



MEDICINAL PLANTS WITH POTENTIAL ANTICANCER ACTIVITIES: A REVIEW

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ABSTRACT

Plants have been the beacon of therapeutic sources for curing diseases from times immemorial. Medicinal plants with their isolated lead molecules are also used as an alternative medicine for treating neoplastic cells. Neoplastic cells are the anomalous proliferation of cells in the body which cause cancer. Diverse efficient compounds derived from natural products have been isolated as anticancer agents. These chemical compounds are formulated with a view to create effective drugs against cancer. Some of the lead molecules isolated from different medicinal plants are already in use to treat cancer and chemotherapeutic side effects. These potential and successful anticancer molecules include Vincristine, Vinblastin, Taxol, Camptothecin and Podophyllotoxin. This paper deals with the selective medicinal plants having anticancer properties which could be further designed to produce cancer curing drugs.

KEYWORDS: Therapeutic, Neoplastic cells, Chemotherapeutic, Taxol, Anticancer

INTRODUCTION

In recent times, medicinal plants occupy an important position for being the paramount sources of drug discovery, irrespective of its categorized groups- herb, shrub or tree. Plants have been indispensable in treating diverse forms of diseases including cancer. According to World Health Organisation, 80% of the people living in the rural areas depend on medicinal plants as primary health care system. These practices are solely based on the knowledge of traditional use of medicinal plants. Natural products are formulated to generate different types of effective drugs to enhance anticancer activities. Proper understanding of the complex synergistic interaction of various constituents of anticancer herbs, would help in formulating the design to attack the cancerous cells without harming the normal cells of the body.^{1, 2}

Cancer is a dreadful disease characterized by the irregular proliferation of the cells. As a cell progresses from normal to cancerous, the biological imperative to survive and perpetuate drives fundamental changes in cells behaviour.³ So the actual cause of the disease in different sections is still to be explored clearly. Cancer is thus, a class of diseases, classified by the type of cell that is initially affected. Today's global scenario indicates that breast cancer and colorectal cancer is the most prominent cancer in case of woman and man. To combat cancer United States National Cancer Institute has undergone 2069 anticancer clinical trials, in which over 150 drug combinations have been successfully recorded against cancer. The search for this cancer drug discovery from Natural sources began with the investigations done by Hartwell and his co-workers in the late 1960's with the application of Podophyllotoxin and its derivatives from the plant *Podophyllum peltatum*. Further discoveries lead to isolate anticancer compounds from plants like *Catharanthus roseus*, *Camptotheca acuminata* and *Taxus brevifolia*. Vincristine, Vinblastine, Camptothecin and Taxol are the established potential anticancer agents derived from these plants which are found to be effective against various types of cancer.⁴

Advances in the clinical researches for anticancer agents have been increased over the years and as a result numbers of drugs have been introduced. Imperative organic compounds present in plants could exaggerate to diminish the toxicity caused due to chemotherapy. Task of modulating the adverse affect is feasible only through requisite perspective regarding the specificity of these molecules with combination therapy.⁵ In this present review, we have focused on some of the medicinal plants containing anticancer properties that would benevolently play a vital role in discovering potential drugs for treating cancer.

Potential plants, which could be evaluated for effective anticancer compounds in future days, are discussed below:-

***Artocarpus obtusus* F.M. Jarrett**

The *Artocarpus obtusus* species belongs to *Moraceae* family. *Artocarpus* is distributed from South East Asia to Oceania. Several *Artocarpus* species have been introduced throughout the tropics and are harvested for food. Different species of *Artocarpus* are also found in Africa, Madagascar, Malay peninsula and also in Sumatra and Thailand.⁶ An investigation of the chemical constituents in *Artocarpus obtusus* species led to the isolation of three new xanthenes, pyranocycloartobiloxanthone A (1), dihydroartoinonesianin C (2), and pyranocycloartobiloxanthone B (3). The compounds were subjected to antiproliferative assay against human promyelocytic leukemia (HL60), human chronicmyeloid leukemia (K562), and human estrogen receptor (ER+) positive breast cancer (MCF7) cell lines. The extracts of *A. obtusus* were found to exhibit good cytotoxic and potential antiproliferative activity against these cell lines. Pyranocycloartobiloxanthone A (1) inhibits the cell proliferation of human promyelocytic leukemia and breast cancer cells. The potent activity of Pyranocycloartobiloxanthone A (1) is exhibited by the presence of both resorcinol moiety in ring B and isoprenyl substituent at C-3 position. This phytochemical investigation of Malaysian *Artocarpus* species can identify new lead compounds as anticancer agents.⁷

***Blumea balsamifera* DC**

Blumea balsamifera (also known as sambong) is a medicinal plant that grows in Southeast Asia. It belongs to the Family *Asteraceae*. The leaves of *B. balsamifera* are used as tea, and to cure certain disorders such as rheumatism and hypertension. Its leaves have attracted attention as this part of the plant has various physiological activities, including plasmin-inhibitory, antifungal, and liver-protective effects.⁸ In Thailand, the dried leaves are cut into small pieces and smoked as a cigarette to relieve sinusitis pain. An infusion of the leaves is used as a stomachic, carminative, diaphoretic, expectorant and emmenagogue. Leaves of *Blumea balsamifera* DC consist of compounds, two dihydroflavonols, dihydroquercetin-4'-methyl ether (1) and dihydroquercetin-7,4'-dimethyl ether (2), two flavanones, 5,7,3',5'-tetrahydroxyflavanone (3) and blumeatin (4), three flavonols, quercetin (5), rhamnetin (6) and tamarixetin (7), two flavones, luteolin (8) and luteolin-7-methyl ether (9).⁹ Methanolic extract of *B. balsamifera* induced cell cycle arrest at G1 phase via decreases in expression of cyclin-E and phosphorylation of retinoblastoma (Rb) protein in both dose- and time-dependent manners. It also reduced the level of a proliferation related ligand which stimulates tumor cell growth. *B. balsamifera* extract is also effective against human hepatocellular carcinoma cells.

***Boerhaavia diffusa* L**

Boerhaavia diffusa L. is a perennial creeping herb which belongs to the family *Nyctaginaceae*. It is commonly known as "punarnava" in the Indian system of medicine. The various parts of the plant are used in the treatment of cancer, jaundice, dyspepsia, inflammation, enlargement of spleen, abdominal pain and as an anti-stress agent. Punarnava possesses punarnavoside, which exhibits a wide range of properties such as diuretic, antifibrinolytic, anticonvulsant and antibacterial. Liriodendrin isolated from the methanol extract of the roots of *B. diffusa* exhibits significant calcium channel antagonistic activity. Punarnavine, an alkaloid from *B. diffusa* enhanced the immune response against metastatic progression of B16F-10 melanoma cells in mice.¹⁰ Ethanolic extract of *B. diffusa* Showed cytotoxicity against HeLa cell line and inhibits the S- phase of the cell cycle. It also suppressed the growth of cancer cells in DMBA- induced cancer carcinogenesis in mice by preventing the promotional events in the mouse skin through free radical scavenging mechanism.¹¹ Two rotenoids isolated from *B. diffusa*, boeravinones G and H, have been found to potently inhibit the drug efflux activity of breast cancer resistance protein (BCRP/ABCG2), a multidrug transporter responsible for cancer cell resistance to chemotherapy.¹²

***Calotropis procera* (Ait.) R. Br.**

Calotropis procera (Ait.) R. Br. has been used for a variety of disease conditions that includes its use in the treatment of leprosy, ulcers, piles and tumors.¹³ It belongs to the family *Asclepiadaceae*. The root extract of *C. procera* has been found to produce a strong cytotoxic effect on COLO 320 tumor cells. Recently, a hemi synthetic derivative of a cardenolide isolated from the root barks of *C. procera* shows a strong cytotoxic effect on several human cancer lines, a high *in vivo* tolerance to tumor growth and prolonged survival in the human xenograft models of nude mice.¹⁴ The aqueous extract of dried latex (DL) of *C. procera* showed a strong *in vivo* chemopreventive effect. The methanolic extract (ME) of DL was evaluated for cytotoxicity using

MTT assay on two different cell lines, viz., Huh-7 and COS-1 cells. ME induced cell death in both cell lines in a concentration dependent manner. The latex of *C. procera* possesses potent anti-inflammatory and antioxidant properties. Choedon et.al tested the latex for its chemopreventive and *in vitro* cytotoxic properties. The cytotoxic effects of DL was evaluated on hepatoma (Huh-7), non-hepatoma (COS-1) and non-cancerous (AML12) cell lines and observed that the cytotoxic activity was associated with one of the polar fractions of DL.¹⁵

***Citrus maxima* (Burm.) Merr.**

The plant *Citrus maxima* Merr. (shaddock or pomelo) of the family *Rutaceae* is indigenous to tropical parts of Asia. The pulp is stated to possess the following properties as reported in ancient and medieval literature: appetizer, antitoxic, cardiac stimulant, and stomach tonic. The major flavanones of pomelo are neohesperidin and naringin, which are high in the seed in case of unripe citrus fruits and its extract showed antioxidant activity through free radical-scavenging *in vitro* and reduced reactive oxygen species in H₂O₂-treated HepG2 cells.¹⁶ The flavonoids and limonoids present in citrus plants are postulated to be the cause of their antitumor and anti-inflammatory effects.¹⁷ Flavonoids have a chemopreventive role in cancer by means of their effect in signal transduction in cell proliferation and angiogenesis. Experiment performed by Kudus et.al. found that intraperitoneal administration of methanolic extract of *Citrus maxima* at the dose levels of 200 and 400 mg/kg BW increased the life span of nonviable tumor cell count and decreased the tumor volume.¹⁸ Immature hexane fruit extract of pomelo has also shown its antiproliferative activity against U937 human leukemia cell line.¹⁹

***Emblica officinalis* Gaertn.**

Emblica officinalis Gaertn. belongs to the family *Euphorbiaceae*. It is commonly known as amla or Indian gooseberry. Emblica has been used as an important traditional herbal medicine in Southeast Asia since ancient times. It is extensively found all over India, as well as Sri Lanka, Malaysia, China, Pakistan and Bangladesh. The fruits contain constituents with variable biological activity. Emblica is a good source of polyphenols, flavones, tannins and other bioactive substances.²⁰ It is a source of hepatoprotective, antioxidant, immune stimulator and antitumor agent. Pyrogallol an active compound of *E. officinalis* has anti-inflammatory effect. Eighteen compounds found in *Emblica* inhibit the growth of gastric, uterine and breast cancer. It enhances natural killer (NK) cells in various tumors and reduced the ascites and solid tumor induced by Dalton's lymphoma ascites cells in mice. Cyclophosphamide is one of the most popular alkylating anticancer drugs in spite of its toxic effects. Haque et.al found that aqueous extract of *Emblica officinalis* reduced the toxic effect, such as immunotoxicity, hematotoxicity and mutagenicity, in mice treated with cyclophosphamide.²¹

***Moringa oleifera* Lam.**

Moringa oleifera Lam. belongs to the monogeneric family, *Moringaceae*. This rapidly growing tree is also known as horseradish tree or drumstick tree, is native to the sub-Himalayan region tract of India, Pakistan, Bangladesh and Afghanistan. All Parts of Moringa tree are edible and have long been consumed by humans. The leaves were used in folk remedies for tumors. *Moringa oleifera* Lam. contains a unique combination of isothiocyanate and glucosinolates.

Isothiocyanates have antitumor activity in cancers of the lung, breast, skin, esophagus, and pancreas. Studies have found that *Moringa* compounds, benzyl isothiocyanate (BITC) and phenethyl isothiocyanate (PEITC) induced apoptosis in ovarian cancer cells *in vitro*. Beta-sitosterol, glycerol-1-(9-octadecanoate), 3-O-(6'-O-oleoyl-beta-D-glucopyranosyl)-beta-sitosterol and beta-sitosterol-3-O-beta-D-glucopyranoside of *Moringa oleifera* have been identified as anticancer agents.²² Benzyl isothiocyanide and the related compound niazimicin were shown to be potent inhibitors of Phorbol ester (TPA)- induced Epstein-Barr-Virus early antigen activation in Lymphoblastoid (Burkitt's Lymphoma) cells. Nair et.al. found that aqueous extract of *Moringa* tree is cytotoxic against HeLa cell lines.²³ One of the interesting facts of *Moringa oleifera* is that its root has unique estrogenic, antiestrogenic, progestational and antiprogestational activities. Higher dose of root bark extract of *Moringa* tree can cause toxic hypotensive and violent uterine contraction which can be fatal.²⁴

***Oroxylum indicum* Vent**

Oroxylum indicum Vent is a member of the family *Bignoniaceae* and is widely used by Indians for the treatment of various ailments. It is a medium sized deciduous tree which is mostly sighted along the riverbanks or slopes of the hills and is distributed throughout India and Southeast Asia. The decoction of *Oroxylum indicum* bark could cure nasopharyngeal cancer. This is also used for curing gastric ulcer while the paste of the bark is applied to mouth for cancer, scabies, tonsil pain and other diseases.²⁵ The bioactive constituents present in the plant are baicalin, Chrysin, baicalein-7-*O*-glucoside and baicalein. Methanolic extract of the fruit of *Oroxylum indicum* inhibited *in vitro* proliferation of HL-60 cells. The flavanoid baicalein was found to be an active component that induced apoptosis in HL-60 cell line.²⁶

***Panax Ginseng* C.A. Meyer**

Panax ginseng C.A. Meyer or Ginseng is one of the best known Korean and Chinese traditional herbal medicines, which is used worldwide. Ginseng belongs to the family *Araliaceae*. The efficiency of ginseng has been demonstrated in the central nervous system and in the cardiovascular, endocrine, immune systems and it has antineoplastic, anti-stress, and antioxidant activities. The most important bioactive components of ginseng are ginsenosides, polyacetylenes, polysaccharides, alkaloids, and phenolic compounds. The ginsenoside is one of the most important secondary metabolites in ginseng and contains glucosyl moiety at carbon-3, -6, and -20.²⁷ *Panax ginseng* and its chemical constituents have been tested for their inhibiting effect on putative carcinogenesis mechanisms such as cell proliferation, apoptosis, immunosurveillance and angiogenesis and in most experiments inhibitory effects were found.²⁸ Cancers of the lip, oral cavity, pharynx, esophagus, stomach, colorectal, liver and pancreas showed decreased odds ratios with increasing ginseng intake. It was found that ginsenoside Rp1 inhibited breast cancer cell proliferation and inhibited both anchorage-dependent and -independent breast cancer cell colony formation.

***Pfaffia paniculata* (Mart.) Kuntze**

Pfaffia paniculata (Brazilian ginseng or Suma) is a native shrubby medicinal plant of Brazil. It belongs to the *Amaranthaceae* family. The roots of these plants have been used traditionally in folk medicine as tonic, aphrodisiac and

for the prevention and treatment of diabetes. Brazilian ginseng is also used to improve physical as well as mental state and to treat various diseases including some types of cancer. The major constituents of *Pfaffia paniculata* are saponins, which are known to have several biological properties due to the complexity in their chemical structure. *P. paniculata* is cytotoxic, cause mitochondrial damage and cell membranes damage. Roots of *Pfaffia paniculata* have been well documented for multifarious therapeutic values and have also been used for cancer therapy in folk medicine. Study has been performed in human breast cancer cell line, MCF-7; where butanolic extract of the roots of *P. paniculata* showed cytotoxic effect on MCF-7 cell line. The main isolated compounds of its roots are stigmaterol, sitosterol, allantoin, pfaffic acid and triterpenoid saponin. The Pfaffic acid, hydrolytic product of the saponins has inhibitory action on the growth Melanoma B-16, HeLa S-3 and Lewis lung carcinoma cells *in vitro*.²⁹

***Rheum officinale* Baill.**

Rheum officinale Baill. of the family *Polygonaceae*, is also known as Da Huang in Chinese herbal medicine. It has been widely used as a laxative, antiphlogistic and haemostatic agent in the treatment of obstipation, gastrointestinal indigestion, diarrhea and Jaundice. In addition, it is one of the herbs commonly used in traditional Chinese medicine formulae prescribed to cancer patients. The major pharmacologic constituents of Da Huang in the rhizome and root portions of the plant are anthraquinone and bianthrone derivatives. Da Huang has been reported to have anti-tumor activity with hepatocarcinoma.³⁰ Da Huang significantly inhibited the proliferation of A549 and MCF-7 cells *in vitro*, confirmed by the cell viability and colony formation assays. Da Huang water extract treatment resulted in internucleosomal DNA cleavage in both A549 and MCF-7 cell lines, while the internucleosomal DNA from untreated cancer cells remained intact. Da Huang water extract has strong dose and time dependent antiproliferative activity on A549 and MCF-7 cells in culture. Aqueous extract of *Rheum officinale* has a general function in suppressing cancerous cell growth but may act through multiple pathways.³¹

***Saxifraga stolonifera* (L) Meeb**

Saxifraga stolonifera (L) Meeb, which belongs to *Saxifragaceae* family, is a perennial herbaceous plant growing at an altitude of 390–3600 m in China, Russia, Japan and Korea. Pharmacological experiments have indicated that constituents and extracts of *S. stolonifera* can block tumors at various sites, e.g. gastric, prostate, breast and leukemia. Studies have also revealed that the extracts of *S. stolonifera* can inhibit proliferation of cancer cells *in vivo* by induction of apoptosis. Ten compounds isolated from ethanolic extracts of *S. stolonifera* plant were identified as n-C31H64 (1), (n-C17H35)2CO (2), b-sitosterol (3), n-C29H60 (4), Bergenin (5), Protocatechuic acid (6), Gallic acid (7), Quercitrin 3-O-a-L-rhamnoside (8), Quercetin (9), and Quercetin 3-O-b-D-glucopyranoside (10). Among them, n-C31H64 (1), (n-C17H35)2CO (2), b-sitosterol (3), and n-C29H60 (4) showed anticancer activities on human gastric carcinoma cell line BGC-823. Chen et.al. studied the effect of the extracts from *S. stolonifera* on human tumor cell lines BGC-823 by MTT assay at concentrations ranging from 5 to 100 μ M. They found that the inhibitory effects of b-sitosterol, gallic acid and quercetin were concentration-dependent. Among these ingredients, quercetin was found to

exhibit high effect on BGC-823 cells, with the growth inhibition ratio of 39.3% after 72 h treatment at 100 μ M, while the growth inhibition ratios of other compounds were considerably lower even at high concentration, ranging from 6.6% to 22.5% after 72 h treatment at 100 μ M.³² Quercetin not only caused growth inhibition in BGC-823 cells, but also brought out morphological changes on the tumor cells. Quercetin can also induce apoptosis on human promyelocytic leukemia cells (HL-60 cells) and kidney tubule epithelial cells (NRK-52E).³³ Quercetin seems to hold a promising component for inducing apoptosis in BGC-823 cells and can be used as a chemopreventive and therapeutic agent for cancers.

***Vitex negundo* Linn.**

Vitex negundo Linn. (Nirgundi in Hindi) which is a species of *Verbenaceae* family, is a large evergreen, climbing, much branched shrub and ascending up to an altitude 1100-1400 ft, is found almost throughout India. Although all parts of *V. negundo* are used as medicine in the indigenous system of medicine, the leaves are the most potent part for medicinal use. It is used for treatment of eye disease, toothache, inflammation, leucoderma, enlargement of the spleen, skin ulcers, in catarhal fever, rheumatoid arthritis, gonorrhoea and bronchitis. They are also used as tonics, vermifuge, lactagogue, emmenagogue, antibacterial, antipyretic and antihistaminic agents. Ethanolic extract of *Vitex negundo* treatment was found to enhance nonviable counts in peritoneal exudates and decrease the viable cell count.³⁴ This extract is effective against the major problems, myelosuppression and anaemia, that are being encountered during chemotherapy and can bring back hemoglobin and RBC count to normal.

***Withania Somnifera* (L.) Dunal**

Withania somnifera (L.) Dunal (also known as ashwagandha), belongs to the family *Solanaceae*, is an important medicinal plant that is widely used as a home remedy for several diseases in the Indian subcontinent and other parts of the world. *W. somnifera* is a dietary supplement composed of various nutrients, polyphenols and alkaloids that have free radical scavenging capacity as well as other chemical constituents that possess anti-inflammatory, antitumor, anti-aging, anti-stress, antioxidant, immunomodulatory, and rejuvenating properties. Over 35 chemical constituents have been identified from *Withania*. The biologically active chemical constituents are alkaloids-isopelletierine and anaferins, steroidal lactones- withanolides and withaferins, saponin containing an additional acyl group-sitoinoside VII and VIII and withanolides with a glucose at carbon 27- sitoindoside IX and X. *Withania somnifera* is also rich in iron.³⁵ *W. somnifera* decreases NF-kB levels, suppresses intercellular tumor necrosis factor and potentiates apoptotic signaling in animal cancerous cell lines. *In vitro* and *in vivo* studies of *W. somnifera* has showed stimulatory effects on cytotoxic T lymphocyte generation and demonstrated the potential to reduce tumor growth.³⁶ The chemopreventive effect of *W. somnifera* root extract was demonstrated in a study on induced skin cancer in Swiss albino mice. A study of an alcohol extract of dried *W. somnifera* roots and the active component withaferin A isolated from the extract showed significant antitumor and radiosensitizing effects in *in vivo* experimental tumors and lacked any noticeable systemic toxicity. These isolated

compounds of *W. somnifera* could provide a potential and relatively safe radiosensitizer or chemotherapeutic agent.³⁷

***Zingiber officinale* Roscoe**

Zingiber officinale Roscoe (Ginger), belonging to the family *Zingiberaceae*, is a commonly used medicinal herb throughout the world. It is a natural dietary component with antioxidant and anticarcinogenic properties. Active phenolic compounds of ginger such as shagaol and gingerol, have antioxidant, anti-angiogenesis, anti-inflammatory, anti-atherosclerotic and anticancer properties. [6]-gingerol, a compound of ginger can inhibit angiogenesis of human endothelial cells and cause cell cycle arrest in the G1 phase through the down regulation of cyclin D1. The oleoresin from the roots of ginger also contains a structurally related vanilloid, [6]-paradol. These compounds suppress the proliferation of human cancer cells through the induction of apoptosis and exert inhibitory effects on the viability of human HL-60 (promyelocytic leukemia) cells. Keum et.al, found that [6]-paradol and other structurally related derivatives like [10]-paradol, [3]-dehydroparadol, [6]-dehydroparadol and [10]-dehydroparadol, induced apoptosis in an oral squamous carcinoma cell line, in a dose dependent manner through a caspase-3-dependent mechanism.³⁸ Beta-Elementene is a novel anticancer drug, which is extracted from the ginger plant. It triggers apoptosis in non-small cell lung cancer cells through a mitochondrial release of the cytochrome *c*- mediated apoptotic pathway. Beta-Elementene also induced caspase-3, -7 and -9 activities and decreased Bcl-2 expression.³⁹

CONCLUSION

Plants are the largest reservoir of secondary metabolites which contribute in combating different diseases from ancient times. This review has shown that plants like *Withania Somnifera* (Ashwagandha), *Oroxylum indicum* which were used in Ayurveda possess potential anticancer properties. Ashwagandha has already proven to be a constituent of anti-aging property. *Vitex negundo* is an important plant with lots of medicinal properties. According to earlier studies it has been shown that *vitex negundo* possess antioxidant properties.⁴⁰ Many bioactive components in the plant material are responsible for their anticancer activity. Active compounds contain in diverse groups of plants are still to be explored scientifically. So, to evaluate the potential anticancer compounds present in medicinal plants with proper methodology is in exigency. This proper exploration would develop in introducing a site specific and safe anticancer drug with higher therapeutic properties to eradicate cancer.

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