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Medicinal plants for cancer treatment: A review approach

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Abstract
Indian system of medicine is seems to be a boon to the world. One among them is the Ayuvedic system, which has a holistic approach of treatment and ameliorates the root cause. Medicinal herbs are the major source of the ayurveda. India is an herbal hub with wide diversity of medicinal plants used in the various ailments from simple fever to deadly cancer. Currently medicinal plants have become the paramount source of drug discovery in research for treating diverse form of diseases including Cancer safely with fewer side effects. In the recent years herbal drugs have become the topic of global importance and also made a remarkable impact on both world health and international trade. Medicinal plants continue to play a central role in the healthcare system of large proportions of the world's population. Indian system of medicine has a major lacuna of documented scientific evidence for their claims. But currently this scenario has been changing by the proper documentation to take the Indian system of medicine to the global standards. Ayurvedic treatment cures many fatal diseases including cancer which is the most threatening and challenging one in the current medical world. Ayurveda claims to cure the cancer using the herbal drugs. Many traditional healers and herbalists have also claimed to treat cancer patients for many years using various medicinal plant species. Despite the long history of cancer treatment using herbal remedies, the knowledge and experience of these herbalists have not been scientifically documented. Considering the rapid rate of deforestation and loss of biodiversity, there is a need for accurate scientific documentation of the knowledge. In this article we covered the information gathered from the plants used previously in the treatment of cancer and recently identified for the anticancer activity.

Keywords: cytotoxicity, cell lines, carcinoma, phytochemicals, secondary metabolites

1. Introduction
In worldwide cancer is the most prominent cause for death. In general cancer defines as uncontrolled growth of immature cell. About 22 million people in the world are cancer patients. Nearly 10 million of people per year are diagnosed with cancer and more than 6 million die of the disease [1]. There are twenty eight types of cancer identified in every state of India. Most common type of cancer is breast cancer, Prostate cancer, basal cell cancer, Melanoma, Colon cancer, lung cancer, leukaemia and Lymphoma. Deaths due to cancer doubled in India from 1990 to 2016. In India due to cancer, 8·3% of the total deaths and 5·0% (4·6–5·5) of the total disability adjusted life years. Breast, cervical and stomach cancers are responsible for the majority of cancer deaths among women in India, while lung, oral and stomach cancers are the leading causes of cancer death in Indian men [2]. Four common types of human's cancer are found in India such as carcinoma (90%), sarcoma (2%), leukemia (8%) and lymphoma [3] (8%). Treatments like chemotherapy and radiotherapy can cause some serious complications. A suitable alternate remedy to overcome this issue is to use and finding a suitable lead compounds from medicinal plants. In India medicinal plants are plays an important role in cure and treatment of various illnesses. There are many advantage are usage of medicinal plants low cost, easy availability and belief that these medicinal plants do not present toxicity and do not trigger side effects. A classes of secondary metabolites such as anthocyanins, terpenoids, alkaloids, carotenoids, anthraquinones, essential oil, flavonoids, etc., were own the potential therapeutic efficacy as anti-tumorigenic agents. There are many naturally or semisynthetic anticancer agents are derived from natural sources Vinca (Vincristine and Vinblastine), Podophyllotoxin (Etiopside and Teniopside), *Taxus spp.* (Taxol) etc. Several research reports describe that the anticancer activity of medicinal plants is due to the presence of antioxidants present in them. Since there is a large number of medicinal plant with anticancer and antioxidant properties, very limited number of medicinal plant has been utilize and exploited so far.

2. Medicinal plants for cancer treatment
2.1 *Indigofera tinctoria*
Indigofera tinctoria Linn belongs to the family Fabaceae, which one used for the treatment of various illnesses. It is available in wold wide counties but widely available in most part of the Asia, tropical Africa and tropical America. It is a shrub attains the height between one to two meter height. In Ayurveda is mentioned as a name of Nili, *Indigofera tinctoria* is one of the drug for the promotion of hair growth [4]. Indirubin or isoindigotin or indigo red were isolated from *Indigofera tictoria* which inhibits DNA synthesis in several cell lines [5]. Treatment of methnolic extract of *Indigofera tictoria*, morphological changes are occurring in NCI-H6P (Human lung carcinoma). Five different concentrations are

prepared and find the percentage cell viability. Among five different concentration, 250µg/ml level concentration shows lowest cell viability percentage of 46%. Flavonoid is one of the major classes of secondary metabolites present in the aerial part of *Indigofera tictoria*, showed cytotoxic on A-549 cell line [6]. The purified indirubin were derived from methonolic extract of *Indigofera tinctoria* by two steps of column chromatography and purified by reverse phase high performance liquid chromatography. The inhibitory effect of indirubin on MCF-7 human breast cancer cells showed that 30mM indirubin strongly inhibited the cell growth of MCF-7 cells about 42% within 24 h. The cell growth inhibition of MCF-7 cells could reduce longer time of treatment and a higher concentration of indirubin [7].

2.2 *Melissa officinalis* L.

Melissa officinalis L. is a medicinal plant commonly known as lemon balm, plays significant role in European and Iranian Traditional Medicine for the treatment of several diseases. In Mediterranean region *Melissa officinalis* is consumed as a traditional herbal tea. Phytochemical screening showed that this plant contains volatile compounds, triterpenoids, phenolic acids and flavonoids. *Melissa officinalis* has been widely used for the treatment of several types of cancer. The citrus-like aroma of *Melissa officinalis* is due to the presence of citral isomers. Citral isomers (geranial and neral), citronellal and geraniol are the important volatile components present in *Melissa officinalis*. Citral, induced apoptosis of GBM cell lines that expressed active MRP1. In the same study, citral induced production of ROS and inhibited MRP1 expression [8]. Citral also reduced the viability of several 27 human tumour cell lines and a mouse melanoma cell line [9]. *Melissa officinalis* extracts is shows the presence of phenolic acids, mainly hydroxy cinnamic acid derivatives such as rosmarinic acid. Decoction of *Melissa officinalis* containing rosmarinic acid and lithospermic acid. The phenolic acids showed growth inhibition activity against different human tumour cell lines against human tumor cell lines, namely against breast (MCF-7), non-small lung (NCI-H460), cervical (HeLa) and hepatocellular carcinoma (HepG2). The best inhibition was detected for MCF-7 cell line and the least affected cell line was the NCI-H460. *Melissa officinalis* proved to be better against HepG2 cell line than other hepatoprotective plants [10]. HCT-116 cells were treated with rosmarinic acid (5–1,000µg/ml) for 24, 48 and 72 hours; a high dose was clearly cytotoxic with a significant decrease in cell number [11].

2.3 *Ammi visnaga*

Ammi visnaga is an aromatic, annual herb attains the height of 1-1.5 metre height with branched stem. *Ammi visnaga* is native to North Africa and commonly known as Khella. Phytochemical screening of *Ammi visnaga* shows different classes of secondary metabolites such flavonoids, volatile oil etc. Many secondary metabolites are isolates from this plant namely Khellol, Khellin, Visnadine, Cimifugin, β-sitosterol, Chromolyn, Quercetin and Kaempferol. The flowering aerial parts of *Ammi visnaga* were investigated for cytotoxicity against T47D (breast ductal carcinoma) using doxorubicin as standard. The petroleum ether and chloroform extracts showed the most significant cytotoxic activity (IC_{50} value of 0.40 mg/ml). On the other hand, the least potency (IC_{50} value of 1.80 mg/ml) was associated with methanol extract [12]. Essential oil extracted by steam distillation from *Ammi visnaga* (camphor α-terpineol and linalool). Cytotoxicity of essential oil were studied with two cancer cell lines namely, human pelvic rhabdomyosarcoma (RD) and mouse cell line (L20B). Results of study showed that the volatile oil caused dose-dependent cytotoxicity [13]. Khellin and visnagin are two furanochromones were isolated from entire plant of *Ammi visnaga* L. Methanolic extract of *Ammi visnaga* are studied against four different cell lines, Hela (cervical carcinoma cell line), Hep-G2 (liver carcinoma cell line, HCT 116 (colon carcinoma cell line) and MCF7 (breast carcinoma cell line) using SBR assay. Doxorubicin, an anticancer drug was used as a positive control. The highest cytotoxic activities were shown against Hep-G2 cell line with IC_{50} value 10.9 ± 0.68 µg/ml and 13.3± 0.78 µg/ml for Visnagin and khellin respectively. Visnagin was also found to show higher potency than khellin against HCT 116 and Hela cells with IC_{50} value 12.3± 0.94 and 35.5± 1.2µg /ml respectively. On the other hand, Khellin showed slightly higher potency against MCF7 cells than visnagin with IC_{50} value 13.3± 0.94 and 13.7± 0.942µg/ml respectively.

2.4 *Boswellia serrata*

Boswellia serrata is one of the most important herbs in Ayurveda belonging to the family Burseraceae. It is deciduous middle sized tree widely distributed in tropical parts of Asia and Africa. The tree produce a gum resin, having pleasant flavour and slightly bitter in taste. The oleo gum resin of *Boswellia serrata* plays a significant role in Unani and Ayurvedic preparation. Major active principle present in the *Boswellia serrata* is boswellic acids that belong to ursane- and oleanane-type pentacyclic triterpenes. HepG2 cell line, petroleum ether and 80% aqueous methanolic extracts elicited the most pronounced cytotoxic activity with IC_{50} values equal 1.58 and 5.82 µg/mL at 48 h, respectively which were comparable to doxorubicin with an IC_{50} equal 4.68 µg/mL at 48 h. With respect to HCT 116 cells, petroleum ether and 80% aqueous methanolic extracts exhibited the most obvious cytotoxic effect; with IC_{50} values equal 0.12 and 6.59 µg/mL at 48 h, respectively which were comparable to 5-fluorouracil with an IC_{50} equal 3.43 µg/ mL at 48 h [11]. Hydro alcoholic extract of *Boswellia serrata* causes death of cervical cancer cells (HeLa cell) and this effect is dependent on dosage and time [12]. The alcoholic extract of oleo gum resin of *Boswellia serrata* caused disturbed in the biosynthesis of DNA and RNA and proteins inhibit the tumour cell growth and induce apoptosis in cancerous cells in mice [14]. In leukemic cells HL60, it was shown that oleo gum resin of *Boswellia serrata* reduces viability of the cells [13].

2.5 *Curcuma longa*

Curcuma longa Linn, is a plant native to India, it is used in culinary purpose. Hence otherwise known as turmeric. Turmeic is a member of the Zingiberaceae family. Turmeric plays an important role in food preparation as a colorants and flavouring agents. Curcumin is a naturally occurring yellow pigment isolated from the rhizome of *Curcuma longa*. Curcumin is well known drug for its antioxidant, anti-

inflammatory, anti-fatigue, anti-parasitic, anti-allergic, anti-microbial, anti-mutagenic and anti-cancer properties. Curcumin inhibits various types of cancer cells due to multi targeting nature, different cancers including leukemia, gastrointestinal cancers, genitourinary cancers, breast cancer, etc. The results of the Curcumin shown to bring down the viability of the rat mammary gland cell line in culture and reduce metastasis of these cells injected into nude mice [15]. Another study shows that curcumin could inhibit the growth of human hepatocellular carcinoma cell line (HepG2). Curcumin promotes cell apoptosis by change the cell surface morphology and followed by pro-apoptotic factor. Cell viability had a dose-dependent relationship with the curcumin concentration [16]. Formation of free radicals and toxic products of oxidative stress play an important role in the development of many diseases, including cancer, and curcumin has antioxidant effects that reduce or inhibit damage caused by free radicals [17].

2.6 *Adenium Obesum*

Adenium Obesum, is a small tree, can grow to shrub or small tree belongs to the plant family Apocynaceae. Traditionally this herb used to treat varieties of ailments including venereal diseases; the root or bark extract is used as a bath or lotion to treat skin diseases and to kill lice, while the latex is applied to decaying teeth and septic wounds to promote healing and restoration. Betulin, a triterpenoid compound was isolated from the stem-bark of the plant. Nearly 30 different types of cardiac glycosides are found in *Adenium Obesum*, digitoigenin, oleandrigenin and gitoigenin are some of the important cardiac glycosides. Four different active pregnane was isolated from the methanolic extract of the leaves. The cytotoxic activities of these four pregnanes on murine leukemia P388 cells were examined. Two of the isolated pregnane shows significant cytotoxic effect on murine leukemia P388 cells [18]. In another study aerial part of methanolic extract of *Adenium Obesum* showed strong activity against HELA cell line. It is a strong inhibitor of the hedgehog Hh/GLI pathway. The hedgehog pathway is an important therapeutic target in cancer; it causes formation and progression of tumors in humans [19].

2.7 *Dysoxylum binectariferum*

Dysoxylum binectariferum, belongs to the family Meliaceae. In this genus nearly 100 species distributed all over the world. Generally it occurs as a trees and shrubs. In traditional systems of medicine, crude extract of the plant are used to treat various illnesses such as neurological disorders, inflammation, tumours, cardiovascular disorder and externally used to treat various skin diseases. Flavopiridol, a semisynthetic flavone derivative of the plant alkaloid rohitukine is isolated from the stems of *Dysoxylum binectariferum*, which one Inhibits cell cycle progression at G_1 or G_2 phase by interfering with the phosphorylation activity of cyclin dependent kinases. This flavone derivative active against various cancer cells such as colorectal, non-small cell lung cancer, renal cell carcinoma, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and also solid tumours [20].

2.8 *Camptotheca acuminate*

Camptotheca acuminata belongs to the family of Nyssaceae. It is a kind of medicinal tree from south China and listed as an endangered species in China. Cytotoxic alkaloid namely Camptothecin is isolated from the bark and stem of the *Camptotheca acuminate*. Camptothecin is having a poor solubility and produce severe toxicity overcome this issue certain analogues of Camptothecin were synthesized. Irinotecan and Topotecan, which are semi-synthetic derivatives of camptothecin have entered clinical routine treatment for ovarian cancer and colon cancer, respectively [21]. These analogs work by inhibiting DNA Topoisomerase I which plays a major role in various DNA functions like replication and transcription. Exatecan is another new camptothecin derivative which having potential anti-tumor activity against various tumors both *in-vitro* and *in-vivo* [22]. This synthetic analog having better aqueous solubility, lesser toxic effects and more tumor efficiency compared to camptothecin and other derivatives [23].

2.9 *Taxus baccata*

Taxus baccata Linn. belongs to the family Taxaceae. Evergreen tree attains the height of 6m in height and 1.5–1.8m in width, found in the temperate Himalayas at an altitude between 1800 and 3300m [24]. In Ayurvedic system of medicine, it was mentioned for the treatment of cancer, diarrhea, asthma, and haemoptysis and also used as a carminative, expectorant and stomachic [25]. Most parts of the tree contain the alkaloid namely taxin. Taxoids belong to the antimitotic family, action is that these active agents bind to the polymerized microtubules which prevent the normal mitosis to occur and thus they are called anti-mitotic drugs [26]. Paclitaxel and docetaxel are two of the best anticancer agents in clinical use today, for the treatment of ovarian cancer, breast cancer and non-small cell lung cancer Paclitaxel is poorly soluble, overcome by Docetaxel and more effective than one another [27].

2.10 *Silybum marianum*

Silybum marianum is otherwise known as Milk thistles belong to the family Asteraceae. In folk medicine it is used as a liver tonic. Silymarin is the secondary metabolite isolated from this plant used to treat liver disorders. Silidianin, Isosilibinin, Silibinin and Silichristin are the four different isomers of Silymarin [28]. Silibinin is a polyphenolic flavonoid and the major biologically active compound of milk thistle. Silibinin has been found to possess multifactorial anti-cancer efficacy. Silibinin having the ability to inhibit the multiple cancer cell lines, including prostate, colon, skin, bladder and lung cancers. Recent research demonstrated that silibinin-reduced HuH7 cell growth was significantly associated with increased AC-H3 and AC-H4 expression, suggesting that increased histone acetylation may mediate silibinin-reduced hepatocellular carcinoma growth [29]. Silibinin is an active compound against prostate cancer. Silibinin has shown the ability to modulate cell signalling, alter cell proliferation, apoptosis, epithelial to mesenchymal transition, invasion, metastasis, and angiogenesis [30]. Another study revealed that

silibinin treatment could inhibit cell proliferation and invasive potential of HepG-2 cells through inhibition of ERK 1/2 cascade both directly and indirectly and also cell growth and proliferation may be inhibited by silibinin through downregulation of Hec1 [31].

2.11 *Betula alba*

Betula alba Linn, belong to the family Betulaceae, is a tree growing to about 30m height, it is otherwise known as "Lady of Woods". Traditionally the plant is used to treat various ailments like rheumatic arthritis, boils, fever, gout, headache, kidney stones, and worms, also used as anti-inflammatory, the leaves are antibacterial, diaphoretic, used in gonorrhea, diarrhea, dysentery and cholera [32]. Essential oil isolated from this wood is used to treat eczema and psoriasis and hair loss in Ayurveda [33]. The anticancer activity of the plant mainly depends on the phytochemical namely betulinic acid. Chemically betulinic acid is 3β, hydroxy-lup-20(29)-en-28-oic acid, a lupine class type, pentacyclic triterpene compound. Betulinic acid have major advantage over other anticancer agents is not toxic *in vivo*. Betulinic acid act as a growth inhibitor of human melanoma in athymic mice and also inducer of apoptosis in neuroblastomas and glioblastomas *in vitro* [34-36].

2.12 *Withania somnifera*

Withania somnifera Dunal, shrub belongs to the family Solnaceae otherwise known as ashwagandha. *Withania somnifera* distributed throughout the hotter part of India. *Withania somnifera* possesses a number of therapeutic actions some importance are general tonic, sedative, hypnotic, narcotic aphrodisiac and anti-inflammatory. In ayurvedic system of medicine *Withania somnifera* used as an immunomodulatory agent. Twelve different types of withanolides are isolated from leaves of the plant. The most important withanolide, Withaferin A was isolated from the extract of the leaves and dried roots of *Withania somnifera*. Leaf extract of *Withania somnifera* inhibit the growth of osteogenic sarcoma and breast cancer cell lines by increased tumor apoptosis [37]. Withanolides shows the chronic myeloid leukemia, embryonic kidney carcinoma, breast adenocarcinoma by NF-κB suppression [38].

3. Conclusion

Traditional medical practice such as Ayurveda, Siddha, Unani, Yoga, Homeopathy and Naturopathy etc. are plays an important role for prevention, maintenance and healing of various ailments. Medicinal plants or combinations of medicinal plants are the major sources in tradition system of medicines. In India, Ayurveda, Siddha and Unani are extensively practised systems of medicines. Both in developed and developing countries cancer and heart diseases are the major public health problems. Many therapeutic procedures such as radiation therapy, chemotherapy, immunotherapy and targeted Therapy etc. are available for the treatment of cancer, where these treatment procedures are producing some undesirable side effects that will affect many other healthy organs also. Treatment with medicinal plants also having a unwanted side effects, but the quantum of unwanted side effects are less when compared with other therapeutic procedures. In traditional system of medicine many medicinal plants or combination of medicinal plants are used to treat cancer. The classes of secondary metabolites in the plants such as anthocyanins, terpenoids, alkaloids, carotenoids, anthraquinones, essential oil, flavonoids, etc have been widely studied for their potential use as anticancer agents. Secondary metabolites presence in those medicinal plants have antioxidant properties, cytotoxicity of cancer cells, inhibition of cancer cell growth, cell cycle arrest, induction of apoptosis, inhibition of angiogenesis in tumour cells. This review had given some of the plants own anticancer activity for various types of cancer. This review can support others to investigate the herbs to further extents.

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