

Recent Scenario of Medicinal Plants of India in Cancer Therapeutics

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Abstract

A severe metabolic syndrome, cancer ranks at the second position as a cause of mortality and morbidity worldwide. Not only is there a high death rate associated with cancer but also are threats of chemotherapeutic resistance and the numbers are increasing each year. Thus novel therapeutics in cancer treatment is aimed to design anti-cancer drug that is having reduced side effects. In this regard, phytotherapeutics is one of the most promising candidates. India has a rich heritage for large number of medicinal and aromatic plants that have been cited in Ancient Hindu texts such as Shushrut Samhita, Atharva Veda and Charak Samhita as well. These plants have several medicinal phytomolecules that are proven to be used for healthcare. In this case, bioactive compound, which is derived from medicinal plants are reported for their lesser or no side effects, and better healing properties and targeted action on cancer cells and not altering normal cells. Tumor development is a very complex process regulated through multiple cellular signaling and gene regulation. Phytochemicals are playing a major role by targeting multiple concerns and hence they are playing a crucial role in drug discovery in Cancer therapeutics studies today. The present article deals with reviewing twelve different medicinal plants of India that have been promising candidates found to be clinically active against various types of cancer cells. The activity of these plants has been mentioned in Ayurveda and ancient scriptures and preliminary studies have proven the same scientifically. However, the attempt of the present article is to review the capabilities of these plants for cancer treatment.

Keywords

Cancer, Medicinal plant, Phytotherapeutics, Bioactive compound

Introduction

Cancer is a heterogeneous disease involving uncontrolled cell growth with potential to invade other parts of the body. According to the World Health Organization (WHO), it is one of the major public concerned and second most life-threatening diseases. The report of International agency for research on cancer gives the estimated number of cancer incidents as 24,500,000 and mortality 12,500,000 by 2030.¹ If we consider 2018 as a base line, the main types of cancer leading to overall cancer mortality each year are: Lung [13,00,000 deaths/year], Stomach [8,03,000 deaths/year], Colorectal [6,39,000 deaths/year], Liver [6,10,000 deaths/year], Breast [5,19,000 deaths/year].² The most frequent type of cancer reported worldwide among men are: lung, stomach, liver, colorectal, esophagus and prostate cancer, while breast, lung, stomach, colorectal and cervical cancer are prevalent among women.²

In Cancer therapeutics, every year there are new breakthroughs in research but the incidences and mortality rates are also increasing for last 30 years. Heterogeneity of cancer leads to complexity in therapeutic research creating new hurdles every time. However, an in-depth understanding of molecular mechanisms leading to malignancy and cancer metastasis is a crucial point to be studied in the current phase of cancer treatment and prevention.

There are several synthetic drugs that are being used currently for cancer treatment in medical science but due to their high cost and vast side effects, clinically they have not succeeded in healing cancer completely as a result. It has pushed to the scientific community to look out for phytotherapeutics option using medicinal plants with these capabilities to cure heterogeneous disease like cancer. Indian flora has been an attraction for scientific community worldwide.

In the recent past, there has been significant advancement in cancer treatment with surgery radiotherapy, chemotherapy, immunotherapy, target therapy, vaccination, combination therapy, stem cell transformation therapy being in its advanced states. However, all these have toxic side effects, poor pharmacodynamics properties, resistance to metastasis, poor bioavailability and non-specificity limiting their clinical utility to a large extent. Recent

anticancer therapy not only cures the diseases but also causes several side effects.³ There are several examples of synthetic drugs reported in literature related with their side effects (Table 1). In human body, there are cells which multiply rapidly under normal physiological conditions like hair follicle cells, bone marrow cells and digestive tract cells. Most of the anticancer drugs target these rapidly dividing normal cells along with cancerous cells leads to harmful side effects like decreased blood production, gastrointestinal tract inflammation, hair loss, immunosuppression, heart diseases and nervous disorders. There is a greater challenge to overcome these side effects that has taken the front seat for clinical intervention. Cell resistance is an another major limitation of these drugs due to their capability to induce mutations for e.g., drug resistant genes (ABCA4 and ABCA12) were highly expressed in human MCF-7 breast cancer cells respectively when docetaxel was used as a treatment. However, by applying curcumin in association with docetaxel, down regulation of drug resistance genes was observed.⁴ There are several studies that have convincingly proved that phytotherapeutics are better than their synthetic counterpart. Thus, treating cancer by combinational therapy including synthetic drug with phyto-constituents has shown promising outcomes than employing mono-target through single chemical agent. Therefore, based on extensive research findings, phytochemicals and their derived analogues proven to be encouraging candidates for treating cancer.

Sr.No	Drug	Mechanism of Action	Side effect
1	Doxorubicin	Topoisomerase inhibitors	Cardiotoxicity
2	Oxaliplatin, Melphalan, Carboplatin and Cyclophosphamide	Alkylating agents	Nephrotoxicity, Gastrointestinal, Cardiovascular toxicity, Pulmonary and Hematologic-toxicity
3	Cisplatin (cis-di ammine, dichloro platinum, DDP)	Cell cycle arrest and apoptosis	Nephrotoxicity
4	Taxanes : Paclitaxel, Docetaxel, Vinblastine and	Tubulin polymerization	Cardiovascular toxicity, Pulmonary and Hematologic-

	Discodermolide		toxicity
5	Gefitinib	Tyrosine kinase inhibitor	Cardiotoxicity
6.	Corticosteroids: Prednisone, Methylprednisolone, Dexamethasone	Allergic reaction prevention	Gastrointestinal Toxicity
7.	Anthracycline: Epirubicin, Idarubicin, Valrubicin	Topoisomerase II Inhibitor	Cardiotoxicity, Febrile neutropenia
8.	Anti-metabolites: Methotrexate, Nelarabine, Pemetrexed (Alimta), Pentostatin, Pralatrexate, Thioguanine	DNA Replication Inhibitor	Inflammation
9.	Nitrosourea: Carmustine, Lomustine, Streptozocin	Act against Brain Tumor	Pulmonary fibrosis

Table 1 : List of Anti-cancer drugs and their side-effects^{3,4}

Medicinal plants and Cancer

There are several plants studied for cancer therapeutics till now. The National Cancer Institute (NCI) has screened approximately 35,000 plant species for possible anticancer activities. However, among them, about 3,000 plant species have demonstrated effective anticancer activity.⁵

Medicinal plants and their bioactive compounds play crucial roles in ancient medicinal practices. Several medicinal plant species and their phytochemicals inhibit the progression and development of cancer and also have demonstrated properties to inhibit cancer cell activity such as inhibiting proliferation of cancer cells and inducing apoptotic cell death.⁶ Ongoing research is being done throughout the world in cancer therapeutics i.e. chemotherapy which includes the high risk dosage of chemical drugs at the same time it leads to high toxicity. Medicinal plants treat cancer through the phytochemicals, naturally present

with antioxidant and anticancer activities that are known to inhibit carcinogenic cells progression without showing any toxicity in individual. Phytochemicals and their derived analogous present in different parts of the plant, e.g., flower, stigmas of flower, pericarp, sprouts, fruits, seeds, roots, rhizomes, stem, leaf, embryo, and bark have several pharmacological functions. Several phyto-constituents like primary and secondary metabolites such as alkaloids, flavonoids, terpenes, taxanes, glycosides, gums, oils, lignans, saponins, biomolecules, vitamins, minerals etc. play significant roles in either inhibiting cancer cell divisions through various pathways (Table 2). In addition to the chemically synthesized anticancer agents, several anticancer compounds with different modes of action have been extracted from different plant sources, such as *Taxus brevifolia* (Paclitaxel, docetaxel), *Catharanthus roseus* (Vinblastine, Vincristine), *Berberis amarensis* (Berbamine), *Aglaia foveolata* (Silvestrol), *Cephalotaxus* species (Homoharringtonine), *Maytenus serrata* (Maytansine), *Dysoxylum binectariferum* (Flavopiridol), *Podophyllum* species (Etoposide, teniposide), *Tabebuia abellanadae* (Beta lepatchone).⁷

Sr. No.	Compound	Mechanism of action
1	Paclitaxel, Docetaxel	Stabilization of microtubules
2	Vinblastine, Vincristine	Inhibition of tubulin polymerization
3	Berbamine	Caspase-3 dependent apoptosis
4	Silvestrol	Triggers apoptosome/mitochondrial pathway
5	Homoharringtonine	Inhibition of protein synthesis
6	Maytansine	Inhibition of microtubule assembly
7	Flavopiridol	Inhibition of cell cycle progression at G1 or G2 phase
8	Etoposide, Teniposide	Inhibition of topoisomerase II
9	Beta lepatchone	Inhibition of topoisomerase I and II

Table 2 : List of Commercially available Anti-cancer phyto-compounds and their role⁷

In several studies for cancer therapeutics, the anticancer properties of plants have been targeted due to their wide availability and no toxicity. The number of plants worldwide continues to be actively researched, some of which showing promising results in cancer therapeutics. According to the World Health Organization (WHO), some nations still rely on plant-based treatment as their main source of medicine and developing nations are utilizing

the benefits of naturally sourced compounds for therapeutic purposes.⁸ There are some plants having Indian origin (Table 3) are showing reproducible anticancer activity has been discussed in following section. The emphasis on these plants is because many of them are edible, regularly used by individuals so as such do not have any toxicity and additionally reveal anti-cancer activities in preclinical and clinical trials.

Important Anticancer plants of India and their proven activities

1. Ferula asafoetida Linn.

Family: Umbelliferae

Common name: Hing

Traditional use: It is used as a spice in food as well as a digestive aid. Plant parts are used in some respiratory disorders like bronchitis, asthma, and cough and in some neural disorders. From root and rhizomes of this plant, gum resin is obtained which is used as antispasmodic, carminative, expectorant, laxative, and sedative.⁹

Anti-cancer activity: *F. asafoetida* has been widely used as health-promoting, food supplements, and medicine.¹⁰ The responsible chemo preventing constituents present in asafoetida are alpha-pinene, alpha terpineol, diallyl-disulfide, ferulic acid, isopimpinellin, luteolin, umbelliferone, and vanillin.¹¹ Apart from the antitumor effect, *F. asafoetida* has shown decreased lung, liver, and kidney metastasis and also decrement in areas of necrosis in the tumor tissue respectively.¹² The treatment of asafoetida has been shown to be effective in decreasing the tumor weight and tumor volume in treated mice.¹² Some reports showed that asafoetida has significant antioxidant and lipoxygenase inhibitory activity.¹³

2. Berberis vulgaris L.

Family: Berberidaceae

Common name: Barberry

Traditional use: Used to treat fever, liver diseases, hyperglycemia, cough and bleeding.¹⁴ The aqueous extract of dried fruits is used to treat acne.¹⁵ Fruits are preferably given to diabetic person.

Anti-cancer activity: Scientific reports have shown that even at only 1 mg/ml concentration of *B. vulgaris*, the crude extract was effective while 9 mg/ml and 12 mg/ml of extract had better anti-cancer activity compared with doxorubicin in MCF-7 cell line however further

scientific validation is still not done.¹⁶ One study evaluated the antioxidant and anti-cancer activity of ethanolic and ethyl acetate extract of root bark of *B. vulgaris* which shows the highest activity in ethanol extract, because of its large cytotoxic activity against the MCF-7 cell line unlike the ethyl acetate extract due to presence of several principal molecules including jatrorrhizine, palmatine, columbamine, berberine, and epiberberine.¹⁷ Berberine, a bioactive compound isolated from this plant plays a crucial role as an anti-cancer agent by inhibiting proliferation and inducing cell death associated with G0/G1 cell cycle arrest in cancerous cells.¹⁸ This bio-active compound also induces apoptotic cell death in human epidermoid carcinoma cells A431 through activation of the caspase-3 pathway and the distraction of mitochondrial membrane potential.¹⁹

3. *Acacia catechu* Linn.

Family: Mimosaceae

Common name: Kattha

Traditional use: Used to treat blood clotting, gingivitis, swelling in liver, skin disorder, constipation and chest pain and for birth control.²⁰

Anti-cancer activity: The abundant amount of polyphenolic and flavonoid compounds is found in the aqueous extract of *A. catechu*.²¹ The antiproliferative activity of methanolic extract of *A. catechu* studied in different cell lines was found in decreasing order as Hep-G2 > MCF-7 > IMR32 > HeLa = A549.²⁰ It has been reported that 70% methanolic extract of “Katha” leads to apoptosis induction by increasing the Bax/Bcl-2 ratio which results in the intrinsic pathway, i.e. activation of caspase-cascade and ultimately leads to the cleavage of Poly adeno ribose polymerase (PARP) in MCF-7 cell line.²² *A. catechu* ethanolic bark extract is useful as a therapeutic agent for the attenuation of oral squamous cell carcinoma.²³

4. *Ficus racemosa* Roxb.

Family: Moraceae

Common name: Gular

Traditional use: Used to treat diabetes, hemorrhoids, inflammation, and urinary diseases.²⁴

Anti-cancer activity: The methanolic extract of *F. racemosa* fruit has shown promising anticancer properties against human hepatocellular carcinoma (HepG-2) cells proven by comet assay and DNA fragmentation assay but this requires further scientific validation is

remaining.²⁵ On the basis of Sulphorodamine B (SRB) assay, the fruit extract of *F. racemosa* has shown cytotoxic and anti-cancer activity in MCF-7 cell line at ≥ 80 $\mu\text{g/ml}$ concentration.²⁶

5. *Cyperus rotundus* L.

Family: Cyperaceae

Common name: Nutgrass

Traditional use: Used to treat gastric disorders, malaria, inflammation, diarrhea, diabetes.²⁷

Anti-cancer activity: Reports show that the n-hexane fraction of *C. rotundus* rhizome has anticancer activity against breast cancer cell line MCF-7 arresting cells in the G₀-G₁ phase through induction of apoptosis.²⁸ In human colon cancer cell line (HCT116) and Ehrlich Ascites Carcinoma (EAC) cell lines, ethanolic extract of *C. rotundus* rhizome has highest cytotoxic effect when compared to traditionally used drug doxorubicin.²⁹

6. *Tinospora cordifolia* (Willd.) Miers

Family: Menispermaceae

Common name: Guduchi

Traditional use: Used to treat diabetes, cholesterol, hay fever, lymphoma, rheumatoid arthritis (RA), hepatitis, peptic ulcer disease (PUD), gonorrhoea, syphilis. It is also used for some common health problems like stomach pain, allergy and fever.³⁰

Anti-cancer activity: The hexane extract of *T. cordifolia* has been reported to inhibit cell proliferation, cell differentiation, and the activity of tumor-associated macrophage in Ehrlich ascites tumor (EAT) in mice and also known to induce apoptosis via caspase-3 DNase induced apoptosis.³¹ Alkaloids isolated from *T. cordifolia* extracts have better antineoplastic activity than compared to doxorubicin treatment.³² It is reported that *T. cordifolia* also has ROS mediated pro-apoptotic effects in breast cancer cells.^{33,34}

7. *Zizyphus mauritiana* Lamk.

Family: Rhamnaceae

Common name: Indian jujube

Traditional use: Used for improving hair growth, muscular strength, weight and wound healing. Used for preventing liver and bladder diseases, bacterial infection, obesity and

stress ulcers. It is also used to reduce constipation, asthma, fever, and to reduce symptoms of some medications.³⁵

Anti-cancer activity: Fruit, leaves and seed extracts of *Z. mauritiana* have been reported to have antioxidant activity and bark and pulp are reported to possess cytotoxic action against cancer cell lines.³⁶⁻⁴² Ethanolic-aqueous seed extracts of *Z. mauritiana* depict the anti-tumor and cytotoxic potential in Human promyelocytic leukaemia cells (HL-60), Human promyelocytic leukaemia cells (Molt-4) and human cervical cancer cells (HeLa).⁴³

8. *Boswellia serrata* Roxb. ex Colebr.

Family: Burseraceae

Common name: Salai guggal

Traditional use: Gum resin extract is used for chronic inflammatory diseases. Different plant parts are used for diarrhea, dysentery, ringworm, boils, fevers (antipyretic), skin and blood diseases, cardiovascular diseases, mouth sores, bad throat, bronchitis, asthma, cough, vaginal discharges, hair-loss, jaundice, hemorrhoids, syphilitic diseases, irregular menses and stimulation of liver.⁴⁴

Anti-cancer activity: Methanolic extract of *B. serrata* shows apoptotic activity in human colon cancer cells (HT-29) by targeting microsomal prostaglandin E synthase-1 of mPGES-1/PGE2 pathway in which extracts inhibits mPGES-1 and decrease the PGE2 level and its downstream targets.⁴⁵ The biologically active constituent of boswellia gum resin is boswellic acid. Some reports have shown that boswellic acid has anti-inflammatory and anti-cancer properties.^{46, 47} No adverse effect of this plant has been reported yet.

9. *Psoralea corylifolia* Linn.

Family: Fabaceae

Common name: Babchi

Traditional use: Used to treat skin disorders, hair treatments. Used to treat bronchial asthma and cough, anemia and edema. Fruits are used to treat inflammatory disease and leaves are used for diarrhea.⁴⁸

Anti-cancer activity: Seed extract of *P. corylifolia* has been reported to have anticancer activity in MCF-7 cell line by increasing apoptotic cell death.⁴⁹ Further scientific validations of this plant remain to be studied.

10. *Pulicaria wightiana* L.

Family: Asteraceae

Common name: Sontikli

Traditional use: The leaf extract is used to treat fever and rheumatism.⁵⁰

Anti-cancer activity: The essential oil of *P. wightiana* has anti-cancer property as indicated by *in vitro* cell growth inhibition and morphological changes in MCF-7 cells.⁵¹ However further investigations is required to understand its exact mechanism of action.

11. *Elephantopus scaber* Linn.

Family: Asteraceae

Common name: Gobhi

Traditional use: Different plant parts are used as an astringent agent, cardiac tonic, and diuretic, and is used for eczema, rheumatism, fever, and bladder stones, nephritis, edema, dampness, chest pain, pneumonia, scabies and leukemia.⁵²

Anti-cancer activity: *E. scaber* contains anti-cancer bioactive compounds. The chloroform extract of *E. scaber* leaf shows highest cytotoxic activity in T47D cells than methanolic and ethanolic extracts.⁵³ The ethanolic extracts has cell growth inhibition effect in sub G₁ phase.⁵³ The dichloromethane fraction of *E. scaber* has anti-cancer property through apoptotic induction in HeLa, A549, MCF-7, and Caco-2 cell lines.⁵⁴

12. *Tecomella undulata* (Sm.) Seem.

Family: Bignoniaceae

Common name: Roheda

Traditional use: The bark obtained from the stem is used as a remedy for syphilis. It is also used in curing urinary disorders, enlargement of spleen, gonorrhoea, leucoderma and liver diseases. Seeds are used against abscess. The plant is used to cure leucorrhoea, leucoderma, enlargement of spleen, traumatic wounds, hepatitis, piles, anorexia, flatulence, tumors, worm infestations and syphilis.⁵⁵

Anti-cancer activity: The chloroform fraction of bark extract indicated apoptosis in chronic myeloid leukemia cell line (K562).⁵⁵ Quercetin (0.03%) has been reported in the bark extract which is proven an anti-cancer bioactive compound.⁵⁵ Further studies are required for insight to its anticancer properties.

Name of Plant	Distribution in India
<i>Ferula asafoetida</i> Linn.	Kashmir and some parts of Punjab
<i>Berberis vulgaris</i> L.	Uttarakhand
<i>Acacia catechu</i> Linn.	Tamil Nadu, Karnataka, Maharashtra, Andhra Pradesh, Gujarat, Madhya Pradesh, Uttar Pradesh and Rajasthan
<i>Ficus racemosa</i> Roxb.	Assam, Bihar, Chhattisgarh, Jharkhand, Madhya Pradesh, Orissa, Sikkim, Meghalaya, W. Bengal
<i>Cyperus rotundus</i> L.	Throughout India
<i>Tinospora cordifolia</i> (Willd.) Miers	Throughout India
<i>Zizyphus mauritiana</i> Lamk.	Throughout India except Jammu & Kashmir, Himachal Pradesh, Sikkim, Arunachal Pradesh.
<i>Boswellia serrata</i> Roxb. ex Colebr.	Assam, Bihar, Maharashtra, Odisha, Punjab, Rajasthan
<i>Psoralea corylifolia</i> Linn.	Central India and Eastern part of Rajasthan, Punjab, and adjoining areas of Uttar Pradesh.
<i>Pulicaria wightiana</i> L.	Karnataka, Tamil Nadu
<i>Elephantopus scaber</i> Linn.	Assam, Meghalaya, Odisha, Uttar Pradesh
<i>Tecomella undulata</i> (Sm.) Seem.	North-West region of India

Table 3: Plants distribution in India ⁵⁶

Current Research gaps

It is known since long time that secondary metabolites and the bio active compounds play crucial role in phytotherapeutics. However, the scientific validation of many of these compounds are yet pending. Most of the studies done so far have mainly focus on single plant extract or poly herbal extract. There are very few studies that have used combinational approach which remains an unexplored area as of now. Scientists have been more focused on the efficacy without efficient and in-depth toxicity profiling of plant derived compounds. It has been reported that the ecological parameters affect the composition and activity of secondary metabolites in plants ⁵⁷ which indicates it is better to do toxicity study for a particular plant sample and then go for therapeutic study. Heavy metals like Pb, Cd, Hg, Cr

etc. interfere the drug delivery during *in vivo* studies.⁵⁸ So it's necessary to evaluate the different types of toxicity parameters to confirm the safety of natural therapeutic compounds. This part of the study reference to phyto-formulation is also an avenue for further research and investigation.

Future Direction

In the fields of Cancer therapeutic research, medicinal plants are gaining significance. Treatment of cancer by use of natural products and traditional medicine by applying the concepts of Ayurvedic formulations is attaining a great significance scope of cancer research. In some plants, the scientific validation and clinical trials are still remaining for their anti-cancer activity which gives discernments for therapeutic research. Also there are currently developments using new technologies such as nanoparticles to be used in administration of anticancer compounds and therapies. Their development could be applied for better drug availability to the specific tissues and help in aims to reduce severe side effects of treatments. The bioactive phyto-compounds and their biological activities mentioned in this review can help researchers to explore these plants for further studies.

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