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A Review on Plants a useful source of anti-cancer drugs

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ABSTRACT

Plant-derived compounds have played very crucial role in the field of anti-cancer drugs. Various important anti-cancer agents like vincristine, vinblastin, camptothecin, paclitaxel and podophyllotoxin have been isolated from the various plant source. Most of the anticancer drugs act on tubulin site. Beauty of these drugs is planar structure because space between a & ß-subunit of tubulin is very less and planar compounds can fit in the gap and bind to ß-Subunit. Several new agents have been found against cancer including combretastatin A4 phosphate, aliphatic esters and lignans. The basic aim of this review is to explore the potential of newly discovered anticancer compounds, from natural resourses, as a lead for anticancer drug development.

Key words: Anticancer drugs, Camptothecins, Combretastatins, Podophyllotoxins, Tubulin inhibitors.

INTRODUCTION

Cancer is an ailment that affects over 200 types of cells. Uncontrolled cell proliferation, differentiation and death of the invaded organs and tissues are the major characteristics. The major difficulties in the treatment of this ailment are toxicity, drug resistance and low specificity[1]. Cancer is one of the most death causing diseases in humans. There is considerable scientific and commercial interest in the continuing discovery of new anticancer agents from natural product sources[2]. The potential of using natural products as anticancer agents was recognized in the 1950s by the U.S. National Cancer Institute (NCI)[3] and has since made major contributions to the discovery of new naturally occurring anticancer agents[4]. The semi-synthetic and synthetic derivatives of active constituents derived from plants are important sources of antitumor drugs[1]. Over 50% of the drugs in clinical trials for anticancer activity were isolated from natural sources or are related to the natural source[5] for example *Vinca* alkaloids, vinblastine and vincristine, were isolated from *Catharanthus roseus* (Apocynaceae) ,similarly the lignans derivatives etoposide and teniposide are semi-synthetic derivatives of epipodophyllotoxin isolated from species of the genus *Podophyllum* (Berberidaceae), as well as the taxanes isolated from species of the genus *Taxus* (Taxaceae) , the semi-synthetic derivatives of camptothecin, irinotecan and topotecan, isolated from *Camptotheca acuminata* (Nyssaceae), and several others .[6-10]

Classification of Cancer

Cancers can be classified in two ways: by the type of tissue from which they arise and by the location in the body from which they start to grow. The first way is known as classification by histology and is defined internationally. The second method of classification is not very useful to clinicians, but the general public may find it easier to talk about cancers as being in the breast, or lung.

There are five major histological classifications:

Carcinoma: These cancers grow from epithelial tissue, which is tissue that makes up the outer and inner lining of the body. Carcinomas account for as much as 90 percent of all cancers.

Sarcoma: These cancers develop in supportive and structural body tissues, like bones, muscles, tendons, cartilage, and fat.

Myeloma: These cancers develop in the plasma cells of the bone marrow. These are cells that produce some of the proteins that circulate in the bloodstream.

Leukemia: These cancers are also called liquid cancers or blood cancers. They start in the bone marrow. They cause an overproduction of white blood cells that do not reach their mature form, but they can also cause cancerous growth of red blood cells.

Lymphoma: These cancers originate in the organs and tissues of the lymphatic system, including lymph nodes, spleen, or tonsils. Since lymph vessels circulate all through the body, a lymphoma may develop in the lymph system of any organ, such as the stomach, breast, or brain.

How Cancer Drugs Work

All cancer drugs on the whole show the same mechanism of action: They block the growth of living cells. But the way by which they achieve this goal differs on the basis of cellular functions on which each drug acts. The characteristics that lead to cell growth can be used against the cell, and this advantage is used in chemotherapy.

MECHANISM OF ACTION

1.By inhibiting Topoisomerase

Topoisomerase inhibitors are agents designed to interfere with the action of topoisomerase enzymes (topoisomerase I :-cuts one strand of a DNA double helix, relaxation occurs, and then the cut strand is reannealed and topoisomerase II:- cuts both strands of one DNA double helix, passes another unbroken DNA helix through it, and then reanneals the cut strand), which are enzymes that control the changes in DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle.

2.Interference with microtubule

Although it is widely accepted that antitubulin agents block cell division by inhibition of the mitotic spindle, the mechanism of action of antitubulin agents on microtubules remains to be determined. There are two types of mechanisms by which microtubule inhibitors can exert their chemotherapeutic effect.

Tubulin stabilizing agents

Normally the tubulin polymerizes to microtubulin and again microtubulin converts into tubulin and this process is in equilibrium. Generally 24-nm microtubulin bundles are formed which leads to cell multiplication process, but taxol makes stabler bundles of microtubulins[11] of size 22 nm. There is a formation of unnatural bundles of microtubules due to defective polymerization process and thus no mitotic spindle. The cancerous cells do not have a check point to detect the absence of a spindle and cell cycle continue, which later leads to cell death. Because of this , taxol is sometimes also referred to as a spindle poison[18] ***Tubulin destabilizing agent.***

According to McGown and Fox the trimethoxy benzene moiety in compounds like colchicine, podophyllotoxin and CA-4 probably provides a favourable binding site for tubulin.[18] It has been concluded that both vinca alkaloids and CA-4, which are colchicine like inhibitor act by preventing polymerization of mi

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crotubules but there binding sites are different . Colchicine binds to a site near the intra-dimer interface and alters lateral contacts within the microbubule, blocking microtubule polymerization.[12] On the other hand vinca alkaloids inhibit microtubule assembly by cross linking at the inter dimer interface; they sterically distort the protofilament and induce tubulin to form alternate spiral polymers.

3.By curbing blood supply to tumor cells.

CA-4P (combretastatin-4, 3-O phosphate) significantly reduces blood flow to the tumor cells in a dose-dependent manner as shown by Magnetic resonance imaging (MRI) experiments[18]. Thus, it acted as an antivascular targeting agent, which blocks tumour blood supply. This study opened the new doors toward the new class of anticancer therapies those act by interfering a tumours blood supply. It is reported that it cause the shutdown of blood flow in many animals tumors leading to extensive tumour necrosis. A sodium phosphate derivative of CA-4 induced a complete vascular shutdown within metastatic tumours , while the reduction in blood flow by CA-4 is up to 70%.[18]

4.By apoptosis induction:

One of the important processes in the development and tissue homeostasis is the Programmed cell death (apoptosis). This mechanism plays role when the cells are exposed to certain toxic agents. Apoptosis is an important process for eliminating cancer cells. Induction-apoptosis is a key mechanism by which anticancer compounds show their action.

Anti-cancer compoundes obtained from various plants:

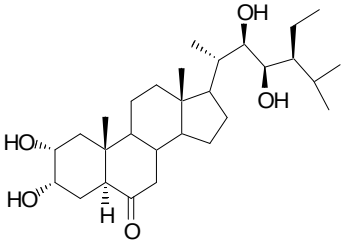
1)Brassinosteroids, Anticancer compounds from *Brassica napus*[13]

Biological Source Rapeseed (*Brassica napus)*
Family Brassicaceae (mustard or cabbage family)
Syn. Rape, oilseed rape, rapa, rapaseed and canola

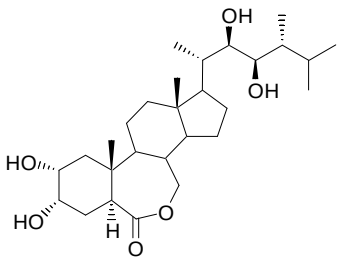
Brassinosteroids (BRs) are polyhydroxy steroidal plant hormones which play important regulatory roles in various physiological processes like growth, differentiation, root and stem elongation, and disease resistance etc. [14, 15]. These were first explored nearly forty years ago by Mitchell et al. The yield of brassinosteriods from 230 kg of *Brassica napus* pollen was only 10 mg. This Brassinosteroids include more than 70 compounds which are distributed throughout the plant kingdom.[13] BRs have been isolated from various parts of plant like seeds, fruits, leaves, galls and pollen[3]. They are the most structurally similar to animal steroid hormones[16]. Brassinolide, the most biologically active BR, was initially isolated from 200 kg of Brassica napusve[17]. Brassinolide has been identified in all plant species examined to date[3].

1.2. Mechanism of action of Brassinosteroids

Natural BRs inhibit the growth of various cancer cell lines at micromolar concentrations, and have minimal effects on normal cells. Information on the mechanisms of action of BRs at a molecular level is still under the shadow of doubt, but they may involve interactions with steroid[15] receptors.



28-homocastasterone



24-epibrassinolide[15]

Both BRs inhibited cell growth in a dose dependent manner in the cancer cell lines. Experiments showed that BR treatment arrested MCF-7, MDA-MB-468 and LNCaP cells in G1 phase of the cell cycle and induced apoptosis in MDA-MB-468, LNCaP, and slightly in the DU-145 cells. Therefore, these plant hormones are promising leads for potential anticancer drugs[15].

1)Camptothecin, Anti cancer compound from *Camptotheca accuminata*[18]

Biological source : Bark and stem of *Camptotheca acuminate*
Family : Cornaceae
Syn. : Happy tree, Cancer tree, Tree of life, Tree of joy, Tree of love

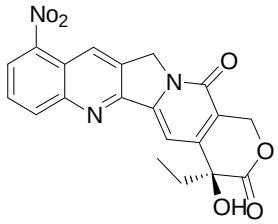
The discovery of camptothecin (CPT, 1) by M. E. Wall and M. C. Wani in 1996 as an anticancer drug with a unique mode of action, (Inhibition of DNA topoisomerase I) added an entirely new dimension to the field of chemotherapy. This cytotoxic quinoline alkaloid was first extracted from the stem wood of the Chinese ornamental tree *Camptotheca acuminate*. It has also been isolated from *Ophiorrhiza pumila* and *Mapia foetida*[18]

2.3. Mechanism of action

DNA topoisomerase-I inhibition progressively become irreversible with increasing concentration and exposure duration. It has also been found that camptothecin is selectively cytotoxic to S-phase cells, arrests cells in the G-2 phase and induces fragmentation of chromosomal DNA[18].

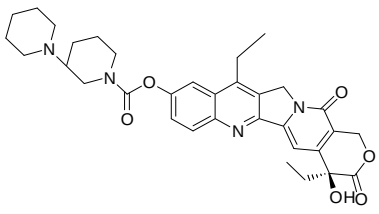
2.2. Chemistry

It consists of a pentacyclic ring structure that includes a pyrrole (3,4b) quinoline moiety it has one asymmetric centre within the a-hydroxy lactone ring with 20(S) configuration (ring E) [18].

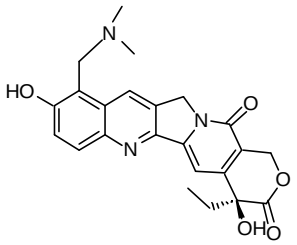


Camptothecin (CPT) [18]

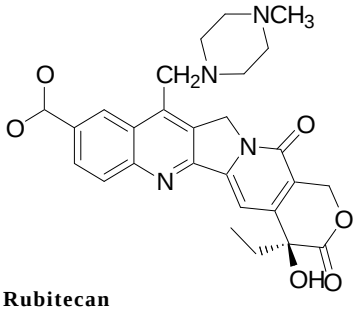
2.5. Semi synthetic derivatives



Irinotecan



Topotecan



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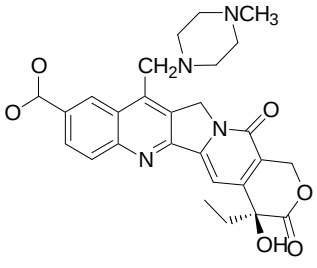


Lurtotecan

We have synthesized topotecan by new approach using methylene chloride,as a single carbon source, under solid-liquid phase transfer catalysis, and a US patent has been granted for the process. (US Patent no. 6,660861 December 9, 2003)[19]. CPT shows anticancer activity mainly for solid tumours. It inhibits DNA topoisomerase I. It shows anticancer activity mainly against colon and pancreatic cancer cells. But its analogues show anticancer activity in breast, liver, prostate and many other malignancies[18].

1)Taxol, Anticancer compound from *Taxus brevifolia*[18,20]

Biological source : Bark of the *Taxus brevifolia*
Family : Taxaceae
Syn. : Pacific Yew or Western Yew

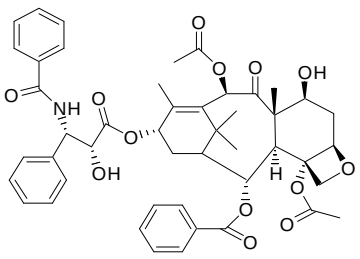
Paclitaxel (Taxol) is a complex polyoxygenated diterpenoid[18] mitotic inhibitor used in cancer chemotherapy. It was discovered in a National Cancer Institute program at the Research Triangle Institute in 1967, Monroe E. Wall and Mansukh C. Wani isolated it from the bark of the Pacific Yew tree, *Taxus brevifolia* and named it 'taxol'. Later on, it was isolated from several other species of taxus including *Taxus wallichiana* (the Himalayan yew). So far, more than 300 taxoids have been isolated and characterized from different species of taxus.

3.3. Mechanism of action

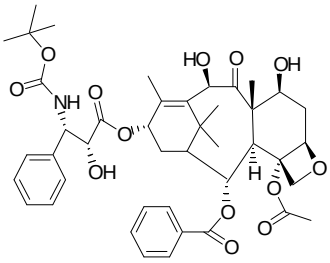
Taxol shows an unique mode of action by acting as microtubulin stabilizing agent.

3.2. Chemistry

It has been found to have a basic [9.3.1.0] pentadecane, tetracyclic ring system and it also has a N-benzoyl-b-phenylisoserine side chain attached at the C-13 hydroxyl as an ester linkage[18].



Taxol



Docetaxol

It is reported that Taxol showed promising results in phase I and phase II clinical trials in lung, ovarian and breast cancers and squamous cell carcinoma of the head and neck. Taxol was approved by US FDA in 1992 for the treatment of drug refractory metastatic ovarian cancer[18]

4. Combretastatin A-4, anticancer compound from *Combretaum caffrum*[18]

Biological Source : Bark of *Combretum caffrum*
Family : Combretaceae
Syn : South African Bush Willow

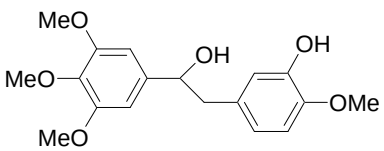
Combretastatins are antimitotic agents which were isolated from the bark of the South African tree *Combretum caffrum*. The most potent combretastatin A-4 [cis-1-(3,4,5-trimethoxyphenyl)- 2-(3'-hydroxy-4'-methoxy phenyl) ethene] is a stilbene which compete with colchicine for binding site on tubulin. CA-4 is a potent cytotoxic agent which strongly inhibits the polymerization of brain tubulin by binding to the colchicine site. CA-4 is thus a promising lead molecule for the development of anticancer drugs[18] Combretastatin A-1 is also a potent cytotoxic agent .

4.3. Mechanism of action[18]

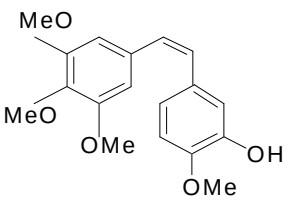
Combretastatin is a member of the colchicine-like inhibitors of microtubulin. CA-4P (combretastatin-4, 3-O phosphate) significantly reduces blood flow to the tumour cells in a dose-dependent manner.

2. Chemistry and Isolation[18]

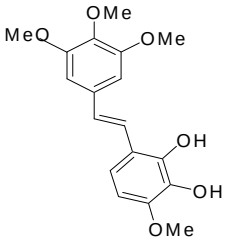
In 1982 Pettit et al isolated, biologically active bibenzyls, stilbenes and phenantherenes from the bark of African willow tree C. *caffrum* at Arizona State University, USA. Combretastatins A-1 and A-4 were isolated by the same group in 1987 and 1989, respectively. Chemically, these stilbene derivatives have two phenyl rings separated by a C-C double bond. Three methoxy groups are there in Ring-A at 3,4,5-positions while in ring B one hydroxyl group is at the C-3 and one methoxy group at the C-4 position.



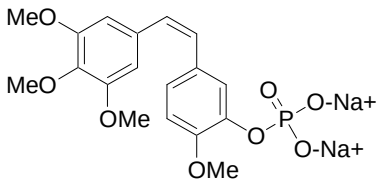
Combretastatin



Combretastati A-4

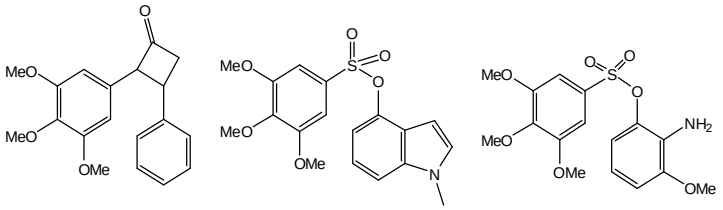


Combretastatin A-1



Prodrug

4.6. Semi synthetic and synthetic derivatives



CA-4 analogues having different moieties; azetidinone and novel sulfonate analogues.CA-4 is found to be active against colon, lung and leukaemia cancers. It is stated that it is the most cytotoxic phytomolecule isolated so far.[18]

The key feature of structurally diverse molecules , like Combretastatins, chalcones, benzophenones and lignans, to share same activity as tubulin inhibitors can be explained on the basis of "Butterfly model" that is from the molecular model view the two aromatic rings in these molecules are arranged like the two wings of butterfly leading to have cisoid disposition of these molecules.

1. Podophyllotoxin, anticancer compound from *Podophyllum peltatum*[18]

Biological Source : Rhizome of American Mayapple (*Podophyllum peltatum*).
Family : Berberidaceae
Syn. : Hogapple, Indian apple, mayflower, Umbrella plant (shape of the leaves), Wild lemon (flavor of the fruit), Wild mandrake, American mandrake (shape of rhizomes) or "devil's apple"

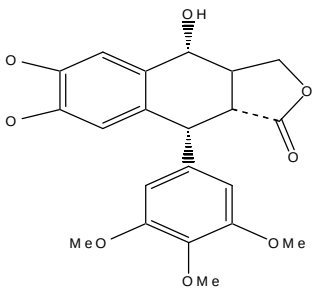
Podwyssotzki isolated Podophyllotoxin (PDT) and deoxypodophyllotoxin which are naturally occurring aryltetralin lignans. Podophyllotoxin, was first isolated in 1880 from the North American plant *Podophyllum peltatum* Linnaeus (American podophyllum), commonly known as the American mandrake or May apple,which was found to be a a non-alkaloidal bioactive lignan. it has also been isolated from *P. emodi* Wall (Indian podophyllum, syn. *P. hexandrum* Royle) and *P. pleianthum* (Taiwanese podophyllum).4-deoxypodophyllotoxin has been isolated from *Anthriscus sylvestris* and *Pulsatilla koreana.*

5.3. Mechanism of action

Podophyllotoxin inhibits assembly of microtubules and supposed to arrest the cell cycle in metaphase.[20]This shows its effect by blocking the catalytic activity of DNA topoisomerase II. It also binds at the colchicine site of the tubulin.

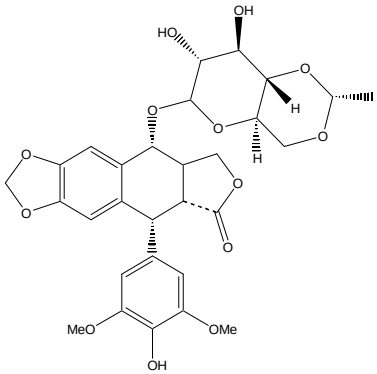
5.2. Chemistry

Chemically, it is found to be an aryltetralin lignan, having a lactone ring.[18]

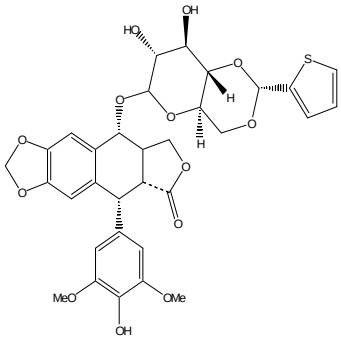


Podophyllotoxin

5.5. Semi synthetic and synthetic epipodophyllotoxin derivatives



Etoposide



Teniposide

In various experiments podophyllotoxin showed strong cytotoxic activity against various cancer cell lines. It is found to be effective in the treatment of Wilms tumours, non- Hodgkins and in various genital tumours as well as in other lymphomas and lung cancer.[18] Due to complicated side effects PDT as such is not used as a drug.[21] Many structure modifications were performed to obtain more potent and less toxic anticancer agents, such as epipodo phyllotoxin, etoposide and teniposide. These are the most widely used derivatives for the treatment of lymphomas, acute leukaemia, testicular cancer, small cell lung cancer, ovarian, bladder, brain cancers, etc.

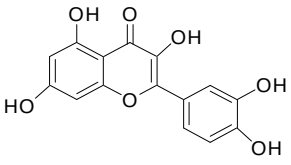
6.Anticancer compound from *Saxifraga stolonifera* (L) Meeb [22]
Biological source : Whole plant of *Saxifraga stolonifera* (L) Meeb
Family : Saxifragaceae

It have been found that some flavones and polyphenols present in traditional Chinese medicines decrease various types of experimental carcinogenesis.[22] *Saxifraga stolonifera* (L) Meeb a traditional chiniese plant which is a dicotyledon, is a perennial herbaceous plant grow at an altitude of 390–3600 m in China, Russia, Japan and Korea. The whole plant is known for its use in Chinese medicines to treat various diseases like measles, tympanitis, erysipelas, hemoptysis, piles, and hair fall.[23] Constituents and extracts of *S. stolonifera* can block tumors at various sites as indicated by various pharmacological experiments, e.g. gastric, prostate, breast and leukemia. it has also been reported that *S. stolonifera* can inhibit proliferation of cancer cells in vivo by induction of apoptosis.[22]

6.5. Mechanism of Action
One of the important processes in the development and tissue homeostasis is the Programmed cell death (apoptosis).

6.2. Method of Isolation
The isolation process for different constituents from *Saxifraga stolonifera* [22].

6.3. Chemistry
Various compounds have been isolated from ethanol extracts and identified as (1)n-C31H64,(2) (n-C17H35)2CO (3) ß-sitosterol (4) n-C29H60 (5) Bergenin (6) Protocatechuic acid (7) Gallic acid (8) Quercitrin 3-O-α-L-rhamnoside (9) Quercetin (10) Quercetin 3-O-ß-D-gluco-pyranoside by analytical and spectral methods.[22] But out of all these Quercetin was found to be most potent.



Quercetin.

Quercetin was found to be most effective on human gastric carcinoma cells BGC-823 cells in a time- and dose-dependent manner e.g. as reported, the growth inhibition ratio of quercetin on BGC-823 cells was 39.3%after 72 h treatment at 100 μM. Quercetin has proved to be of potential use as a chemo-preventive and therapeutic agent for cancers[22].

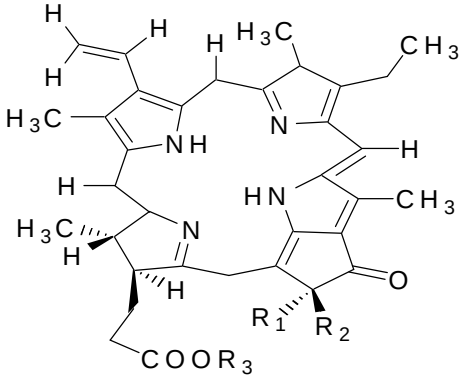
7. Anti-cancer compound from *Typhonium flagelliforme*[24]
Biological Source : Juice of whole plant ***Typhonium flagelliforme***
Family : Araceae
Syn. : Rodent tuber (English), Keladi tikus (Malay)

It is a herbal plant which is used in Malaysia to treat various types of cancer

7.5. Mechanism of action[24]
It exerts its anticancer effect by inducing apoptosis in the cells as confirmed in invitro experiments on NCI-H23 cell lines.

7.2.Isolation and Chemistry[24]
Many chemical constituents have been isolated but none has been tested for the anticancer activity. Isolated chemical constituents include phenyltridecanoic acid, methyl 13-phenyltridecanoate , several aliphatic esters , coniferin, its methyl derivative , ß-sitosterol, ß-daucosterol and 1-O-ß-glucopyranosyl-2- (hydroxyloctadecanoyl)amido-4,8-octadecadiene-1,3-diol.Recently 11 more chemical constituents have been identified in the dichloromethane extract of *Typhonium flagelliforme*[24].

(1) pheophorbide-a (2) pheophorbide-a' (3) pyropheophorbide-a (4) methyl pyropheophorbide-a (5) hexadecanoic acid (6) oleic acid (7) linoleic acid (8) linolenic acid (9) campesterol (10) stigmasterol and (11) sitosterol. Although **1-4** are the main constituents but anticancer effect of *Typhonium flagelliforme* may be due to synergistic effect of several substances because evidence shows that the individual constituents of the plant were not as active as the fraction, which is of a combination of all these substances.



1.R1 = $COOCH_3$; R2 = H ; R3 = H
2.R1 = H ; R2 = $COOCH_3$; R3 = H
3.R1 = H ; R2 = H ; R3 = H
R1 = H ; R2 = H ; R3 = CH_3

Tabebuia impetiginosa is an evergreen, canopy tree and has rosy (or purple) flowers. This plant is indigenous to the Amazon rain forest, but found all over Argentina, Bolivia, Brazil, Colombia, Ecuador, French etc. This plant is commonly known as Pau d'arco (bowtree) in Portuguese. Its common names are ipê roxo (red thick bark), taheebo (ant wood), *tajy* ("to have strength and vigor") and red (or purple) lapacho [29]. The family name *Tabebuia* has been derived from an Indian language spoken in Brazil, while the species name *impetiginosa has been* derived from the use of the bark against impetigo[30].

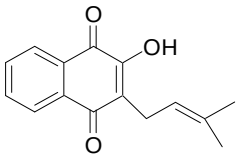
8.4. Mechanism of action[29]
As reported ß-lapachone showed ability to inhibit topoisomerase I. reported that ß-lapachone inhibited catalytic activity of eukaryotic topoisomerase I, but not topoisomerase I-mediated DNA cleavage. Another mechanism by which ß-lapachone shows it anticancer activity was given by Lee and co-workers. They showed that ß-lapachone exerts its effect by re-activating the apoptotic pathways which cleared the cancerous cells from the body through an increase of Bax/Bcl2 and activation of Caspase 3, It also cause loss of prostaglandin-E2 and telomerase activity by inhibition of COX-2 and hTERT expression.

8.2. Isolation[29]
Active constituents were isolted from methanolic extract and many techniques were applied for the isolation, like solvent assisted flavour evaporation (SAFE), Steam distillation under reduced pressure, followed by continuous liquid-to-liquid

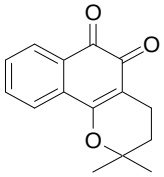
extraction (DRP-LLE) and high-flow dynamic headspace sampling (DHS).

8.3. Chemistry and Structures of compounds

There are a number of naturally occurring compounds in the bark and heart-wood of Red Lapacho , particularly in the methanolic extract (Park et al., 2004)[31],mainly these compounds are flavonoids , cyclopentene dialdehydes, benzoic acid and benzaldehyde derivatives, quinones, furanonaphthoquinones and, most importantly, naphtoquinones and anthraquinones[29]. Lapachol and ß- lapachone were the two main compounds among the numbers of the isolated compounds but lapachol was discarded by the NCI because it lacked anticancer chemotherapeutic value, on the other hand ß -lapachone has been selected as a research molecule in cancer therapy.



Lapachol



ß- lapachone

It is said about the Red Lapacho that it is one of the "miraculous" cures for cancer and tumours. It has attracted quite attention in Brazil and Argentina as a 'wonder drug'[29].

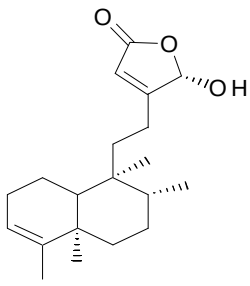
As reported *Tabebuia impetiginosa* has shown activity against the many cancer cell lines like: carcinoma (Walker 256), prostate cancer (DU-145, PC-3, LNCaP)[32], human promyelocytic leukaemia (HL- 60), breast carcinoma, ovarian carcinoma, epidermoid laryngeal carcinoma (HEp-2) [33], radio-resistant human malignant melanoma (U1-Mel) also against human breast cancer (MCF-7:WS8) [34], human lung adenocarcinoma (A549), human cervical cancer (HeLa) and osteosarcoma (HuO9)[35].

9. Anti-cancer compounds from *Polyalthia cerasoides* seeds[36]

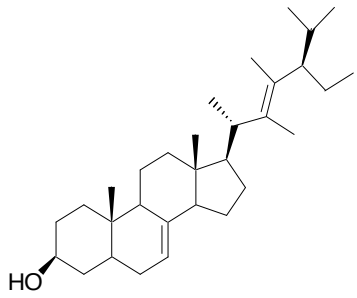
Biological source : *Polyalthia cerasoides* (Roxb.)Bedd.
Family : Annonaceae

Polyalthia cerasoide (Roxb.)Bedd. (Annonaceae) is a medium sized tree which is found in almost all forests of Deccan India upto 3000ft .The stem bark of this plant is used as tonic to combat stress (Padma et al.2001)[37] by clinicians of Tamilnadu, India. The active constituents of the plant have antibacterial, anti-fungal, cytotoxic and antimalarial properties.

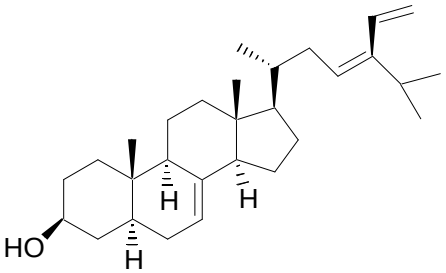
9.2. Isolation & Structure[36]



Clerodane diterpinoid



Spinasterol



α- Spinosterol

9.4. Mechanism of action

Initial experimental results had shown that the compounds induce apoptosis.treated cells showed apoptotic morphology, condensed nuclei, membrane blebbing and formation of apoptotic bodies compared to control cells, which had cellular and nuclear architecture[36]. Results showed that Clerodane diterpenoids induce apoptosis by topoisomarase poisoning (Richter et al.2004)[38] and phytosterols induce apoptosis by Bax activation (Choi et al. 2003)[39]. a-Spinasterol is also proved to be a potent inhibitor of glomerular mesangial cell proliferation and its inhibitory potency was found to be 1000 times higher than that of simvastatin.

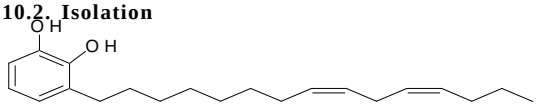
Isolated compounds showed Anti-proliferative activity against colon cancer cell lines (Caco2)[36]

10. Anticancer catechol from *Semecarpus anacardium*[40]

Biological Source :Fruits of S*emicarpus anacardium*
Family :Anacardiaceae
Syn. :Bhallatak, Ker beeja, Marking Nut

Semecarpus anacardium is a tropical tree growing wild in the Indian subcontinent, the fruits of this plant are used extensively for the treatment of human cancers in the Ayurvedic medicine. "Kalpaamruthaa" is nut milk extract of *semecarpus anacardium*, used in Sidda medicine which have antioxidant, analgesic, antipyretic and ulcerogenic properties. The nut extract also possess antitumor activity due to the suppression of hypoxic and angiogenic factors (hypoxia inducible factor-1 alpha, vascular endothelial growth factor, and inducible nitric oxide synthase). It is reported by Chakraborthy et al., that the oil of *semecarpus anacardium* nut have cytotoxic effects against acute myeloblastic leukemia (HL-60), chronic myelogeinc leukemia (K-562), breast adenocarcinoma (MCF-7) and cervical epithelial carcinoma (HeLa) cell lines [41].

10.2. Isolation



Chemical structure of 3-(8'(Z), 11'(Z)-pentadecadienyl) catechol .

It was found to be active against Colon cancer cell lines, Breast cancer cell lines and Multidrug resistance cell lines as well.

11. Vinca alkaloids from *Cantharanthus roseus*[42]

Biological source : Dried whole plant of *Cantharanthus roseus*
Family : Apocynaceae
Syn. : Catharanthus,Periwinkle.Madagascar,Sadabahar

11.3. Mechanism of action

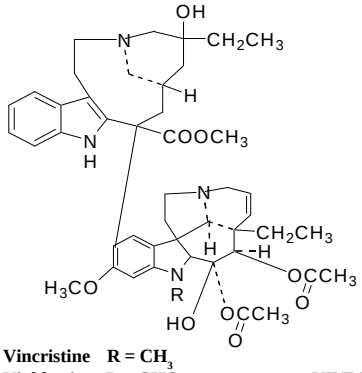
Vinca alkaloids are anti-mitotic and anti-microtubule agents.

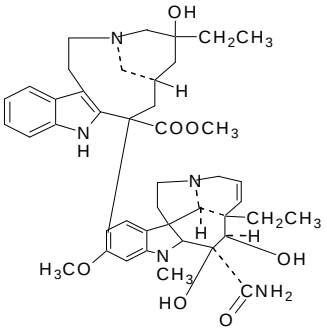
Vincristine shows it action by acting as antimitotic agent and arresting mitosis at the metaphase Vinblastine arrest mitosis at metaphase and also shows interference in amino acid synthesis by tumors cells

11.2. Chemistry

The vinca alkaloid antimitotic agents are asymmetrical dimeric compounds

11.4. Structure



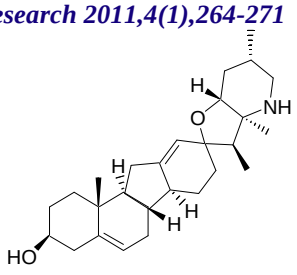


Vincristine R = CH_3
Vinblastine R = CHO **VINDESINE**

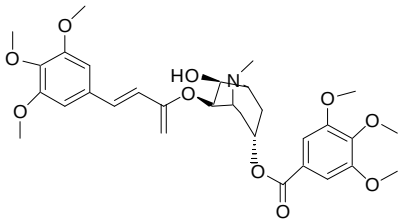
Vinblastine Hodgkin's lymphoma, non-small cell lung cancer, breast cancer, head and neck cancer, and testicular
cancer Vincristine Hodgkin's lymphoma acute lymphoblastic leukemia, nephroblastoma (Wilms tumor, a kidney tumor common in children).
Vindesine Leukaemia, lymphoma, melanoma, breast cancer, and lung cancer.
Vinorlbine Breast cancer and non-small cell lung cancer.

Table. Various other plants which possess anticancer activity and their chemical constituents

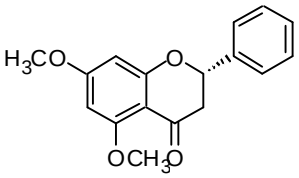
S.No	Plant	Family	Active constituent
1	*Cephalotaxus harringtonia*	Cephalotaxaceae	Homoharringtonine[43]
2	*Bleckeria vitensis A.C.Sm.*	Apocynaceae	1.Elliptinium[43](Derivative of ellipticine)
3	*Raphanus sativus L.*	Brassicaceae	Olomucine[43]
4	*Thapsia garganica L.*	Apiaceae	2.Thapsigargin[43](Precursor of Roseovitine)
5	*Brucea antidysenterica J.F. Mill*	Simaroubaceae	3.Bruceantin[43]
6	*Betula Spp.*	Betalaceae	4.Betulinic acid[43]
7	*Indigofera tinctoria*	leguminosae	5.Indirubins[43]
8	*Veratrum californium*	Malanthiaceae	6.Cyclopamine[44]
9	*Erythroxylum Pervillei Baillon*	Erythroxylaceae	7.Pervilleine A[43](under clinical trials)
10	*Caesalpinia Pulcherrina*	Leguminosae	8.5,7-dimethoxy-3',4'- Methylene Dioxyflavanone and isobonducellin[45]
11	*Waltheria indica*	Sterculiaceae	Tiliroside[45]
12	*Phyllanus polyphyllus*	Euphorbiaceae	Phyllamyricin C[45]
13	*Coffea canephora* and *C. arabica.*	Rubiaceae	Caffeic acid[46]
14	*A. karakolicum Raspc*	Ranunculaceae	8-O-Azeloyl-14-benzoylaconine[47]
15	*Diospyros Montana*	Ebenaceae	Diospyrin[48]



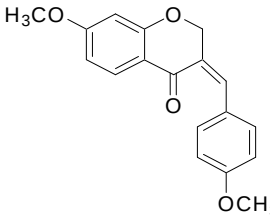
Cyclopamine



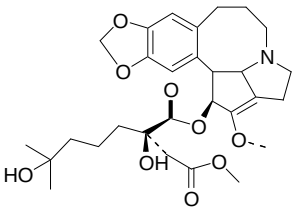
Pervilleine A



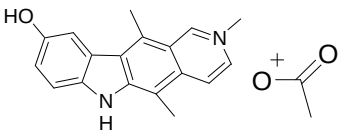
5,7-dimethoxy-3',4'- Methylenedioxyflavanone



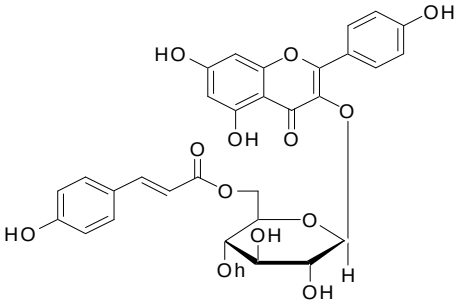
Isobonducellin



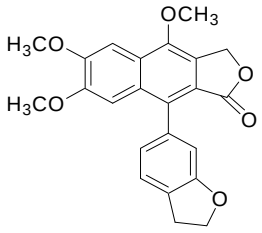
Homoharringtonine



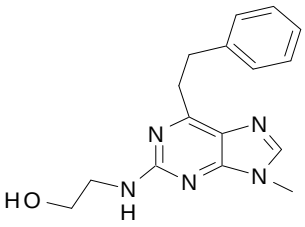
Elliptinium



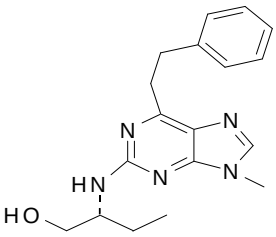
Tiliroside



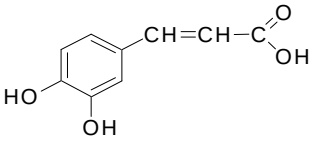
Phyllamyricin C



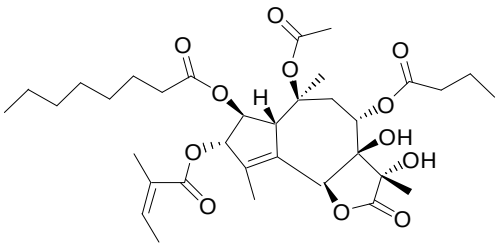
Olomucin



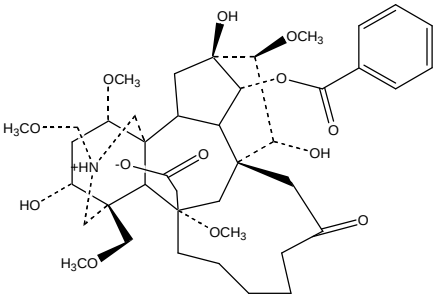
Roscovitin



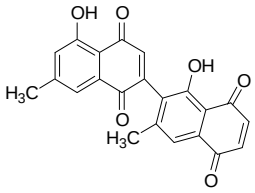
Caffeic acid (Hydroxy cinnamic acid)



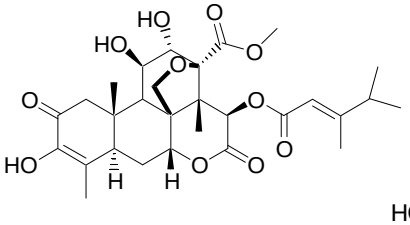
Thapsigargin



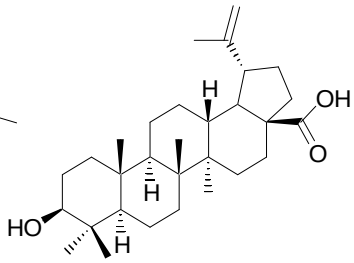
8-O-Azeloyl-14-benzoylaconine



Diospyrin



Bruceantin



Betulinic acid

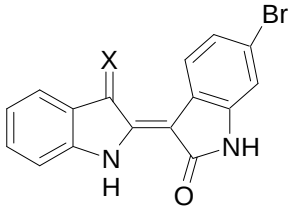
Extracts of some plants having anticancer activity

1.Extract of *Iris tectorum*[4]

Biological Source : Rhizomes of *Iris tectorum* Maxim.
Family : Iridacea
Syn. : Japanese Roof Iris

2.Anticancer activity of plants of *Scutellaria* genus[50]

Biological Source : *Scutellaria orientalis ssp.Carica*
S. barbata
S. baicalensis
S. rivularis
Family :Labiatae



X=O

Bromo indirubin X=N-OH Oxime of Indirubin

3.Extracts of Mediterranean dietary plants[51]

Name of the plant	MCF-7	LNCaP	C32	ACHN
Borago officinalis (Boraginaceae)	15.27 ± 0.31	*NA*	4.40 ± 0.13	*NA*
Capparis sicula Veill (Capparaceae)	42.67 ± 0.85	47.58± 0.87	65.79 ± 1.15	77.69 ± 1.25
Carrduus pycnocephalus (Asteraceae)	NA	17.52± 0.36	*NA*	*NA*
Cichorium intybus leaves (Asteraceae)	NA	3.67 ± 0.12	NA	NA
Cichorium intybus roots (Asteraceae)	12.65 ± 0.26	NA	30.78 ± 0.75	14.93 ± 0.29
Clematis vitalba (Ranunculaceae)	6.54 ± 0.18	6.39 ± 0.19	NA	NA
Cynara cardunculus ssp. Cardunculus (Asteraceae)	22.74 ± 0.42	5.46 ± 0.31	2.28 ± 0.09	NA
Echium vulgare (Boraginaceae)	3.80 ± 0.11	2.97 ± 0.31	NA	NA
Foeniculum vulgare ssp. piperitum (Apiaceae)	7.82 ± 0.19	NA	15.32 ± 0.33	16.59 ± 0.31
Lepidium sativum (Brassicaceae)	2.68 ± 0.09	NA	4.32 ± 0.14	NA
Mentha aquatica (Lamiaceae)	44.71 ± 0.95	5.48 ± 0.17	NA	NA
Picris hieracioides (Asteraceae)	8.83 ± 0.23	1.49 ± 0.08	NA	NA
Sonchus oleraceus (Asteraceae)	8.36 ± 0.25	NA	3.77 ± 0.12	NA

Note: NA = no activity; MCF- 7: human breast cancer cells; LNCaP: human prostate cancer cells; ACHN: renal cell adenocarcinoma; C32: amelanotic melanoma cells.

4.Anti cancer activity of coix seed extract[52]
Biological source : *Coix lacryma-jobi*
Family : Poaceae
Syn. : Job's Tears adlay, or adlai, Coixseed

Coix seed extract inhibit FAS activity. The other mechanism of action of Coix seed extract, as a
(1) Experiments showed that the extract inhibits the mitosis of tumor cells during the G2/M phases
(2) Leads apoptosis of tumor cells
(3) Up-regulate FAS/Apo-1 gene expression and down-regulating Bc1-2 gene expression thus affects the genetic expression of tumor cells
(4) Inhibits tumor angiogenesis

5.Antiproliferative action of methanolic extract of *Geum quellyon* Sweet roots[53]

Biological Source : Dried roots of *Geum quellgon*
Family : Roseaceae
Syn. : Geum chilense

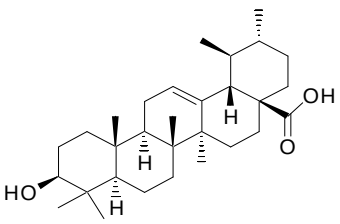
Cause DNA fragmentation and cellular membrane breakage

6.Anticancer activity of extract of *Pereskia bleo* (kunth) DC against Breast carcinoma T-97D cell[54] lines

Biological source : Dried leaves and stem of *Pereskia bleo* (kunth) DC
Family : Cactaceae
Dose : EC_{50} 2.0 µg /ml
It shows its anticancer activity by inducing apoptosis in the cancerous cells

7.Bark water extract of *Uncaria tomentosa* (Willd.) DC[55]
Biological source : Bark of *Uncaria tomentosa*
Family : Rubiaceae
Syn : Cat's claw,Vilcacora

Water extracts showed delayed-type apoptosis. One of the main constituents of extract is ursolic acid which has very strong anti proliferative properties and induces apoptosis in various human cancer cell lines like : A549 (lung cancer), SK-OV-3 (ovary cancer), SK-MEL-2 (skin cancer), XF498 (brain tumor), HCT-15 (leukemia) and B16-F-0 (melanoma).



Ursolic acid

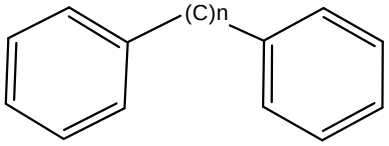
Some other plants having ursolic acid and anticancer activity

APPLE
Biological source : Pomaceous fruit
Family : Rosaceaea

BASIL
Biological source : Leaves of *Ocimum basilicum*
Family : Lamiaceae

BILBERRY
Biological source : Fruit of *Vaccinium myrtillus* L
Family : Ericaceae

CONCLUSION:
Plants have been important source of highly effective conventional drugs for the treatment of different types of cancer. In many cases it has been found that actual compounds isolated from the plants may not serve as the drug, but leads to the development of potential anticancer agents. With the development of new drug delivery system, the ability to attach anticancer agent to carrier molecules directed to the specific tumor site, of highly cytotoxic natural products to the tumor avoiding their toxic side effects on the normal cells.Also the compounds having minimum structural feature like



n=1-4

Where n=1 to 4

Show tubulin inhibiton activity e.g benzophenones, combretastatins, chalcones and lignin,.in these molecules terminal rings are arranged like the two wings of the butterfly having certain dihedral angle between them.Therefore a "Butterfly model" with two aromatic rings as the two wings of the butterfly is proposed an important structural feature responsible for their anti-tubulin activity. Though there appears to be a lot of structural diversity but from the three dimensional structures, the peripheral shape of two phenyl aromatic rings in all these molecules look similar

ACKNOWLEDGEMENTS
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