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REVIEW ON MEDICINAL PLANTS AS POTENTIAL SOURCES OF CANCER PREVENTION AND TREATMENT

Adel Abdel-Moneim* and Alaa Magdy**

*Physiology Division, Zoology Department, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt.
**Zoology/Chemistry Student, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt.

*** Corresponding Author: Adel Abdel-Moneim**
Physiology Division, Zoology Department, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt.

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ABSTRACT
Cancer is a major public health problem in all the developed and undeveloped countries and it is considered the second disease that causes death after cardiovascular diseases in the world. Nowadays, no absolute preventative and curable agent has been found for cancer. The current cancer treatments such as; surgery, chemotherapy, radiation, immunotherapy, hormone therapy and gene therapy etc., showed adverse effects such as; nausea, vomiting, fatigue, loss of appetite, hair loss, decreased blood cell and platelet, liver and kidney failure and decreased immune response. The high mortality and the increasing incidence of certain cancers justify a growing interest for the identification of new pharmacological agents efficient in cancer prevention and treatment. Moreover, several drugs in cancer care originated from natural products. The mechanism of action of antitumor plants could be; anti-oxidative, anti-proliferative, anti-differentiation, anti-apoptosis effects, cell cycle arrest and inhibition of angiogenic and proliferation process. However, there is a continuing need for development of new potential novel anticancer drugs and chemotherapy strategies, by methodical and scientific exploration of natural products that give more efficiency, less toxicity and cost effective. The present study reviews the most recent information in the field of natural anticancer compounds and the phytochemical components and their mode of action in cancer treatment and prevention.

KEYWORD: Tumors, current medications, anticancer plants, mode of action, cancer prevention and treatments.

INTRODUCTION
Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. Also, cancer is a complex disease involving numerous tempo-spatial changes in cell physiology, which ultimately lead to malignant tumors.[1] Prevalence estimates for 2012 show that there were 32.6 million people (over the age of 15 years) alive who had had a cancer diagnosed in the previous five years. The most commonly diagnosed cancers worldwide were those of the lung (1.8 million, 13.0% of the total), breast (1.7 million, 11.9%) and colorectum (1.4 million, 9.7%). The most common causes of cancer death were cancers of the lung, liver and stomach.[2]

For thousands of year's natural products have played a very important role in health care and prevention of diseases. The ancient civilizations of the Chinese, Indians and North Africans provide written evidence for the use of natural sources for curing various diseases.[3] The earliest known written document is a 4000 year old Sumerian clay tablet that records remedies for various illnesses.[4] In recent years, the interest in medicinal plants and their biologically active derivatives has increased.[5] Complementary and alternative medicine modalities are commonly used for cancer prevention and care. The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity.[6] Over 3000 species of plants with antitumor properties have been reported.[7] The antitumor activity and the possible applications of medicines from medicinal plants for cancer prevention have been recently described.[8] Medicinal plants have played an important role as a source of effective anticancer agents and it is significant that over 60% of currently used anti-cancer agents are derived in one way or another from natural sources, including plants, marine organisms and micro-organisms.[9] However, there is a continuing need for development of new anticancer drugs, drug combinations and chemotherapy strategies, by methodical and scientific exploration of enormous pool of synthetic, biological and natural products. Although more than 1500 anticancer drugs are in active development with over 500 of the drugs under clinical trials, there is an urgent need to develop much effective and less toxic drugs.[10] The present study aimed to summarize the current anti-cancer drugs and different plants used for

treatment and prevention of cancer. Also, the review discusses the plants therapeutic agents and various mechanisms of action.

Conventional cancer treatment

Surgery, radiation therapy, chemotherapy (drug therapy), hormonal therapy, immunotherapy, gene therapy and nano-therapy are the main tools of conventional cancer treatment. Surgery is the oldest and still most effective mainstream treatment for solid tumors. Radiation and most anticancer drugs damage DNA, suppress DNA replication, killing rapidly growing tumor cells. After the surgical ablation of progressive cancer, however, metastasized tumor cells continue to progress and this is one of the causes making cancer treatment difficult (table 2).[11] Chemotherapy and their consequent side effects (as listed in the drugs package inserts for physicians), which include: destruction of the immune system, leukopenia, hemorrhage, gonadal suppression, bone marrow depression, severe cellulites, fever, chills, nausea, prolonged vomiting, partial or total hair loss, disorientation, dysarthria, anorexia, stomatitis, erythema, anemia, liver and kidney failure and finally, death.[12]

Medicinal plants in cancer treatment

The search for anticancer agents from plant sources started in earnest in the 1950s with the discovery and development of the vinca alkaloids, vinblastine and vincristine and the isolation of the cytotoxic podophyllotoxins. As a result, the United States National Cancer Institute (NCI) initiated an extensive plant collection program in 1960, focused mainly in temperate regions. This led to the discovery of many novel chemotypes showing a range of cytotoxic activities[13], including the taxanes and camptothecins, but their development into clinically active agents spanned a period of some 30 years, from the early 1960s to the 1990s.(4) Since 1961, nine plant-derived compounds have been approved for use as anticancer drugs in the US: vinblastine (Velban), vincristine (Oncovin), etoposide (VP-16, **1**), teniposide (VM-26, **2**), Taxol (paclitaxel), navelbine (Vinorelbine), taxotere (Docetaxel), topotecan (Hycamtin) and irinotecan (Camptosar). The last three drugs were approved by the Food and Drug Administration in 1996.[14]

A number of other secondary metabolites and their derivatives of plant origin, as well as natural products of marine and microbial origin, are currently in preclinical and clinical trials as potential anticancer agents.[15] Maitake D-fraction (PDF) has been also approved by FDA for the investigational new drug (IND) application for a phase II pilot study on patients with advanced breast and prostate cancer.[16] Herbal medicine is very common and the use of herbal remedies (including dietary supplements) gains popularity day by day, even in healthy people.[17] The treatment approach for the cancer based on allopath is expensive and also shows an adverse effect. Alternative approach as safe, effective and affordable is needed to control the disease development and progression.[18] Active ingredients such as alkaloids, flavonoids, terpenoids, polysaccharide and saponin obtained from natural products have potent biological properties such as antitumor, analgesia, anti-inflammatory, immunomodulation, antiviral activities. The antitumor activity of most natural antineoplastic drugs often do not kill tumor cells directly, but regulates the human immune function to achieve the purpose or both.[19]

Herbal compounds with anticancer agents

Various classes of anti-cancer agents derived from plants are currently available for clinical use owing to their diverse mechanism of action. Some of them are vinca alkaloids, podophyllotoxin derivatives, taxanes, flavonoids, polysccharids, lectines, tannis, lignins, terpenoids and saponins.

Phenolic compounds

The human diet contains a complex mixture of plant polyphenols and it is believed that human individuals may consume as much as one gram of plant phenols per day in their diet.[20] Studies have shown that these phenols have cytotoxic effects on different tumors. Mechanisms of these compounds are carried out through apoptosis. Curcumin (Di-ferolelyl methane) is a phenol compound derived from rhizome of curcuma specie.[21] Using cucrcumin, pre-clinical cancer research has shown that this plant inhibits carcinogenic procedure in the most cancers including colorectal, pancreas, gastric, and prostate. It is also effective on different stages of carcinogens, proliferation, angiogenesis and metastasis as in table 3.[22]

Flavonoids

Flavonoids are a group of more than 4000 polyphenolic compounds that occur naturally in foods of plant origin. These compounds possess a common phenylbenzopyrone structure (C6-C3-C6) and they are categorized according to the saturation level and opening of the central pyran ring, mainly into flavones, flavanols, isoflavones, flavonols, flavanones and flavanonols (table 1).[23] Licorice is a common chinese medicinal herb and studies conducted showed that liquiritigenin, the flavonoid compound in licorice can effectively inhibit the proliferation of human cervical carcinoma cell of tumors xenografts in nude mice.[24] A flow cytometric analysis[25], suggested that genistein (a hydroxyisoflavone) induced apoptosis in human pro-myelocytic HL-60 leukaemic cells. Genistein is also reported to inhibit tyrosine kinase[26], angiogenesis[27] and cell cycle progression[28] (table 3). Apigenin, a widely distributed plant flavonoid has also been shown to inhibit the growth of HeLa cells and was reported to be a potential antitumor agent.[29]

Table 1. Anticancer activities of flavonoids in various cancer cell lines

Flavonoids	Cell lines	Cancer type	References
Flavanones, isoflavans, EGC, chalcones, EGCG, curcumin, genistein, ECG, quercetin, cisplatin	HSC-2,HSG, SCC-25	Human oral cancer	[30][31]
Flavanones, daidzein, genistein quercetin, luteolin	MCF-7	Human breastcancer	[32][33]
Genistein, apigenin, kaempferol, chrysin, luteolin, biochanin A	ARO,NPA,WRO	Human thyroid cancer	[34][35]
Flavone, quercetin	SKLU1,SW900,H441,H661,haGo-K-1, A549	Human lung cancer	[36][37]
Catechin, epicatechin, quercetin, kaempferol, luteolin, genistein, apigenin, myricetin, silymarin	LNCaP,PC3, DU145	Human prostate cancer	[38][39]
Flavone, quercetin, genistein, anthocyanin	Caco-2,HT-29, IEC-6,HCT-15	Human colon cancer	[40][41]
Apigenin, quercetin, myricetin, chalcones	HL60,K562, Jurkat	Human leukemia	[42][43]
Chalcones	4A5	B16 mouse melanoma	[44]

Alkaloids

Alkaloids are organic compounds containing nitrogen, which have obvious biological activity and are mostly present in plants. Vinblastine and vincristine are the bisindole alkaloids isolated from the Madagascar periwinkle, Catharanthus roseus. Vinblastine and vincristine are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of different types of cancers, including leukemias, lymphomas, testicular cancer, breast and lung cancers, and Kaposi's sarcoma.[45] Vinflunine, a bis-fluorinated vinorelbine derivative, has been synthesized by super acid chemistry.[46] Due to its favorable preclinical antitumor activities, vinflunine is now being widely studied in phase I–III clinical trials.[47] Solamargine, an alkaloid purified from Solanum incanum, has been observed to induce apoptosis (table 3) in human hepatocyte (Hep-3B) and normal skin fibroblast cells in culture. In addition, the gene expression of tumor necrosis factor TNF receptor I was up-regulated within 30 min of solamargine treatment.[48] (table 3).

Polysaccharides

Polysaccharide play antitumor role by a variety of approaches and level of participation and regulation in the immune system, such as regulating phagocytic function of the reticulo-endothelial system, improve the natural killer (NK) cell activity, activate macrophages, induce the expression of immune-regulatory factors, affect cell metabolism, inhibit tumor cell cycle, inhibit the activity of SOD in tumor tissues.[49] Several studies reported that polysaccharopeptide (PSP) possesses selective anti-cancer activity against certain cancer cells in vitro. PSP in dose-dependent and time-dependent manners suppresses proliferation of human cancer cell lines.[50] Moreover, PSP markedly inhibited the growth of several human cancer cell lines including lung cancer cell lines *in vitro*.[51] It is hypothesised that the polysaccharides extracted from different parts of Ganoderma lucidum induce different immune responses with varying immune potencies.[52] (table 3).

Lectines

Lectins are highly specific proteins that bind to carbohydrates and are found in many plants, animals, and bacteria.[53] For several years, Viscum album L. (VAL) has been used in adjuvant cancer therapy. VAL stimulates immune system specifically increases the activity and number of NK cells and neutrophils as in table 3.[21] Lectins such as Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN), Natural killer-receptors (NK-receptors) and selectins including P-selectin, L-selectin and E-selectin are all part of the superfamily called C-type lectin. C-type lectins are known to be involved in immune response, cell proliferation and programmed cell death making them expected targets for research. Also, another study found DC-SIGN can recognize and bind to certain Le glycans expressed in human colorectal carcinoma cells leading to increased immune-functioning.[54]

Tannis and Lignin

Tannins are a large group of polyphenolic compounds which have received attention in recent years due to their claimed ability to cure a variety of diseases.[55] Tannins are subdivided into two groups: hydrolysable tannins and proantocyanidins (condensed tannins). Hydrolysable tannins are gallic acid and ellagic acid esters of core molecules that consist of polyols such as sugars. Proantohocyanidins are polymers of flavan-3-ols (for example catechin) and flavan-3, 4-diols linked through an interflavan bond that is not susceptible to hydrolysis.[56] Cuphiin D1 (CD1) is new macrocyclic hydrolysable tannin, it was isolated from Cuphea hyssopifolia (Lythraceae) and it has been shown to exert antitumor activity against to HL-60 cells.[57] Moreover, Ellitannin isolated from the C. ladanifer (Cistaceae), showed inhibit the proliferation of M220 pancreatic cancer cells and MCF7/HER2 and JIMT-1 breast cancer cells.[58] So, Pomegranate (Punica granatum L.) fruits are widely consumed as tannin extracts were evaluated for anti-proliferative activity in vitro on human oral, colon and prostate tumor cells and apoptotic effects were evaluated against the HT-29 and HCT116 colon cancer cell lines.[59] (table 3).

Terpenoids

Triterpenes are one of the possible pharmaceutically active compounds contributing to the medicinal activities of Ganoderma lucidum (table 3).[60] Triterpenes is a subtype of Terpene, composed of one or more isoprene units. Many subtypes of Terpenes have been found to have anti-inflammatory, anti-tumourigenic and hypolipidemic activity.[61] There are over 140 species of triterpenes and triterpenoids identified in G. lucidum.[62] A study reported that 8-epi-xanthatin and its epoxide, two xanthanolide sesquiterpene lactones from the methanolic extract of the leaves of Xanthium strumarium L. potently inhibited proliferation of cultured human tumor cells.[63]

Taxanes

Taxanes currently known to suppress and inhibit cell growth, differentiation and proliferation in indefinitely known cancer cell lines.[64] Taxus baccata was reported to use in the Indian Ayurvedic medicine for the treatment of cancer. Paclitaxel (Taxol®) derived from the bark of Taxus brevifolia (Taxaceae) is another success in natural product drug discovery. Also, paclitaxel is used against ovarian cancer, advanced breast cancer, small and non-small cell lung cancer.[65] (table 3).

Saponins

Saponin is a diverse group of compounds widely distributed in the plant kingdom, which are usually characterized by their structure containing a steroidal or triterpenoid aglycone and one or more sugar chains.[66] It has antioxidant and anticancer properties.[67] The Saponins from the plant of china, Clematis manshrica has obvious antitumor effects against various transplanted tumor on mice[68] (table 3). Studies have proven that ginsenoside can inducing apoptosis of hepatocellular carcinoma cell line and also have effect on glioma and on other cancers.[69] Ginsenoside can treat leukemia by blocking the cell cycle, treat pancreatic cancer by inhibiting proliferation, migration, invasion and inducing apoptosis of cancer cells.[70]

Mechanisms of action of antitumor plants

Antiproliferation

The use of medicinal plants is becoming increasingly appreciated in suppressing cancer growth and cancer prevention. The antiproliferative effects of the water extracts of previously obtained ethanolic dry extracts of three different medicinal plants (Camellia sinensis, Frangula alnus from two different places and Rosmarinus officinalis) using cell lines derived from human cervix adenocarcinoma (HeLa cells) were investigated. The extract of Camellia sinensis exhibited significant cytotoxic effect against HeLa cells (table 3).[71]

Cell cycle arrest

In general, the plant extracts or its constituent, cause cellular toxicity in cervical cancer cells and result in cell death by two primary pathways-cell cycle arrest and apoptosis. The arrest primarily occurs at G1 and G2/M phase although arrest at other stages (figure 1). Cell cycle arrest results into fragmentation or degradation of DNA, a hallmark of induction of apoptosis. Additionally the plant extracts or its derivatives also induces the proapoptotic proteins such as Bcl-2–associated X protein (Bax) and represses antiapoptotic protein B-cell lymphoma 2(Bcl-2) and Bcl-XL.[72] Studies have shown that triterpene extracts from G. lucidum can arrest the cell cycle at the G1 phase.[73] Many extracts of plants could cause cell cycle arrest in cancer cell like; Plumbago scandens[74], Mangifera indica[75], Citrus aurantifolia[76] and Olea europaea[77] as summarized in table 2,3.

Anti-apoptosis effect

Apoptosis, a physiological process for killing cells, is critical for the normal development and function of multi cellular organisms. Abnormalities in cell death control can contribute to a variety of diseases, including cancer, autoimmunity and degenerative disorders.[78] Apoptosis pathways can be initiated at the level of the mitochondria by the release of apoptogenic factors such as cytochrome c, second mitochondria-derived activator of caspase (Smac) or apoptosis inducing factor (AIF) from the mitochondrial intermembrane space into the cytosol (mitochondrial or intrinsic pathway)(figure 1). In table (2,3) several extracts of plants have anti apoptotic effect like Eugenia caryophyllata[79], Chelidonium majus.[80][81]

Decrease in differentiation

The flavones genistein, apigenin, luteolin, quercetin, and phloretin were found to induce differentiation of human acute myelogenous leukemia HL-60 cells into granulocytes and monocytes.[82] Deregulation of growth control ultimately leads to selection of clonal lines of cells that replicate at embryonic pace and yet fail to respond to differentiation and maturation signals. Nonphysiological inducers of terminal differentiation have been used as novel therapies for the prevention and therapy of cancer.[83] In table (2,3) examples of plants with antidifferentiation effect like: Achyranthes aspera[84], Capparis sepiaria[85] and Derris scandens.[86]

Inhibition of angiogenic process

Considering the fact that tumor growth and metastasis are fully dependent on angiogenesis formation of competent new blood vessels. However, it can be inhibited either by regulation of the main angiogenic cytokines VEGF (vascular endothelial growth factor) and bFGF (basic fibroblast growth factor) released by tumor cells or prevention of endothelial cell angiogenic processes.[87] Moreover, Cao and Lin (2006) showed that a polysaccharide peptide (Gl-PP) isolated from G. lucidum inhibits the proliferation of human umbilical cord vascular endothelial cells (HUVEC) in a dose-dependent manner. Therefore, Gl-PP may inhibit angiogenesis via inhibiting secretion of pro-angiogenic factors and inhibition of vascular endothelial cell proliferation. Additionally, anti-angiogenic activity was elucidated in curcuma specie[21] (table 2,3).

Modulation of multidrug resistance

Multidrug resistance due to P-glycoprotein (Pgp) or multidrug resistance associated protein (MRP) is a serious impediment to successful chemotherapy of cancer. Modulation by flavonoids of cell multidrug resistance mediated by Pgp may be through (i) inhibiting the over expression of multidrug resistance gene-1 (MDR1),[88] (ii) direct binding to NBDs with high affinity,[89] (iii) inhibiting ATPase activity, nucleotide hydrolysis and energy-dependent drug interaction with transporter-enriched membranes.[90] Plants with modulation of multi drug resistant effect are shown in table 5 such as; Curcuma longa Linn[91], Erythroxylum pervillei Baill[92] and Acanthosper mum hispidum[93] (table 2,3).

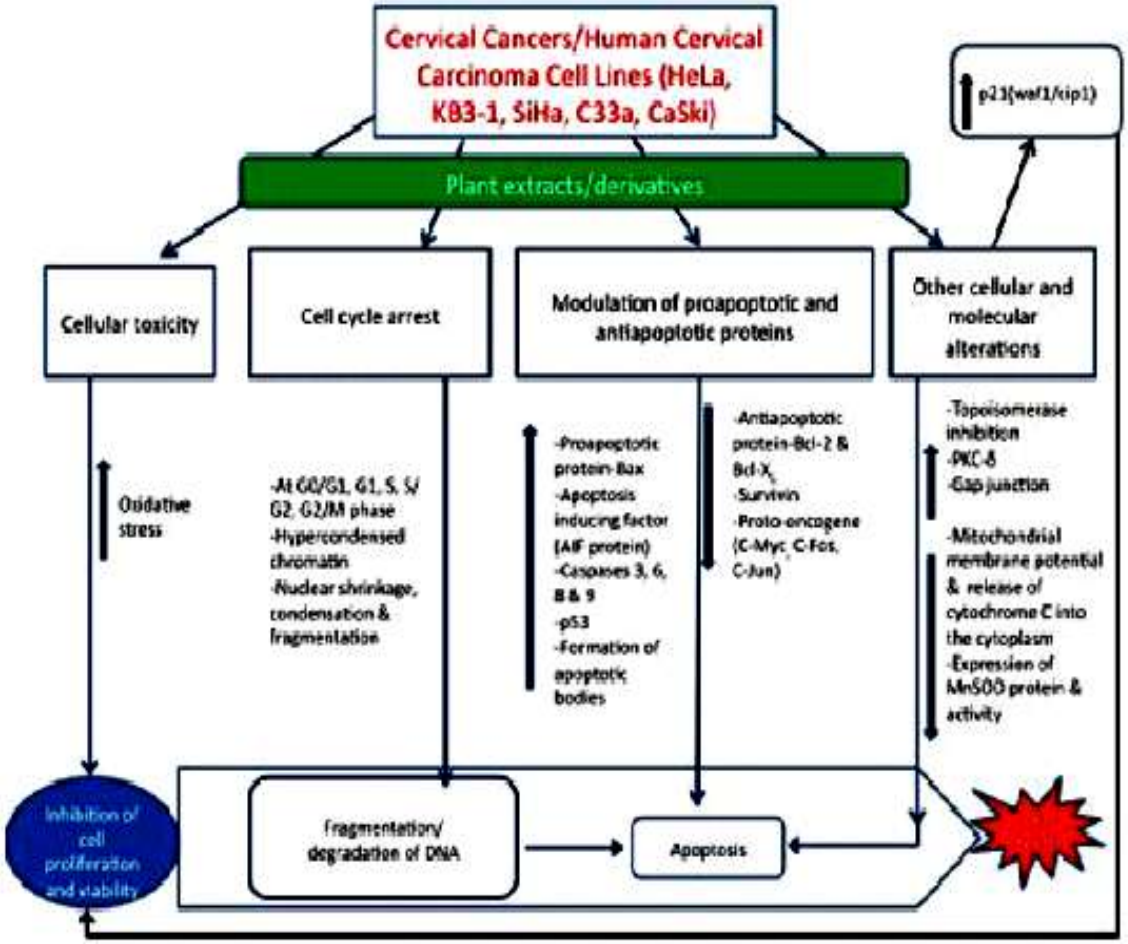

Figure1. General Mechanism of Action of Plant Products or its Constituent on Cervical Cancer/Cervical Carcinoma Cell Lines.[94]

Table 2. Some anticancer plants that mimetic effect of many current treatments.

Treatment name	Therapeutic action	Examples of medicinal plants with the same action
1. Radiation therapy	Decrease the differentiation and inhibition of angiogenic process.	Scutellaria baicalensis, Chrysanthemum indicum Linn[95], Rhus verniciflua Stokes[96], blackseed.[97]
2.chemotherapy a. Chemotherapy by alkylating agents	Can impair DNA polymerase and act as anticancer agents, In in vitro cell lines.	Male Fern Rhizome (Dryopteris Crassirhizoma).[98]
b. Chemotherapy by antimetabolism	DNA fragmentation and formation of DNA ladders, transduce the apoptotic signal via ROS generation.	Eugenia caryophyllata.[79]
c. Chemotherapy by taxanes	Activation of the mitochondrial apoptotic pathway, Significant block of G1 to S phase transition manifested by the increase of cell number in G0/G1 phase	Olea europaea.[77] [99]

d. Chemotherapy by anthracylines	Exhibits anti-proliferative activity in HL-60 cells by inhibiting DNA synthesis and apoptosis	Maytenus ilicifolia.[100]
e. Chemotherapy by platinum based	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	Acanthospermum Hispidum.[93]
3.Immunotherapy	Modulation of multidrug resistance and apoptosis	Bauhinia Purpurea[101], Allium tuberosum[102] , The seed of Strychnos nux-vomica [103].
4.Gene therapy	Decrease differentiation, Modulation of multi drug resistance and Inhibition angiogenic process	Solanum nigrum L.[76], Annona glabra[104], Ganoder malucidum[105] [106], onion and garlic.[107]

Examples of anticancer medicinal plants

Medicinal plants have been used by humans for centuries in folklore medicine.[108] The plants are a rich source of secondary metabolites with interesting biological activities.[109][110] Sixty percent of drugs confirmed by FDA from 1984 to 1994 were isolated from natural sources specially plants.[111] Therefore, attention has been paid to natural, active substances.

1. Taxus brevifolia

Taxus brevifolia is a conifer native to the Pacific Northwest of North America. The isolation of a large number of taxoids as well as lignans, flavonoids, steroids and sugar derivatives has been reported from different parts of various Taxus species.[112] Paclitaxel is a complex taxane diterpene isolated from the bark of T. brevifolia.[113] Microtubule stabilizing agents (MSA) is a class of these drugs that includes taxanes (paclitaxel and docetaxel), which inhibit the metaphase anaphase transition through suppressing spindle microtubule dynamics, which block mitosis and induce apoptosis (table 3).[114]

2. Annona glabra

Annona glabra (pond apple), a tropical tree growing wild in the Americas and Asia, is used in traditional medicine against several human ailments, including cancer. The extracts were highly cytotoxic to drug sensitive (CEM) and multidrug-resistant leukemia (CEM/VLB) cell lines as mentioned in table 3. Treatment of CEM and CEM/VLB cells with seed extract induced apoptosis and necrosis in both sensitive and resistant leukemia cells in a concentration dependent manner.[104]

3. Andrographolide

Andrographolide (ANDRO), an active compound isolated from A. paniculata, is known to possess various physiological regulatory characteristics such as anti-inflammatory, antibacterial and hepatoprotection. ANDRO inhibited the growth of hepatoma cells by activation of c-Jun NH2-terminal kinase (JNK) and reduction of GSH levels.[115] ANDRO also caused reactive oxygen species ROS-stimulated cycle arrest (table 3) leading to the hypothesized crosstalk between JNK activation, cellular GSH homeostasis and cytotoxicity in hepatoma cells.[116]

4. Black seeds (Nigella sativa)

Nigella sativa is one the most revered medicinal seeds in history. Nigella sativa seeds extracts contains amino acids, proteins, carbohydrates, alkaloids, saponins, fixed and volatile oils, and many others. Among the volatile oil, thymoquinone (TQ) is the main active compound[117] TQ affects multiple targets, including suppression of, anti-apoptotic genes expression and thus enhances apoptosis induction as in table (3).[118] Moreover, TQ inhibited cell proliferation of many types of cancer cell lines, including breast adenocarcinoma, ovarian adenocarcinoma[97], human pancreatic adenocarcinoma, colorectal cancer[119], uterine sarcoma[120], human osteosarcoma[121] and fibrosarcoma, lung carcinoma.[118] More recently, it was reported that TQ blocks tumor angiogenesis (table 3) in vivo (mouse model) and in vitro (human umbilical vein endothelial cell.

5. Garcinia Fruit (Garcinia Cambogia)

It is rich in prenylated xanthones from mangosteen fruit with inhibitory properties against anti-neoplastic lesions in colon.[123] It showed cytotoxic effects to leukemia, breast, gastric, lung, liver cancer cell lines. However, xanthones mediate anticancer effects through down regulation of c-MYC mRNA expression/telomerase reverse transcriptase gene and initiate apoptosis, arresting immortalization, proliferation (table 3) of human cancer cells.[124] It arrested tumor cell proliferation, migration, cell adhesion, inhibition of MAPK/ERK, PI3K/Akt, membrane adhesion kinase phosphorylation, augmented expression of BAX, caspase 2/3 activation, released cytochrome C, PARP-1 cleavage in human cancer cell lines.[125]

Prevention of cancer by medicinal plants

Many of the plants and their derivatives have been under evaluation for their effects in cancer prevention. Among them, there are biologically active components such as curcumin, lycopene, capsaicin, gingerol, catechins, isothiocyanates, isoflovanes, vitamin E and C and selenium. Flavonoids, tannins, isoprenoids and phytosterols are commonly investigated. All of these agents are thought to have anti-inflammatory effect that may influence the carcinogenesis.[126] Free radicals are constantly generated resulting in extensive damage to tissues and biomolecules leading to various disease conditions. So, the medicinal plants with antioxidant

property are employed as an alternative source of medicine to mitigate the diseases associated with oxidative stress.[127] Antioxidants are the substances that inhibit oxidation prevent damage caused by free radicals.[128]

Mode of actions

Antioxidative activity

An antioxidant is "any substance that delays, prevents or removes oxidative damage to a target molecule".[129] Antioxidants can act by diverse mechanisms in the oxidative sequence. The human body complex antioxidant defense system consists of the dietary intake of antioxidants, as well as the endogenous production of antioxidative compounds, such as glutathione, etc.[130] Antioxidants can be classified into a number of different groups as enzymatic and non-enzymatic strategies. The enzymatic antioxidant involve superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, while non-enzymatic antioxidants include the vitamins A, C and E, glutathione and lipoic acid, mixed carotenoids, several bioflavonoid, antioxidant minerals (copper, zinc, manganese and selenium),[131] Several studies have shown that plant derived antioxidant scavenge free radicals and modulate oxidative stress. Free radicals are the cause of many diseases such as cancer, atherosclerosis, diabetes and aging. Different experimental and clinical studies have proved that higher intake of antioxidant rich food is associated with decreased risk of cardiovascular diseases and cancer. The free radical neutralizing properties of several plants have been screened by various researchers. Plants have been used in the prevention of cancer such as; Solanum nigrum[76], Bauhinia Purpurea[101], Sweet Myrrh[132], Semecarpus Anacardium[133] as mentioned in table 3.

Preventing carcinogens metabolic activation

Studies in vitro and in vivo have shown that some flavonoids modulate the metabolism and disposition of carcinogens and can contribute to cancer prevention.[134] One important mechanism by which flavonoids may exert their effects is through their interaction with phase I metabolizing enzymes (e.g., cytochrome P450), which metabolically activate a large number of procarcinogens to reactive intermediates that can interact with cellular nucleophiles and ultimately trigger carcinogenesis (table 1).[135] Thus, they are likely to have a protective role against the induction of cellular damage by the activation of carcinogens. Another mechanism of action is the induction of phase II metabolizing enzymes such as glutathione-S-transferase, quinone reductase, and UDP-glucuronyl transferase[136] and by which carcinogens are detoxified and thus more readily eliminated from the body.[137]

Examples on plants prevent cancer

a. Melia azedarach L. (Margosa)

Chemical constituents; Azaridine, sterols, tannins, paraisine, rutin and seeds are rich in fatty oil consisting of palmitic, oleic, linoleic acid (table 3). It showed that the extract of Melia azedarach, which contains highest amount of phenolic compounds, exhibited the greatest antioxidant activity. The high scavenging property may be due to hydroxyl groups existing in the phenolic compounds chemical structure that can provide the necessary components as a radical scavenger.[138]

b. Zingiber officinale Roscoe

Zingiber officinale Roscoe (ZO) in the family Zingiberaceae is a herbaceous, rhizomatous perennial plant widely distributed throughout the tropical and subtropical regions. The rhizome of ZO, commonly known as ginger, is a common condiment for various foods and beverages and is used in folk medicine in Asia and other tropical countries for various purposes such as for the relief of cold, fever and for treatment of inflammation, rheumatic disorder, hypercholesterolemia.[139] Ginger and its constituents show antioxidant activity as mentioned in table 3 and prevent the damage of macromolecules, caused by the free radicals/oxidative stress.[140] Ginger also acts as antitumor via modulation of genetic pathways such as activation tumor suppressor gene, modulation of apoptosis (table 3).[141]

c. Dates fruits

Dates fruits are used as staple food in the Middle East for thousands of years. Various types of dates are found worldwide mainly Khodry, Khalas, Ruthana, Sukkary, Sefri, Segae, Ajwa, Hilali and Munifi and each type of dates has shown medicinal value in various type of disease prevention. Dates and their constituents show a role in diseases prevention through antioxidant and anti-inflammatory activity. Antioxidant activity (table 3) is recognized due to the wide range of phenolic compounds present in dates including p-coumaric, ferulic, and sinapic acids, flavonoids and procyanidins.[142] The dates fruits constituents have shown the antitumor activity but its exact mechanism of action of dates and their constituents in the prevention of tumor is not known exactly.[143]

d. Allium sativum

Allium sativum L. (garlic) is among the oldest of all cultivated plants being used as a food, having a unique taste and odor along with some medicinal qualities. Modern scientific research has revealed that the wide variety of dietary and medicinal functions of garlic can be because of the sulfur compounds present in it.[144] Different garlic preparations including fresh garlic extract, aged garlic, garlic oil and a number of organo sulfur compounds derived from garlic shown to have chemo preventive activity. The chemo preventive activity (table 3) has been attributed to the presence of organo sulfur compounds in garlic. The two major compounds in aged garlic, S-allylcysteine and S-allylmercapto-L-cysteine possess the highest radical scavenging activity.[145]

e. Daucus carrota Linn. (Carrot)

Seed oil of daucus carrota contain Carotol, daucol, terbenolene, sabinene, carotenoid, carotene, flavonoids, α tocopherol, ascorbic acid, camphene, γ-terpinene, histidine Antitoxin.[146] Antioxidant and radical scavenging activities (table 3) are much higher in carrot peel than phloem and xylem tissue. Phenolic acids and flavonoids made greater contribution to the total antioxidant capacity. The quality of the antioxidants in the extracts is determined by the IC50 values.[147]

Table 3: **Shows different medicinal plants and their effect on cancer prevention and treatment.**

No.	Medicinal plant name	Family name	Action or effect	references
1.	Alangium salvifolium	Alangiaceae	inhibition and damage the DNA (cell cycle arrest and apoptosis)	[148]
2.	Bupleurum falcatum	Apiaceae	Increasing the expression of p53 and induction of Fas/APO1 (apoptosis)	[149][150]
3.	Solanum incanum	Solanaceae	Increased the release of cytochrome c. and caspase-3 activity (apoptosis)	[151]
4.	Forsteronia refracta Müll.	Apocynaceae	Inhibits proliferation of the human breast cancer cellline MCF-7 by inducing cell cycle arrest at the G1 phase (cell cycle arrest and apoptosis)	[152]
5.	Ananas comosus	Bromeliaceae	in vivo antitumoral/ anti-leukemic activity	[153]
6.	Chenopodium ambrosioides	Chenopodiaceae	exhibits antitumour activity, anti-neoplastic activity in different tumor cell lines	[154]
7.	Bidens pilosa	Asteraceae	toxic with a half maximal inhibitory concentration(IC50) (antiproliferation)	[155]
8.	Securidaca longepedunculata	Polygalaceae	cytotoxic activity and possible pro-apoptotic effect	[156]
9.	Erythroxylum pervillei Baill	Erythroxylaceae	selectively cytotoxic against a multi-drug resistant (MDR) oral epidermoid cancer cell line	[92]
10.	Artocarpus obtusus	moraceae	Exhibits good cytotoxic and potential antiproleferative activity against cell lines	[157]
11.	Onion (Allium cepa	Liliaceae	Onion oil inhibited tumor promotion by DMBA/TPA	[158][159]
12.	Maytenus ilicifolia	Celastraceae	exhibits anti-proliferative activity in HL-60 cells by inhibiting DNA synthesis and apoptosis	[100]
13.	Morinda citrifolia Linn.	Rubiaceae	suppress tumor growth directly by stimulating the immune system (antiprolifratio)	[160]
14.	Aloe vera	Liliaceae	S-phase arrest promoted the release of apoptosis-inducing factor (AIF), (apoptosis)	[161]
15.	Silybum marianum	Asteraceae	cell cycle arrest at the G1 phase	[162]
16.	Santalum album)	Santalaceae	The mechanism of its activity is due, in part, to the inhibition of TPA-induced epidermal ODC activity	[163]
17.	Alpinia galanga	Zingiberaceae	DNA fragmentation where a characteristic DNA laddering was noticed in treated tumor cell line (cell cycle arrest)	[164]
18.	Derris scandens	Fabaceae	Identified as a potent radio-sensitizer of human colon cancer HT29 cells. Cell death mechanisms (cell cycle arrest and antidifferentiation)	[86]
19.	Melissa officinalis	Lamiaceae	antiproliferative properties of Melissa officinalis on breast cancer.	[165]
20.	Vitis vinifera	Vitaceae	Antitumor and antioxidant activity antitumor effect and antioxidant role was determined by using tumor volume, packed cell volume	[166]
21.	Manihot esculenta Crantz	Euphorbiaceae	cytotoxic activity against cervical and ovarian adenocarcinoma cells (antiproliferative)	[167]
22.	Withania somnifera	Solanaceae	anti-oxidant and immune-modulatory properties., antitumor, In vitro cytotoxicity (anti-oxidation, cell cycle arrest and anti-proliferation)	[168]
23.	Curcuma longa Linn	Zingiberaceae	Chemo preventive effect on DNA damage in human normal cell. (modulation of multi drug resistant)	[169][91]
24.	Ocimum basilicum	Lamiaceae	Induced a significant decrease in the percentage of cells in anaphase/telophase stages (antidifferentiation)	[170]

25.	Amaranthus tricolor	Amaranthaceae	inhibited the growth of AGS,SF-268,HCT116, tumor cell (cell cycle arrest)	[171]
26.	Semecarpus anacardium Linn.	Anacardiaceae	anticancer and hepato-protective activity, protective role on deranged cell membrane in AFB1 induced hepato-carcinoma.(antioxidation and multi drug resistant)	[133]
27.	Sweet Myrrh	Burseraceae	antioxidant properties, apoptosis, antiproliferation in lung, pancreas, breast, prostate cancers (antio-xidation,apoptoss and anti-proliferation)	[132]
28.	White Cherry Bark (Prunus Serotina)	Rosaceae	Anticancer properties suchas antiproliferative apoptotic effects in colorectal cancer (antiproliferatin, cell cycle arrest and apoptosis)	[172]
29.	Eugenia caryophyllata	Myrtaceae	DNA fragmentation and formation of DNA ladders, transduce the apoptotic signal	[79]
30.	Capparis sepiaria	CapparaceaE	Decreases the tumor volume, packed cell volume (antioxidation effect, antidifferentiation)	[85]
31.	Chelidonium majus	Papaveraceae	induce cell death by apoptosis, cell death of pancreatic cancer cells via cell cycle arrest at prophase and metaphase	[80][81]
32.	Elaeis guineensis	Arecaceae	vitro cytotoxicity, induce an inhibitory action on the human breast cancer cells (antiprolifration and cell cycle arrest)	[173][174] [175] [176]
33.	Bauhinia Purpurea	CaesalpiniacEae	elevated antioxidant defense enzyme activities, induction of apoptosis.	[101]
34.	Solanum nigrum	Solanaceae	antioxidant, cytotoxic properties.	[76]
35.	Garcinia Fruit (Garcinia Cambogia)	Clusiaceae	cytotoxic effects to leukemia, breast, gastric, lung, liver cancer cell lines. initiate apoptosis, arresting immortalization, proliferation of human cancer cells.	[124]
36.	Acanthospermum hispidum	Asteraceae	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(multi drug resistant, apoptosis)	[93]
37.	Balanites aegyptiaca	Balanitaceae	Decrease the [ATP] induces in turn a marked disorganization of the Actin cytoskeleton (multi drug resistance)	[177]
38.	MaleFern Rihzome (Dryopteris Crassirhizoma)	Dryopteridaceae	can impair DNA polymerase and act as anticancer agents and arrested cancer growth through S-phase arrest and resulting apoptosis	[98] [178]
39.	Salvia libanotica Boiss	Labiatae)	inhibit tumor promotio by DMBA/TPA	[179]
40.	Plumbago scandens	Plumbaginaceae	exhibit cytotoxic activity against breast cancer and melanoma cells, induces apoptosis and cell cycle arrest in a small cell	[180] [181]
41.	Citrus aurantifolia	Rutaceae.	inhibition of human colon cancer cells DNA fragmentation and induction of apoptosis.	[76]
42.	Trigonella foenum	Fabaceae	alternative cell death processes and para-apoptosis	[182] [183] [184]
43.	Camellia sinensis	Theaceae	Antioxidant, antitumor and cancer preventive activities.	[185]
44.	Mangifera indica	Anacardiaceae	anticancer properties of polyphenolic extracts in cancer lines, (cell cycle arrest)	[75]
45.	Achyranthes aspera	Amaranthaceae	suppressed two stage carcinogenesis by DMBA/TPA(antiprolefration and antidifferentiation)	[84]
46.	Azadirachta indica	Meliaceae.	inhibit tumor promotion by DMBA/ TPA, Inhibition of carcinogenesis	[186]
47.	Olea europaea	Oleaceae	Activation apoptotic pathway, block of G1 to S phase	[77] [99]

48.	Silybum marianum	Asteraceae	Induces G1 arrest in cell cycle progression. Activates apoptotic machinery in human prostate cancer cells.	[187][188]
49.	Plantago lanceolata	Plantaginaceae	DNA damage and cytotoxic potential (cell cycle arrest)	[189]
50.	Aglaia sylvestris	Meliaceae	cytotoxic to several human cancer cell lines (antiprolefration and cell cycle arrest)	[190]
51.	Kigelia Africana	Bignoniaceae	cytotoxic activities and treating melanoma and renal carcinoma	[191]
52.	Viola odorata	Violaceae	cytotoxic activity against ten different cancer cell lines (antiproliferation)	[192]
53.	Goniothalamus macrophyllus	Annonacae	anticancer properties, DNA damage, DNA fragmentation, apoptosis, cytotoxicity effect against cervical cancer cells (Hela) and the cell	[193]
54.	Eclipta alba	Asteraceae	DNA damage leading to apoptosis.	[194]
55.	Licorice	Fabaceae	inhibit the proliferation of human cervical carcinoma cell of tumors. It inhibits cell cycle and induces cell apoptosis in cancerous cells	[24]
56.	Stephania sutchuenensis	Menispermaceae	Inducing cell growth inhibition and apoptosis.	[195]
57.	Ganoderma lucidum	Ganodermataceae	Cell cycle arrest, inhibit proliferation, anti-angiogenic activity and can also inhibit the production of nitric oxide, an inducing agent of angiogenesis over expressed in tumours	[105] [106]
58.	Viscum album (coloratum)	Viscaceae	Cytotoxic and apoptosis against cancer cell	[21]
59.	Red maple (Acer rubrum)	Sapindaceae	Anticancer effect against human tumorigenic(colon, HCT-116; Breast, MCF-7)	[196]
60.	Cuphea hyssopifolia	Lythraceae	Antitumor activity against HL-60 (antiproliferation)	[57]
61.	C. landaifer	Cistaceae	Inhibit proliferation of pancreatic and breast cancer cell	[58]
62.	Punica grantum	Lythraceae	Anti-proliferative activity and apoptotic effect against colon cancer cell lines	[59]
63.	Xanthium strumarium	Asteraceae	Inhibit proliferation of human tumor cells	[63]
64.	clematis manshrica	Ranunculaceae	Antitumor effects against various transplanted tumor	[68]
65.	Frangula alnus	Rhamnaceae	Anti-proliferation on tumor cell	[71]
66.	Rosmarinus officinalis	Lamiaceae	Anti-proliferation effect	[71]
67.	Taxus brevifolia	Taxaceae	Anti-proliferation effect on cancer cell	[71]
68.	Annona globra (pond apple)	Annonaceae	Cytotoxic effect, multidrug resistant against leukemia	[104]
69.	Tinospora cordifolia (Wild) Miers	Menispermaceae	Immunomodulatory and anti-oxidant activities.	[197][198]
70.	Andrographis paniculata	Acanthaceae	Cytotoxicity and cell cycle arrest against cancer cell.	[199][116]
71.	Nigella sativa (Black seed)	Ranunculaceae	Apoptotic induction, antiproliferation, blocks tumor angiogensis	[118][97]
72.	Garcinia cambogia	Clusiaceae or Gutti ferae	Cytotoxic effect, anti-proliferation, reduction apoptosis, cell arrest.	[124][125]
73.	Melia azedarach L.(Margosa)	Meliaceae	Antioxidant effect for prevention of tumor	[138]
74.	Zingiber officinale Roscoe	Zingiberaceae	Anti-oxidation, induction of apoptosis	[140][141]
75.	Dates fruits	Arecaceae	Antioxidant effect for prevention of tumor	[143]
76.	Allium sativum(garlic)	Amaryllidaceae	Chemo-preventive and anti-oxidant activity	[145]
77.	Daucus carrota Linn (carrot)	Apiaceae	Antioxidant effect for prevention of tumor	[147]
78.	Camptotheca acuminata	Cornaceae	Inhibits the DNA enzyme topoisomerase I, leading to DNA damage and apoptosis	[200]
79.	Catharanthus	Apocynaceae	Treats leukemia, It binds tubulin, thereby inhibiting the assembly of microtubules thus prevent separation ofchromosomes during mitosis.	[200]
80.	Strychnos nux-vomica	Loganiaceae	Cell cycle analysis showed G2/M phase arrest and apoptosis	[103]

4. Conclusion and future prospective

Cancer is the most deadly disease that causes the serious health problems around the world. In present study, herbs are surveyed to demonstrate their benefits in human health and possible use as anticancer prevention and treatments. The pharmacological action and biochemical mechanisms of herbs are highlighted for their possible effects on anticancer action. A possible herbal anticancer composition is proposed for make effective anticancer herbal formula. Therefore, it is need for new therapeutic strategy to improve the efficacy of natural compounds, alone or combine with chemical drugs to reduce toxicity as well as side effects, increase selectivity and reduce the risk of using the current drugs. It should be interest to explore the anticancer potential of the medicinal plants extracts for isolation and characterization of the active anticancer constituents so that better, safer and cost effective drugs can be developed for treating cancer. Several plants contain chemical therapeutic agent that help in cancer prevention and early treatment by different mechanisms. Indeed, the struggle to combat cancer is one of the greatest challenges of mankind. It will be needed to develop novel plant-derived natural products and their analogs for anticancer activity to synthesize new derivatives with more efficiency and save and less cost.

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