



Natural Products Effective for Management of Cancer - Review

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Abstract

Cancer is one of the foremost causes of death and worldwide the numbers of cases of cancer are increasing progressively. Presently numerous medicines existing in the market to treat the various types of cancer but no drug is found to be fully effective and safe. The synthetic drugs are associated with huge adverse effects and patient also vanish immune system. Natural products have been the backbone and proved effective and safe in the treatment and management of cancers. Natural products remain an important source of new drugs, new drug leads and new chemical entities. The plant based drug discovery resulted mainly in the development of anticancer agents including plants, marine organisms and micro-organisms sources. Consequently, natural products are likely to deliver numerous of the chief structures with potent anticancer activity. These novel compounds enhanced anticancer activity by transforming in suitable dosage form. In this review, we emphasized the natural products traditionally used as anti-cancer agents and the new plant species scientifically validated for the anticancer activity.

1 Introduction

Cancer is one of the ten leading causes of mortality in India. It is estimated that the point prevalence for cancer in India is approximately 2-2.5 million. The incidence of detection of new cases of cancer in India is estimated to be more than seven lakh per year. Similarly, and cancer-related mortality is estimated to be more than three lakh per year in our country. The National Cancer Registry Program of the Government of India states that the leading sites of cancer are oral cavity, lungs, esophagus and stomach among men and cervix, breast and oral cavity amongst women. It also states that the most common causes of cancer-related mortality are the cancers of oral cavity and lungs in males and that of cervix and breast in females which account for more than 50% of all cancer-related deaths in India.

Cancer is defined as a disease that is caused by an uncontrolled division of abnormal cells in a part of the body. Cancers, derived from the Latin word for crab, i.e., they adhere to any part that they seize in an obstinate manner, similar to a crab's behavior. Hence the cancerous growth can invade and destroy adjacent structures and spread to distant sites

(metastasize) to cause death. Cancer can affect all living cells in the body, at all ages and in both genders.

In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous. Benign tumors do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body. They will only cause a problem if they grow very large, becoming uncomfortable or press on other organs - for example a brain tumour inside the skull. Malignant tumours are faster growing than benign tumours and have the ability to spread and destroy neighbouring tissue. Cells of malignant tumours can break off from the main tumour and spread to other parts of the body through a process known as metastasis.

2 Various Types of Cancer^{1,2}

2.1 Leukemia

Leukemia or leukaemia is a type of cancer of the blood or bone marrow characterized by an abnormal increase of immature white blood cells called "blasts." Leukemia is a broad term

covering a spectrum of diseases. In turn, it is part of the even broader group of diseases affecting the blood, bone marrow, and lymphoid system, which are all known as hematological neoplasms.

leukemia is subdivided into acute and chronic leukemia:

Acute leukemia is characterized by a rapid increase in the number of immature blood cells. Crowding due to such cells makes the bone marrow unable to produce healthy blood cells. Immediate treatment is required in acute leukemia due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. Acute forms of leukemia are the most common forms of leukemia in children.

Chronic leukemia is characterized by the excessive build up of relatively mature, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal, resulting in many abnormal white blood cells. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group.

2.2 Carcinoma

Carcinoma is the medical term for the most common type of cancer occurring in humans. Put simply, a carcinoma is a cancer that begins in a tissue that lines the inner or outer surfaces of the body, and that generally arises from cells originating in the endodermal or ectodermal germ layer during embryogenesis. More specifically, a carcinoma is tumor tissue derived from putative epithelial cells whose genome has become altered or damaged to such an extent that the cells become transformed, and begin to exhibit abnormal malignant properties. Carcinomas may invade the surrounding tissues and organs and metastasise to the lymph nodes and other areas of the body. The most common forms of cancer in this group are breast, prostate, lung and colon cancer.

2.3 Sarcoma

A type of malignant tumour of the bone or soft tissue (fat, muscle, blood vessels, nerves and other connective tissues that support and surround organs). The most common forms of sarcoma are leiomyosarcoma, liposarcoma and osteosarcoma.

2.4 Lymphoma

Lymphoma is a cancer of the lymphatic system, which runs all through the body, and can therefore occur anywhere. The two main forms are non-Hodgkin's which begins with uncontrolled growth of the - white blood cells -lymphocytes - of the immune system) and Hodgkin's lymphoma in which cells of the lymph nodes become cancerous.

3 Causes³⁻⁶

Cancer-causing substances called carcinogens. Genes are coded messages inside a cell that tell it how to behave. Mutation or changes to the gene, such as damage or loss, can alter how that cell behaves. For example, a mutation may mean that too much protein is made, or that protein is not made at all. Significantly, there needs to be a number of genetic mutations within a cell before it becomes cancerous. Something that damages a cell, changing its behaviour and makes it more likely to be cancerous is called a 'carcinogen'.

3.1 Age

Many types of cancer become more prevalent with age. The longer people live, the more exposure there is to carcinogens and the more time there is for genetic changes or mutations to occur within their cells.

3.2 Genetics

Some people are unfortunately born with a genetically inherited high risk for a specific cancer ('genetic predisposition'). This does not mean developing cancer is guaranteed, but a genetic predisposition makes the disease more likely.

3.3 Immune system

People who have weakened immune systems are more at risk of developing some types of cancer. This includes people who have had organ transplants and take drugs to suppress their immune systems to stop organ rejection, plus people who have HIV or AIDS, or other medical conditions which reduce their immunity to disease.

Lifestyle and environmental causes are to a large extent controllable or avoidable. Examples include:

3.4 Bodyweight, diet and physical activity

Cancer experts estimate that maintaining a healthy bodyweight, making changes to our diet and taking regular physical activity could prevent about one in three deaths from cancer. Many people eat too much red and processed meat and not enough fresh fruit and vegetables. This type of diet is known to increase the risk of cancer.

3.5 Overweight or obesity

'Obese' means being more than about 25% overweight. Overweight or obese people have an increased risk of bowel and pancreatic cancer, probably due to a tendency towards higher insulin levels. Obesity can also increase the risk of cancer of the foodpipe (oesophageal cancer), kidney and gallbladder cancer, as well as breast or womb (uterine) cancer in women

3.6 Alcohol

The evidence that all types of alcoholic drinks are a cause of a number of cancers is now stronger than ever before. Alcohol can increase the risk of a number of cancers, including mouth, throat (which includes pharyngeal cancer), laryngeal and cancer of the foodpipe, plus liver, breast and bowel cancer (in men). Even moderate alcohol intake increases the risk of cancer⁷.

3.7 Tobacco⁸

Tobacco smoke contains at least 80 different cancer-causing substances (carcinogenic agents). When smoke is inhaled the chemicals enter the lungs, pass into the blood stream and are transported throughout the body. This is why smoking or chewing tobacco not only causes lung cancer and mouth cancers, but is also related to many other cancers. The more a person smokes, the younger they start, and the longer they keep smoking, all further increase the risk of cancer.

3.8 Ionising radiation

Manmade sources of radiation can cause cancer and are a risk for workers. The main risk is however, prolonged and unprotected exposure to ultraviolet radiations from the sun which can lead to melanoma and skin malignancies. Fair skinned people, those with lot of moles or who have a relative who has had melanoma or nonmelanoma skin cancer, are at highest risk.

3.9 Work place hazards

Some people risk being exposed to a cancer causing substance because of the work that they do. For example, workers in the chemical dye industry have been found to have a higher incidence than normal of bladder cancer. Asbestos is a well-known work place cause of cancer - particularly a cancer called mesothelioma, which most commonly affects the covering of the lungs (pleura).

3.10 Infection

A proportion of cancers can be caused by infection with a virus. However, this does not mean that these cancers can be caught like an infection; rather the virus can cause changes in cells that make them more likely to become cancerous⁹.

Chronic inflammation resulting from noninfectious sources can also lead to cancer.

4 Herbs with anticancer activity

Herbal medicines have a vital role in the prevention and treatment of cancer and medicinal herbs are commonly available and comparatively economical. A great deal of pharmaceutical research done in technologically advanced countries like USA, Germany, France, Japan and China has considerably improved quality of the herbal medicines used in the treatment of cancer. Medicinal herbs are also significant

source of synthetic and herbal drugs. So far, pharmaceutical companies have screened more than 25,000 plants for anti-cancer drugs. The list of plants along with their chemical constituents responsible for anticancer activity are given below;

Aloe vera¹⁰

Aloe vera contains aloe-emodin, which activates the macrophages to fight cancer. Aloe vera also contains acemannan, which enhances activity of the immune cells against cancer and the plant has been found to inhibit metastases.

Aegle marmelos

Lupeol, isolated from pulp and seeds of *A. marmelos*, possesses strong anticancer activity against breast cancer, malignant lymphoma, malignant melanoma, malignant ascites and leukaemia. *A. marmelos* possesses significant antioxidant activity and reduces side effects of chemotherapy and radiotherapy.

Allium cepa

Allium cepa contain Diallyl disulphide, quercetin flavonoid, allicin, allin inhibits stomach cancer, and quercetin may cure lung and other Cancers¹¹.

Andrographis paniculata

Andrographolide (active diterpine component), isolated from whole plant of *A. paniculata*, has immunoenhancing and strong anticancer activity against cancers of breast, ovary, stomach, colon, prostate, kidney and nasopharynx, malignant melanoma, and leukaemia.

Alpinia galanga

Acetoxy-chavicol-acetate, Pinocembrin and Galangin isolated from *Alpinia galanga* possesses significant anticancer activity against cancers of breast, lung, stomach, colon and prostate, multiple myeloma, and leukaemia¹².

Aphanamixis polystachya

Amooranin (a triterpene acid), isolated from *A. polystachya* stem bark, inhibits growth and spread of breast and cervical cancers by arresting G2/M phase of the cell cycle and by inducing apoptosis.

Artocarpus obtusus

Artocarpus obtusus consists three new xanthenes, pyranocycloartobioxanthone A, dihydroartoinonesianin C, and pyranocycloartobioxanthone B, which exhibit anticancer activity. The compounds were subjected to antiproliferative assay against human promyelocytic leukemia (HL60), human chronicmyeloid leukemia (K562), and human estrogen receptor (ER+) positive breast cancer (MCF7) cell lines¹³.

Azadirachta indica

Azadirachta indica contains liminoids, Nimbolide which exhibit anticancer activity. Liminoids regress growth and spread of various cancers, e.g., cancers of breast, lung, liver, stomach, prostate and skin. Ethanolic extract of *A. indica* inhibits growth and spread of prostate cancer by inducing apoptosis and its antiandrogenic effect. This herb reduces side effects of chemotherapy and radiotherapy.

Bauhinia variegata

Cyanidin glucoside, malvidin glucoside, peonidin glucoside and kaempferol galactoside, isolated from root, stem bark and flower of *B. variegata*, inhibit growth and spread of various cancers, e.g., cancers of breast, lung, liver, oral cavity and larynx, and malignant ascites.

Berberis vulgaris

B. vulgaris root bark contains berberine, berbamine which possesses anticancer properties.

Blumea balsamifera

Leaves of *Blumea balsamifera* consist of compounds, two dihydroflavonols (dihydroquercetin-4'-methyl ether and dihydroquercetin-7,4'-dimethyl ether), two flavanones (5,7,3',5'- tetrahydroxyflavanone and blumeatin), three flavonols (quercetin, rhamnetin and tamarixetin), two flavones (luteolin and luteolin-7-methyl ether) which possesses anticancer properties. It reduced the level of a proliferation related ligand which stimulates tumor cell growth. *B. balsamifera* extract is also effective against human hepatocellular carcinoma cells.

Boerhaavia diffusa

Liriodendrin, Punarnavine, and Two rotenoids isolated from *B. diffusa*, boeravinones G and H, have been found to potently inhibit the drug efflux activity of breast cancer resistance protein (BCRP/ABCG2), a multidrug transporter responsible for cancer cell resistance to chemotherapy¹⁴.

Catharanthus roseus

Catharanthus roseus consist vinblastine (leurocristine), alstonine, ajmalicine and reserpine. Vinca alkaloids execute the anticancer effect. Vinblastine is used in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma and cancers of the kidney. Vincristine is usually given in combination with other anticancer agents to treat acute lymphocytic leukaemia, Wilm's tumour, neuroblastoma, lymphoma and cancers of the breast.

Citrus limon

Citrus limon (Nibu) fruit contains flavonoid, flavone, limonoid, limonene, nobiletin and tangeretin. The flavonoid, tangeretin and nobiletin are potent inhibitors of tumor cell growth and can activate the detoxifying P450 enzyme system. Limonoids inhibit

tumour formation by stimulating the GST enzyme. The limonene (a terpenoid) also possesses anticancer activity. Nibu fruit is used for inhibition of human breast cancer cell proliferation and delaying of mammary tumorigenesis. It is also used in metastasis and leukemia

Curcuma longa

Curcuma longa contains curcumin, which inhibits the growth of cancer by preventing production of harmful eicosanoid such as PGE-2. The anticancer effect of curcumin has been demonstrated in all the steps of cancer development, i.e. initiation, promotion and progression of cancer. Curcumin is used to treat squamous cell carcinoma of the skin and the ulcerating oral cancer¹⁵.

Embllica officinalis

E. officinalis fruit contains Emblicanins A and B (tannins), possess strong anticancer properties. *E. officinalis* inhibits growth and spread of various cancers, including that of the breast, uterus, pancreas, stomach and liver, and malignant ascites. Amla fruit contains 18 compounds that inhibit growth of gastric, uterine and breast cancers. It enhances natural killer cell activity in various tumours.

Fragaria vesca

Flavonoid, tannin, borneol, ellagic acid, vitamin C, bioflavonoid and chalcone of *F. vesca* leaf and fruit possess antioxidant and anticancer activities. *F. vesca* acts against various cancers.

Ginkgo biloba

Ginkgetin and ginkgolides (A and B), isolated from *G. biloba*, inhibits growth and spread of various aggressive cancers such as invasive oestrogen-receptor negative breast cancer, glioblastoma, hepatocellular carcinoma, and cancers of ovary, colon, prostate and liver by inducing apoptosis¹⁶.

Glycyrrhiza glabra

Glycyrrhiza glabra contain Licochalcone- A, inhibits growth and spread of various cancers particularly the androgen-refractory prostate cancer by inducing apoptosis and arresting cancer cells division. Triterpenoid saponins (e.g., glycyrrhizin and glabranin) also isolated from *G. glabra* inhibits growth and spread of lung cancer and fibrosarcomas¹⁷.

Ipomoea batatas

The derivatives (viz. chlorogenic, dicaffeoylquinic and tricaffeoylquinic acids) of caffeoylquinic acid contained in *Ipomoea batatas* tubers (Shakarkand) have potential cancer chemoprotective effect. 4-Ipomeanol (a furanoterpenoid) isolated from *I. batatas* has been found to exhibit anticancer activity against non-small cell lung cancer lines

Morinda citrifolia

Damnacanthol, NB10 and NB11, isolated from *M.citrifolia* fruit, possess strong anticancer activity against various cancers, particularly lung cancer and sarcomas¹⁸.

Moringa peregrina

Apigenin is a flavone present in *Moringa peregrina*. It demonstrates cytotoxic activities against breast cancer cell lines (MCF 7), colon cell line (HCT 116), and its cytotoxic activity is comparable to that of doxorubicin. Apigenin is also being considered as a mediator for chemoprevention in the cancerous process and induces a process of autophagia but may induce resistance against chemotherapy. It induces apoptosis in human colon cancer cells reduces azoxymethane (AOM) induced aberrant crypt foci (ACF) formation in male Sprague-Dawley rats, and increases apoptosis which may contribute to the colon cancer prevention.

Moringa oleifera

Moringa oleifera contains a unique combination of isothiocyanate and glucosinolates. Isothiocyanates have antitumor activity in cancers of the lung, breast, skin, esophagus, and pancreas. Studies have found that Moringa compounds, benzyl isothiocyanate (BITC) and phenethyl isothiocyanate (PEITC) induced apoptosis in ovarian cancer cells in vitro¹⁹.

Nigella sativa

Thymoquinone and dithymoquinone, isolated from *Nigella sativa* seeds, have strong anticancer activity against various cancers, including cancers of colon, prostate, pancreas and uterus, malignant ascites, malignant lymphoma, malignant melanoma, sarcomas, and leukaemia. *N. sativa* kills cancer cells by binding to the asialofectin (lectin) on the surface of cancerous cells, causing their aggregation and clumping.

Ocimum sanctum

O. sanctum leaves contain volatile oils Eugenol, orientin and vicenin inhibit growth and spread of various cancers such as breast cancer, liver cancer and sarcomas, particularly fibrosarcoma by blocking supply of oxygen and nutrients to cancer cells and killing them by starving²⁰.

Oldenlandia diffusa

The whole plant of *O.diffusa* contains oldenlandosides, stigmasterol, ursolic acid, oleanolic acid, beta-sitosterol, p-coumaric acid and flavonoid glycosides. Ursolic acid inhibits growth and spread of various cancers such as cancers of lung, ovary, uterus, stomach, liver, colon, rectum and brain, malignant melanoma, malignant ascites, lymphosarcoma, and leukaemia.

Oroxylum indicum

The bioactive constituents present in the plant are baicalin, Chrysin, baicalein-7-O-glucoside and baicalein which inhibited

in vitro proliferation of HL-60 cells. The flavanoid baicalein was found to be an active component that induced apoptosis in HL-60 cell line²¹.

Panax ginseng

Ginsenosides (panaxadiol and panaxatriol saponins), isolated from *P. ginseng*, inhibits the growth and spread of various cancers such as cancers of breast, ovary, lung, prostate and colon, renal cell carcinoma, malignant melanoma, malignant lymphoma, and leukaemia²².

Pfaffia paniculata

The major constituents of *Pfaffia paniculata* are saponins, stigmasterol, sitosterol, allantoin, pfaffic acid and triterpenoid saponin. The Pfaffic acid, hydrolytic product of the saponins has inhibitory action on the growth Melanoma B-16, Hela S-3 and Lewis lung carcinoma cells in vitro²³.

Plumbago zeylanica

Plumbagin, isolated from *P. zeylanica* root inhibits growth and spread of breast cancer, liver cancer, fibrosarcoma, malignant ascites and leukaemia by inhibiting cancer cell proliferation.

Prunella vulgaris

Ursolic acid and oleanolic acid, isolated from *P. vulgaris*, inhibit growth and spread of various cancers such as cancers of the breast, cervix, lung, oral cavity, oesophagus, stomach, colon and thyroid, malignant lymphoma, intracranial tumours and leukaemia.

Psoralea corylifolia

Bavachinin, corylfolinin and psoralen, isolated from *P. corylifolia*, possess strong anticancer activity against lung cancer, liver cancer, osteosarcoma, fibrosarcoma, malignant ascites and leukaemia.

Punica granatum

Fruit (Anar) of *P. granatum* contains alkaloids, anthocyanidines and vitamin C. *P. granatum* acted against solid tumour and ascites tumour in albino mice.

Rheum officinale

The major pharmacologic constituents of *Rheum officinale* are anthraquinone and bianthrone derivatives which possess anti-tumor activity²⁴.

Rubia cordifolia

Root of *R. cordifolia* contains rubidianin, rubiadin, rosemary acids, carnosic acid, purpurin, pseudopurpurin, alizarin and xanthopurpurin which inhibits growth and spread of breast, ovary, cervix, colon and lung cancers, malignant ascites, malignant lymphoma, malignant melanoma (B16 melanoma), P388 cells, L1210 cells, sarcoma, and leukaemia.

Saxifraga stolonifera

Saxifraga stolonifera contains nC31H64, (n-C17H35)2CO, b-sitosterol, nC29H60, and quercetin which showed anticancer activities on human gastric carcinoma cell line BGC-823. Quercetin was found to exhibit high effect on BGC-823 cells and brought out morphological changes on the tumor cells. Quercetin can also induce apoptosis on human promyelocytic leukemia cells (HL-60 cells) and kidney tubule epithelial cells (NRK-52E). Quercetin seems to hold a promising component for inducing apoptosis in BGC-823 cells and can be used as a chemopreventive and therapeutic agent for cancers²⁵.

Solanum nigrum

Solanum nigrum contains solamargine, solasonine, spirostane, furostane, spirosolane, Pregnane and Glycoproteins which inhibit growth and spread of various cancers, including breast, liver, lung and cyst cancers, choriocarcinoma or chorioadenoma, and leukaemia. Solanine and solamergine have very strong anticancer actions against murine tumours¹¹.

Tinospora cordifolia

Stem bark and fruit of *T. cordifolia* contain berberine, tinosporine, giloin, giloinin, Sesquiterpenes and diterpenes, inhibit growth and spread of various cancers, including cancers of lung, cervix and throat, and malignant ascites.

Viscum album

Lectins (e.g., viscumin), polypeptides (viscotoxins) and phenolic compounds (e.g., digallic acid), isolated from *V. album* inhibit growth and spread of various cancers, including that of breast, cervix, ovary, lung, stomach, colon, rectum, kidney, urinary bladder and testis, malignant melanoma, sarcoma, fibrosarcoma, malignant ascites, lung metastasis, and leukaemia by inducing apoptosis and antiangiogenesis activity¹¹.

Withania somnifera

Withania somnifera contains withanolides, Withaferin A and withanolide D inhibit growth of breast, central nervous system, lung, and colon cancer. Plant also contain withaniol, acylsteryl glucosides, starch, reducing sugar, hantreacotane and ducitol which enhances the therapeutic effect of radiotherapy²⁶.

Zingiber officinalis

Zingiber officinalis rhizomes rich of gingerols-phenolic antioxidants that inhibit various cancers. The anticancer properties of ginger are attributed to the presence of certain pungent vallinoids, viz. [6]-gingerol and [6]-paradol, as well as some other constituents like shogaols, zingerone etc. Ginger also contains curcumin, which assists in the elimination of cancer causing substances from the body²⁷⁻²⁸.

5 Conflict of interests

The authors have no current conflict of interests in this work.

6 Author's contributions

AC and SS carried out literature review and draft the manuscript. All authors read and approved the final manuscript.

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