

**REVIEW ON HERBAL PLANTS HAVING
ANTI-CANCER ACTIVITY**

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Summary

Cancer is a class of diseases characterized by uncontrolled cell growth. Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except in the case of leukemia when cancer prohibits normal blood function by abnormal cell division in the blood stream). Cancer treatment involves surgery, radiation and drug therapy, singly or in combination. Majority of anticancer drugs act by interfering with cancerous cell growth, however these drugs commonly affect not only the cancerous cells but other cells that reproduce quickly like the cancer cells. e.g. 5-fluorouracil, daunorubicin, doxorubicin, methotrexate and etoposide etc. Therapeutic effect of anticancer herbs is executed by inhibiting the cancer activating enzymes, stimulating DNA repair mechanism, promoting production of protective enzymes, including antioxidant action and by enhancing activity of the immune cells. Certain biological response modifiers derived from herbs are known to inhibit growth of cancer by modulating the activity of specific hormones and enzymes. Some herbs reduce toxic side effects of chemotherapy and radiotherapy. In the following review various plants having anticancer activity have been discussed.

Key words: Anticancer, leukemia, tumors, herbal drugs.

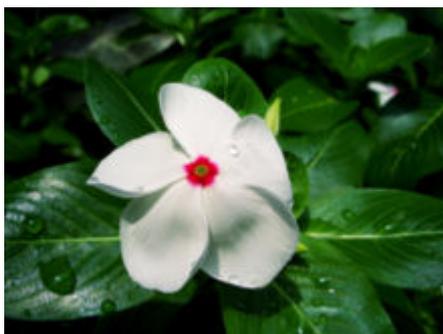
Introduction

Medicinal plants are nature's gift to mankind and are rich ancient heritage of India. Our ancient literature has references of plants reported to cure difficult and incurable diseases. The Aryans of Indus valley wrote three treatises viz., the Rigveda (2000 BC), Atharvaveda (2000-1000BC) and Ayurveda (100-600BC) which mention several medicinal plants and their uses. The Charaka Samhita, an encyclopedia of Indian medicine published at Varanasi, between 1000BC and 100AD, is a comprehensive record of medicinal plants and their uses. Hippocrates rejected magical-ritual treatment of the disease and stated that medicine was a science and not a myth. He is regarded as the "father of modern medicine". A system of medicine is not a discovery, but a gradual evolution during successive periods of history [1].

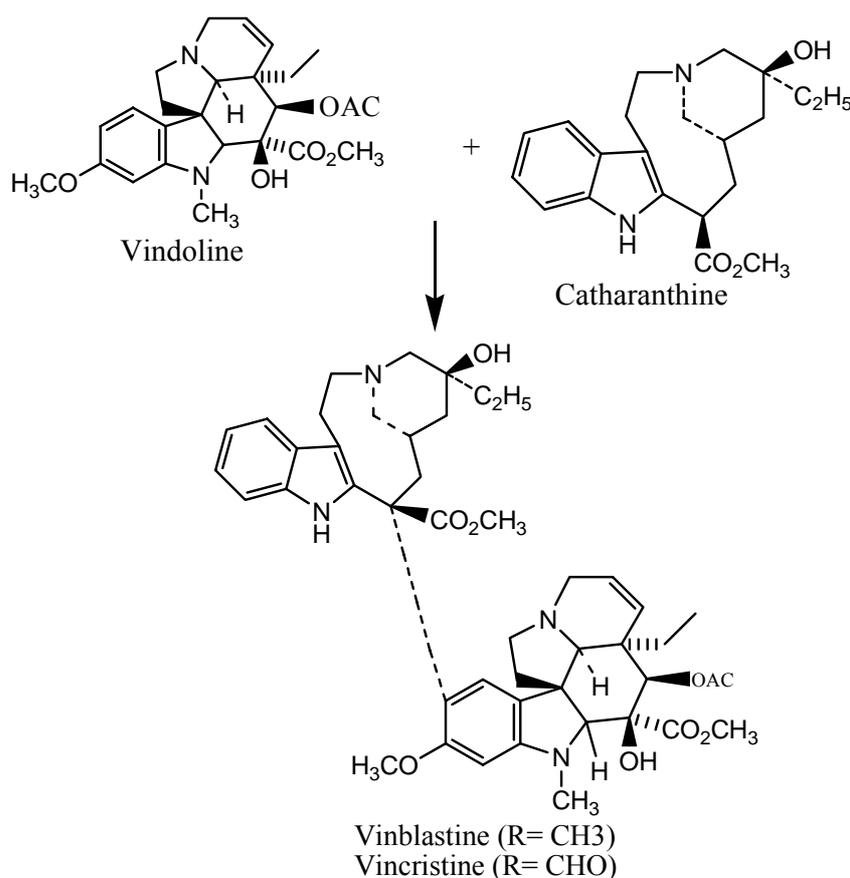
In the present review we are discussing some plants which are used for their anticancer and antitumor activity. Plants having anticancer activity are growing popularly now a day because they contain several anticancer phytochemicals.

The anticancer drugs either kill cancer cells or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy. In addition to their prominent role in leukemia and lymphomas, drugs are used in conjunction with surgery, radiotherapy and immunotherapy in the combined modality approach for many solid tumors, especially metastatic.

Majority of the cytotoxic drugs have more profound effect on rapidly multiplying cells, because the most important target of action are the nucleic acids and their precursors; rapid nucleic acid synthesis occurs during cell division. Many cancer (especially large solid tumors) have a lower growth fraction (lower percentage of cells are in division) than normal bone marrow, epithelial linings, reticuloendothelial (RE) system and gonads. The tissues are particularly affected in a dose-dependent manner by majority of drugs [2].

Vinca rosea (*Catharanthus roseus*) [3]

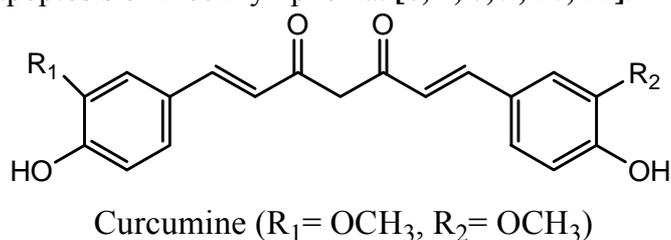
Catharanthus roseus is a perennial tropical plant belonging to the family *Apocynaceae* that produces more than 100 monoterpene indoles including two commercially important cytotoxic dimeric alkaloids used in cancer chemotherapy. These two bis-indole alkaloids, vinblastin and vincristine, accumulate in trace amounts in leaves and are formed from the oxidative coupling of catharanthine and vindoline. Vinblastin kills actively dividing cells in G₁ and M phase and vincristine in the M phase only [4].



Turmeric (*Curcuma longa*) [5]

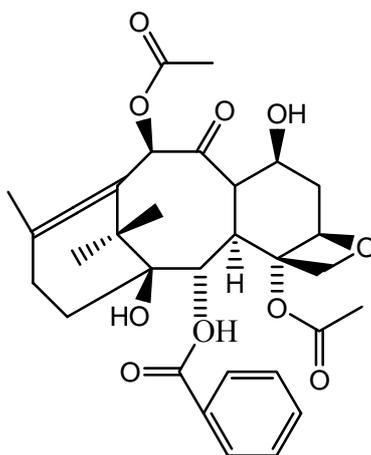
Turmeric consists of dried as well as fresh rhizomes of the plant known as *Curcuma longa* Linn. (*C. domestica*), belonging to the family *Zingiberaceae*. Curcumin, a common dietary pigment possesses a wide range of therapeutic utilities in traditional Indian medicine. Curcumin (difeuryloymethane) is a polyphenolic phytochemical has been currently accepted as a potent anticancer agent. The tumoricidal effect of curcumin has been studied on a wide range of cell lines like mouse sarcoma (S 180), human colon cancer cells (HT-29), human kidney cell line 293 and hepatocellular carcinoma (Hep G2 cells). Curcumin also showed antiproliferative activity on human breast tumor MCF-7 cells.

The tumoricidal action of curcumin is due to the inhibition of protein tyrosine kinase activity, protein kinase activity and arachidonic acid metabolism. Curcumin causes growth arrest and apoptosis of B cell lymphoma. [6, 7, 8, 9, 10, 11].

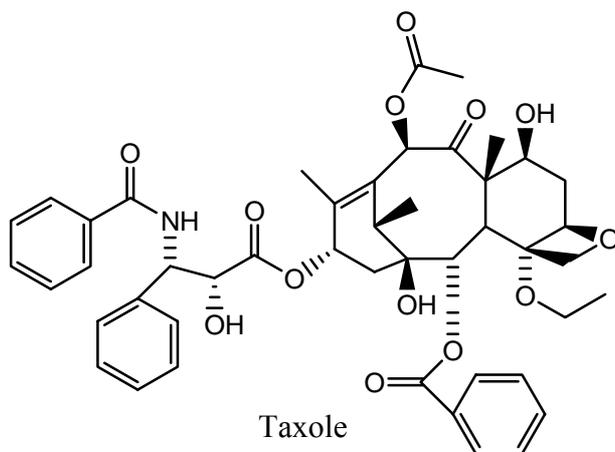
**Taxus (*Taxus baccata*) [12]**

Taxus is a naturally occurring diterpenoid belonging to taxane group of compounds present in genus *Taxus* under family *Taxaceae*. Taxol is a valuable plant-derived drug showing activity against various cancer types. Paclitaxel is a very important anticancer drug commonly called Taxol. Another taxane used as anticancer drug is docetaxel, commonly called Taxotere. The active ingredients in taxol and taxotere are mainly derived via chemical semisynthesis from advanced taxoid 10-deacetyl baccatin III. It has been found that the enzyme activity of secondary metabolic pathways was stimulated, which was particularly responsible for enhanced Paclitaxel production.

Toxoids are complex molecules that are chemically similar to paclitaxel. Paclitaxel enhances polymerization of tubulin: a mechanism opposite to that of the vinca alkaloids. The microtubules are stabilized and their depolymerization is prevented [13].



13-dehydroxy baccatin III



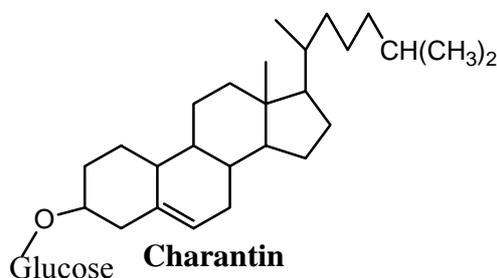
Taxole

Bitter gourd (*Momordica charantia*) [14]

Momordica charantia (MC), a climber belonging to the family *Cucurbitaceae*, is commonly known as bitter gourd or bitter melon in English and karela in Hindi. *Momordica* means, “to bite”-referring to the jagged edges of the leaf, which appears as if bitten [15].

Momordica charantia contains biologically active chemicals that include glycosides, saponins, alkaloids, fixed oils, triterpenes, proteins and steroids. Several phytochemicals such as α & β -momorcharins, momordenol, charantin, charine, cryptoxanthine, cucurbitins, cucurbitacins, cycloartenols and diosgenin etc. have been isolated. α -momorcharin was found to have tumor suppressive properties [16, 17, 18].

Various preliminary studies (*in vitro* as well as *in vivo*) with crude MC extract and its various purified fraction-including MAP 30 (Mitogen activating protein 30) have shown anticancer activity against lymphoid leukemia, choriocarcinoma, melanoma, breast cancer, squamous carcinoma of tongue and larynx, human bladder carcinomas and Hodgkins disease [19, 20, 21].



Gripe weed (Phyllanthus urinaria) [22]

Phyllanthus urinaria is a herbal plant belonging to the genus phyllanthus (*Euphorbiaceae*), is widely distributed in China, Southern India and Southern America. It was tested for its antitumor effect *in vivo* for the first time. The antitumor activity in *P.urinaria* extract was evaluated by its effect on tumor developed in C57BL/6J mice implantation of Lewis lung carcinoma cells. The oral administration of *P.urinaria* to mice caused significant inhibition of tumor development with lower occurrence rate and markedly reduced tumor size. *Phyllanthus amarus* protected the liver from hepatocarcinogenesis induced by N-nitrosodiethylamine in animal models. Roots of *Phyllanthus acuminatus* also has been shown to inhibit the growth of murine P-388 lymphocytic leukemia and B-16 melanoma cell lines. Recently, 7' hydroxy 3',4',5,9,9'-Pentamethoxy-3,4-methylene dioxy lignan isolated from the ethyl acetate extract of *P.urinaria* was shown to exhibit anticancer activity by inducing apoptosis through the inhibition of telomerase activity and Bcl-2 expression. Since the inhibition of angiogenesis could result in a suppression of tumor growth. It was also investigated in the potential anti-angiogenic effect of *P. urinaria* by examining the neovascularization of the tumor developed in C57BL/6J mice with the implantation of Lewis lung carcinoma cells [23, 24, 25, 26, 27].

Turpeth (*Operculina turpethum*) [28]

Operculina turpethum (Linn) Silva Manso belongs to the family *Convolvulaceae* and is commonly known as Indian

Jalap in Indian medicine. Reactive oxygen species (ROS) directly or indirectly involved in multistage process of carcinogenesis. Antioxidant activity of methanolic extract of *Operculina turpethum* stems (MEOT) on 7,12-dimethyl benzo(a)anthracene (DMBA) induced breast cancer was investigated in female sprague-Dawley rats.

Polycyclic aromatic hydrocarbons (PAHs) are products formed by incomplete combustions of organic matter. Sources of PAHs include industrial and domestic oil furnaces, gasoline and diesel engines. PAHs are widely distributed in our environment and are implicated in various types of cancer. Enzymatic activation of PAHs leads to the generation of active oxygen species such as peroxide and superoxides anion radicals, which include oxidative stress in the form of lipid peroxidation.[29, 30].

Antioxidant acts as free radical scavenger inhibiting LPO and other free radical-mediated processes there by protecting the human body from various diseases. *O.turpethum* contains bioactive compounds like turpethin, α and β rhamnase, fructose, scopoletin, etc. Turpethinic acids (A, B, C, D and E) are isolated from the resin of the plant and lupeol, betulin, and β -sitosterol are isolated from stem. Recently, their structurally related compounds like lupeol, betulin and sitosterol have been identified to possess anticancer activity. Sitosterol possesses cytotoxic and anticancer activity in MCF-7 breast cancer cell lines [31, 32, 33, 34].

Ginger (*Zingiber officinalis*) [35]



Zinger consists of rhizomes of *Zingiber officinalis* Roscoe, belongs to a tropical and sub-tropical family - *Zingiberaceae*, originating in South-East Asia and introduced to many parts of the globe, has been cultivated for thousands of years as a spice and for medicinal purposes [36].

The volatile oil component in ginger consists mainly of

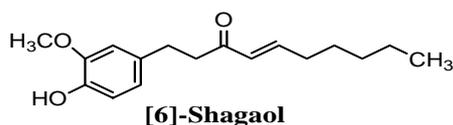
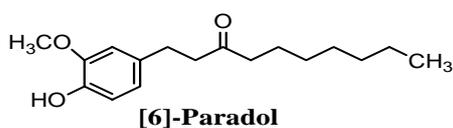
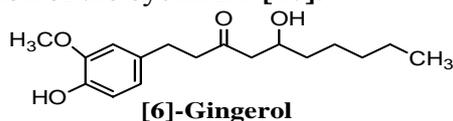
sesquiterpene hydrocarbons, predominantly zingerene, curcumene and farnesene with lesser amounts of bisabolene and b-sesquiphellandrene [37].

The non-volatile pungent principles are gingerols, shogales, paradols and zingerone that produce a “hot” sensation in the mouth. The gingeroles, a series of chemical homologs differentiated by the length of their unbranched alkyl chains, were identified as the major active components in the fresh rhizome [37].

The anticancer properties of ginger are attributed due to the presence of certain pungent vallinoids viz. 6-gingerol and 6-paradol, as well as some other constituents like 6-shagaol, zingerone etc. [38].

The alcoholic extract of the ginger inhibited cell growth at concentration of 0.2-1mg/ml *in vitro* and 0.12-0.3mg/ml in tissue culture as well as inhibited thymidine uptake into DNA. *Helicobacter pylori* is the primary etiological agent associated with peptic ulcer disease and development of gastric and colon cancer. The anti-H pylori effects of ginger and its constituents were tested *in vitro* [39].

6-Gingerol inhibited angiogenesis of human endothelial cells and caused cell cycle arrest in the G1 phase through the down-regulation of the cyclin D1 [40].



Jequirity (*Abrus precatorius*) [41]

Abrus precatorius is commonly known as Jequirity, Crab's eye, Rosary pea, and Licorice belong to family- *Leguminosae-papilionaceae*. It is a legume with long, pinnate-leafleted leaves, also known as Gunja in Sanskrit. Plant is native to Indonesia and grows in tropical and subtropical areas of world where it has been introduced. From the seeds of *Abrus precatorius* abrus abrin is isolated, which is a hetero-dimeric glycoprotein of 63-k Da molecular weight. Abrus abrin is composed of two nonidentical polypeptied chains (A- and B-chain) cross-linked through a single disulfide bond [42].

It belongs to the type II ribosome inactivating protein family (RIP II) with a protein synthesis inhibitory concentration (IC_{50}) of 10 ng/ml and a lethal dose (LD_{50}) of 20 μ /Kg body weight in mice [43].

The abrin binds to the cell-surface receptors containing terminal galactose through the B subunit, enter cells by receptor mediated endocytosis and A subunit inhibits the protein synthesis by modification of the ribosomal subunits of the cells. In addition, abrin induces apoptosis followed by the inhibition of protein synthesis. The apoptosis is triggered through intrinsic mitochondrial pathway by caspase 3-activation involving mitochondrial membrane potential damage and reactive oxygen species production [44, 45].

Peptides derived from larger molecules that are important modulators in cancer regression are becoming leads for development of therapeutic drugs. It has been reported that abrus abrin showed *in vitro* and *in vivo* antitumor properties by the induction of apoptosis. The study was designed to evaluate the *in vivo* therapeutic effectiveness of abrin-derived peptide (ABP) fraction in Dalton's lymphoma (DL) mice model. The lethal dose (LD_{50}) of ABP was found to be 2.25mg/kg body weight and further the acute toxicity was determined with sublethal doses in normal mice. The

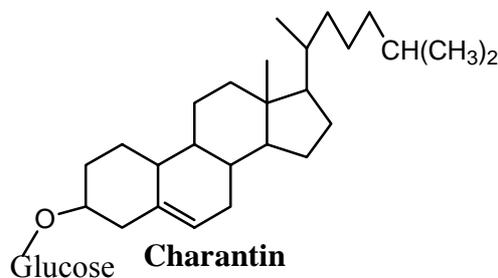
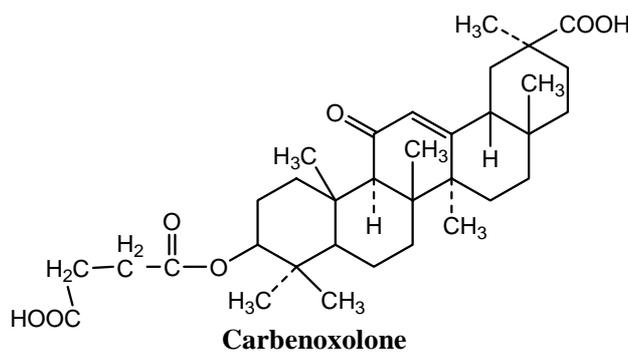
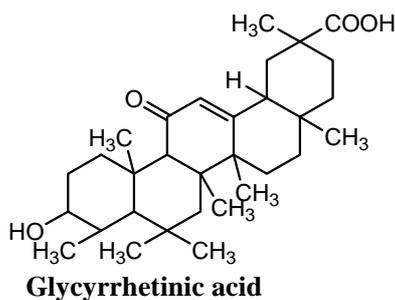
sublethal dose of ABP showed very significant growth inhibitory properties *in vivo* DL mice model. There were 24%, 70.8% and 89.7% reductions in DL cell survival in 25, 50 and 100 µg/kg body weight of ABP, respectively [46, 47].

Liquorice (*Glycyrrhiza glabra*) and **Yellow sophora** (*Sophora flavescens*) [48, 49]



Glycyrrhiza (Liquorice) consists of dried, peeled and unpeeled, roots and stolon of *Glycyrrhiza glabra* Linn., belonging to the family *Leguminosae*. The liquorice plant is a legume (related to beans and peas), native to southern Europe and parts of Asia. *Sophora flavescens*, a perennial herb, is a species of plant in the genus *Sophora* belongs to the family *papilionaceous*. It is a traditional Chinese medicine. Matrine (Mat), a component extract from *Sophora flavescens* Ait. has a wide spectrum of pharmacological activities. Glycyrrhizin (Gly), a major active constituent of liquorice (*Glycyrrhiza glabra*) root has various pharmacological effects. Glycyrrhizinic acid is a glycoside and on hydrolysis yields glycyrrhetic acid, which has a triterpenoid structure. Gly and Mat is ancillary drug used clinically in china for protection of liver function and treatment of tumors. Combined use of Gly and Mat could offer better liver protection and antihepatocarcinogenic effects than Gly or Mat alone, and whether it could reduce the adverse effects of Gly alone by acetaminophen induced hepatotoxicity, diethylnitrosamine–induced hepatocarcinogenesis [50, 51, 52].

Glycyrrhizin (Gly) molecular formula: (C₄₂H₂₄N₂O), a triterpene glycoside and a conjugative compound of enoxolone and glucuronic acid as an active component of liquorice has been used in prevention of liver cancer [53, 54, 55, 56, 57].



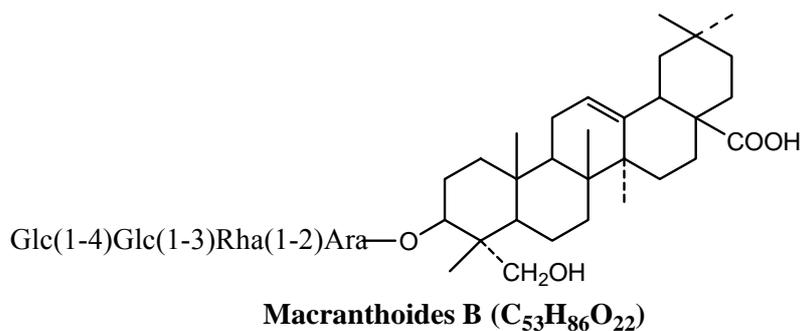
***Lonicera macranthoides* [58]**



Lonicera macranthoides is a species of Flos *Lonicera*, belonging to the family *Caprifoliaceae*. It is found in the Asian countries. Macranthoside B (MB) (3-O- β -D-glucopyranosyl (1-4)- β -D-glucopyranosyl (1-3)- α -L-rhamnopyranosyl (1-2) α -L-arab inopyranosyl hederagenin, MB) is a hederagenin saponin extracted from flower buds of *Lonicera macranthosides*. The anticancer effect of MB was tested both *in vitro* and *in vivo* using cell proliferation assays and xenograft tumor assays. MB inhibits the proliferation of

various kinds of cancer cells with IC_{50} values in the range of 10-20 μ M. Moreover, the volume and weight of xenograft tumors in nude mice treated with 5mg/kg MB were decreased remarkably compared to those of the vehicle control group. Further more, DAPI (4', 6-diamidino-2-phenylindole) staining and flow cytometry analysis with annexin V/PI (propidium iodide) double staining revealed that more apoptotic cells were observed following MB treatment. In addition, degradation of PARP (Poly-ADP-ribose polymerase), and activation of the caspase for intrinsic pathway were observed. MB exhibited strong antitumor effect and mitochondrion-mediated apoptosis induction in it.

MB could inhibit the proliferation of tumor cells and suppressed the growth of HepG2 human hepatocarcinoma in xenograft tumor in athymic BALB/Ca nude mice [59, 60, 61, 62, 63].



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