Natural Products Based Anticancer Agents

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Abstract: Natural products have been a rich source of anticancer compounds. Several anticancer "lead" compounds have been isolated and identified from different natural sources. These lead compounds after proper chemical modifications and bioevaluations afforded potential drugs. In the present article the sources, chemistry and bioactivities of some promising natural anticancer compounds have been discussed. The structure-activity relationship of these natural products and the discovery of useful drugs derived from them have also been highlighted.

Keywords: Natural products, anticancer compounds, sources, bioactivities, mode of action, structure-activity relationship, commercial drugs.

1. INTRODUCTION

Cancer has recently been a major killer of human population. It is the second leading cause of deaths after cardiovascular diseases. It is a growing public health problem and worldwide more than six million new cases of this disease are reported every year [1]. Chemists and biologists have been actively engaged for a long time in searching of potent anticancer compounds from natural sources. A large number of plants are known to exhibit potent anticancer properties [2]. Extensive chemical and biochemical investigations on the constituents of some of these plants have resulted in the identification of certain "lead compounds" to develop cancer chemotherapeutic agents. Various terrestrial plants, microorganisms and marine species have been thoroughly examined. It has reported that 63% of anticancer drugs introduced over the last twenty five years have been obtained from natural sources [3]. The lead compounds have been chemically modified to generate more potent and less toxic molecules. The anticancer properties as well as the mode of action of these compounds have been studied. As a result, several synthetic and semisynthetic analogues have shown more promising results than the parent compounds [4].

In recent years several review articles on natural anticancer agents have been published [5]. However, in some articles only the general discussion has been provided. The present article contains the lucid description of the sources, biological properties and mode of actions of some representative potent natural anticancer compounds. The structure-activity relationships of these lead compounds and the discovery of anticancer drugs have also been described. Some recent examples of natural anticancer molecules and their sources have been mentioned. The work on this topic carried out in our laboratory has also been reported.

2. NATURAL ANTICANCER COMPOUNDS

From the natural sources various anticancer compounds have been isolated and identified. Some of the impressive compounds are given below (Table **1**).

3. CHEMISTRY AND BIOLOGY

The chemistry, bioactivity, the mode of action and the synthesis of analogues of some most promising naturally occurring anticancer compounds have been discussed here. The drugs derived from these compounds are also briefly mentioned.

3.1. Podophyllotoxin

Podophyllotoxin (**2**) was isolated from podophyllum resin obtained from the rhizomes of the species of the genra *Phodophyllum* (Berberidaceae) [7a]. Several *phodophyllum* species such as *P. peltatum*, *P. emodi* and *P. pleianthum* have been investigated for isolation of the compound [24]. Podophyllotoxin resin was used earlier in medicine as cathartics and cholagogue and later its cytostatic properties have been discovered. Along with podophyllotoxin several other related lignans have been isolated from this resin.

Podophyllotoxin (**2**) is an aryltetralin lignan containing four consecutive chiral centers. The molecule possesses a lactone ring and a hydroxy, three methoxy and a methylenedioxy functionalities. The compound is stable and abundant in nature.

As per biological activity is considered, podophyllotoxin exhibits prominent cytotoxic properties against different cancer cell lines [24]. It is effective in the treatment of genital tumours and of non-Hodgkin's and other lymphomas and lung cancers. However, it cannot be used as such due to its complicated side effects. The anticancer activity of podophyllotoxin can be attributed to the inhibition of assembly of microtubules caused by the compound. It arrests the cell cycle in metaphase [25].

Various semisynthetic and synthetic analogues of podophyllotoxin have been prepared to evaluate their anticancer properties [26, 27]. The structure-activity relationship demonstrated the importance of the lactone ring of podophyllotoxin to tubulin assembly. The methylenedioxy group is also essential. The modifications of the hydroxy group are highly encouraged to enhance anticancer as well as topoisomerase activity.

As a part of the discovery of more potent and less toxic analogues some cyclic acetals and ketals of 4'-demethyl-epipodophyllotoxin-β-D-glucopyranosides were prepared. Two of these compounds, the ethylidene derivative, etoposide (**2a**) and the thenylidene derivative, teniposide (**2b**) showed promising activity to develop as anticancer drugs [28]. Etoposide is effective for treatment of small-cell lung cancer, testicular cancer, lymphoma and leukemia while teniposide for treatment of acute lymphatic leukemia, neuroblastoma and brain tumour. These two compounds show anticancer activity by interacting with DNA topoisomerase II. They affect cell division in the late S or G_2 phase of the cell cycle. This is related to the enzyme-mediated DNA cleavage which leads to the death of the tumour cells [29].

3.2. Vinbalstine and Vincristine

Two naturally occurring highly promising anticancer compounds are vinblastine (**3**) and vincristine (**4**). These two compounds were isolated [8, 9b] from *Catharanthus roseus* G Don (formerly known as *Vinca rosea* Linn). The earlier names of vinblastine and vincristine were vincaleukoblastin and leurocristine respectively. The leaf extract of *Catharanthus* species was known to possess oral hypoglycemic properties and later its anticancer activity was discovered leading to the isolation of its alkaloid constituents.

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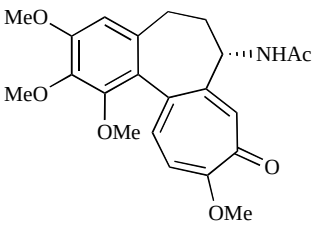
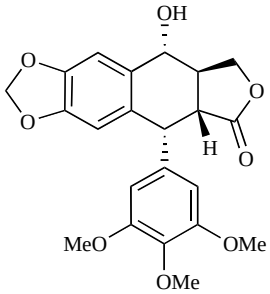
Table 1. Anticancer Molecules from Natural Sources

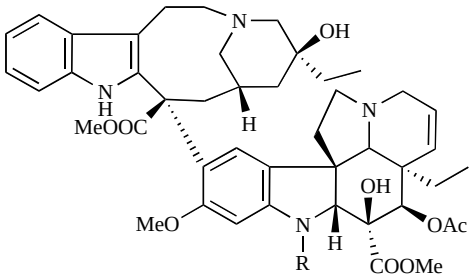
S. No	Name	Source	Structure	Reference
1	Colchicine	*Colchicum antumnale* (Libiaceae)	**1**	[6]
2	Podophyllotoxin	*Podophyllum emodi* and other *Podophyllum* species (Berberidaceae)	**2**	[7]
3	Vinblastin	*Catharanthus roseus* (Apocyanaceae)	**3**	[8]
4	Vincristine	*Catharanthus roseus* (Apocyanaceae)	**4**	[9]
5	Ellipticine	Ochrosia elliptica (Apocyanaceae)	**5**	[10]
6	Parthenin	Parthenium hystophus (Asteraceae)	**6**	[11]
7	Ferulenol	Feula communis (Umbelliferae)	**7**	[12]
8	Camptothecin	Camptotheca acuminata (Nyssaceae) *Mappia foctida* (Icacinaceae)	**8**	[13]
9	Jatrophone	*Jatropha gossypifolia* and other *Jatropha* sp. (Euphabiaceae)	**9**	[14]
10	Taxol	*Taxus brevifolia* and other *Taxus* species (Taxaceae)	**10**	[15]
11	Laulimalide	*Hyattella* sp. and other marine species	**11**	[16]
12	Discodermolide	*Discoduma dissolute* (marine sponge)	**12**	[17]
13	Dynemicin A	*Micromonospora chersina* (Microorganism)	**13**	[18]
14	Combretastatin A-4	*Combretum caffrum* (Combretaceae)	**14**	[19]
15	Epothilone A	*Soragium cellulosum* (myxobacterium)	**15**	[20]
16	Epothilone B	*Soragium cellulosum* (myxobacterium)	**16**	[20]
17	Eleutherobin	*Eleutherobia* sp. (Soft coral)	**17**	[21]
18	Ceratamine A	*Pseudocerotina* sp. (marine sponge)	**18**	[22]
19	Ceratamine B	*Pseudocerotina* sp. (marine sponge)	**19**	[22]
20	Orthodiffene A	*Orthosiphon diffuses* (Lamiaceae)	**20**	[23]



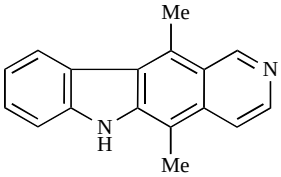
Colchicine (**1**)



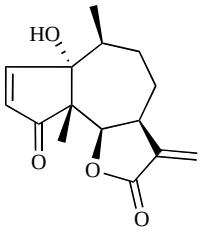
Podophyllotoxin (**2**)



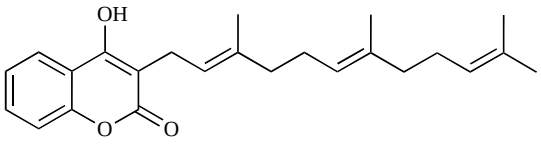
R=Me Vinblastin (**3**)
R=CHO Vincristine (**4**)



Ellipticine (**5**)

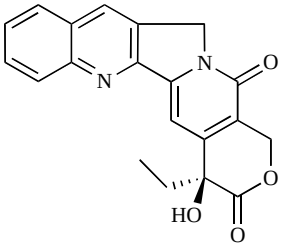


Parthenin (**6**)

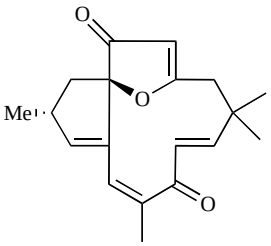


Ferulenol (**7**)

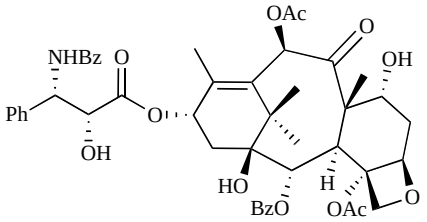
Fig. (1). contd….



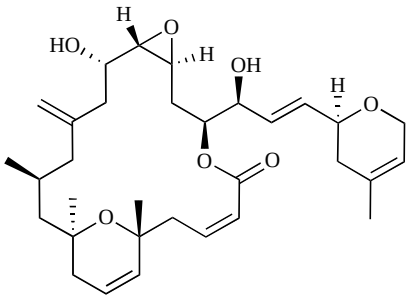
Camptothecin (**8**)



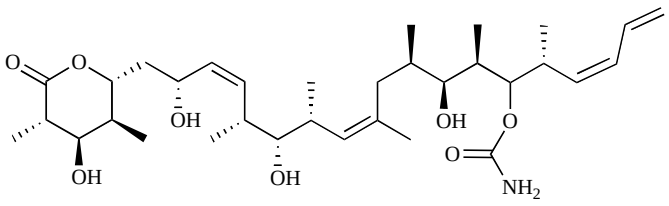
Jatrophone (**9**)



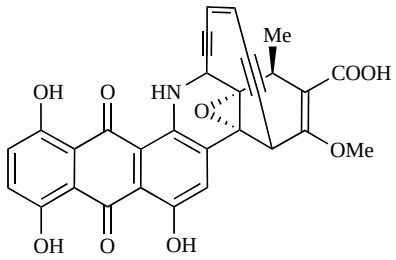
Taxol (**10**)



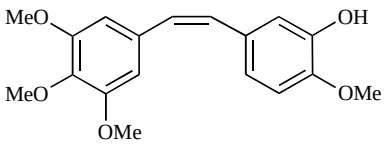
Laulimalide (**11**)



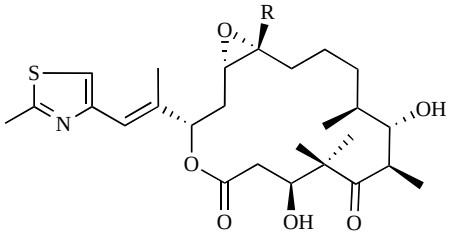
Discodermolide (**12**)



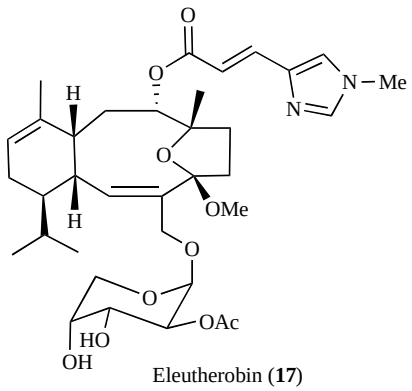
Dynemicin A (**13**)



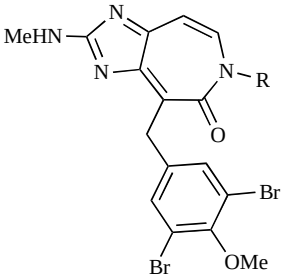
Combretastatin A-4 (**14**)



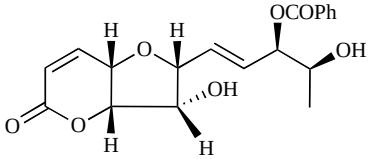
R=H Epothilone A (**15**)
R=Me Epothilone B (**16**)



Eleutherobin (**17**)



R=Me Ceratamine A (**18**)
R=H Ceratamine B (**19**)



Orthodiffene A (**20**)

Fig. (1).

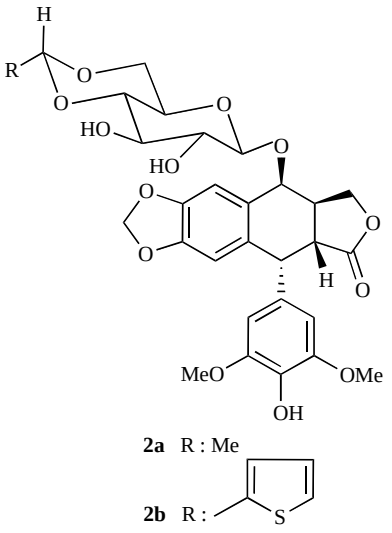


Fig. (2).

Chemically vinblastine (**3**) and vincristine (**4**) are indole-dihydroindole alkaloids. The compounds contain two subunits: an upper catharanthin ring system linked to a lower vindoline ring system by a single bond. The structures of the compounds were established through chemical and spectroscopic evidence [30]. Vincristine methiodide dihydrate was analyzed by X-ray crystallography [31].

Vinblastine (**3**) and vincristine (**4**) are highly important in phytochemistry and medicinal chemistry due to their complex structures and impressive anticancer activity. The compounds represent a novel class of natural oncolytic agents which extensively applied in the chemotherapeutic management of various human neoplasms. The chemical success of vincristine (**4**) has marked the compound as a "miracle drug" [32]. Vinblastine (**3**) is effective in the treatment of choriocarcinoma, Hodgkin's disease, non-Hodgkin's lymphomas and renal, testicular, neck and head cancers [32, 33]. Vincristine (**4**), on the other hand, is applicable for treatment of lymphocytic leukemia, lymphosarcoma, small cell lung cancer and cervical and breast cancers [32, 34]. VAMP (combination of vincristine, amethopterin, 6- mercaptopurine and prednisone) has shown a great success to ménage leukemia [35]. Vinblastine (**3**) and vincristine (**4**) are inhibitors of tubulin polymerization. At very low concentration they suppress microtubule dynamics and at higher concentration they reduce microtubule polymer mass. They arrest the cells at metaphase and produce a typical C-mitotic effect with micronuclei [36].

Various structural modifications of vinblastine (**3**) and vincristine (**4**) were accomplished to generate better analogues with higher potency and less toxicity. Vindesine (**3a**) is one of the most impressive analogues to enter clinic uses [37]. The molecule is structurally related to vinblastine (**3**) but it has an amide function instead of methyl ester on the vindoline ring and it lacks the acetyl group on the same ring. So far activity is still concerned, it resembles vincristine (**4**) but its neurotoxic potential is less. It shows the absence of cross-resistance with vincristine in the treatment of acute lymphoid leukemia.

Vinorelbine (**3b**) is another important analogue of vinblastine (**3**). The indole ring in the former has been connected to the piperidine nitrogen by one carbon and water has been eliminated from the piperidine ring. The compound is useful for the treatment of nonmetastatic breast cancer [38].

3.3. Camptothecin

Camptothecin (**8**) was isolated from the rare Chinese plant, *Camptotheca acuminata* (Nyssaceae) [13a]. The compound was obtained in minor quantity. Indian *Nothapodytes foetida* (Icacinaceae) is an important source of the compound [13b, 39]. The structure of the camptothecin (**8**) was established from its spectral properties, chemical reactions and X-ray crystallographic studies [13a, 40]. The molecule consists of a pentacyclic ring structure including a pyrrole (3, 4-) quinoline moiety and one asymmetric center within a hydroxylactone ring having (*S*)- configuration. The biogenetic formation of camptothecin was proposed from monoterpene indole intermediate [41]. Camptothecin (**8**) was biologically evaluated to be a promising anticancer compound. It was found to possess remarkable activity against murine L1210 and P388 leukaemia and B16 melanocarcinoma [13a, 42]. Subsequently it was used to treat liver carcinoma and tumours of head and neck [43]. It was approved by U.S. Food and Drug Administration (FDA) in the 1970s against colon carcinoma [44].

Camptothecin (**8**) possess an interesting mechanism of action for its biological activity. It is a specific inhibitor of DNA topoisomerase I and inhibitor of its anticancer activity [45]. Camptothecin binds reversibly to a Topo1-DNA cleavable complex to form a stable ternary complex. Camptothecin (**8**) as such could not be used as a drug as it is highly toxic and insoluble in water. Numerous studies on the synthesis of its analogues have been accomplished to define structure- activity relationship and to discover derivatives with lower toxicity, higher solubility and more activity. The structure-activity relationship indicated that (a) the conjugated fused rings ABCD is necessary for both *in vitro* and *in vivo* activities of camptothecin; (b) hydroxy lactone moiety at ring E is essential; (c) the hydroxy group at C-20 should be with (*S*)- configuration and (d) D-ring pyridine is required.

On the basis of the results of structure-activity relationship different analogues of camptothecin were prepared and their anticancer activity was evaluated. Two most successful water-soluble analogues, irinotecan (CPT-11) (**8a**) [46] and topotecan (**8b**) [47] have been approved for clinical uses. Irinotecan has shown broad spectrum of activity for treatment of lung, cervical, ovarian and breast cancers. Topotecan, on the other hand, is applied to metastatic ovar-

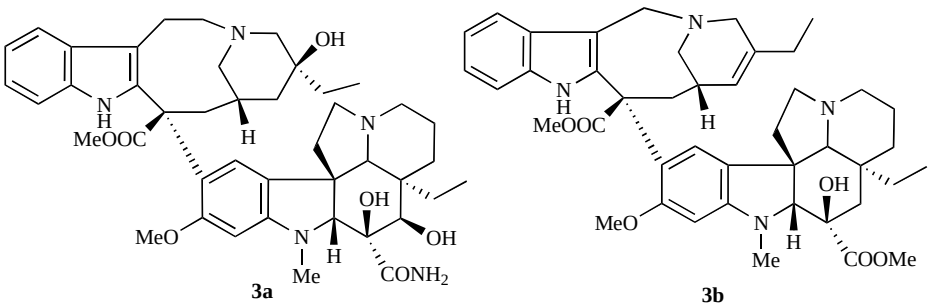


Fig. (3).

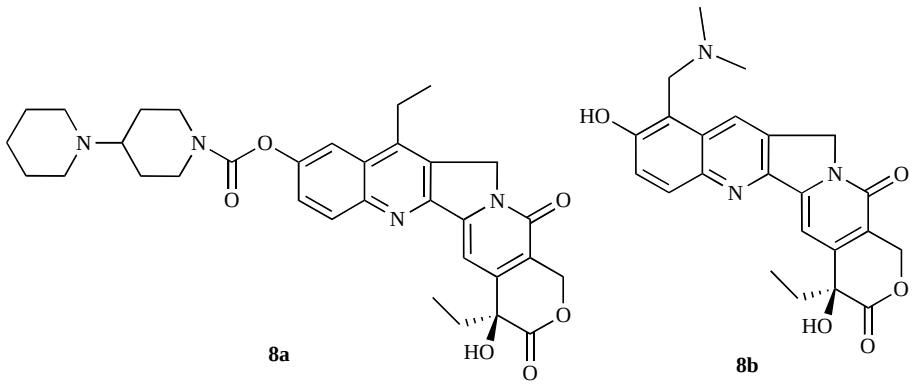


Fig. (4).

ian and small-cell lung cancers. Several new camptothecins are also under consideration for clinical implementation.

3.4. Taxol

Taxol (taxol A, paclitaxel, taxol®) (**10**), an exceptionally promising anticancer compound, was originally isolated from the Pacific yew, *Taxus brevifolia* (Taxaceae) [15a]. The yield of taxol was found to be 0.02% from the dried bark of this plant. It has been examined that taxol concentration is highest in the bark, followed by roots, needles and wood [48]. Various other *Taxus* species were subsequently investigated for their taxol content [49]. The needles and the other parts of the Himalaya yew (*Taxus baccata* Lin = *Taxus wallichiana* Zucc) contain appreciable quantity of taxol together with several other taxoids and phenolics [15d, 50]. The needles are the bioregenomable part of the yew and thus they may be considered as an important source of taxol.

The structure determination of taxol (**10**) faced a difficult problem. The combination of chemical reactions, spectral properties and X-ray crystallographic analysis of different fragments generated by chemical reactions resulted in the establishment of its molecular structure [15a]. The compound is a complex novel diterpenoid possessing a tetracyclic ring system. It bears a large number of chiral centers. Moreover, it contains a N-benzoyl-β-phenylisoserine moiety at the side chain and an oxetane ring as the vital parts of the molecule.

The anticancer activity of taxol is highly impressive [51]. The compound has been called by the National Cancer Institute (NCI) "the best anticancer agent developed in recent years". The compound shows strong cytotoxicity against KB cells and impressive antitumour activity against various leukemia models such as L1210 P1534 and P388 [15a]. It is highly effective against several human cancer diseases, such as ovarian, melanoma and breast cancers [52]. It has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of refractory advanced ovarian cancer and metastatic breast cancer.

Taxol (**10**) shows a unique mode of action on the tubulin-microtubules system [53]. The compound stabilizes microtubules and inhibits depolymerization back to tubulin. However, several other antimitotic agents bind to soluble tubulins and inhibit depolymerization of tubulin to form microtubules. No significant effect of taxol on DNA, RNA and protien synthesis has been observed [54].

Though taxol is a highly promising anticancer compound, its poor solubility and high toxicity are the major problems. To generate better drugs, a large number of modifications of taxol have been carried out and the structure-activity relationship has been thoroughly studied [15b, 55]. The major structural requirements are as follows: a) taxone core; b) phenylisoserine side chain; c) N-acyl group at the side chain and d) oxetane ring. Several novel analogues of taxol with these structural requirements have been synthesized and biologically evaluated. The most promising analogue is taxotene (docetaxel) (**10a**) [56]. The compound is more soluble than taxol. A series of important prodrugs of taxol which are esters derived from the hydroxyl group of the side chain have been introduced [57]. These compounds are known as "protaxols". The compounds are stable and have acceptable water solubility. Under toxic conditions protaxols generate taxol and this mechanism is relevant in the basic microenvironment of tumour cells.

The poor availability of taxol is another problem to develop the compound as a drug. This problem has been somewhat solved by its semisynthesis from 10-decacetyl baccatin (**10b**) which is a major taxoid constituent of the needles of *Taxus baccata* and other yew species [5d]. This sermisynthetic method has been adopted for commercial production of taxol. The total synthesis of the molecule is a challenging target to the organic chemists. The novel tetracyclic system, various functionalities and complex stereochemical features of the compound create serious problems to proceed for its synthesis. The total synthesis of the compound has been achieved independently by Holton *et al*. [58] and by Nicolaou *et al.* [59].

Biotechnological production of taxol is an important method to eliminate the crisis of supply of the compound. Different *Taxus* species have been considered for this purpose. The yield of taxol from *Taxus brevifolia* callus cultures has been claimed to the 0.05%. The cell culture of *Taxus cuspidate* has shown more impressive results. The yields of taxol from callus and suspension cultures of this species have been found to be 0.02% and 0.12% respectively [60].

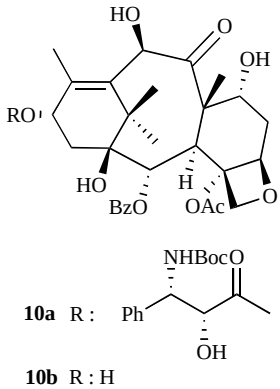


Fig. (5).

3.5. Discodermolide

Discodermolide (**12**) was isolated from the Caribbean marine sponge, *Discodermia dissolute*, which was known as inhibit P388 murine leukemia cells [16, 61]. The yield of the compound was

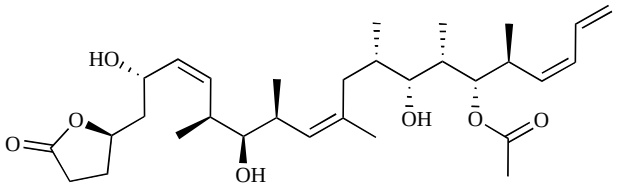
0.002%. Initially the compound was identified as an immunosuppressive and antifungal agent but subsequently its anticancer activity was recognized. The structure of the compound was established from its 2D NMR spectra and finally by X- ray crystallographic analysis. Structurally, discodermolide (**12**) is a novel lactone containing a polyhydroxylated side chain. The side chain possesses four olefinic bonds, six methyl groups and an amide moiety. The molecule is associated with a large number of chiral centers.

Discodermolide (**12**) is active against the proliferative cultured murine P388 leukemia cells and suppresses the two-way mixed lymphocytes and human peripheral blood lymphocytes [16]. The compound has been shown to be a microtubule stabilizing agent which promotes microtubule assembly more actively than taxol [62]. In the presence of discodermolide near-total polymerization takes place with tubulin and microtubule-associated proteins under conditions in which taxol cannot bring any effective change.

Discodermolide inhibits the proliferation of human cells by arresting the cell cycle in G2 and M- phase. The hyper stabilization of the mitotic spindle caused by the compound results in cell cycle arrest and cell death by apoptosis [62]. The compound is also effective in taxol- and epothilone-resisted cancer cells [63].

Several structural modifications of discodermolide (**12**) have been carried out [64]. The total syntheses of the compound and its analogues have also been accomplished [65]. Some of these total syntheses are highly efficient and are applicable for the large-scale production of the natural product. The biological studies on these synthetic and semisynthetic analogues established the structure activity relationship. The lactone moiety of discodermolide (**12**) was found to be very tolerant. However, the second double bond (from the end of the lactone ring) with *cis* (*Z*)- configuration is an absolute requirement.

Considering the structure-activity relationship a new analogue (**12a**) of discodermolide has been discovered. The compound is much more active against the human breast carcinoma cell line compared to the parent compound [66].



12a

Fig. (6).

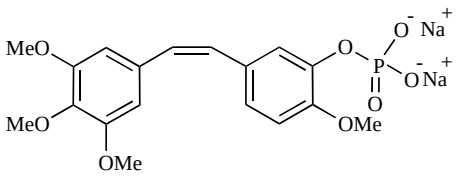
3.6. Combretastatin A-4

Combretastatin A-4 (**14**) is a most important member of combretastatins isolated from *Combretum caffrum* (Combretaceae) [18]. The compound is a simple stilbene derivative containing two phenyl rings separated by a carbon-carbon double bond. One of the phenyl rings (ring-A) possesses three methoxy groups at 3, 4, 5-positions while the other (ring-B) a hydroxy group at C-3 and a methoxy group at C-4. The configuration of the carbon-carbon double bond is *cis* (*Z*).

Combretastatin A-4 (**14**) is a highly cytotoxic phytomolecule. It exhibits significant cytotoxicity against various human cancer cell lines including MDR cancer cell lines [67, 68]. It is active against leukemia, colon and lung cancers. It shows an ID_{50} value of 0.007 μM against murine L1210 leukemia cell lines [69]. The compound competes with colchincines for binding sites on tubin [70]. It targets the microtuble, inhibiting the polymerization of tubulin to microtubles. However, the problem is that it is much more cytotoxic than its activity.

Several analogues of combretastatin A-4 (**14**) have been prepared to define the structure-activity relationship. It has been observed [71] that (a) two aryl groups separated by a *cis* (*Z*)-double bond or having conformationally restricted arrangement (b) trimethoxy benzene segment and (c) 4-methoxy or methyl group in ring B are essential for the activity of a combretastatin related compound. 3-Hydroxy group in ring B of combretastatin A-4 is not required but incorporation of an amino group in this ring increases its activity [72].

Combretastatin A-4 phosphate (CA-4P) (**14a**) is a simple derivative of the natural product. It is soluble in water. It significantly reduces the blood flow to the tumour cells at well-tolerated doses. Thus it acts as a vascular disrupting agent. It can cause the shutdown of blood flow resulting in extensive tumour necrosis [73]. Several other phosphate derivatives of combretastatin A-4 have been prepared and biologically evolved but none of them is so active as **14a**.



14a

Fig. (7).

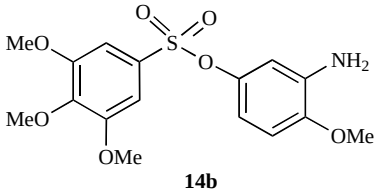
Two compounds, **14b** and **14c**, prepared in keeping a sulfonate group between two aryl groups for their restricted rotation, were found to exhibit cytotoxicity comparable to combretastatin A-4 (**14**) [74].

3.7. Epothilones A and B

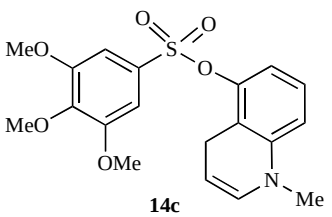
Epothilones A (**15**) and B (**16**) were isolated from the fermentation broths of the mycobacterium *Sorangium cellulosum* [19, 75]. The compounds were originally discovered on the basis of a screening for new antifungal agents but their potential anticancer activity was quickly recognized [76]. Their structures were established from detailed NMR spectral studies and X-ray crystallographic analysis.

The compounds are polyketide-derived novel 16-membered macrolides possessing various chiral centers. They contain a side chain with a thiazole ring. The size of the diterpenoid core of these compounds corresponds approximately to that of taxol.

Epothilones are highly active against breast and colon tumours [19, 75]. Tubulin polymerization studies, cytotoxicity and mitosis inhibition analysis suggested that they exhibit almost identical



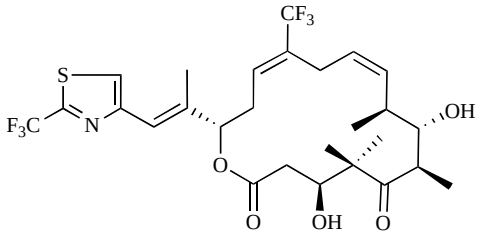
14b



14c

Fig. (8).

mode of action to that of taxol – they induce tubulins to form microtubules and can stabilize these microtubules [76]. The epothilones, like taxol, can work without GTP and microtubule associated proteins [77]. Epothilone B (**16**) promotes microtubule assembly more strongly than epothilones A (**15**) [77]. Both of these compounds have much higher activity against multidrug resistant tumour lines compound to taxol. They can also competitively displace taxol from microtubules, suggesting that microtubule binding occurs at the taxol site in β-tubulin. A multidrug resistant colon carcinoma line and the taxol resistant ovarian cancer cell line retained sensitivity to epothilones [76]. The solubility of epothilones in water is better than that of taxol and their availability is also higher. As a result, several modifications of epothilones have been carried out to discover better drugs [78]. The replacement of the epoxide ring with other functionalities and expansion of the epoxide ring have been thoroughly examined. However, it was observed that the epoxide moiety is not an absolute requirement for the activity of epothiloes [79b, 80]. The transformation of the side chain with benzothiazole moiety has yielded the analogues with higher activity than the natural epothilones [78, 81]. Considering the structures of the synthetic and semisynthetic analogues of epothilones and their biological activity some of these compounds have been recognized as potential candidates for anticancer drugs. The fluorinated analogue, fludelone (**15a**) has shown promising aspects in such drug discovery direction [82].



15a

Fig. (9).

CONCLUSION

The present discussion demonstrates the significance of natural products as an important source of anticancer agents. Several compounds with impressive activity have been discovered from plants and marine species. The areas of anticancer drug discovery and development have been dependent mainly on the "privileged compounds obtained from Nature". The combination of chemistry and biology has put a high impact on this investigation. The isolation and purification of natural products with simultaneous bioevaluations followed by proper clinical trials have identified the promising drugs to control cancer. Chemical synthesis (partial and total) have played an important role in supplying the natural products in large quantities and in preparing novel analogues for biological studies to discover the activity and the mode of action. Biotechnological approaches have also been helpful to supply the active constituents. In fact, various chemical and biological processes are now under trials for successful implementation of natural products to cancer chemotherapy. The present discussion on some impressive naturally occurring anticancer compounds has briefly highlighted these efforts.

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CONFLICT OF INTEREST

None declared.

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