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G Fareeda
Assistant Professor, Department of Biochemistry, Agricultural College, Mahanandi, Andhra Pradesh, India

Corresponding Author:
G Fareeda
Assistant Professor, Department of Biochemistry, Agricultural College, Mahanandi, Andhra Pradesh, India

Green cancer drugs

G Fareeda

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Abstract
Globally cancer is a disease which severely effects the human population. Cancer occurs when alterations of genetic material create an abnormal function leading to unregulated proliferation of cells in the body. There is a constant demand for new therapies to treat and prevent this life-threatening disease. Scientific and research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. The plant kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. With the success of these compounds that have been developed into staple drugs for cancer treatment new technologies are emerging to develop the area further. This review discusses the demand for naturally-derived compounds from medicinal plants and their properties which make them targets for potential anticancer treatments.

Keywords: Anti-cancer agents, cancer, natural plant products

1. Introduction
Cancer is a general term applied of series of malignant diseases that may affect different parts of body. These diseases are characterized by a rapid and uncontrolled formation of abnormal cells, which may mass together to form a growth or tumor, or proliferate throughout the body, initiating abnormal growth at other sites. If the process is not arrested, it may progress until it causes the death of the organism. The main forms of treatment for advance stage cancer in humans are surgery, radiation and drugs (cancer chemotherapeutic agents). Cancer chemotherapeutic agents can often provide temporary relief of symptoms and occasionally cures In recent years, a lot of effort has been applied to the synthesis of potential anticancer drugs. Many hundreds of chemical variants of known class of cancer chemotherapeutic agents have been synthesized but have a more side effects. A successful anticancer drug should kill or incapacitate cancer cells without causing excessive damage to normal cells. An appraisal of the currently used anticancer agents showed that many anticancer drugs are mainly from natural origin as well as their semi-synthetic products (Sivaraj *et al.*, 2014) [33].

2. Cancer therapy via phytochemicals
2.1 Vinca Alkaloids: The first agents introduced in clinical use were vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the *Catharanthus roseus* G. Don. (Apocynaceae) (Fig 1a). Vinorelbine (VRLB) and vindesine (VDS) (Fig 1b). Vinorelbine (VRLB) and vindesine (VDS) are primarily using alone or in combination with other chemotherapeutic drugs to combat a variety of cancers. VLB is using for the treatment of lymphomas, leukemias, breast cancer, testicular cancer, lung cancers and Kaposi's sarcoma (Xie and Zhou, 2017) [37].

Fig 1a: *Catharanthus roseus*

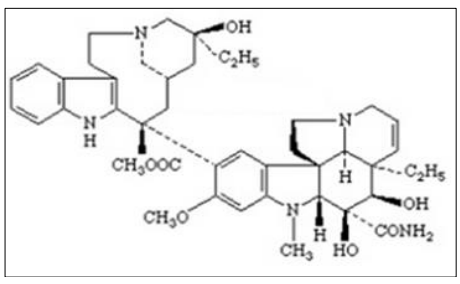

Fig 1b: *Vindesine*

2.2 Taxanes: A more recent advancement in the development of plant derived chemotherapeutic agents are taxanes. Paclitaxel also names as taxol was first isolated from the bark of *Taxus brevifolia* Nutt. (Taxaceae) (Fig 2a**)**. Paclitaxel is used in the treatment of wide variety of cancers including breast, ovarian and non-small-cell lung cancer, and has also shown efficacy against Kaposi sarcoma (Ojima *et al.*, 2016) [30] (Fig 2b).

Fig 2a: *Taxus brevifolia*

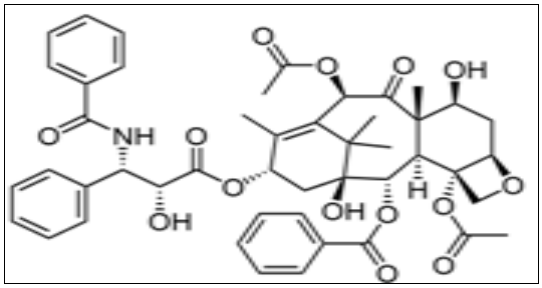

Fig 2b: Taxol

2.3 Camptothecin (CPT): Another advancement that was made in the anti-cancer drug is the class of clinically-active agents derived from camptothecin, isolated from the Chinese ornamental tree, *Camptotheca acuminata* Decne (Nyssaceae) (Fig 3a), and known in China as the tree of joy. The extract of *C. acuminata* was the only extract out of 1000 various plant extracts tested for anti-tumor activity which showed efficacy and the active constituents was identified as camptothecin (Lorence *et al.*, 2004) [23] (Fig 3b).

Fig 3a: *Camptotheca acuminate*

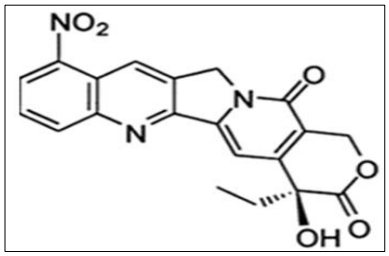

Fig 3b: Campothecin

2.4 Podophyllotoxin: It is obtained from the roots of Podophyllum species, namely, *Podophyllum peltatum Linnaeus* and *Podophyllum emodi Wallich* (Fig 4a). Epipodophyllotoxin is an isomer of podophyllotoxin (Fig 4b). The two clinically important semi-synthetic analogs generated from Epipodophyllotoxin are Etoposide and Teniposide which were found very potential in treating lymphomas, bronchial and testicular cancers (Thomson and Ali, 2003) [36].

Fig 4a: *Podophyllum peltatum*

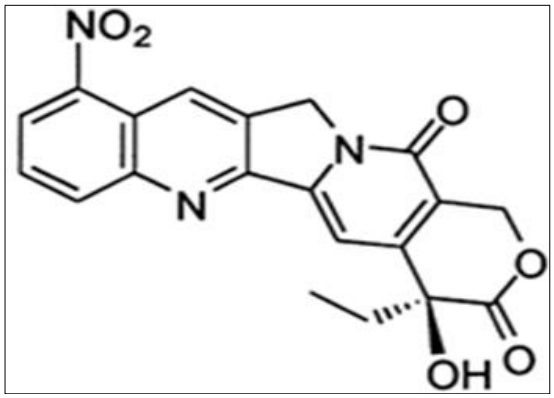

Fig 4b: Podophyllotoxin

3. Natural anti cancer plants

3.1 Achyranthes aspera: *Achyranthes aspera* Linn. (Family-Amaranthaceae) is a commonly found herb as a weed on road sides throughout India (Fig 5a). The methanol extract of *Achyranthes aspera*, its alkaloid, non-alkaloid and saponin fractions has been exhibited significant inhibitory effects on the *Epstein-Barr* virus early antigen activation induced by the carcinogen 12-O-tetradecanoylphorbol-13-acetate (at a concentration of 100µg) (Bhoomika *et al.*, 2007) [4].

3.2 Allium sativum (Allicin): *Allium sativum* (garlic, lasun) is used to treat a wide variety of diseases in India (Fig 5b). Allicin is a major component of raw garlic and some organo-sulfur compounds from garlic, like S-allylcysteine, are reported to retard the growth of chemically induced and transplantable tumors in several animal models (Thomson and Ali, 2003) [36]. Thus the consumption of garlic may beneficial providing some kind of protection from cancer.

3.3 Andrographis paniculata: Phytochemical investigation of the ethanol extract of the aerial parts of *Andographis paniculata* (Fig 5c) has been reported the isolation of 14 compounds; a majority of them are flavonoids and labdane diterpenoids and the cytotoxic activities of these compounds have been evaluated against various cell lines and found that these isolates have a potent tumour inhibitory activity against all investigated cell lines (Geethangili *et al.*, 2008) [10].

3.4 Annona muricata: Graviola is known as *Annona muricata* (Fig 5d). The important class of medicinal components found in graviola is acetogenins, found in the fruit, seeds, leaves, and bark of the graviola plant. Some specific acetogenins have been reportedly identified to be toxic for various cancer cell lines like lung solid human-breast cancer, tumor carcinoma, pancreatic carcinoma, prostatic adenocarcinoma, colonic adenocarcinoma, human lymphoma, liver cancer, and multiple-drug resistant human-breast adenocarcinoma (Lannuzel *et al.*, 2002) [20].

3.5 Bidens pilosa: *Bidens pilosa* is a folk medicine reported with the presence of polyacetylenes, flavonoids, terpenoids, phenylpropanoids and others (Fig 5e). Hexane, chloroform and methanol extracts of *Bidens pilosa* and their fractions were tested on various cancer cell lines and exhibited the antitumor activity of extracts among which hexane extract pronounced the most remarkable activity (Sundararajan *et al.*, 2006) [34].

3.6 Bolbostemma paniculatum : Extraction and further fractionation of chinese herb *Bolbostemma paniculatum* (Cucurbitaceae) (Fig 5f) led to the isolation and characterization of a triterpenoid saponin Tubeimoside-V revealed the apoptotic killing nature on glioblastoma cells, thus suggesting its critical role in antitumor chemotherapy (Guang *et al.*, 2006) [11].

3.7 Cannabis sativa: *In vitro* studies of components *Cannabis sativa* indicate a potential to inhibit human breast cancer cells and to produce tumor eradications (Fig 5g). The active components of *Cannabis sativa* are cannabinoids, their derivatives exert palliative effects in cancer patients by preventing nausea, vomiting and pain and also stimulated the appetite and these compounds have also been shown anti-tumor activity in cell culture and animal models by modulating key cell-signalling pathways (Manuel, 2003) [24].

3.8 Centaurea ainetensis: The cytotoxic activity of *Centaurea ainetensis* crude extracts has been studied in human colon carcinoma cells (Fig 5h). The extract of *Centaurea ainetensis* inhibited the proliferation of a host of colon-derived cancer cells (Najjar, 2008) [26].

3.9 Camellia sinensis (Green Tea): Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol in *Camellia sinensis* (Fig 5i) and inhibit the invasion and migration of human colon and oral cancer cells (Ho *et al.*, 2007) [13]. Apart from EGCG other flavonoids such as rutin, quercetin also linked with anticarcinogencity through inhibition of oxidative activation (Hu *et al.*, 2005) [14].

3.10 Daphne mezereum: *Daphne mezereum* is a plant widely used for treating cancer like symptoms (Fig 5j). A hydro alcohol extract of *Daphne mezereum*has exhibited a potent antileukemic activity against lymphocytic leukemia in mice (Kupchan and Baxter, 1975) [19].

3.11 Gossypium hirsutum: *Gossypium hirustum* (Fig 5k) also called as Gossypol or cottonseed oil and used as a male contraceptive in the treatment of metastatic carcinoma of endometrium or ovary and also used in HIV (Coyle *et al.*, 1994) [6]. Some *in vivo* and *in vitro* studies revealed the antitumor properties of gossypol on many cytosolic and mitochondrial enzyme systems that is fundamental for tumor cell growth, including melanoma, endometrial, colon, lung, prostate, breast, brain, and adrenocortical cancer (Liang *et al.*, 1995) [22].

3.12 Hydrocotyle asiatica: *Hydrocotyle asiatica* (Fig 5l) is the scientific name of Gotu kola, brahmi, synonyms with *Centella asiatica*. In early studies on animal tissue, brahmi exhibited cytotoxic and antitumor properties. An aqueous extract of leaves of brahmi has shown prominent cytotoxic activity against mouse melanoma, human breast cancer, rat glioma cell lines (Frederico *et al.*, 2009) [8].

3.13 Hypericum perforatum: Hypericin is the active constituent which was isolated and characterized from *Hypericum perforatum* (Fig 5m) and inhibits serotoninre uptake and thus reduces cell growth on several cancer cell lines, *in vitro* and *in vivo* (Martarelli *et al.*, 2004) [25].

3.14 Mangifera indica: M*angifera indica* is a nutritional supplement used in several tribes and countries as a folklore remedy (Fig 5n). This aqueous extract is considered in Cuba beneficial and used in healthy people to reduce environmental, nutritional risk factors, and also prolong the quality of life through increasing free radical scavenging mechanism (Garrido-Garrido *et al.*, 2007) [9]. Ethno-botanical studies resulted in a great improvement of life quality in cancer patients (Tamayo *et al.*, 2001) [35]. The principle active constituents of mango consists of a mixture of terpenoids, polyphenols, steroids, fatty acids and microelements that imparts properties and provide antioxidant supplements (Nunez *et al.*, 2002) [29].

3.15 Nervilia fordii: *Nervelia fordii* is a drug used in China as a folklore remedy. Petroleum ether and ethyl acetate extracts of *Nervilia fordii* (Fig 5o) has been screened out for its anticancer properties using mice models and have shown prominent anticancer effects when administered to S-180 mice and H-22 mice models; also prolong the life of cancer bearing mice (Zhen, 2007) [38]. This study suggests, *Nervilia fordii* can exploit as cancer inhibiting agent and further research work is required to isolate active constituent/s present in drug drug.

3.16 Oroxylum indicum: ***O****roxylum indicum* (Sonapatha) is used in various polyherbal formulations in Indian system of medicine. Studies have proved anticancer potential of *Oroxylum indicum* (Fig 5p) using various models. A 95% ethanol extract exhibited cytotoxic activity against Hep2 cell lines at a concentration of 0.05% (Narisa *et al.*, 2006) [27]. Flavonoid baicalein present in *Oroxylum indicum* has anti-tumour effect on human cancer cell lines and inhibited the 50% proliferation of HL-60 cell lines at a concentration of 25-30 microM (Roy *et al.*, 2007) [31].

3.17 Picrorrhiza kurroa*:* *Picrorrhiza kurroa* (Kutki) used as a hepatoprotective remedy in Indian system of medicine, inhibited liver cancer growth formed due to exposure of chemicals in animal studies (Fig 5q). Kutkin is the active constituent of herb which is a combination of picrosides and kutkosides. Kutkin is found to inhibit level of lipid peroxidases, hydroperoxidases, free radical producing agents and also facilitates the recovery of antioxidant SOD, which is needed to prevent the liver from oxidative damage (Jenna *et al.*, 1999) [16].

3.18 Rubia cordifolia: The hexapeptides and quinones found in *Rubia cordifolia* (Fig 5r) have showed a prominent antitumor activity by binding to eukaryotic 80S ribosomes. This binding resulted in inhibition of aminoacyl-tRNA binding and peptidyl-tRNA translocation, which is a necessary mechanism for protein synthesis (Itokawa *et al.*, 2005) [15]. Mollugin is a constituent that was isolated from chloroform extract of *Rubia cordifolia* roots and showed a significant activity against lymphoid leukemia in mice and also showed the inhibition of passive cutaneous anaphylaxis, protection of mast cells degranulation in rats (Gupta *et al.*, 1999) [12].

3.19 Salvia miltiorrhiza: Tanshinone-I was isolated from traditional herb *Salvia miltiorrhizae* (Fig 5s) was investigated on the expression of intercellular adhesion molecule. The study revealed a potential anticancer effect of tanshinone I on breast cancer cells, suggesting that tanshinone-I may serve as an effective drug for the treatment of breast cancer (Nizamutdinova *et al.*, 2008) [28].

3.20 Silybum marianum: Silymarinis a flavonoid compound isolated from the milk thistle plant *Silybum marianum* (Fig 5t). *S*ilymarin was studied against UV radiation induced skin cancer in mice (Kim *et al.*, 2009) [18]. The probable mechanism of silymarin can be its suppression of proliferation of tumor cells; this is accomplished through cell cycle arrest at the G1/S-phase, induction of cyclin-dependent kinase inhibitors, down-regulation of anti-apoptotic gene products, inhibition of cell-survival kinases and inhibition of inflammatory transcription factors. Silymarin was also found to down regulate gene products associated in the proliferation of tumor cells, invasion, angiogenesis and metastasis (Agarwal *et al.*, 2006) [2].

3.21 Terminalia chebula*:* *Terminalia chebula*is a source of hydrolysable tannis and its antimutagenic activity in *Salmonella typhimurium* (Fig 5u) has been documented (Kaur *et al.*, 1998) [17]. Phenols like chebulinic acid, tannic acid, ellagic acid are the cancer growth inhibitors found in the fruits of *Terminalia chebula* (Arora *et al.*, 2003) [3]. *Terminalia chebula* fruits powder and its acetone extract of bark have been reported with promising antimutagenic and anticarcinogenic activity (Saleem *et al.*, 2002) [32].

3.22 Vernonia amygdalina: *Vernonia amygdalina* (VA), member of the Compositae family, is a small shrub that grows in the tropical Africa (Fig 5v). Immuno histochemical data revealed that *Vernonia amygdalina* increased basal apoptotic but decreased angiogenic activities in both breast cancernoma cells (Lecia *et al.*, 2008) [21].

3.23 Withania somnifera (Withanolides): Withaferin-A is a withanolide isolated from the roots of *Withania somnifera* (Fig 5w). Withaferin-A has been shown a significant tumor reducing activity in carcinomas like carcinoma of nasopharynx, Sarcoma 180, Sarcoma Black and E 0771 mammary adenocarcinoma. *Withania somnifera* is highly appreciated in Ayurveda for cancer patients and also used as a folklore remedy for combating the cancer like conditions, also prolong the life (Devi *et al.*, 1996) [7].

3.24 Zingiber officinale: *Zingiber officinale* ethanol extract was investigated to find out its antitumor effects in skin tumorigenesis model (Fig 5x). Ginger's natural bio-actives, specifically ginger extract and 6-gigerol, have also been investigated for their *in vitro* inhibition of two key aspects of colon cancer biology, cancer cell proliferation and angiogenic potential of endothelial cell tubule formation. These active ginger constituents linked to a direct effect on cancer cells (Brown, 2008) [5]. The suggested mechanism of action of Ginger extract on colon cancer cells may be its suppression and arresting the G0/G1-phase, reducing DNA synthesis and inducing apoptosis (Abdullah *et al.*, 2010) [1].

a. Achyranthes aspera

b. Allium sativum

c. Andrographis paniculata

d. Annona muricata

e. Bidens pilosa

f. Bolbostemma paniculatum

g. Cannabis sativa

h. Centaurea ainetensis

i. Camellia sinensis *j. Daphne mezereum* *k. Gossypium hirsutum* *l. Hydrocotyle asiatica*

m. Hypericum perforatum n. *Mangifera indica* o. *Nervilia fordii* p. *Oroxylum indicum*

q. Picrorrhiza kurroa *r. Rubia cordifolia* *s. Salvia miltiorrhiza* *t. Silybum marianum*

u. Terminalia chebula *v. Vernonia amygdalina* *w. Withania somnifera* *x. Zingiber officinale*

Fig 5: Natural anti-cancer plants

4. Conclusion

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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