Review Article

A Review on Medicinal Plants as a Potential Source for Cancer

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Accepted on: 07-03-2014; **Finalized on:** 30-04-2014.

ABSTRACT

Cancer is a major health problem in both developed and developing countries. Cancer is the second leading cause of death after cardiovascular disease. Due to high death rate associated with cancer and serious side effects of chemotherapy and radiation therapy, many cancer patients seek alternative and/or complementary methods of treatment. India, which are being used traditionally for the prevention and treatment of cancer. However, only few medicinal plants have attracted the interest of scientists to investigate the remedy for neoplasm (tumor or cancer). Hence, an attempt has been made to review some medicinal plants used to prove scientific validation for the prevention and treatment of cancer. This article considers 82 medicinal plants belonging to 46 families and information on the Botanical name, family name, parts used, experimental model and mechanism of action were presented. This article provides basic handful information for researchers who are interested to work on medicinal plants for innovation of active biological compounds that to work on cancer as a principle mechanism.

Keywords: Anti cancer activity, Cancer, Cytotoxicity, Medicinal plants.

INTRODUCTION

Cancer is a degenerative disease. Accumulation of toxins through carcinogenic food like fast food, colas, habits like smoking, drinking, paan chewing, stressful lifestyle, toxic medicines and environmental pollution lowers immunity causing cancer. There are 10.9 million new cases, 6.7 million deaths, and 24.6 million persons alive with cancer. The most commonly diagnosed cancers are lung (1.35 million), breast (1.15 million), and colorectal (1 million); the most common causes of cancer death are lung cancer (1.18 million deaths), stomach cancer (700,000 deaths), and liver cancer (598,000 deaths).[1] Internationally the cancer burden doubled between 1975 and 2000 and is set to double again by 2020 and nearly triple by 2030. There were around 12 million new cancer cases and 7 million cancer deaths worldwide in 2008, with 20-26 million new cases and 13-17 million deaths projected for 2030.[2] In India Every year about 8, 50,000 new cancer cases being diagnosed, resulting about 5, 80,000 cancer related death every year.[3] The control of cancer, one of the leading cause of death worldwide, may benefit from the potential that resides in alternative therapies. Conventional therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Better cancer treatments with milder side effects are desperately needed. There is thus the need to utilize alternative concepts or approaches to the prevention of cancer.[4]

However natural therapies, such as the use of the plants or plant derived natural products are being beneficial to combat cancer. Plants produce an array of active ingredients that are known as secondary metabolites. Many secondary metabolites have been utilized by human beings for various purposes, specially for making medicines and as healing agents by people of Homeopathy, Unani, Ayurvedic medicine producers and practitioners.[5] Plants, since ancient time, are using for health benefits by all cultures as well as source of medicines. It has been estimated that about 80-85% of global population rely on traditional medicines for their primarily health care needs and it is assumed that a major part of traditional therapy involves the use of plant extracts or their active principles.[6] The Indian system of holistic medicine known as "Ayurveda" uses mainly plant-based drugs or formulations to treat various ailments, including cancer. Of the at least 877 small-molecule drugs introduced worldwide between 1981 and 2002, the origins of most (61%) can be traced to natural products.[7] Recent phytochemical examination of plants which have a suitable history of use in folklore for the treatment of cancer.[3] Among many recent advances in cancer chemotherapy, plant natural products play an important role in having contributed considerably to the approximately 60 available cancer chemotherapeutic drugs. There are now four classes of anticancer agents used clinically in the United States are plant-derived, namely, the Vinca alkaloids, the epidodophyllotoxin, the taxanes, and the camptothecin derivatives.[8] Here an attempt is being made through this review to highlights the new plant species identified with anti-cancer properties either *in vivo* or *in vitro*.

Causes of cancer are as follows

1. Viruses such as Epstein-Barr-Virus (EBV), Hepatitis- B-Virus (HBV), Human Papilloma Virus (HPV).
2. Environmental and occupational exposure such as ionizing, UV radiation, exposure to chemicals including vinyl chloride, benzene and asbestos.

3. Life style factors such as high-fat, low fiber diets, tobacco, ethanol etc.
4. Medication such as alkylating agents and immunosuppressant's.
5. Genetic factors such as inherited mutations, cancer causing genes, defective tumor suppressor genes.[3]

Types of Cancers

1. Cancers of Blood and Lymphatic Systems

a) Hodgkin's disease b) Leukemias c) Lymphomas d) Multiple myeloma e) Waldenstrom's disease.

2. Skin Cancers

a) Malignant Melanoma

3. Cancers of Digestive Systems

a) Esophageal cancer b) Stomach cancer c) Cancer of pancreas d) Liver cancer e) Colon and Rectal cancer f) Anal cancer

4. Cancers of Urinary system

a) Kidney cancer b) Bladder cancer c) Testis cancer d) Prostate cancer

5. Cancers in women

a) Breast cancer, b) Ovarian cancer, c) Gynecological cancer, d) Choriocarcinoma

6. Miscellaneous cancers

a) Brain cancer, b) Bone cancer, c) Carcinoid cancer, d) Nasopharyngeal cancer, e) Retroperitoneal sarcomas f) Soft tissue cancer g) Thyroid cancer.[9]

The mechanism on cancer therapy

1. Inhibiting cancer cell proliferation directly by stimulating macrophage phagocytosis, enhancing natural killer cell activity.
2. Promoting apoptosis of cancer cells by increasing production of interferon, interleukin-2 immunoglobulin and complement in blood serum.
3. Enforcing the necrosis of tumor and inhibiting its translocation and spread by blocking the blood source of tumor tissue.
4. Enhancing the number of leukocytes and platelets by stimulating the hemopoietic function.
5. Promoting the reverse transformation from tumor cells into normal cells.
6. Promoting metabolism and preventing carcinogenesis of normal cells.
7. Stimulating appetite, improving quality of sleep, relieving pain, thus benefiting patient's health.[10]

Cancer-Classical systems

Ayurveda, the oldest Indian indigenous medicine system of plant drugs is known from very early times for preventing or suppressing various tumors using natural drugs. Nowadays scientists are keener to researches on complementary and alternative medicine for the management of cancer. In Ayurvedic concept, according to 'Charaka' and 'Sushruta Samhitas' cancer is described as inflammatory or non-inflammatory swelling and mentioned either as 'Granthi' (minor neoplasm) or 'Arbuda' (major neoplasm).[11] The therapeutic approach of Ayurveda has been divided into four categories as *Prakritisthapani chikitsa* (health maintenance), *Roganashani chikitsa* (disease cure), *Rasayana chikitsa* (restoration of normal function) and *Naishthiki chikitsa* (spiritual approach).[12] Balachandran and *Govindarajan*[13] review to discuss about the pathology and therapeutic management of various cancers described in Ayurveda and give a list of anticancer drugs of plant origin revealed identification of newer ayurvedic drugs that are not mentioned in the ancient texts.

Siddha system is one of the oldest systems of medicine in India. The term Siddha means achievements and Siddhars were saintly persons who achieved results in medicine. According to Indian history prior to Aryans migration, the Dravidian was the first inhabitant of India of whom the Tamilians were the most prominent. The Siddha medicine for cancer contains metals and compounds such as ferrous sulphate, mica, magnetized iron ore, sulphur, antimony, mercury, tin etc. The siddha medicine aims at providing immunity to the body and is devoid of any side effects. Based on the reports available, as a whole, the siddha system of medicine seems to provide a promising cure for many types of cancer. *Tridosha* is the physiological base around which the Siddha system of medicine revolves. Three basic functions operating through a constant interplay between the environment and the individual are thought to be required to maintain the integrity of a living system. In benign neoplasm one or two of the three bodily systems are out of control and is not too harmful to the body as the body could overcome this condition. Malignant tumors (*Vippuruthi, Putru*)[14] are very harmful because all the three major humours loose mutual coordination and thus cannot prevent tissue proliferation resulting in deadly morbid condition. Siddha literature deals with various types of malignancies, mentioned by Siddhars. Jeeva *et al*[15] can review Siddha classical literature and evidence based research data were emphasized to explore the Siddha medicinal plants with potent anticancer activity.

SCIENTIFIC PRINCIPLES OF ANTICANCER DRUGS

Two sets of genes are controlling cancer development. Oncogenes are the first set of genes and are involved in different cell activities including cell division. However, over expression of these genes transforms a normal cell into a cancer cell. On the other hand, the second set of genes (tumor suppressor genes) inhibits cancer cell

formation by different mechanisms. Tumor suppressor genes are under expressed in cancer cells while, oncogenes are over expressed. Oncogenes and their products represent good targets for cancer therapy. Other targets include enzymes involved in cell division like topoisomerases that unwind the DNA during replication. The diversity of plant derived natural products can provide therapeutic products attacking different targets in cancer cells.[16] Medicinal plants have played an important role in treatment of cancer. In this review nearly 82 anti cancer plants belonging to 46 families have been presented in scientific name, Family, Part in which solvent it is extracted, Experimental model and Mechanism action in a chronological order. These plants possess good immuno modulatry and biochemical alterations leading to anticancer activity (Table 1).

Table 1: List of Medicinal plants for anti cancer with scientific validation

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Acanthospermum hispidum	Asteraceae	Aqueous ethanolic whole plant extract	Dalton's ascites lymphoma	Inhibiting the activation of transcription factor NF Kappa B, the central mediator of apoptosis and immune response by directly targeting DNA binding activity of gene P50, down regulation and expression of mRNA of MDR cells and also possess non cytotoxic anti-tumor affect through inhibition of Farnesyl Protein Transferase (FPT) and Histone-deacetylase.[17]
Achyranthes aspera	Amaranthaceae	Methanolic leaf extract	Pancreatic cancer cell lines	Extract selectively suppressed the transcription of metalloproteases (MMP-1 and -2), inhibitors of MMPs (TIMP-2) and angiogenic factors (VEGF-A and VEGF-B).[18]
Acorus calamus	Araceae	Methanolic and aqueous rhizome extracts	MDA-MB-435S and Hep3B cell lines	The IC 50 Values of methanolic extracts in MDA-MB-435S and Hep3B cell lines is 13.71 ± 6.66 µg/ml and 32.74 ± 4.55 µg/ml respectively to reduce the viability of cells.[19]
Aerva lanata	Amaranthaceae	Ethnolic aerial parts extract	Lung, Leukaemia, Prostate, Colon and Cervix cancer.	Inhibition of cellular levels of NADH and glucose levels.[20]
Agave americana	Agavaceae	Ethanolic leaf extract	PA-1 human cell line of ovarian teratocarcinoma.	LC50 value for extract leaves is found to be lower than 1000µg/ml to reduce the viability of cells.[21]
Ageratum conyzoides	Asteraceae	Kaempferol from ethylacetate leaf extract	Human non-small cell lung carcinoma (A-549), human colon adenocarcinoma (HT-29), human gastric carcinoma (SGC-7901), human golima (U-251), human breast carcinoma (MDA-MB-231), human prostate carcinoma (DU-145), human hepatic carcinoma (BEL-7402), and mouse leukemia (P-388) cancer cell lines.	Extract exhibited the highest cytotoxic activity on A-549 and P-388 cancer cells with IC_{50} values of 0.68 and 0.0003 µg/ml, respectively. Extract containing Kaempferol rapidly scavenged DPPH at a concentration of 130.07 ± 17.36 g/kg.[22]
Ailanthus excelsa	Simaroubaceae	Chloroform root bark extract	Human embryonic kidney cell line (HEK 293), Mouse melanoma B16F10 cells (B16F10), Human breast carcinoma (MDA-MB-231), Human breast adeno-carcinoma (MCF-7) and Human prostate (PC3) cells	Increased expression of tumor suppressor proteins P53/P21, reduction in the expression of Oncogene c-Myc and down regulation of Cyclin D1 and cdk 4. Inhibited cell proliferation and induced death in B16F10, MDA-MB-231, SMCF 7 and PC3 Cell lines.[23]

Table 1: List of Medicinal plants for anti cancer with scientific validation (Continued.....)

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Alangium salvifolium	Alangiaceae	Methanolic stem and leaf extract	Dalton's ascitic lymphoma	Dihydrofolate reductase inhibition and damage the DNA.[24]
Allium sativum	Liliaceae	Hydro-alcoholic bulbs extract	HepG2 (human liver) cell line and Diethylnitrosomine (DEN) induced liver cancer rat model	Induced apoptosis in both cell lines and cancer induced animals, able to scavenge reactive oxygen species (ROS) and normalize the altered Alpha fetoprotein (AFP) levels in liver cancer induced rat model. mRNA expression of NF-κB was markedly decreased in vitro and in vivo upon treated with the plant extract.[25]
Aloe vera	Liliaceae	Aloe-emodin from leaves	Human tongue squamous carcinoma SCC-4 cells	S-phase arrest through promoted p53, p21 and p27, but inhibited cyclin A, E, thymidylate synthase and Cdc25A levels. Promoted the release of apoptosis-inducing factor (AIF), endonuclease G (Endo G), pro-caspase-9 and cytochrome c from the mitochondria via a loss of the mitochondrial membrane potential which was associated with a increase in the ratio of B-cell lymphoma 2-associated X protein (Bax)/B cell lymphoma/leukemia-2 (Bcl-2) and activation of caspase-9 and -3. The free radical scavenger N-acetylcysteine (NAC) and caspase inhibitors markedly blocked aloe-emodin-induced apoptosis.[26]
Alpinia galanga	Zingiberaceae	Ethanolic root extract	Adeno carcinoma of human prostate cell line.	DNA fragmentation where a characteristic DNA laddering was noticed in treated tumor cell line.[27]
Amaranthus spinosus	Amaranthaceae	Ethanolic leaf extract	Ehrlich ascites carcinoma in Swiss albino mice	Decreasing the nutritional fluid volume and arresting the tumor growth.[28]
Amaranthus tricolor	Amaranthaceae	Galactosyl diacylglycerols 1-3 from leaf and stem extract	Human AGS (gastric), CNS (central nervous system; SF-268), HCT-116 (colon), NCI-H460 (lung), and MCF-7 (breast) cancer cell lines	Compound 1 inhibited the growth of AGS, SF-268, HCT-116, NCI-H460, and MCF-7 tumor cell lines with IC50 values of 49.1, 71.8, 42.8, 62.5, and 39.2 mug/mL, respectively. For AGS, HCT-116, and MCF-7 tumor cell lines, the IC50 values of compounds 2 and 3 were 74.3, 71.3, and 58.7 microg/mL and 83.4, 73.1, and 85.4, respectively.[29]
Ananas comosus	Bromeliaceae	Bromelain from aqueous Stem extract	P-388 leukemia, sarcoma (S-37), Ehrlich ascitic tumor (EAT), Lewis lung carcinoma (LLC), MB-F10 melanoma and ADC-755 mammary adenocarcinoma	Bromelain significantly reduce the number of lung metastasis induced by LLC transplantation, as observed with 5-FU. The antitumoral activity of bromelain against S-37 and EAT, which are tumor models sensitive to immune system mediators, and the unchanged tumor progression in the metastatic model suggests that the anti metastatic action results from a mechanism independent of the primary anti tumoral effect.[30]
Andrographis paniculata	Acanthaceae	Andrographolide	human cancer	Cell-cycle arrest at G0/G1 phase through induction of cell-cycle inhibitory protein p27 and decreased expression of cyclin-dependent kinase 4 (CDK4). Increased proliferation of lymphocytes and production of interleukin-2, enhance the tumor necrosis factor-alpha production and CD marker expression.[31]

Table 1: List of Medicinal plants for anti cancer with scientific validation (Continued.....)

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Anisomeles indica	Lamiaceae	Apigenin, ovatodiolide, β-sitosterol and acteoside from crude leaf extract	12-O-tetradecanoylphorbol-13-acetate (TPA)-induced human breast adenocarcinoma MCF-7 cells	Suppressed the migration and invasion, down regulated the matrix metalloproteinase (MMP)-9 enzymatic activities and its mRNA expression, nuclear factor (NF)-κB subunit p65, and activator protein (AP)-1 subunit c-Fos proteins expression in nucleus and, transcriptional activity of NF-κB and AP-1.[32]
Anisomeles malabarica	Lamiaceae	n-hexane and chloroform whole plant extracts	human cervical cancer cells	Shows arrest in S- and G2/M phases.[33]
Annona muricata	Annonaceae	Ethanolic leaf extract	7,12-dimethylbenza(α) anthracene /Croton induced skin papillomagenesis	Shows only slight hyperplasia and absence of keratin pearls and rete ridges.[34]
Annona reticulata	Annonaceae	Ethanol and aqueous root extracts	A-549 (Human lung carcinoma), K-562 (Human chronic myelogenous leukemia bone marrow), HeLa (Human cervix) and MDA-MB (Human adenocarcinoma mammary gland) cancer cell lines	Ethanol extract exhibited a prominent inhibitory effect against A-549, K-562, HeLa and MDA-MB human cancer cell lines at a concentration range between 10 and 40 µg/ml, whereas the aqueous extract showed a lower activity at the same concentration.[35]
Aristolochia indica	Aristolochia ceae	Aristolochic acid from ethonolic Whole plant extract	4-nitroquinoline 1-oxide induced oral cancer in Albino rats	Reduction of GGT and 5'-nucleotidase levels.[36]
Asparagus racemosus	Liliaceae	Ethyl acetate fraction of shatavarin IV from root extract	Human breast cancer, Human colon adenocarcinoma and Human kidney carcinoma of MCF-7, HT-29 and A-498 cell lines.	Reduction in percent increase in body weight, tumor volume, packed cell volume, viable tumor cell count, and increased non-viable cell count and also restoration of hematological parameters towards normalcy.[37]
Azadirachta indica	Meliaceae	Aqueous leaf extract	N-nitrosodiethylamine (NDEA)-induced hepatic cancer	Showed severe alterations in organelle organization, cellular arrangement, and degree of differentiation, cellular metabolism, and morphology of the hepatocytes.[38]
Bacopa Monnieri	*scrophularia ceae*	Ethanolic whole plant extract	Daltons lymphoma ascites tumor celkls	The possible mechanism is due to radiomimetic, nucleotoxic and cytotoxic effect and acts in a manner similar to that of spindle poison and inhibits cell mitosis.[39]
Balanites aegyptiaca	Balanitacea e	Balanitin-6&7 from aqueous kernel extract	A549 non-small cell lung cancer and U373 glioblastoma bearing murine L1210 leukemia grafts	Decrease the $[ATP]_i$ induces in turn a marked disorganization of the Actin cytoskeleton.[40]
Bauhinia Purpurea	Caesalpiniac eae	Methanolic Whole plant extract	Hepatocarcinogenesis in Wistar rats	Decreased the levels of serum toxicity markers, elevated antioxidant defense enzyme activities, suppressed the expression of ODC and PCNA and P53 along with the induction of apoptosis.[41]
Bauhinia variegata	Caesalpiniac eae	Ethanolic extract	N-nitrosodiethylamine induced experimental liver tumor in rats and human cancer cell lines, human epithelial larynx cancer (HEp2) and human breast cancer (HBL-100) cell lines.	Suppressed elevated levels of serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase (ALP), total bilirubin, gamma glutamate transpeptidase (GGTP), lipid peroxidase (LPO), glutathione peroxidase (GPx) and glutathione S-transferase (GST). Increases in enzymatic antioxidant (superoxide dismutase and catalase) levels and total proteins.[42]

Table 1: List of Medicinal plants for anti cancer with scientific validation (Continued.....)

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Bidens pilosa	Asteraceae	Hydroalcoholic crude extracts, chloroform	Ehrlich ascites carcinoma in isogenic BALB/c mice	Chloroform fraction was the most toxic with a half maximal inhibitory concentration (IC50) of 97 ± 7.2 and 83 ± 5.2 μg/mL.[43]
Biophytum sensitivum	Oxalidaceae		B16F-10 melanoma cells	Inhibit the invasion and motility of B16F-10 cells in a dose-dependent manner; inhibit the expression of MMP-2 and MMP-9, whereas it activated STAT-1 expression in metastatic tumor-bearing lungs. Similarly, inhibition of prolyl hydroxylase, lysyl oxidase, ERK-1, ERK-2, and vascular endothelial growth factor (VEGF) expression but activation of nm23. Down regulate the expression of tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, and granulocyte monocyte-colony stimulating factor in metastatic tumor-bearing lungs. In B16F-10 cells, B sensitivum also inhibited the production of proinflammatory cytokines.[44]
Bixa orellana	Bixaceae	Hydroalcoholic seed extract	Radiation induced chromosomal aberration in Swiss albino mice	Pre-treatment with the extract compounds resulted in a significant reduction in the percentage of aberrant metaphases as well as in the different types of aberration scored.[45]
Boerhaavia diffusa	Nyctaginaceae	Ethanolic root extract	HeLa cells	Causes cell death via apoptosis as evident from DNA fragmentation and caspase-9 activation.[46]
Borreria hispida	Rubiaceae	Protein (F3) from ethanolic seed extract		lung cancer (A549) and cervical cancer (HeLa) cell lines.[47]
Boswellia serrata	Burseraceae	Acetyl-11-keto-beta-boswellic acid	Human myeloid KBM-5 cells, Mouse macrophage Raw 264.7 cells, Human lung adenocarcinoma H1299 cells, Human embryonic kidney HEK A293 cells, and Human squamous cell carcinoma SCC-4 and MDA1986 cell lines	Can potentiate apoptosis, inhibit invasion, and abolish osteoclastogenesis. Suppress the nuclear factor jB (NF-jB) and NF-jB-regulated gene expression.[48]
Butea monosperma	Fabaceae	Aqueous Flower extract	HBV-related X15-myc mouse model for hepatocellular carcinoma	Inhibit the cell proliferation and accumulation of cells in G_1 phase, reduction in the levels of activated Erk1/2 and SAPK/JNK and induction of apoptotic cell death.[49]
Caesalpinia bonducella	Caesalpiniaceae	Methnolic extract	Ehrlich Ascites Carcinoma induced in Swiss albino mice.	Significantly decrease the levels of lipid peroxidation and increasd the levels of GSH, SOD, and CAT.[50]
Calendula officinalis	Asteraceae	Aqueous flower extract	Human and Murine tumor cell lines	Cell cycle arrest in G0/G1 phase and Caspase-3-induced apoptosis.[51]
Calophyllum inophyllum	Clusiaceae	Ten natural 4-phenyl-coumarins from dried aerial parts	Epstein–Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-ace-tate in Raji cells.	Calocoumarin-A (5) exhibited the most potent inhibitory activity, suggesting that the prenyl sidechain is a structure in increasing the anti-tumor promoting effect.[52]
Calotropis procera	*Asclepiadaceae*	*Laticifer proteins from latex*	*SF295 and MDA-MB-435 cell lines*	*Inhibit DNA synthesis due to alterations in the topology of DNA. Interfere in topoisomerase I activity by somehow acting upon DNA.*[53]
Capparis sepiaria	*Capparaceae*	*Methanolic bark extract*	*Dalton's Ascites Lymphoma in swiss albino mice*	Decreases the tumor volume, packed cell volume and viable cell count, prolonged the life span of induced mice. Hematological profile converted to more or less normal levels in extract-treated mice. The lipid peroxidation is increased in tumor bearing animals, after treatment antioxidant levels are increased significantly.[54]

Table 1: List of Medicinal plants for anti cancer with scientific validation (Continued.....)

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Cardiospermum halicacabum	*Sapindaceae*	Ethanolic leaf extract	Lung A-549 carcinoma cell lines	Denatures the ribosome and suppresses the expression of enzymes and proteins.[55]
Carissa spinarum	Apocynaceae	Aqueous Stem extract and n-butanol fraction	Human leukaemia HL-60 cell lines	Decrease the Annexin V binding, DNA laddering, apoptotic body formation and an increase in hypodiploid sub G_0 DNA content. Moreover, persistent levels of reactive oxygen species caused translocation of Bax to mitochondria and Bcl-2 degradation, which led to loss of mitochondrial membrane potential and release of cytochrome c to the cytosol. Significant activation of caspase-3, caspase-6 and caspase-9 leading to poly (ADP-ribose) polymerase cleavage.[56]
Carthamus tinctorius	Asteraceae	Dichloromethane, methanol and hexane flower extracts	Human colon cancer (SW 620 cell line)	Upregulation of Caspase 3, 7 and 9 and down regulation of Bcl2 transcripts. Stimulatory effect on the lymphocyte proliferation.[57]
Cassia fistula	Fabaceae	Rhein from hexane flower extract	Human colon cancer cell line COLO 320 DM	Cells treated with Rhein shoed the characters of apoptosis.[58]
Cassia tora	Fabaceae	Methanolic leaf extract	Human cervical cancer cell lines (HeLa)	Induce a marked concentration dependent inhibition on proliferation, reduced DNA content and apoptosis in HeLa.[59]
Cassytha filiformis	Lauraceae	Aporphine alkaloids (actinodaphnine, cassythine, and dicentrine)	human cervical cancer cells (HeLa)	Alkaloids bind effectively to DNA and behave as typical intercalating agents. Actinoda-phnine, cassythine, dicentrine interfere with the catalytic activity of topoisomerases.[60]
Celastrus paniculatus	Celastraceae	3 β-dihydroagarofuranoid sesquiterpenes from whole plant	MCF-7 breast cancer cell lines	Growth inhibition leads to apoptosis, LC3B-II accumulation, indicative of autophagy. Signaling effectors related to survival and cell cycle progression, including Akt, NF-κB, p53, and MAP kinases.[61]
Cinnamomum cassia	Lauraceae	Aqueous bark extract	Human cervical carcinoma cell line (SiHa)	Exhibit reduced migration potential that could be explained due to down regulation of MMP-2 expression. Expression of Her-2 oncoprotein was significantly reduced in the presence of ACE-*c*. Induce apoptosis in the cervical cancer cells through increase in intracellular calcium signaling as well as loss of mitochondrial membrane potential.[62]
Cleome gynandra	Cleomaceae	Methanolic extract	Swiss albino mice against Ehrlich Ascites Carcinoma	Shows significant decrease in tumor volume, viable cell count, tumor weight and elevated the life span mice. RBC, hemoglobin, WBC and lymphocyte count reverted to normal level.[63]
Clerodendrum serratum	Verbenaceae	Methanolic leaf extract	Testis in 7, 12-dimethylbenz [a] anthracene induced skin carcinogenesis in Swiss albino mice	Significantly curtailed tumor development and counteracted all the biochemical effects. Increases the body and testis weight, DNA, RNA, protein, glycogen, GSH level, SDH, AKP, SOD, CAT and GST activities. Decreases the cholesterol content, LDH, ACP activities and TBARS level.[64]
Dillenia indica	Dilleniaceae	Betulinic acid from ethyl acetate and Methanolic fruits extract	Human leukemic cell lines U937, HL60 and K562	Induces cell death in U937, HL60 and K562 cell lines by inducing apoptosis.[65]
Echinacea angustifolia	Asteraceae	Ethyl acetate root fraction	Cervical and breast cancer cell lines	Affects cell proliferation despite cancer treatment and increased cell growth.[66]
Eclipta alba	Asteraceae	hydro-alcoholic leaf extract	*HepG2, C6 glioma and A498 cell lines*	DNA damage leading to apoptosis. Down-regulated the expression f NF-kB.[67]

Table 1: List of Medicinal plants for anti cancer with scientific validation (Continued.....)

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Emblica officinalis	Euphorbiaceae	Aqueous extract	Dalton's lymphoma-bearing mice	Reduce the in Ascitic volume and solid tumor growth, significantly reduced the solid tumors and prolonged survival time. Inhibit the cell cycle-regulating enzyme, Cdc25 phosphatase.[68]
Eugenia caryophyllata	Myrtaceae	Eugenol from seeds	Human promyelocytic leukemia cells (HL-60)	DNA fragmentation and formation of DNA ladders, transduce the apoptotic signal via ROS generation, thereby inducing mitochondrial permeability transition (MPT), reducing anti-apoptotic protein bcl-2 level, inducing cytochrome c release to the cytosol, and subsequent apoptotic cell death.[69]
Ferula asafoetida	Umbelliferae	Asafoetida from seeds	N-methyl-N-nitrosourea (MNU)-induced mammary carcinogenesis in Sprague-Dawley rats	Significantly reduce the levels of cytochrome P450 and b5, enhance the activities of glutathione S-transferase, DT-diaphorase, superoxide dismutase and catalase.[70]
Gardenia gummifera	Rubiaceae	Dikamaliartane-A is from benzene gum resin extract	HeLa (cervical cancer) and MCF-7 (breast cancer) cell lines	Significantly decreased the tumor volume, packed cell volume and viable tumor cell count. Increases the hemoglobin and red blood cell levels, decreases the white blood cell levels.[71]
Glycyrrhiza glabra	Fabaceae	Aqueous root extract	Ehrlich ascites tumor cell lines	In the levels of the cytokine VEGF and micro vessel density count in the peritoneum of mice treated with plant extract decreased VEGF production and the cytokine induced neovascularization.[72]
Grewia hirsuta	Tiliaceae	Methanolic leaf extract	Hep G2 cell lines	Induces the Cell cycle arrest.[73]
Gymnema sylvestre	Asclepiadaceae	Ethanolic leaf extract	A375 cells (human skin melanoma)	Increased DNA fragmentation and showed an increases level of mRNA expression of apoptotic signal related genes cytochrome c, caspase 3, PARP, Bax, and reduced expression level of ICAD, EGFR, and the anti-apoptotic gene Bcl2.[74]
Holoptelea integrifolia	Ulmaceae	Ethanolic leaf extract	Dalton's ascetic lymphoma in Swiss albino mice	Brought back hemoglobin content and RBC count to normal. Analysis of the other hematological parameters showed minimum toxic effect in the mice which were treated with extract.[75]
Ichnocarpus frutescens	*Apocynaceae*	Two triterpenes α-amyrin and ursolic acid from Methanolic root extract	MCF-7 (Human breast cancer cell line), BEL-7402 (Human hepato-cellular carcinoma cell line), SPC-A-1 (Human lung cancer cell line) and SGC-7901 (Human gastric cancer cell line)	Ursolic acid shows anticancer activity on four cancer cell lines with IC50 values 8.5±0.29, 9.9±0.12, 8.1±0.40 and 6.2±0.23 respectively, while IC50 values for α-amyrin on four cancer cell lines was found to be 7.2±0.12, 8.2±0.29, 7.6±0.06 and 5.0±0.12 respectively.[76]
Ipomoea obscura	Convolvulaceae	Indole alkaloid fraction of Ipobscurine	B16F-10 melanoma cancer lines	Inhibit the proliferation, migration, and invasion of pro-metastatic genes such as matrix metallo proteinases (MMPs) and inflammatory mediators-cyclooxygenase-2 (COX-2), Ipobscurine may also promote apoptosis by up-regulating pro-apoptotic molecules such as caspase-3, p53, and Bax and down-regulating anti-apoptotic Bcl-2 and also suppresses various transcription factors such as nuclear factor-κB (NF-κB) and activator protein. Inhibit cell growth with arrest at G1 and reduce transition to the S and G2/M phases of the cell cycle.[77]

Table 1: List of Medicinal plants for anti cancer with scientific validation (Continued.....)

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Momordica charantia	Cucurbitaceae	Aqueous green fruits extract	1321N1, Gos-3, U87-MG, Sk Mel, Corl -23, Weri Rb-1 and L6 cell lines	Increase the release of Caspase - 3 and caspase-9 and Cytochrome-c and elevated [Ca^{2+}] to avoid the damage of Mitochandria.[78]
Ocimum basilicum	Lamiaceae	Ursolic acid from methanolic leaf extract	Human cancer cell lines HT-144, MCF-7, NCL-H460 and SF-268 cell linces.	Induced a significant decrease in the percentage of cells in anaphase/telophase stages along with F-actin aggregation and nitotic spindle distortion.[79]
Ocimum sanctum	Lamiaceae	Ethanolic extract	Human non small cell lung carcinoma A549 cells and Lewis lung carcinoma (LLC) animal model	Increases the sub-G1 population and exhibited apoptotic bodies in A549 cells, cleaved poly (ADP-ribose) polymerase (PARP), released cytochrome C into cytosol and simultaneously activated caspase-9 and -3 proteins. Also increases the ratio of proapoptotic protein Bax/antiapoptotic protein Bcl-2 and inhibited the phosphorylation of Akt and extracellular signal regulated kinase (ERK) in A549 cancer cells, suppress the growth of Lewis lung carcinoma inoculated onto C57BL/6 mice in a dose-dependent manner.[80]
Oldenlandia diffusa	Rubiaceae	Ursolic and Oleanolic acids	Human breast cancer cells through ERα/Sp1-mediated p53 activation.	Strongly inhibit anchorage-dependent and-independent cell growth and induced apoptosis in estrogen receptor alpha (ERα)-positive breast cancer cells. Mechanistically the extracts enhance the tumor suppressor p53 expression as a result of an increased binding of ERα/Sp1 complex to the p53 promoter region.[81]
Oroxylum indicum	Bignoniaceae	Flavonoid Baicalein	HL-60 cell line	Proliferation inhibition at a higher dose may be associated with induction by apoptosis AND nuclear fragmentation.[82]
Oxalis corniculata	Oxalidaceae	Ethanolic Whole plant extract	Ehrlich ascites carcinoma in Swiss albino mice	Decreases the nutritional fluid volume and arresting the tumor growth.[83]
Peperomia pellucida	*Piperaceae*	Methanolic leaf extract	Human breast adenocarcinoma (MCF-7) cell line	*Inhibit DPPH and free radicals.*[84]
Phyllanthus amarus	Euphorbiaceae	*Aqueous extract*	Solid and Ascites tumor development in mice induced by Dalton's lymphoma ascites (DLA) cells	Induces the formation of apoptotic bodies with characteristic features like plasma membrane invagination, elongation, fragmentation, and chromatin condensation. Induces DNA fragmentation, expression of caspase-3 expression of Bcl-2.[85]
Phyllanthus polyphyllus	Euphorbiaceae	Methanolic leaf extract	Ehrlich ascites carcinoma and human breast cancer (MCF7), colon cancer (HT29), and liver cancer (HepG2) cell lines	*Decreases the levels of lipid peroxidation (LPO), glutathione peroxidase (GPx), glutathione S-transferase (GST), and increases the levels of superoxide dismutase (SOD)* and catalase (CAT).[86]
Piper longum	Piperaceae	Alcoholic fruit extract and its component piperine	Dalton's lymphoma ascites (DLA) cells and Ehrlich ascites carcinoma (EAC) cells	Increases the total WBC count, Bone marrow cellularity and alpha-esterase positive cells.[87]
Plumbago zeylanica	Plumbaginaceae	Plumbagin	Human non-small cell lung cancer cell lines A549, H292 and H460	Increases the intracellular level of ROS, and inhibited the activation of NK-κB, NF-κB/p65 nuclear translocation. Suppressed the degradation of IκBκ. ROS scavenger NAC highly reversed the effect of plumbagin on apoptosis and inactivation of NK-κB in H460 cell line, Increases the activity of caspase-9 and caspase-3, down regulated the expression of Bcl-2, up regulated the expression of Bax, Bak, and CytC.[88]

Table 1: List of Medicinal plants for anti cancer with scientific validation (Continued.....)

Scientific Name	Family	Part with extracted solvent	Experimental Model	Mechanism of Action
Pupalia lappacea	*Amaranthaceae*	Ethanolic aerial parts extract	Chronic Myeloid Leukemia K562 cells	Decreases the growth, induction of apoptosis and activation of p53. Inhibit PCNA, decrease in Bcl2/Bax ratio, decrease in the mito-chondrial membrane potential resulting in release of cytochrome c, activation of multi caspase and cleavage of PARP.[89]
Smilax zeylanica	Smilacaceae	Methanolic leaf extract	Benzo (a) pyrene induced experimental lung cancer Swiss albino mice	Decreases the extent of lipid peroxidation with concomitant increase in the activities of enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione-S-transferase) and non-enzymatic antioxidants (reduced glutathione, vitamin C and vitamin E) levels.[90]
Solanum nigrum	Solanaceae	Polyphenols and antho-cyanidin iso-lated from aqueous leaf extract	AU565 breast cancer cells	A lower doses of extract induced autophagy but not apoptosis. Higher doses of leaf extract could inhibit the level of p-Akt and cause cell death due to the induction of autophagy and apoptosis.[91]
Tinospora cordifolia	Menispermaceae	Dichlormethane extracts of whole plant	HeLa S3 cell lines	Decline the clonogenicity, glutathione-S-transferase (GST) activity and a concentration-dependent increase in lipid peroxidation and lactate dehydrogenase.[92]
Tylophora indica	Asclepiadaceae	Tylophorine alkaloid isolated from leaves	Human umbilical vein endothelial cells in vitro and Ehrlich ascites carcinoma tumor in vivo	Significantly inhibit neovascularization, inhibit tumor angiogenesis and tumor growth *in vivo*. Molecular docking simulation indicated that tylophorine could form hydrogen bonds and aromatic interactions within the ATP-binding region of the VEGFR2 kinase unit.[93]
Triumfetta rhomboidea	Tiliaceae	Methanolic leaf extract	Ehrlich Ascites Carcinoma	Effect on peritoneal macrophages or other components of the immune system.[94]
Vernonia cinerea	Asteraceae	Vernolide-A fraction isolated from whole plant	C57BL/6 mice B16F-10 melanoma cells and K-562 cells	Enhances the production of interleukin (IL)-2 and interferon-gamma (IFN-γ) in metastatic tumor-bearing animals. Significantly down-regulated the serum levels of proinflammatory cytokines such as IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and granulocyte–macrophage colony-stimulating factor (GM-CSF).[95]
Withania somnifera	Solanaceae	Aqueous extract of whole plant	Azoxymethane induced colon cancer in Swiss albino mice	Significantly altered the level of leucocytes, lymphocytes, neutrophils, immune complexes and immunoglobulins (Ig) A, G and M.[96]
Zingiber officinale	Zingiberaceae	Terpenes isolated from Steam Distilled Extract	Endometrial cancer cell lines	Rapid and strong increase in intracellular calcium and a 20-40% decrease in the mitochondrial membrane potential. Ser-15 of p53 was phosphorylated. This increase in p53 was associated with 90% decrease in Bcl2 whereas no effect was observed on Bax. Inhibitor of p53, pifithrin-α, attenuated the anti-cancer effects and apoptosis was also not observed in the p53 (neg) SKOV-3 cells.[97]
Ziziphus mauritiana	Rhamnaceae	Aqueous Ethanolic Seed Extract	(HL-60, Molt-4, HeLa, and normal cell line HGF) Ehrich ascites carcinoma bearing Swiss albino mice	Markedly inhibit the proliferation of HL-60 cells. Annexin and PI binding of treated HL-60 cells indicated apoptosis induction by extract. Prominent increase in sub Go population. Significantly reduces tumor volume and viable tumor cell count and improved hemoglobin content, RBC count, mean survival time, tumor inhibition, and percentage life span.[98]

The aim of this article is to provide a general outline or descriptions of what type of mechanisms do plant extracts to inhibit cancer. Due to this *in vivo* and *in vitro* induced cancers are proved with scientific principles to ameliorate the cancers with use of these plant extracts. Apoptosis can be induced in cells under *in vitro* conditions by a number of ways. One of the classical systems is exposure of thymocytes to glucocorticoids. Other methodologies include DNA damage either by irradiation, exposure to drugs that inhibit topoisomerase, withdrawal of growth factors from growth media, cell cycle perturbation, exposure to inhibitors/activators of kinases or phosphatases, interference with Ca^{2+} homeostasis, over expression of p^{53}, members of Ced-3/ICE and many more. This article reviews the available literature regarding researches on anti-cancerous plants.

CONCLUSION

Anti-cancer drugs destroy cancer cells by stopping growth or multiplication at some point in their life cycles. Overall, this review has shown that the cytotoxicity of plants that down-regulate the anti-apoptotic genes such COX-2, iNOS, TNFa, Bcl-2 and up-regulation of proapoptotic genes such p53, p21, Bax, caspase and cytochrome C. Interference of NF-kB activity downstream by cryptolepis/cryptolepine may be exploited in cancer treatment or to enhance sensitivity of cancer cells to chemotherapy and radiotherapy. To understand the mechanism of action, the researchers have worked at molecular level and several significant phytochemicals have been isolated based on the activity analysis of the medicinal plant extracts with different solvents. The understanding of the mechanisms that alter growth and metabolism in cancer cells search for new pharmacologically active compounds for drug development is an important issue, but not the only one, as the trend toward using standardized plant extracts of high quality, safety and efficacy will continue. Therefore, all efforts have to be targeted to reveal the properties of the plant extracts and clearly suggest that they have prospects as anticancer agents.

Acknowledgement: The authors are thankful to DST-SERB for financial support.

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Source of Support: Nil, **Conflict of Interest:** None.