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Medicinal Plants Used as Anticancer Agents: A Review

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ABSTRACT

The present review gives information about the common medicinal plants in India possessing anticancer properties. Large numbers of synthetic drugs with anticancer property are available in practice but their side effects as well as the drug interactions made restrictions in its usage. The wide therapeutic effects with the fewer side effects of herbal medicines are now gaining attention as important sources of potent anticancer agents. Many medicinal plants contain various secondary metabolites which include alkaloids, flavonoids, phenolics, tannins etc. which are responsible for the antioxidant and anticancer properties. In this review, we have summarized the current advancements in the research of some common medicinal plants possessing anticancer properties.



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INTRODUCTION

Major part of all the traditional systems of medicine constitutes herbal drugs. From time immemorial, the plants have been used for medicine due to their ease in availability, accessibility and all the more it is less expensive. Natural products have traditionally provided most of the drugs in use. Despite the achievements of synthetic chemistry and the advances towards rational drug design, natural products continue to be essential in providing medicinal compounds and as starting material for the development of synthetic analogues. With the increasing interest in the reservoir of untested natural products, many future drug developments will be based on natural products.¹

The process of cancer development in humans generally takes many years through initiation, promotion and progression. For the control of early cancer development, cancer chemoprevention is highly desirable. Cancer chemoprevention means the use of natural or synthetic agents to reverse, suppress or prevent carcinogenic progression to invasive cancer.² The WHO has also recommended the initiation of studies to identify and characterize new herbal preparations from traditionally known plants and the development of new effective therapeutic agents especially in the areas where we lack safe modern drugs to treat chronic diseases.³

Cancer is a serious health problem showing significant impact on human health care system, even with advancements in diagnosis, prevention and therapy, cancer still affecting millions of people worldwide. According to GLOBOCAN 2018, Asia accounts for nearly half of the new cancer cases and more than half of cancer deaths. Estimated suggest that Asia and Africa have a higher proportion of cancer deaths (7.3% and 57.3% respectively) compared with their incidence (5.8% and 48.4% respectively).⁴

Ancient people were very much aware of the rich potential of herbs curing different types of ailments. A substance with pronounced antioxidant and anti-inflammatory effects is anticipated to act as an antitumor promoter.⁵ Nature has bestowed on us a very rich botanical wealth and a large number of diverse types of plants grow wild in different parts of the country. Our knowledge of medicinal plants has mostly been inherited traditionally and the uses of plants for curing various ailments are not confined to the doctors only but several households as well. There is a growing tendency all over the world to shift from synthetic to

natural based products including medicinal plants. It is also timely now to consider neglected and little known medicinal plants.⁶

India is the largest producer of medicinal plants and is rightly called the Botanical garden of the world. Among the 8000 species of the medicinal plants, Indian accounts for almost 50% of it. In recent years, researches on plant based traditional medicine information have gained considerable interest. Even though many plants have been used by traditional healers, many of them do not have scientific support for their anticancer activity. Current literature review on medicinal plants possessing anticancer property provided enormous beneficial evidences that increase the demand for medicinal plants in the treatment of cancer.

Common medicinal plants possessing anticancer property

1. *Aloe vera*

Aloe vera is a perennial succulent belonging to the Liliaceae family and is called the healing plant or the silent healer. It grows mainly in the dry regions of Africa, Asia, Europe and America. In India, it is found in Rajasthan, Andhra Pradesh, Gujarat, Maharashtra and Tamil Nadu. *Aloe vera* contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, anthraquinone glycosides and amino acids.⁷⁻¹¹ *Aloe vera* juice enables the body to heal itself from cancer and also from the damage caused by radio and chemotherapy that destroys healthy immune cells crucial for the recovery. Emodin, an anthraquinone glycoside, has the ability to suppress or inhibit the growth of malignant cancer cells making it to have antineoplastic properties.¹² The role of *Aloe* in carcinogenicity has not been evaluated well. The chronic abuse of anthranoid-containing laxatives has been hypothesized to play a role in colorectal cancer.¹³ *Aloe vera* tincture and melatonin administration was studied as standard therapy against metastatic solid tumors.¹⁴

2. *Allium sativum*:

Allium sativum belongs to the family Alliaceae and native to the region between Mediterranean and China. It contains ajoene, allicin, alliin, allixin, γ -glutamyl-S-2-propenyl cysteine, diallyl disulfide, methyl allyl disulfide, S-allyl-cysteine and 1,2-vinyldiithin. Allicin shows antitumor activity in L5178Y lymphoma bearing mice. Methanolic extract of *A. sativum* (MEAS) shows anticancer activity against MCF7, A549 & DU145 and cell carcinoma of the bladder.^{15, 16}

3. *Annona muricata*

Annona muricata belongs to the family Annonaceae and is commonly known as Graviola. It contains acetogenins, β -sitosterol, stigmasterol, phenols, alkaloids, annonioside, annoionol A, B, C, lycopene, lutein etc. It is distributed in the tropical regions of Central and South America, Western Africa and Southeast Asia. Acetogenins is the main compound and found in the leaves, seeds, bark and fruit of this plant. Acetogenins block the adenosine triphosphate production which inhibits the pump that removes cancer drug from the cell¹⁷. Acetogenins is identified to be toxic for various cancer cell lines such as pancreatic cancer, breast cancer, colonic adenocarcinoma, liver cancer and lymphoma.¹⁸

4. *Azadirachta indica*

Azadirachta indica belongs to the Meliaceae family and found in India and Indian subcontinent. It contains Nimbin, nimbinine, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and amino acid, nimbiol, etc. It has been used for the treatment of skin cancer, buccal cancer, mammary cancer, prostate cancer and gastric cancer.¹⁹ Ethanolic extract of *Azadirachta indica* causes prostate cancer cell death by apoptosis induction. It acts in a dose dependent manner and increase the fragmentation of DNA.²⁰

5. *Catharanthus roseus*

Catharanthus roseus is an important medicinal plant and belongs to the Apocynaceae family. It is commonly known as Madagascar periwinkle. It contains vinblastine, vincristine, vindesine, vindoline, tabersonine etc. *Catharanthus* is native to Madagascar but nowadays it is being cultivated in Tanzania, Kenya, Kisi and many other countries.²¹ This plant is used for the treatment of cancer, diabetes, fever and hypertension.²² Vinblastine and vincristine are commonly used for the treatment of leukemia and lymphoma.²³

6. *Curcuma longa*

Curcuma longa is commonly known as Haldi in Hindi, harida in Sanskrit and turmeric in English. It belongs to the Zingiberaceae family. This plant is native to Southern Asia and is also used as a colouring agent in Bangladeshi cuisine, Indian cuisine and also for many other purposes. It contains curcumin, curcuminoids, essential oil, turmerone, monoterpenes, diarylpentanoids, diterpenes, sesquiterpenes, triterpenoids, sterols, alkaloid, etc. Curcumin is

the active ingredient of this plant, which is a polyphenol derived from plant rhizome and this plant is used for both cancer prevention and treatment. Curcumin shows protective effect by inhibiting the growth of several angiogenesis associates and tumor associated genes.²⁴ Curcumin possesses antiproliferative property by downregulating the numerous gene expressions which includes activator protein 1, NF-kappa B, cyclooxygenase 2, epidermal growth receptor 1, nitric oxidase synthase and tumor necrosis factor.²⁵

7. *Emblica officinalis*

Emblica officinalis is an important medicinal plant belonging to the family Euphorbiaceae. It contains ellagic acid, gallic acid, quercetin, kaempferol, phyllembin, flavonoids, glycosides and proanthocyanidins. *Emblica officinalis* is valued for its unique tannins and flavonoids, which possess powerful antioxidant and anticancer properties. Ellagic acid is a powerful antioxidant and has the ability to inhibit mutations in genes. Ellagic acid also repairs chromosomal abnormalities. Quercetin, isolated from *Emblica officinalis* has hepatoprotective effect. *Emblica officinalis* inhibits growth and spread of various cancers including that of the breast, uterus, pancreas, stomach, liver and malignant ascites. *Emblica officinalis* is an excellent rejuvenator and antioxidant herb. It is highly nutritious and an important source of Vitamin C, minerals and amino acids. *Emblica officinalis* protects against much cancer particularly the liver cancer and it reduces the side effects of chemotherapy & radiotherapy.²⁶

8. *Glycine max*

Glycine max belongs to the Fabaceae family and native to East Asia. It is commonly known as Soya bean and is rich in selenium, zinc, vitamins, isoflavones, amino acids, phytosterols and saponons. A study reported that soybean-agglutinin inhibits the tumor growth in rats. Isoflavones convert cancer cells to normal by inducing cell differentiation.²⁷

9. *Podophyllum hexandrum*

Podophyllum hexeandrum belongs to the family Berberidaceae and is a native to Himalayan region (Uttarkashi) in India. It is commonly known as May apple and contains podophyllotoxin, kaempferol, quercetin, asiragalin, essential oil, podophyllin. Podophyllotoxin has been used for the treatment of testicular and lung cancers as well as in certain leukemias. Podophyllotoxin is majorly found in the roots and is used for the treatment

of cancers, ulcers, wounds, constipation and tuberculosis. Controlled clinical trials demonstrated that podophyllotoxin exerts a colchicine like effect by arresting mitosis in metaphase resulting in epithelial cell death. The antimetabolic effects of podophyllotoxin are the result of the drug's ability to act as an inhibitor of microtubule assembly. Podophyllotoxin also appears to attach to cell proteins and acts by increasing the incorporation of amino acids into proteins, inhibition of purine synthesis and inhibition of purine incorporation into RNA.²⁸

10. *Ocimum sanctum*

Ocimum sanctum, commonly called Tulsi or Holy basil belongs to the family Lamiaceae. The leaves of *Ocimum sanctum* contain 0.7% volatile oil comprising about 71% eugenol and 20% methyl eugenol. The oil also contains carvacrol and sesquiterpene hydrocarbon caryophyllene. Fresh leaves and stem of *Ocimum sanctum* extract yielded some phenolic compounds (antioxidants) such as cirsilineol, cirsimaritin, isothymusin, apigenin and rosameric acid, and appreciable quantities of eugenol. Two flavonoids, viz., orientin and vicenin from aqueous leaf extract of OS have been isolated. Ursolic acid, apigenin, luteolin, apigenin-7-O-glucuronide, luteolin-7-O glucuronide, orientin and molludistin have also been isolated from the leaf extract⁶. *Ocimum sanctum* also contains a number of sesquiterpenes and monoterpenes viz., bornyl acetate, elemene, neral, and pinenes, camphene, campesterol, cholesterol, stigmasterol and sitosterol. Eugenol, orientin and vicenin inhibits growth & spread of various cancers such as breast cancer, liver cancer and sarcomas particularly fibrosarcoma by blocking supply of oxygen and nutrients to the cancer cells and killing them by starving. Ursolic acid isolated from *Ocimum sanctum* has immune-enhancing and tissue-protective properties. Polysaccharides isolated from *Ocimum sanctum* have antioxidant and radioprotective properties. *Ocimum sanctum* protects against various cancers particularly breast cancer and reduces side effects of chemotherapy and radiotherapy.²⁹

11. *Oroxylum indicum*

Oroxylum indicum belongs to the Bigoniaceae family and is native to the Indian subcontinent. It contains baicalein, chrysin, oroxylin, scutellarein, pinostrobin, stigmast-7-en-3-ol. Several studies have shown the anticancer potential of this plant in various models. Ethanol extract (95%) of this plant showed cytotoxic effects against the Hep2 cell lines at 0.05% concentration.³⁰ Baicalein showed the antitumor effect on the human cancer cell lines

and inhibits proliferation of HL-60 cell lines up to 50% at 25-30 μ M concentration.³¹ Aqueous and methanolic extract of *Oroxylum indicum* showed cytotoxicity in selected tested cell lines and both the extracts exhibited moderate level of DNA protection against the oxidative stress.³²

12. *Punica granatum*

Punica granatum belongs to the Lythraceae family and fruit bearing deciduous shrub which is commonly known as pomegranate. It is originated in Iran and has been cultivated since ancient times throughout the Mediterranean region and northern India. It is a rich source of phenolic compounds, ellagitannins (ETs) and ellagic acid (EA) that metabolically convert to urolithins by the gut microbiota. Urolithins are found in high concentrations in colorectal cancer patients and urolithins inhibit proliferation of cancer cells and interfere with cell cycle²⁷. In a study, potential of pomegranate ellagitannins-derived compounds exhibited anti-proliferative and anti aromatase activities in breast cancer cells.²⁸

13. *Solanum nigrum*

Solanum nigrum commonly known as Black nightshade belongs to the family Solanaceae. Flavonoids (e.g., quercetin) and alkaloids (viz., solasodine, solanine and solamargine) are the main phytoconstituents of *Solanum nigrum* whole plant or fruit which have been reported to act in various tumours. Solamargine and solasonine inhibit growth and spread of various cancers, including breast, liver, lung and cyst cancers, choriocarcinoma or choriadenoma, and leukaemia. Solanine and solamergine have very strong anticancer actions against murine tumours. Steroidal glycosides (spirostane, furostane, spirosolane and pregnane), isolated from *Solanum nigrum*, inhibit growth and spread of colon cancer and pheochromocytoma. Glycoproteins obtained from *Solanu. nigrum* have antiproliferative and apoptotic effects on colon and breast cancers. Polysaccharides of this herb have significant inhibitory effect on growth of cervical cancer. *S. nigrum* inhibits growth and spread of liver cancer by two distinct anticancer activities, i.e., apoptosis (programmed cell death) and autophagy (autophagocytosis). Higher doses of *Solanum nigrum* induce apoptotic cell death, while lower doses lead to autophagocytic death of cancer cells. Lunasin, isolated from *S. nigrum* is a cancer-preventive peptide. *S. nigrum* and *S. lyrati* inhibit growth and spread of stomach cancer, sarcomas, malignant ascites and leukaemia. *Solanum nigrum* leaves extract has inhibitory effect against S 180, V 14 and Ec tumour models.³³

14. *Withania somnifera*

Withania somnifera is commonly known as ashwagandha in Hindi and Sanskrit, winter cherry in English. It belongs to the Solanaceae family and contains withanolides, withaferins, anferine, isopellertierine and sitoindosise. This plant grows majorly in India (especially Madhya Pradesh), Pakistan, Bangladesh, Sri Lanka and parts of Northern Africa. Due to its medicinal properties, leaves and roots have been used in the Indian traditional system of medicine and marketed globally.²¹ Withanolides isolated from *Withania somnifera*, are similar to ginsenosides (the active principles of *Panax ginseng*) in both structure and activity. Withanolides (including Withaferin A, Sitoindoside IX, Physagulin D, Withanoside IV and Viscosalactone B) inhibit growth & spread of various cancers such as cancers of the breast, lung, colon and central nervous system due to their antiproliferative and antiangiogenic properties. Withaferin-A (the most important withanolides) inhibit growth and spread of various cancers including that of the breast, cervix, colon, prostate, nasopharynx, larynx, malignant ascites and sarcomas by inducing apoptosis. Withaferin A is effective in both androgen-responsive and androgen-refractory prostate cancers. Sitoindosides VII-X and Withaferin A have strong antioxidant, antistress, immunomodulatory, anti-inflammatory and antiaging properties. Withanolide D inhibits the metastatic colony formation in the lungs by malignant melanoma. Ashwagandhanolide, a new dimeric withanolide, isolated from *Withania somnifera*, inhibits growth and spread in cancers of breast, stomach, colon, lung and central nervous system. *Withania somnifera* also possesses immunoenhancing, haemopoietic and neuroprotective properties and reduces side effects of radiotherapy and chemotherapy.²¹

15. *Zingiber officinale*

Gingerols isolated from *Zingiber officinale* inhibit growth & spread of various cancers including that of the ovary, cervix, colon, rectum, liver, urinary bladder, oral cavity, neuroblastoma and leukaemia by inducing apoptosis. The most active individual component, 6-shogaol, isolated from *Zingiber officinale*, inhibit growth & spread of many cancers particularly ovarian cancer by blocking formation of new blood vessels and by inducing apoptosis & autophagy. It is effective even in chemotherapy resistant ovarian cancer. *Zingiber officinale* also possesses antioxidant, antimutagenic and anti-inflammatory properties and reduces side effects of chemotherapy and radiotherapy.

Table 1: Major groups of anticancer compounds derived from plant:

SI No:	Plant source	Phytoconstituent	Properties
1	<i>Aloe vera</i> , Liliaceae	Aloe emodin	Induction of apoptosis
2	<i>Allium sativum</i> , Liliaceae	Organo sulfur compounds	Induce apoptosis
3	<i>Annona muricata</i> , Annonaceae	Acetogenins	Inhibits mitochondrial complex I, involved in oxidative phosphorylation and ATP synthesis.
4	<i>Azadirachta indica</i> , Meliaceae	Triterpenoids- Nimbine, Nimbinine, Nimbidic acid	Inhibit proliferation, induce apoptosis, reduce cellular oxidative stress
5	<i>Catharanthus roseus</i> , Apocynaceae	Vincristine , Vinblastine	Arrest cancer cell proliferation by binding to tubulin in mitotic spindle.
6	<i>Curcuma longa</i> , Zingiberaceae	Curcumin	Induce apoptosis, inhibit proliferation
7	<i>Embilica officinalis</i> , Euphorbiaceae	Ellagic acid	Induce apoptosis
8	<i>Glycine max</i> , Fabaceae	Genistein	Arrest cell growth and proliferatin
9	<i>Podophyllum hexandrum</i> , Berberidaceae	Podophyllotoxin	Inhibit mitogen induced lymphocytic proliferation and immunoglobulin synthesis.
10	<i>Ocimum sanctum</i> , Lamiaceae	Eugenol, orientin, vicenin	Blocks the supply of oxygen and nutrients to cancer cells and kill them by starving.
11	<i>Oroxylum indicum</i> , Bigoniaceae	Baicalein	Inhibits the proliferation of cancer cells.
12	<i>Punica granatum</i> , Lythraceae	Ellagitannins, Ellagic acid	Inhibits the proliferation of cancer cells by gets converted to urolithins.
13	<i>Solanum nigrum</i> , Solanaceae	Solamargine, solasonine	Kills the cancer cells by apoptosis and autophagy.
14	<i>Withania somnifera</i> , Solanaceae	Withanolides	Inhibits proliferation and induce apoptosis.
15	<i>Zingiber officinale</i> , Zingiberaceae	Gingeroles	Induce apoptosis and autophagy.

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