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MEDICINAL PLANTS AS SOURCE OF ANTICANCER DRUG DISCOVERY

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Abstract

Medicinal plants represent an important source of new drugs. Moreover, medicinal plants played a good role in health care and prevention of different diseases. The knowledge about medicinal plants and their study of the scientific chemical constituents may led to the discovery of newer and cheaper drugs. Cancer is the most severe health problem in the world and it causes the death of millions of people each year. This review gives available information about medicinal plants that have significant anticancer activity and can be as source of anticancer drug after further clinical evaluations.

Keywords: Medicinal plants, Anticancer activity

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INTRODUCTION

The plants were used as medicines since a long history in the treatment of various diseases. The first reports on the medicinal properties of the plants were in about 2600 BC [1]. Plant secondary metabolites as flavonoids, alkaloids and others proved to be a good source of new medical compounds.

Cancer is a population of abnormal cells which may divide without control, with the ability to invade other tissues. Cancer is the second cause of death in the world and it can be described as a complex disease that is associated with a wide range of escalating effects both at the molecular and cellular levels. Since 1990, there is 22% increase in cancer cases where lung, stomach, liver, and colorectal cancers are the most deadly cancers [2].

Some factors cause cancer as incorrect diet, genetic predisposition, environmental factors as smoking, and infectious diseases and also chemicals and radiation. More than 95% of all cancer types can be caused by life style and some current calculations from the American Cancer Society and also from the International Union against cancer showed that more than 12 million of cancer cases were discovered last year and more than 7% million deaths in the world and these calculations will be increased to double by 2030 [3].

Drug discovery of medicinal plants and natural compounds became very important in cancer treatment and the major of new clinical applications from bioactive compounds of the plant have been applied towards combating cancer [4, 5].

In this review, the potent anti-cancer activity of some medicinal plants is mentioned.

Medicinal plants have potent anticancer activity

The history of medicinal plants as anticancer source began since a long time. Many of the plants proved a significant anticancer efficiency.

Achyranthes aspera

The total methanol extract from *A. aspera*, the alkaloidal, non-alkaloid and saponin fractions showed potent inhibitory activity on Epstein-Barr virus early antigen activation in Raji cells and this promising anticancer activity was observed at the dose of 100µg. In a further *in vivo* studies, the total methanol extract from *A. aspera* proved a promising cytotoxic activity [6].

Andrographis paniculata

This medicinal plant was reported that ethanol extract of the aerial parts contained flavonoids and labdane diterpenoids. The cytotoxic effects of the mentioned compounds were tested against

different cancer cell lines. The results proved a significant antitumor activity against all the tested cancer cell lines [7]. Dichloromethane fraction from the total methanol extract of *A. paniculata* was reported that it contained bioactive constituents proved cytotoxic effect and also potent immunostimulating effect [8].

***Allium sativum* (garlic)**

This medicinal plant is used as a medicinal agent since a long time. Allicin represents the major component of raw garlic. *A. Sativum* showed a cytotoxic effect in the range of 2-50 µg/ml [9].

S-allylcysteine compound of *A. Sativum* can retard the growth of transplantable tumors in several animal models [10].



S-allylcysteine

Annona muricata

Annona muricata is well known as graviola. This medicinal plant has medicinal components known as acetogenins. Previous reports showed that acetogenin has chemotherapeutic potential [11]. Some acetogenins from other *Annona* species were reported that they had a potent cytotoxic effect for different cancer cell lines as lung, breast, pancreatic, and liver cancers [12].



Annonacin compound as example of acetogenins

Apis mellifera

This medicinal plant represents the scientific name of honey bee. A protein from the honey bee was reported to enhance proliferation of primary-cultured rat hepatocytes and suppresses apoptosis [13].

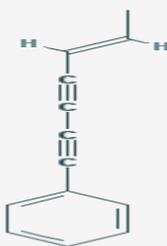
Astralagus hedysarum

This medicinal plant was well known for its anticancer effect where a polysaccharide from this plant proved anti-tumor activity. *A. hedysarum* has immuno-potentiating action and it can be very

useful in cancer chemotherapy [14]. Some species from *Astragalus* as *A. membranaceus* was studied for its cytotoxic effect. The results proved that *A. membranaceus* has the ability to induce monocytic differentiation of human and murine cells *in vitro* [15].

Bidens pilosa

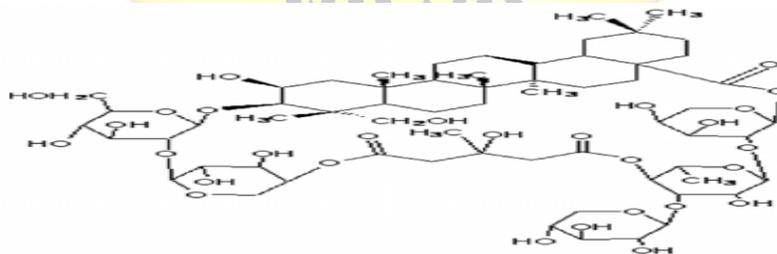
This medicinal plant contained polyacetylenes, flavonoids, terpenoids, and others. Previous phytochemical investigations on the different extracts of *B. pilosa* afforded phenyl-1, 3, 5-heptatriyne. This compound showed a toxic effect on normal blood cells in erythrocyte osmotic fragility experiments [16]. Some non polar extracts (hexane and chloroform) and methanol were test for their antitumor effects. The results indicated that n-hexane extract was the most potent as antitumor [17].



Phenyl-1, 3, 5-heptatriyne

Bolbostemma paniculatum

Previous reports showed that it contained a very promising a triterpenoid saponin Tubeimoside-V. Biological studies on that compound indicated the apoptotic killing nature on glioblastoma cells, and this may explain its significant role in antitumor chemotherapy [18]. Also previous reports indicated that other tubeimosides as tubeimosides-I, and tubeimoside-II showed a promising cytotoxic effect [19].

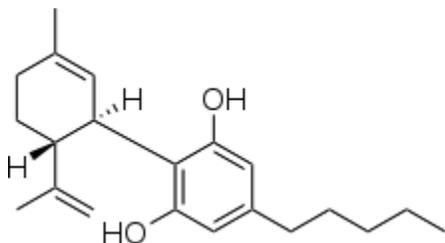


A triterpenoid saponin Tubeimoside-V

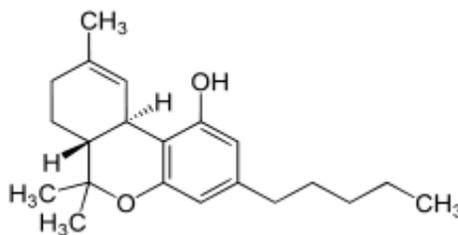
Cannabis sativa

C. sativa has a significant antitumor effect for malignant brain tumors in *in vitro* [20]. This medicinal plant has components named, cannabinoids that have the ability to inhibit human breast

cancer cells [21]. Moreover these active constituents proved anti-tumor activity in cell culture and animal models [22].



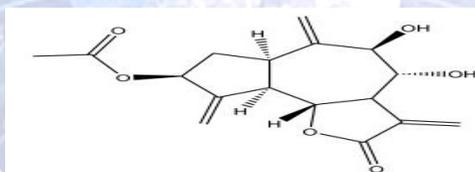
Cannabidiol



Tetrahydrocannabinol

Centaurea ainetensis

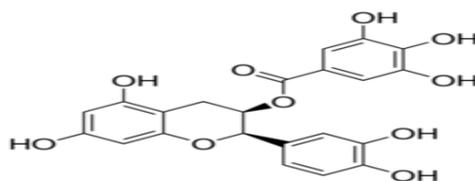
This medicinal plant extract was tested for its antitumor effect against human colon carcinoma cells. The results indicated that the extract has the ability to inhibit the proliferation of a host of colon-derived cancer cells. Moreover the administration of *C. ainetensis* extract reduced the number of tumors. Previous phytochemical investigations on this extract revealed the identification of the bioactive component salograviolide-A. This compound has the ability to reduce the growth of colon cancer cell lines at non-cytotoxic concentrations, moreover that active compound indicated a significant cytotoxic effect against epidermal squamous cell carcinogenesis [23, 24].



Salograviolide-A

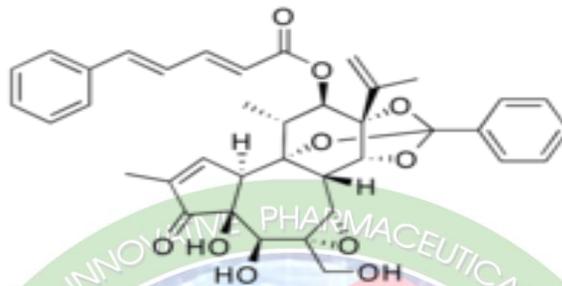
Camellia sinensis (Green Tea)

This medicinal plant contained a major polyphenol component named, Epigallocatechin-3-gallate (EGCG). Some experimental studies on that compound indicated that EGCG has the ability to inhibit the invasion and migration of human colon and oral cancer cells. Also some previous reports indicated that EGCG inhibited the growth of some cancer cell lines as hepatocellular carcinoma through induction of cell cycle arrest [25].



Epigallocatechin-3-gallate***Daphne mezereum***

Daphne mezereum is used as remedy for treating cancer. *D. mezereum* methanol extract proved a potent antileukemic effect against lymphocytic leukemia in mice. This observed activity is due to mezerein which is a potent antileukemic compound [26].

**Mezerein*****Gossypium hirsutum***

This medicinal plant is also named as cotton seed oil and it is used in the treatment of metastatic carcinoma of ovary. Previous reports proved antitumor potential of this plant on many cytosolic and mitochondrial enzyme systems [27, 28, 29].

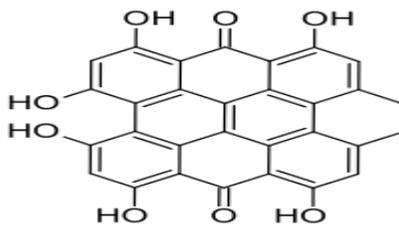
Hydrocotyle asiatica

This medicinal plant has known as gotu kola. Reports of some previous studies on animal tissue indicated this plant proved cytotoxic and antitumor potentials. It was reported that the plant increased the life-span of tumor-bearing mice [30]. The aqueous extract from the leaves of that plant indicated cytotoxic activity against mouse melanoma and human breast cancer [31].

Hypericum perforatum

This medicinal plant has bioactive compound, hypericin. This compound has the ability to reduce the glioma cell lines growth *in vitro*.

The antitumor activity of hypericin to inhibit glioma cells was greater than tamoxifen which was used as reference standard [32, 33]. The potent inhibitory activity of this plant was due to its components [34].

**Hypericin**

***Mangifera indica* (Mango)**

This medicinal plant is used as a nutritional supplement in many countries. The aqueous extract of that plant is used to improve the quality of life through increasing free radical scavenging mechanism [35].

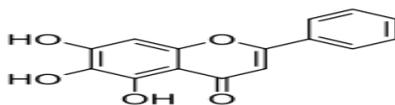
Some previous ethno-botanical studies of that plant resulted in a good improvement of life quality in cancer patients [36]. Also some previous evaluations proved immune-modulator effects of the plant in various cell lines. The active constituents of mango are terpenoids, polyphenols, steroids, and some fatty acids that provide antioxidant supplements [37].

Nervilia fordii

This medicinal plant is used as a drug in China. Both of petroleum ether and ethyl acetate extracts of *N. fordii* were tested for their anticancer effect by using mice models. The two extracts proved a significant anticancer activity. Moreover, the two extracts prolonged the life of mice that has cancer disease. This study indicated that this medicinal plant can act as cancer inhibiting agent and so deep phytochemical study is necessary to identify the bioactive constituents that are present in that medicinal plant [38].

Oroxylum indicum

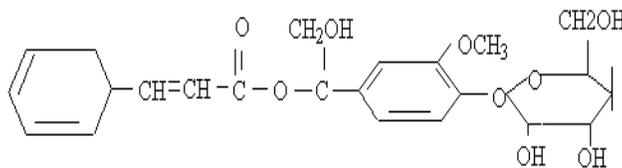
This medicinal plant is named as sonapatha. Some previous studies have indicated anticancer activity of *O. indicum* where ethanol extract showed cytotoxic effect against liver cancer cell lines [39]. Baicalein, a flavonoid compound which is present in *O. indicum* proved anticancer activity on human cancer cell lines and also it inhibited 50% proliferation of human promyelocytic leukemia cells at the dose of 25-30 microM [40]. The methanolic and aqueous extracts of *O. indicum* proved cytotoxic effect in selected tested tumor cell lines and both the extracts showed moderate levels of DNA protection against oxidative stress [41].



Baicalein

Picrorrhiza kurroa

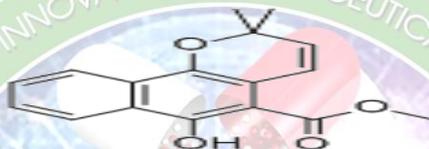
This medicinal plant inhibited liver cancer growth. The bioactive compound of this plant is named as kutkin. This compound has the ability to inhibit level of lipid peroxidases, and hydroperoxidases [42].



Kutkin

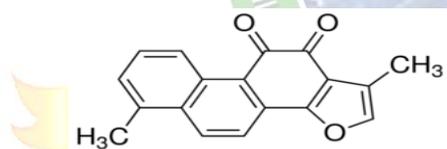
Rubia cordifolia

This medicinal plant is rich with hexapeptides and quinones and these compounds proved potent antitumor effect (43, 44). A compound named, Mollugin which was identified from chloroform extract of *R. cordifolia* roots proved a potent antitumor effect against lymphoid leukemia in mice [45].

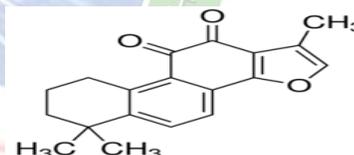


Mollugin

An active compound named, tanshinone-I was identified of *S. miltiorrhizae*. The reports showed that significant effect of tanshinone I on breast cancer cells, and this suggested that compound may be an effective drug for the treatment of breast cancers [46]. Another active compound named, tanshinone II-A, identified from *S. miltiorrhiza*, induced apoptosis [47].



Tanshinone-I



Tanshinone-II-A

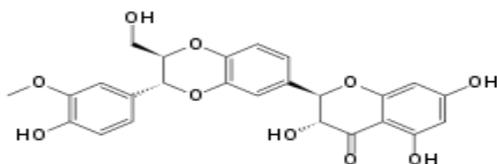
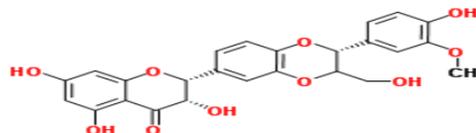
Scutellaria

This genus proved potent anti-cancer activity. *Scutellaria barbata*, this medicinal plant showed antitumor activity against human lung cancer cell line, where the ethanol extract of that plant proved antitumor effect with IC₅₀ value of 0.21 mg/ml [48]. Also a compound named, Tanshinone IIA identified from that plant has anticancer effect on breast cancers, signal transduction, and cell proliferation, [49].

Silybum marianum

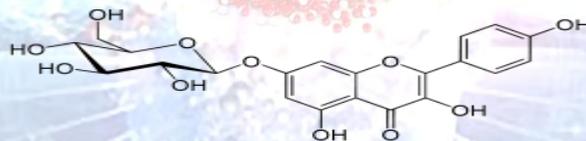
This medicinal plant contained bioactive flavonolignan compound named, silymarin. This compound was tested against skin cancer in mice. The compound showed a very significant anticancer effect where it reduced the chances of tumor incidence to 90% [50]. Another bioactive

compound named, silibinin identified from the fruits of *S. marianum* was very active against human breast cancer cells [51].

**Silibinin****Silymarin**

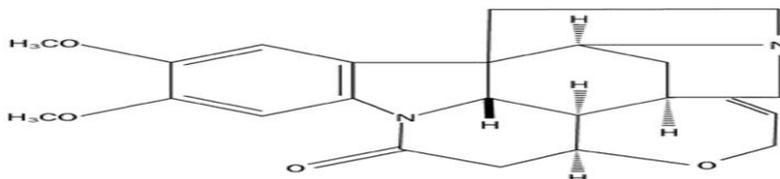
Smilax china

This medicinal plant contained a bioactive flavonoid glycoside named, kaempferol-7-O- β -D-glucoside, identified from *Smilax china L.* rhizomes. This compound proved a potent anticancer activity on cervix carcinoma. Moreover, it showed its cytotoxic effect through arresting of cell cycle and induction of apoptosis in cells, and thus the compound may be used as a therapeutic agent for cervix carcinoma [52, 53].

**Kaempferol-7-O- β -D-glucoside**

Strychnos nuxvomica

This plant showed cytotoxic effect against multiple myeloma cell lines. *S. nuxvomica* root extract was tested for its antitumor effect. The results indicated that the extract revealed anticancer effect in a dose dependent manner [54]. The major compounds of that medicinal plant are alkaloids and the alkaloids of that plant were active against liver cells proliferation, where the alkaloidal compound named, brucine proceed liver cells death through apoptosis [55].

**Brucine**

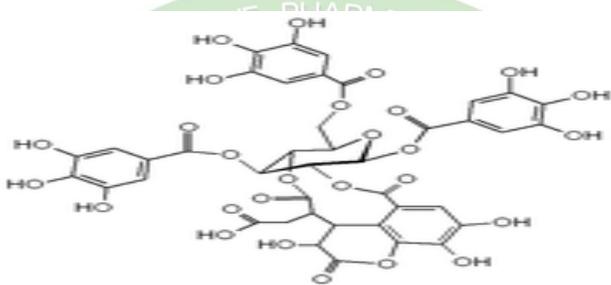
Taraxacum officinale

This medicinal plant was used in several countries for treatment of cancer. The extracts of leaves, flowers and roots were tested against breast cancer cell line. The most active extract of *T.*

officinale was leaves extract which reduced the growth of breast cancer cells [56]. Moreover, this medicinal plant has the ability to decrease the cell viability and also can increase necrosis factor [57].

Terminalia chebula

This medicinal plant is very rich with hydrolysable tannins and it has antimutagenic effect [58]. The fruits of that plant has bioactive constituents named, chebulinic acid, tannic acid, and ellagic acid. These compounds are well known as inhibitors for the cancer growth [59]. The fruits powder and the acetone extract from the bark of *T. chebula* were reported that they have significant antimutagenic and anticarcinogenic effects [60].



Chebulinic acid

Vernonia amygdalina

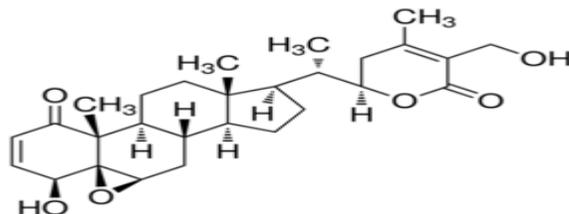
Some *in vivo* studies proved anticancer activity from that plant where the plant completely eliminated the tumors of the animals tested [61].

Withania Somnifera

This medicinal plant is rich with bioactive compounds named, withanolides. A compound named, Withaferin-A was isolated from *W. somnifera* roots. This active compound had a promising tumor reducing activity in carcinomas as carcinoma of nasopharynx. This active plant used as a folklore remedy for combating the cancer [62, 63, 64]. *W. somnifera* root extract has chemopreventive effect for skin cancer [65].

Previous reports indicated that withanolides identified from *W. somnifera* have the ability to reduce the growth of cancer cells in human as breast, lung, and colon cancer cell lines comparable to doxorubicin (the standard drug), where withaferin A compound has anticancer effect more than doxorubicin [66]. Another study was carried out to evaluate anticancer effect of the plant in urethane induced lung adenomas in adult male albino mice. The histological appearance of the lungs of the animals treated with the extract of *W. somnifera* were very similar to the lungs of control animals [67]. The extract from *W. somnifera* has the ability to decrease the cancer cell

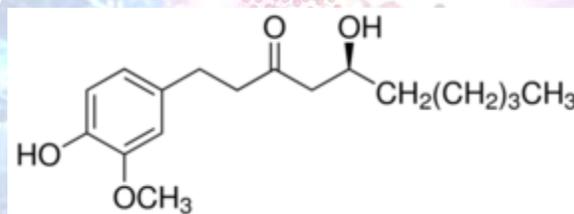
number in the tumour-induced mice and this suggests that that plant has protective effect in carcinogens [68].



Withaferin-A

Zingiber officinale

The ethanol extract of *Z. officinale* was tested for its antitumor activity in skin tumorigenesis model. The extract proved a promising inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA). *Z. officinale* which is named as ginger has bio active compound as 6-gingerol and this compound was tested for its antitumor effect on colon cancer biology. The compound caused a significant antitumor activity at the lower doses resulted in inhibition of endothelial cell tube formation [69].

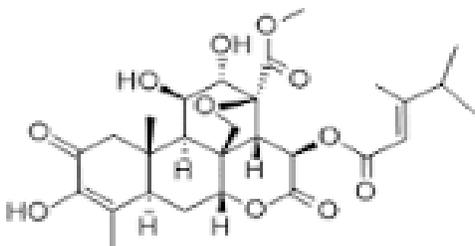


6-gingerol

Ailanthus altissima

The chloroform extract of that plant was tested for its anticancer effect on human lung cancer cell line. The results showed that the extract has a good anti-cancer effect [70].

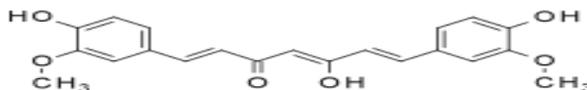
The plant and all *Simaroubaceae* family have bioactive compounds named, quassinoids (highly oxygenated triterpenes) that proved many of biological activities among that anticancer activity. A quassinoid named, Bruceantin was very active against melanoma, colon and leukemia cancers [71, 72].



Bruceantin

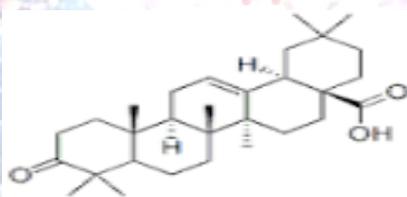
***Curcuma longa* (Turmeric)**

This medicinal plant proved a potent anticancer activity against different tumors as tongue carcinoma, colon cancer, and human breast cancer cells [73-78]. The plant has bioactive constituent named, curcumin which is a good anticancer agent against skin tumors [79].

**Curcumin*****Lantana camara***

This medicinal plant is known as wild Sage. Leaves of *L. camara* showed cytotoxic effect on vero cell line. The methanol extract at dose of 500 µg/ml inhibited growth of the tumor cells. Moreover, the leaves of *L. camara* have anticancer activity against laryngeal cancer and lung cancer cell lines [80, 81].

L. camara has oleanonic acid which is tested for its anticancer effect against Ehrlich ascites carcinoma, and other human cancer cells. Oleanonic acid showed a promising cytotoxic effect against malignant skin melanoma [82].

**Oleanonic acid*****Pygeum africanum***

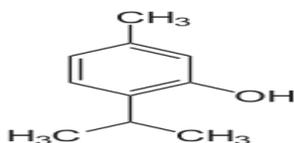
P. africanum bark extract was used in Europe for the prevention and treatment of prostate disorders. This plant is very rich with phytosterols as β-sitosterol which plays a role in the activity of *P. africanum* as anticancer agent for prostate cancer [83].

A recent study reported that therapeutic formulation from *P. africanum* and *Saw palmetto* was used for prostate health and this suggests that *P. africanum* may be used as a supplement for people at high risk for developing prostate cancer [83].

Thymus vulgaris

Thymus genus are from the important medicinal plants. This plant was used for treatment of different diseases due to its high content of the essential oil constituents. Gas chromatography-mass spectrometry of that plant oil revealed that the major constituent was thymol with the percent of 54.26%. The oil from *T. vulgaris* was tested for its anticancer effect against several

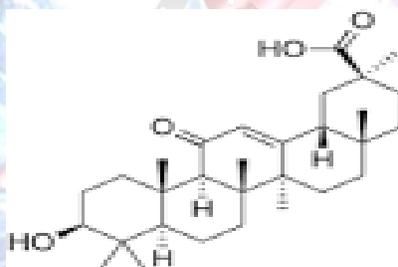
tumor cell lines. The results proved that the oil was very active against breast carcinoma, human alveolar basal epithelial and hepatocellular carcinoma with IC_{50} values of 75, 60 and $41\mu\text{g/mL}$, respectively [84].



Thymol

Glycyrrhiza glabra

The plant contained bioactive compound named, glycyrrhetic acid. *In-vitro* cytotoxic studies of that compound on breast cancer and vero-normal cell line by using MTT method were done. The compound gave an inhibition for the cancer by the percentage of 45.71% for vero-normal cell line and 78.78% for breast cancer cell line [85, 86].



Glycyrrhetic acid

Tabebuia rosea

This medicinal plant is known as pink trumpet tree. The methanol extract from the plant seeds was tested for its antitumor effect. The extract of *T. rosea* was given at doses of 100 mg/kg, and 200 mg/kg in mice for 14 days. The study showed that the methanol extract proved a significant antitumor and anti-oxidant activities *in vivo*. The results support the traditional use of *T. rosea* plant and its alcoholic seed extract as potent anticancer compounds [87].

***Citrus aurantium* (bitter orange)**

This plant has a good role in prevention from cancer. Previous studies on the plant reported anti-proliferative activity of the peels from *C. aurantium* along with its effect on apoptosis. The crude methanol extract of the peels from *C. aurantium* was tested for its anticancer effect by using human leukemia cells. The growth of leukemia cells was inhibited by *C. aurantium* methanol extract in a dose-dependent manner. The extract induced caspase-dependent apoptosis and thus this study proved anticancer activity from *C. aurantium* methanol extract on human leukemia cells [88].

Carica papaya

The different parts of this plant have many of medicinal applications. The different extracts of *C. papaya* may have the ability to alter the growth of several types of cancer cell lines. The juice from *C. papaya* was screened for antiproliferative effect on human breast and liver cancer cell lines. The reports indicated that papaya juice caused cell death in the liver cancer cell line with the half maximal inhibitory concentration (IC₅₀) of 20 mg/mL [89]. Another study reported the high quality of the extract of papaya parts for the prevention, treatment for some types of cancer as stomach, lung, pancreatic, colon, ovarian, leukemia cancers and other blood cancers [90].

CONCLUSION

Plants are widely used as medicines since centuries for the treatment of different types of diseases. People since a long time have relied on traditional herbal agents to meet their health care requirements. Although the presence of conventional drugs, herbal medicines are still have a place in treatment due to their wide range of healing properties. Natural products are considered as a wonderful source for the development of anti-cancer drugs. Secondary metabolites as flavonoids, alkaloids, saponins and others, obtained from different plants are mainly responsible for their several medicinal properties. Further and deep research is going on for the development of new anti-cancer drugs where recent medications for the treatment of cancer show various adverse side effects which may be overcome by replacing that with plant derived compounds. The immense potential of plants in cancer therapy still remains unexplored and need more deep research studies. It is necessary to develop newer anti-cancer drugs from plant materials which may be a good way to a non-toxic mode of cancer control and also it is importance to make people aware of the health benefits of different plant products and its potent role in cancer prevention and treatment as it might provide a unique means of cancer therapy and management.

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