

A Review on: Plants as Anticancer

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ABSTRACT

Cancer is a disease characterized by out-of-control cell growth. There are various types of cancer, and is classified by the type of cell that is affected. Cancer harms the body when altered cells divide uncontrollably to form lumps or masses of tissue called tumors. The recent treatments include chemotherapy, radiotherapy and Surgery. But this treatment accomplished by several side effect like the destruction of bone marrow cell, alopecia etc. So there is a need for the new drug for treatment of cancer. Plant-derived chemical may act as anticancer in many studies. The Plant produces secondary metabolites which are being evaluated for the anticancer activities leading to the development of new drugs. So in this review we have study different plants which act as anticancer. And this will encourage further scientific study of traditionally used plants.

Keywords: Anticancer, Plants, Secondary metabolite

INTRODUCTION

The cancer disease is characterized continuous multiplication of cell with the inability to be controlled or stopped consequently, forming tumors of malignant cells with the potential to be metastatic. Current treatments include chemotherapy, radiotherapy and chemically derived drugs. Treatments such as chemotherapy can put patients under a lot of strain and further damage their health. Therefore, there is a focus on using alternative treatments and therapies against cancer. [Ochwang'I DO et al. 2014]

For many years herbal medicines have been used and are still used in developing countries as the primary source of medical treatment. Plants have been used in medicine for their natural different properties. The plants extracts preparation shows a potential anticancer effect for the treatment of different types of cancer. [Sivaraj R et al. 2014]

There is need for new drugs evaluation for the treatment of cancer from fruits, vegetables, herbs and spices. Ethnotraditional use of different plant-derived natural products plays a significant role in the discovery and development of potential medicinal agents. [Torres MP et al. 2012]

GRAPE SEEDS (VITIS VINIFERA)

Grape seeds are a good source of polyphenols, which showed a potent antioxidant activity. Thus, grape seed extract (GES) can be used to treat number of deadly diseases like cancer (skin cancer, colon cancer & colorectal cancer) and various bacterial infections. The petroleum ether extracted of Grape seeds analyzed for the cytotoxicity against skin cancer cell lines A431 it showed maximum cell lysis at the concentration of 500 µg/mL. The IC₅₀ value is 480 µg/mL, which indicated that such concentration could lyse 50% of skin cancer cell lines. The morphological changes occurs in treated A431 cell lines when visualized under an inverted light microscope showed that the detachment of the cells from the substratum, cell shrinkage, nuclear condensation and fragmentation. The morphological changes included the reduction in the size of the cells and the cells gradually became shrunken with the appearance of small bodies. Nature and its differential features occurred in the cancer cells it clearly defined the cellular morphological characteristics, which was typical of cell death. The GSE could be used in ointments and also injected as injectable in skin cancer patients to treat skin cancer. [Mohansrinivasan V et al. 2015]

Tumor cells trigger angiogenesis through over expression of various angiogenic factors including vascular endothelial growth factor (VEGF) and

angiopoietin 1 (Ang1). Therefore, inhibition of the expression of both VEGF and Ang1, the initial step of tumor angiogenesis, is a promising strategy for cancer chemoprevention and therapy. Grape seed proanthocyanidins (GSPs) are widely consumed as a dietary supplements that showed antitumor activity. Due to their polymeric structure, GSPs are poorly absorbed along the gastrointestinal tract and can reach the colon at high concentrations, allowing these chemicals to act as chemopreventive agents for colon cancer. GSPs inhibited colon tumor-induced angiogenesis and, thus, the growth of colon tumor xenografts on the chick chorioallantoic membranes. The mechanisms of action were related to inhibiting the expression of both VEGF and Ang1 through scavenging reactive oxygen species. [Huang S *et al.* 2012]

The grape seed extract (GSE) has the ability to target colorectal cancer (CRC) cells and delineated its mechanisms involved in GSE-induced CRC cell death. GSE have selectively causes apoptotic cell death in human CRC cells; and its efficacy increased as the metastatic potential of the cancer cells increased. GSE intervention may serve as a multi-targeted CRC therapeutic which is capable of inducing selective cancer cell death. [Derry M *et al.* 2013]



Fig.1 Grape seeds

GINGER (*ZINGIBER OFFICINALE*)

Ginger (*Zingiber officinale*) is a naturally used as dietary component which showed antioxidant and anticarcinogenic properties. The active chemical component present in ginger is [6]-gingerol has been shown to exert anti-inflammatory effects through the mediation of NF-kappaB. The NF-kappaB can be constitutively activated in case of epithelial ovarian cancer cells and may contribute towards increased

transcription and translation of angiogenic factors. The effect of ginger and the major ginger components on cell growth was determined in a panel of epithelial ovarian cancer cell lines. Activation of NF-kappa B and production of VEGF (Vascular Endothelial Growth Factor) and IL-8 (interleukin-8) was determined in the presence or absence of ginger. Ginger treatment of cultured ovarian cancer cells induced profound growth inhibition in all cell lines tested. Ginger treatment resulted in inhibition of NF-kB activation as well as diminished secretion of VEGF and IL-8. Ginger inhibits growth and modulates of secretion of angiogenic factors in ovarian cancer cells. The use of dietary agents such as ginger may have potential use in the treatment and prevention of ovarian cancer. [Rhode J *et al.* 2007]

Despite potential efficacy of [6]-gingerol in cancer, the mechanism by which it exerts chemopreventive effects remains elusive. The leukotriene A(4) hydrolase (LTA(4)H) is a protein which regarded as a relevant target for cancer therapy. In case of In-silico method prediction using a reverse-docking approach revealed that LTA(4)H might be a potential target of [6]-gingerol. [6]-gingerol effectively causes suppression of tumor growth in In-vivo nude mice, and its effect that was mediated by inhibition of LTA(4)H activity. [Jeong CH *et al.* 2009]



Fig.2 Ginger

ALOE-EMODIN

Aloe-emodin (1,8-dihydroxy-3-[hydroxymethyl]-anthraquinone), which is purified from aloe vera leaves, has been reported to have antitumor activity. The anticancer effects of Aloe-emodin in the T24 human bladder cancer cell line were studied. Cell

viability, cell cycle and apoptosis were determined. Levels of cyclins, cyclin-dependent kinase 1 and other enzyme were examined by Western blotting methods. Aloe-emodin which inhibited cell viability, and causes induction of G2/M arrest and apoptosis in case of T24 cells. Aloe-emodin increased the levels of Wee1 and cdc25c, and may have led to inhibition of the levels of cyclin-dependent kinase 1 and cyclin B1, which cause G2/M arrest. AE causes induced of p53 expression and also accompanied by the induction of p21 and caspase-3 activation, which was associated with apoptosis. In addition, AE was associated with a marked increase in Fas/APO1 receptor and Bax expression but it inhibited Bcl-2 expression. Aloe-emodin causes apoptosis in T24 cells which mediated through the activation of p53, p21, Fas/APO-1, Bax and caspase-3.[Lin JG *et al.* 2006]



Fig.3 Aloe-emodin

LICORICE ROOT (GLYCYRRHIZA GLABRA)

Licorice root is a botanical, a shrub native to southern Europe and Asia, which primarily has desirable qualities in sweetening and herbal medicine. Licorice root is one of the oldest and most frequently employed botanicals in Chinese medicine. In the United States, licorice products are most often used as a flavoring and sweetening agents in food products. Constituents of licorice include triterpenoids, such as glycyrrhizin and its aglycone glycyrrhizic acid, various polyphenols, and polysaccharides. A number of pharmacological effects of licorice are known or suspected (anti-inflammatory, antiviral, antiulcer, anticarcinogenesis, and others). Licorice and its derivatives may protect against carcinogen-induced DNA damage and may be suppressive agents as well. Glycyrrhizic acid is act as an inhibitor of lipooxygenase and cyclooxygenase, which inhibits protein kinase C,

and down regulates the epidermal growth factor receptor. Licorice polyphenols induce apoptosis in cancer cells. These and other activities of licorice are reviewed, and a rationale is suggested for combinations of agents in preventive clinical trials.[Wang ZY *et al.* 2001]

Licorice (*Glycyrrhiza uralensis* Fisch) root also inhibits active cell proliferation on human breast cancer cell. The cell proliferation study demonstrated that licorice root reduced the proliferation of MCF-7 cells in a dose- and time-dependent manner. The extracts were fractionated in Chloroform, Ethyl acetate, Hexane, and Methanol-Water (70:30), and these extracts of licorice root (50µg/mL) induced DNA fragmentation demonstrated by Hoechst staining. These results were consistent with specific cleavage of PARP and antiapoptotic protein Bcl-2 and up-regulation of proapoptotic protein Bax demonstrated by Western blotting. The licorice root may also possesses chemopreventive effects against human breast cancer through the modulation of the expression of the Bcl-2/Bax family of apoptotic regulatory factors.[Jo EH *et al.* 2004]



Fig.4 Licorice root (*Glycyrrhiza glabra*)

ARTEMISIA ANNUA

Artemisia annua is sometimes also called as sweet Annie, sweet fern, sweet wormwood or annual wormwood. This little known plant recently became the subject of attention when two researchers at the University of Washington noted in 2001 that this wormwood had the potential to become a powerful anti-cancer herb. *Artemisia annua* showed Antitumor and antiviral properties of the antimalaria drug artemisinin from *Artemisia annua*. Novel artemisinin derivatives (AD1-AD8) evaluated using in vitro models of liver/colon cancer and viral hepatitis B and C. Cell viability assays after treating human cell lines from hepatoblastoma (HepG2), hepatocarcinoma (SK-HEP-1), and colon

adenocarcinoma (LS174T) with AD1-AD8 for a short (6h) and long (72h) period revealed that AD5 combined low acute toxicity together with high antiproliferative effect ($IC_{50}=1-5\mu M$). Ferrosanol, but not hemin, enhanced antiproliferative activity of AD5 if the cells were preloaded with AD5, but not if both compounds were added together. Five derivatives (AD1>AD2>AD7>AD3>AD8) were able to inhibit the cytopathic effect of bovine viral diarrhoea virus (BVDV). Moreover, AD1 and AD2 inhibited the release of BVDV-RNA to the culture medium. Co-treatment with hemin or ferrosanol resulted in enhanced anti-Flaviviridae activity of AD1. In HepG2 cells permanently infected with hepatitis B virus (HBV), AD1 and AD4, at non-toxic concentrations for the host cells were able to reduce the release of HBV-DNA to the medium. [Blazquez AG *et al.* 2013]



Fig.5 Artemisia annua

TEA (CAMELLIA SINENSIS)

The black, green and herbal tea leaves contain a biologically active amino acid (2,4-dinitrophenyltheanine). 80% ethanol/water extracts of the tea leaves showed anticarcinogenic effect in MTT (tetrazolium microculture) assay. Compared to untreated controls, most catechins, theaflavins, theanine, and all tea extracts reduced the numbers of the human cancer cell lines: breast (MCF-7), colon (HT-29), hepatoma (liver) (HepG2), and prostate (PC-3) as well as normal human liver cells (Chang). The growth of normal human lung (HEL299) cells was not inhibited. The destruction of cancer cells was also observed. The anticarcinogenic effects of tea compounds and of tea leaf extracts varied widely and were concentration dependent over the ranges from 50 to 400 $\mu g/mL$ of tea compound and from 50 to 400 $\mu g/g$ of tea solids. The different cancer cells varied in their susceptibilities to destruction. [Friedman M *et al.* 2007]



Fig.6 Tea

ONION (*ALLIUM CEPA*)

Onion (*Allium cepa* L.) is botanically included in the family Liliaceae and the species are found across a wide range of latitudes and altitudes in Europe, Asia, N. America and Africa. World onion production has been increased by at least 25% over the past 10 years with current production being around 44 million tones making it the second most important horticultural crop after tomatoes. Because of their long term storage characteristics and durability for shipping, onions have always been traded more widely than most vegetables. Onions are versatile and are often used as an ingredient in many dishes and are accepted by almost all traditions and cultures. Onion (*Allium cepa*) consumption is increasing significantly, day by day particularly in the USA and this is partly because of heavy promotion that links flavour and health. Onions are rich in two chemical groups that have perceived benefits to human health. These are the flavonoids and the alk(en)yl cysteine sulphoxides (ACSOs). Two flavonoid components are found in onion, the first anthocyanins, which impart a red or purple colour to some varieties and flavanols also while second quercetin and its derivatives responsible for the yellow and brown skins of many other varieties. The alk(en)yl cysteine sulphoxides are the flavour precursors, which, when breakdown by the enzyme alliinase, generate the characteristic odour and taste of onion. The downstream products of onion is a complex mixture of compounds which include thiosulphinates, thiosulphonates, mono-, di- and tri-sulphides. Onions contain several anti-cancer compounds, including quercetin, anthocyanins, organosulfur compounds such as diallyl disulfide (DDS), S-allylcysteine (SAC) and S-methylcysteine (SMC) and onionin A (ONA). Onion can be used to suppress epithelial ovarian cancer. [Griffiths G *et al.* 2002]



Fig.7 Onion

FOXGLOVE

The various study on Foxglove showed possible anticancer properties. There are two varieties of this plant, *Digitalis purpurea* L and *Digitalis lanata* Ehrh. These two have been looked at for their vitro cytotoxicity after polypeptide isolation and extraction. 100 fractionated plant extracts were screened in vitro for cytotoxicity following extraction and fractionation (polypeptide isolation). Of these 100 extracts, 30 were selected for preliminarily for antitumor potency by testing them on cell lines, primary cultures of human tumor cells. On the basis of cytotoxicity potency, 10 of the extracts were further characterized for anticancer activity in 10 human tumor cell lines. This final testing resulted in seven potential lead plants with superior evidence of antitumor potential: *Colchicum autumnale* L. (Colchicaceae), *Digitalis lanata* Ehrh. and *Digitalis purpurea* L. (Plantaginaceae), *Helleborus cyclophyllus* Boiss. (Ranunculaceae), *Menyanthes trifoliata* L. (Menyanthaceae), and *Viola arvensis* Murr. and *Viola patrinii* Ging. (Violaceae).[Lindholm P *et al.* 2002]



Fig.8 Foxglove

Milk thistle

The study on Milk thistle reported that it showed anti-cancer properties. Milk thistle (*Silybum*

eburneum or *Silybum marianum*) has an active ingredient in their seeds contain a wide mixture of flavonolignans such as silibinin, silidianin, silicristin, and isosilibinin. Prostate cancer (PCA) is the most common cancer diagnosed in men and the second most common cause of death due to cancers after lung cancer. Metastasis of cancer cells involves multiple processes and various cytophysiological changes, including changed adhesion capability between cells and extracellular matrix (ECM) and damaged intercellular interaction. Silibinin, is a flavonoid which found in Milk thistle, which showed antioxidant and potent antiproliferative effect against various malignant cell lines. PC-3 cells were incubated with various concentrations of silibinin for different times; then, cell cytotoxicity, cell adhesion and cell motility were assessed using MTT assay, cell-matrix adhesion assay and cell migration assay, respectively. The results showed that silibinin exerted a dose- and time-dependent inhibitory effect on the viability, motility and adhesion of highly metastatic PC-3 cells. These observations indicate that silibinin can probably inhibit metastasis in PCA. [Mokhtari MJ *et al.* 2008]



Fig.9 Milk thistle

Saffron (*Crocus sativus*)

Saffron is the dry stigmas of the plant *Crocus sativus* L., contains a carotenoid called crocetin. Saffron used as a spice, a food colorant and also used as an herbal remedy for various ailments including cancer by the ancient Arabian, Indian and Chinese cultures. Crocetin, have a significant antitumor agent in animal model and cell culture system. Crocetin affects the growth of cancer cells by inhibiting nucleic acid synthesis in cell, enhancing anti-oxidative system, inducing apoptosis and hindering

growth factor signaling pathways.[Gutheil WG *et al.* 2012]



Fig.10 Saffron

Graviola (*Annona muricata*)

Graviola, is fruit, having natural anti-cancer properties. Graviola (*Annona muricata*) is an evergreen tree that is used as a remedy for coughs, bacterial and parasite infections, herpes, and arthritis. The extract of Graviola, shows anticancer activity on PC cells. It is revealed that Graviola induced necrosis of PC cells by inhibiting cellular metabolism.[Torres MP *et al.* 2012]



Fig.11 Graviola

Dandelions (*Taraxacum officinale*)

The *Taraxacum officinale*, is commonly known as dandelions, have used as traditional medicine in Chinese, Arabian and Native American to treat cancer. The crude extract of *Taraxacum officinale* shows anticancer effect on MCF-7 cell line by inhibiting the growth of MCF-7 breast cancer cells in an ERK-dependent manner, while the aqueous extracts of dandelion flower (DFE) and root (DRE) had no effect on the growth on MCF-7 [Sigstedt SC *et al.* 2008]



Fig.12 Dandelions

TESSARIA ABSINTHIOIDES

Tessaria absinthioides extract exhibits cytotoxicity against cancer cell lines, with no-toxic effects and significant antitumoral effects in colorectal cancer when is orally administrated. The phytochemical analysis of *Tessaria absinthioides* shows the presence of flavonoids, carbohydrates, sterols, terpenes and tannins. Oral administration of the aqueous extract does not induce acute nor dose-repeated toxicity at doses up to 2000 mg/kg and 1000 mg/kg/day, respectively. The antitumoral effect was confirmed by a significant increase in a median survival from 24 weeks (non-treated) to 30 weeks (*Tessaria absinthioides* treated). *Tessaria absinthioides* possesses selective cytotoxicity and antitumoral activities, making its plant derivatives products promising for cancer research and treatment.[Persia FA *et al.* 2017]



Fig.13 *Tessaria absinthioides*

TRITERPENOIDS

Secondary metabolites produced by plants are used as therapeutic agents for various diseases, like cancer. Triterpenes are a category of secondary metabolites that exert inhibitory activity against

multiple intracellular and extracellular targets in eukaryotic cells. These targets are proteins involved in apoptosis, cell development and differentiation, angiogenesis, metastasis and inflammatory processes. The inhibition of their functions leads to decreased cellular growth, differentiation and migration, resulting in antitumor activity, as shown by the numerous published experimental results. The synthetic triterpenoids derivatives shows a potent anticancer activity. [Peron G *et al.* 2017]



Fig.14 Triterpenoids Source

RUBUS FAIRHOLMIANUS

Rubus fairholmianus is a berry used in folkloric medicine. The methanolic column subfraction of *Rubus fairholmianus* root (RFM) shows the presence of alpha-tocopherol, flavonol glycoside and apigenin. The methanolic column subfraction of *Rubus fairholmianus* root (RFM) significantly reduced solid and ascites tumors in mice in 100 mg/kg dose. The morphological features of RFM treated MCF-7 cells showed the cell damage and decreased cell numbers. The viability of treated cells decreased with 67.73% at 20 µg/mL against 96.50% in untreated cells. The treated cells (20 µg/mL) resulted in a substantial decrease ($p < 0.001$) in cellular ATP proliferation, increased the LDH cytotoxicity, increased apoptotic cells population (33.92%) and reduced the population of viable cells (Annexin V-PI-) (45.56%). This is the first evidence about in vitro and in vivo anticancer activity of *R. fairholmianus* phenolics. The major phenolics such as alpha-tocopherol, flavonol glycoside, and apigenin might be the reason behind the caspase-mediated apoptosis. [George BP *et al.* 2017]



Fig.15 *Rubus fairholmianus*

Quercetin

The flavonoid quercetin (3,3',4',5,7-pentahydroxyflavone) is present in plants, foods, and beverages and shows antioxidant, radical-scavenging, anti-inflammatory, antibacterial, antiviral, gastroprotective and immune-modulator. Besides, quercetin is used in neurological disorders and having protection against mitochondrial damages. The various in vitro studies showed the anticancer effects of quercetin, but there mechanism of action is not known. The quercetin has low bioavailability, poor solubility, rapid body clearance, fast metabolism and enzymatic degradation which restrict the use of quercetin as therapeutic agent, so intense research focused on the modification of the quercetin scaffold to obtain analogs with potentially improved properties for therapeutic use. [Massi A *et al.* 2017]

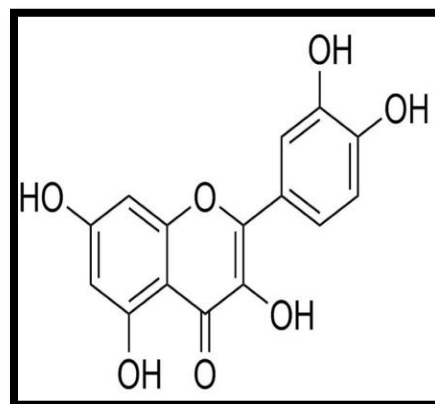


Fig.16 Structure of Quercetin

STEPHANIA TETRANDBRA

The fangchinoline, alkaloid from *Stephania tetrandra*, has inactivator of nuclear NR4A1 and it

inhibits cell proliferation via the NR4A1-dependent pro-apoptotic pathways in human pancreatic cancer cells. It decreased expression of the antiapoptotic protein survivin by inhibiting Sp1-mediated transcription and induced oxidative stress-mediated endoplasmic reticulum (ER) stress in pancreatic cancer cells. [Lee HS *et al.* 2017]



Fig.17 *Stephania tetrandra*

SAUSSUREA LAPPA

The ethanolic extract of *Saussurea lappa* (ESL) has curative effect against prostate cancer. ESL treatment decreased the viability of LNCaP cells and increased Bax expression while suppressing the expression of pro-caspases-8/9/3, PARP, Bid, and Bcl-2, thereby inducing apoptosis in LNCaP cells. So it shows that ESL exerts anticancer effects through the induction of both cellular apoptosis and autophagy, and apoptotic cell death can be facilitated by blocking autophagy in ESL-treated LNCaP cells. Therefore, ESL might be a potential anticancer agent for the treatment of prostate cancer. [Tian X *et al.* 2017]



Fig.18 *Saussurea lappa*

CORDIA DICHOTOMA

Mechanisms of antioxidant and apoptosis induction may be involved in the management of cancer by medicinal plants. The methanolic extract of *Cordia dichotoma* leaves (MECD) shows anticancer activity against a human prostate carcinoma cell line, PC3. Flavonoid content was found to be 160 mg QE/g extract. IC₅₀ values for MECD treatment in various assays based on scavenging of 2,2-diphenyl-1-picrylhydrazyl, 2,2-azinobis(3-ethylenebenzothiazoline-6-sulfonic acid), nitric oxide, peroxy radical, superoxide anion, hydroxy radical were found to be 315.5, 38, 476, 523, 197, 82 µg/ml respectively. MECD exposure to PC3 cells significantly increased the cell death ($p < 0.001$, IC₅₀ = 74.5 µg/ml), nuclear condensation, apoptosis ($p < 0.001$) and induced production of ROS ($p < 0.001$) initiating apoptotic cascade in a dose dependent manner. Flavonoids in MECD may be responsible for these activities due to dual antioxidant and pro-oxidant properties. [Rahman MA *et al.* 2017]



Fig.19 *Cordia dichotoma*

CONCLUSION

Cancer is a disease characterized by out-of-control cell growth. It is difficult to treat cancer. The available treatment for the cancer today is like chemotherapy, Radiation and surgery etc. But it is having various side effects. To minimize the side effect which caused by the chemotherapy we can use a plant-derived substance. So this review article gives information regarding some plant which acts as anticancer. And further, it encourages to explore different plants for the possibility of anticancer.

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