

Chelidonium majus:

Celandine, an active agent isolated from *Chelidonium majus* (family- Papaveraceae) may have anti-cancer properties. In a study, NSC-631570, a semi-synthetic derivative of chelidonine, was shown to disrupt the cell cycle in pancreatic cancer cells but not in normal cells. This leads the authors for the study and concludes that NSC-631570 "might be a new therapeutic option in cancer therapy". The mechanism is thought to involve a disruption of tubulin polymerization. Tubulin is protein that is critically important in stages of the cell cycle leading to cell division. By selectively attacking the ability of cancer cells to divide, it is possible to stop cancer cells without affecting normal cells. [25]

Catharanthus roseus:

Catharanthus, apocynaceae family, well known for being rich in alkaloids. A screening program incidentally discovered that Catharanthus extracts were antineoplastic *in vitro*, leading ultimately to the licensing of the alkaloids vinblastine and vincristine, as well as some synthetic analogs today, as highly toxic chemotherapy drugs. The absolute levels of vinblastine and vincristine are considered far too low to explain the activity of crude extracts of Catharanthus. Various studies show the presence of other antineoplastic alkaloids in the plant. [26-27] Crude extracts of Catharanthus made using 50% and 100% methanol had significant anticancer activity against numerous cell types *in vitro* (at <15 mcg/ml). [28] Greatest activity was seen against multidrug resistant tumor types, suggesting there were compounds in Catharanthus that were synergistic or additive with antineoplastic elements by inhibiting resistance to them. Crude decoction of (200 mg and 1 g herb/ml water) Catharanthus showed a moderate anti-angiogenesis affect *in vitro*. [29] Vincristine and vinblastine, have been isolated from the plant and each has been used effectively against a number of different forms of cancer including childhood leukemia and Hodgkin's disease. In India, this plant has been used by native plant healers to treat diabetes.

Taxus baccata:

Taxus baccata belonging to family Taxaceae, and used for treatment of cancer reported in Indian ayurvedic medicine. [30] It has been reported that several conifers possess cytotoxic activities on some human tumor cell

lines. Taxol as a natural cytotoxic compound has been extracted. In a program to screen the cytotoxic effects of natural resources, male and female branchlets, fruit or bark of two different species of conifers were collected, identified and the cytotoxic effects of their hydroalcoholic extracts on three human tumor cell lines were determined. Different concentrations of extracts were added to cultured cells and incubated for 72 h. Cell survival was evaluated using MTT assay. Extracts from bark of female *Taxus baccata* showed inhibitory activities against Hela cells. The extracts of the branchlets of male and female *T. baccata* and branchlets of *Cupressus horizontalis* showed inhibitory activities against MDAMB-468 cells, whereas the extracts of branchlets of female *T. baccata* showed inhibitory activities against KB cells. The bark extract of *T. baccata* showed a comparable cytotoxic effect to doxorubicin against Hela cells. [31] In an another study, taxane diterpeneoid 2-deacetoxytaxinine J (2-DAT-J) has been isolated from the bark of Himalayan yew, *Taxus baccata* and its anticancer activity against breast cancer cell lines (MCF-7 and MDA-MB-231) and normal human kidney epithelial cell line (HEK-293) has been studied. 2-DAT-J showed significant *in vitro* activity against breast cancer cell line at a concentration of 20 μ M and 10 μ M in MCF-7 and MDA-MB-231 respectively. Few novel taxoids were derived (Epipodophyllotoxin, Etoposide, Homoharringtonine, Elliptinium, Flavopiridol and Roscovitine) from the naturally occurring 2-DAT-J and screened for their anticancer activity. The structure-activity relationship studies also indicated that the cinnamoyl group on C-5 and acetyl group on C-10 is essential for the anticancer activity. 2-DAT-J was also tested for its *in vivo* activity on DMBA-induced mammary tumors in virgin female Sprague Dawley rats at a dose of 10 mg/kg body weight orally for 30 days and showed significant regression in mammary tumors as compared to vehicle treated group. [30, 32]

Curcuma longa:

Curcuma longa (family Zingiberaceae) may be used for the treatment of leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma and neurological cancers. The target for treatment are cyclin D1 and cyclin E, apoptosis (by activation of caspases and downregulation of antiapoptotic gene products), proliferation (HER-2, EGFR, AP-1), survival (P13K/AKT PATHWAY), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4) and inflammation (nf-kappa B, TNF, IL-1, COX-2 and 5-LOX). Their main activity occurs with the interference in the above mentioned specified target molecules. [33-35]

Berberis amurensis:

Berberine, a bisbenzylisoquinoline alkaloid was isolated from the herb named *Berberis amurensis* (Berberidaceae). It was reported that Gleevec was responsible for bcr/abl tyrosine kinase inhibition and therefore used in the treatment of chronic myeloid leukemia. But few patients developed resistance against this drug. It was found that berberine effectively causes cell apoptosis of both Gleevec sensitive and resistant Ph+ chronic myeloid leukemia cells. They work by inducing caspase-3-dependent apoptosis of leukemic NB4 cells by the survivin-mediated pathway. [36-37]

Salvia prionitis:

Salvicine, a diterpenoid quinone is obtained as a derivative of the naturally occurring lead saprothoquinone compound. This lead product is isolated from a medicinal plant species, *Salvia prionitis* Hance (Labiatae). Salvicine reported significant *in-vitro* and *in-vivo* activity against malignant tumors by inhibiting the activity of Topoisomerase II. [38]

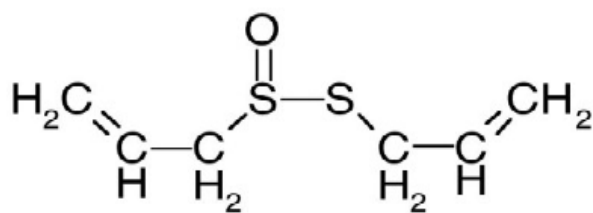
OTHERS:

Some other isolated agents or plants are also included in this review which has little information regarding their anticancer activity. Two alkaloids schischkinnin and montamine have been isolated from the seeds of *Centaurea schischkinii* (Asteraceae) and *Centaurea Montana* (Asteraceae). Both alkaloids exhibited significant cytotoxicity against human colon cancer cell lines. [30] *Anethum graveolens* (Dill) belonging to family Apiaceae has also been reported as anticancer. [39] According to ayurveda *Digitalis lanata* and *Digitalis purpurea* (family- Plantaginaceae), comes under plants having anticancer activity but present data to confirm the activity is not purely available. [40]

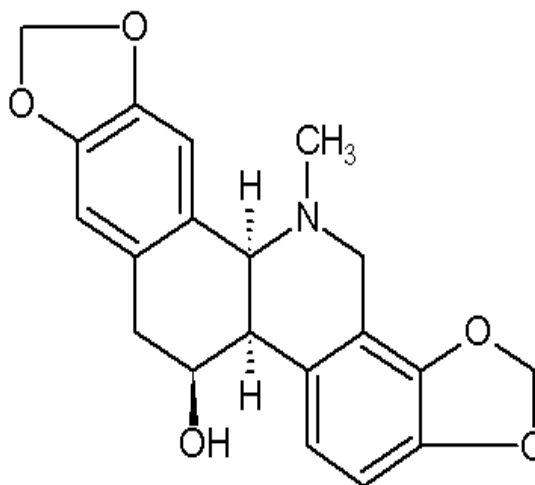
1. Some fruits of various medicinal plants also included in this review which showed anticancer activity, like brucea, psoralea etc. Brucea fruit extract is used in the treatment of carcinomas of the uterine cervix, rectum, anus, esophagus, liver, breast, lung, skin, colon, and thyroid. For carcinomas of the digestive tract and skin, it kills tumor cells when it is topically applied. Brucea fruit is also used in the treatment of dysentery, chronic diarrhea, malaria, dermatitis, eczema and flat condyloma in skin. Psoralea fruit extract in the treatment of heart failure, coronary heart disease, leukoderma, urine bladder atonia, prostatitis, and night bed-wetting. Seeds of this herb contain psoralen which is a photosensitizer. Psoralen damages to membrane of normal cells and tumor cells. Psoralen also binds to DNA of cells that induce apoptosis and death of both normal cells, diseased cells and tumor cells. Psoralea fruit extract is also used in the treatment of

psoriasis and other skin diseases. Glossy Privet fruit is also used for treatment of cancer. If it is used alone, it may give about 20 to 30% anti-cancer efficacy in some patients with leukemia or lymphoma but it may cause some adverse

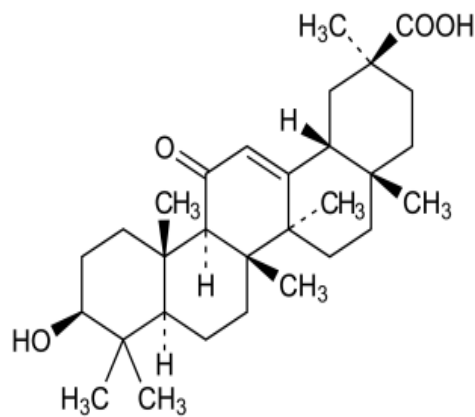
effects. When combines with Milkvetch root herb and others that may attain 90% anti-cancer efficacy and brings about 10% side-effects. [6]



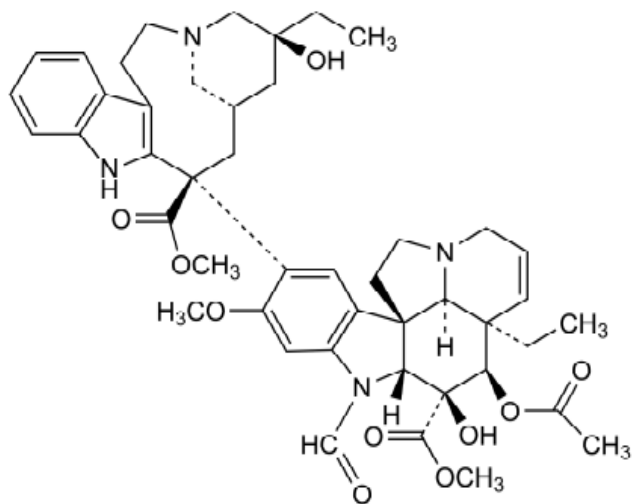
Allicin



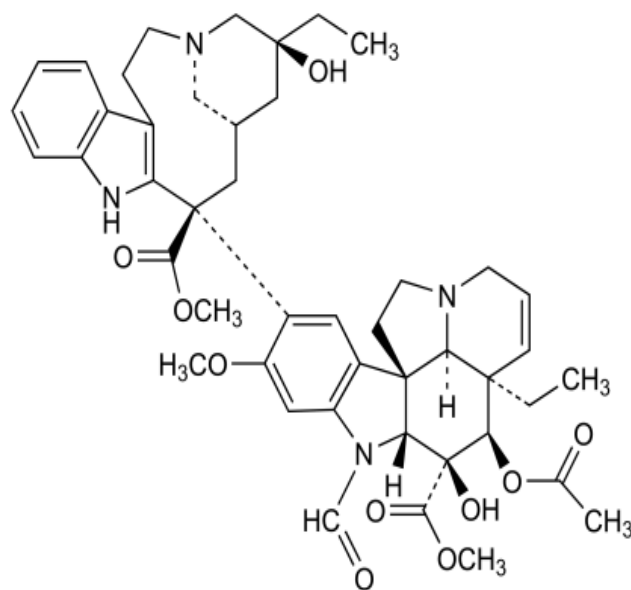
Chelidonium



Glycyrrhetic Acid



Vincristine



Vincristine

CONCLUSION:

A brief description of plants having anticancer activity is given. An impressive number of modern drugs have been developed from the plants. Plant secondary metabolites have proved to be an excellent reservoir of new medical compounds.

ACKNOWLEDGEMENT:

We are grateful to the authors/editors of all those articles has been reviewed and discussed.

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Conflict of Interest: None Declared