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Mini-Review

Natural plant resources in anti-cancer therapy-A review

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Cancer is one of the most common devastating disease affecting millions of people per year. Cancer has been estimated as the second leading cause of death in humans. So there has been an intense search on various biological sources to develop a novel anti-cancer drug to combat this disease. Plants have proved to be an important natural source of anti-cancer therapy for several years. About 30 plant derived compounds have been isolated so far and are currently under clinical trials. These anti-cancer compounds have been found to be clinically active against various types of cancer cells. Further research in this area may lead to better treatment of cancer.

Key words: anti-cancer, apoptosis, clinical trials, plant derivative.

Importance of plant secondary metabolites

Plant secondary metabolites have proved to be an excellent reservoir of new medical compounds. Many anti-cancer agents have been isolated from various plant sources like *Catharanthus roseus*, *Podophyllum* species, *Taxus brevifolia*, *Camptotheca acuminate*, *Betula alba*, *Cephalotaxus* species, *Erythroxylum pervillei*, *Curcuma longa*, *Ipomoeca batatas*, *Centaurea schischkinii* and many others. Scientists are still attempting to explore the bioavailability of anti-cancerous compounds in unexplored plant species.

Anti-cancerous drugs under clinical trials

There are four major structural classifications of plant-derived anti-cancerous compounds *viz*., Vinca alkaloids, Epipodophyllotoxin lignans, Taxane diterpenoids and Camptothecin quinoline alkaloid derivatives. Different anti-cancer compounds that have been identified and reported by scientists have been reviewed under.

1. Vinca alkaloids

Vinca alkaloids belong to an important class of anti-cancer drugs. The mechanism of action of Vinca alkaloids is that they inhibit the cell proliferation by affecting the microtubular dynamics during mitosis, and this causes a characteristic block during mitosis leading to apoptosis. Certain semi-synthetic analogues have been developed to increase the therapeutic index.

Vinblastine (VLB) and Vincristine (VCR) are the two major naturally occurring active compounds obtained from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (Apocynaceae). These compounds reported potential activity against lymphocytic leukemia in mice. Vinorelbine (VRLB) and Vindesine (VDS) are the two semi synthetic analogs obtained from the active compounds. They showed potential activity against leukemia's, lymphomas, advanced testicular cancer, breast cancer, lung cancer and Kaposi's sarcoma when

treated in combination with other chemotherapeutic drugs (Cragg and Newman, 2005). Vinflunine, a bifluorinated derivative of vinorelbine exhibits a superior anti-tumor activity compared to other vinca alkaloids. This novel Vinca alkaloid is currently under Phase II clinical trials. Both Vinflunine and Vinorelbine exhibits reduced toxicity in animal models (Okouneva et al., 2003; Simeons et al., 2008).

2. Podophyllotoxin

Podophyllotoxin is obtained from the roots of *Podophyllum* species, namely, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich. This was isolated in 1880s, and their structure was elucidated in 1950s. Epipodophyllotoxin is an isomer of podophyllotoxin. 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 (Shoeb, 2006).

3. Taxanes

Paclitaxel (Taxol®) is obtained from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae). Their structure was first identified in the year 1971 and they entered the market since 1990s. Another species, *Taxus baccata*, an Indian Ayurvedic medicine have also been in use for cancer therapy (Kingston, 2007). Paclitaxel was found poorly water-soluble and toxic, hence, a water-soluble compound, Docetaxel was derived.

Docetaxel (Taxotere®), a semi-synthetic derivative of paclitaxel was found more effective. Docetaxel can be used in patients who are resistant to paclitaxel. Both docetaxel and paclitaxel are used as first- and second-line treatment in patients suffering from metastatic cancer, breast cancer and ovarian cancer. These drugs are also found active against lung cancer, prostate cancer and also lymphoid malignancies. The mechanism of action is that these active agents bind to the polymerized microtubules which prevent the normal mitosis to occur and thus they are called anti-mitotic drugs (Hait et al., 2007).

4. Camptothecin (CPT)

Camptothecin is a cytotoxic alkaloid isolated mainly from the bark and stem of the Chinese ornamental tree, *Camptotheca acuminate*. It showed poor solubility and severe toxicity, and, because of this reason, certain analogues of CPT were synthesized to overcome these disadvantages. They are topotecan, irinotecan (CPT-11), 9-aminocamptothecin (9-AC), lurtotecan and rubitecan. These analogs work by inhibiting DNA Topoisomerase I which plays a major role in various DNA functions like replication and transcription. It is made up of a pentacyclic ring structure which contains a pyrrole (3, 4 β) quinoline moiety (Srivastava et al., 2005). The camptothecin molecule has an *S*-configured lactone form and a carboxylate form which is responsible for the anti-cancer activity.

Topotecan is found clinically effective in patients with epithelial ovarian cancer and small cell lung cancer as a second-line treatment (Creemers et al., 1996). Irinotecan acts as first- and second-line treatment for metastatic colorectal cancer (Fuchs et al., 2006). DX-8951f (Exatecan) is yet another new camptothecin (CPT) derivative which demonstrated potential anti-tumor activity against various tumors both in-vitro and in-vivo (Mineko et al., 2000). This synthetic analog seems to have better aqueous solubility, tumor efficiency and lesser toxic effects compared to camptothecin and other derivatives (Reichardt et al., 2007). SN-38 (7-ethyl-10-hydroxycamptothecin), an active metabolite of CPT-11 is found to show high cytotoxic activity as compared to CPT-11. Due to the poor solubility of this topoisomerase I inhibitor, it is now designed as a liposome-based formulation. This LE-

SN-38 shows increased cytotoxic effects in various cancer cell lines (Zhang et al., 2004). CZ-48 acts as effective anti-cancer agent, with not much toxicity effects in mice. Research is still undergoing for human clinical trials also (Cao et al., 2009).

5. Berbamine

Berbamine, a bisbenzylisoquinoline alkaloid was isolated from the Chinese herb named *Berberis* amurensis. It was reported that Gleevec was responsible for bcr/abl tyrosine kinase inhibition and therefore used in the treatment of chronic myeloid leukemia. But few patients developed resistance against this drug. It was found that berbamine effectively causes cell apoptosis of both Gleevec sensitive and resistant Ph^+ chronic myeloid leukemia cells. They work by inducing caspase-3-dependent apoptosis of leukemic NB4 cells by the survivin-mediated pathway (Xie et al., 2009; Xu et al. 2006).

6. Berberine

Berberine, an isoquinoline plant alkaloid is obtained from different plant species including *Hydrastis Canadensis* L., (Ranuncufaceae), *Berberineeris* species (Berberidaceae) and *Arcungelisia* flaw (Menispermaceae). They showed anti-tumor activity both in-vivo and in-vitro report show that berberine has found effective against osteosarcoma, lung, liver, prostate and breast cancer (Wang et al., 2011; Patil et al., 2010).

7. Beta-lapachone

Beta-lapachone (3, 4-dihydro-2, 2-dimethyl-2H-naphthol [1, 2-b] pyran-5, 6-dione), a water-insoluble orthonapthoquinone compound, was obtained from the heartwood of South American Lapacho tree (*Tabebuia avellanedae*) (Li et al., 2000). This compound has a broad spectrum of antineoplastic activity against breast cancer, prostate cancer, lung cancer, pancreatic cancer and also in promyelocytic leukemic cells. They work by inhibiting Topoisomerase I and II (De Almeida, 2009). But this drug is found to have poor solubility, systemic toxicity and non-specific distribution. So, gold nanoparticles are being used as a carrier in delivering the drug in the nano form to enhance the radiotherapeutic efficiency (Jeong et al., 2009).

8. Betulinic acid

Betulinic acid (3β, hydroxy-lup-20(29)-en-28-oic acid), a lupine class type, pentacyclic triterpene compound is obtained naturally from various plant species. This compound is obtained in good amounts from the bark of many trees, including white-barked birch trees (*Betula alba*). The mechanism of action of betulinic acid is that they trigger the mitochondrial pathway of apoptosis which causes cancer cell death. Thus this compound exhibits potent anti-cancer activity in humans (Fulda, 2008).

9. Bruceatin

Bruceantin, a plant derivative exhibits anti-tumor activity. This anti-tumor compound work by irreversible inhibition of protein synthesis in HeLa cells, rabbit reticulocytes, and reticulocyte lysates. It is seen that bruceantin exhibits secondary effect on the synthesis of DNA (Liaoo et al., 1976).

10. Colchicine

Colchicine is a plant secondary metabolite extracted from *Colchicum autumnale* and *Gloriosa superba* L. It causes mitotic arrest during cell cycle and thus they are considered as potent anti-mitotic drug both in-vitro and in-vivo. Due to severe toxic effects, certain derivatives of colchicine were synthesized namely, 3-demethyl colchicine, colchicoside, thiocolchicocide which showed improved activity against certain leukemic cells and solid tumors. Research is still undergone in the area of anti-cancer therapy (Dubey et al., 2008).

11. Combretastatin A-4

Combretastatin A-4 is a naturally occurring stilbene compound obtained from the South African bush willow tree, *Combretum caffrum* Kuntze. This vascular targeting agent disrupts the tubulin structure and the change in morphology of endothelial cells causes deprivation of nutrients to tumor cells by impeding the blood flow through capillaries. Due to its poor solubility, a water-soluble prodrug called Combretastatin A-4 disodium phosphate has been formulated for experimental purpose which is currently under phase II clinical trials (Thomson et al., 2006; Ley et al., 2007).

12. Cucurbitacin

Cucurbitacin, a tetracyclic triterpenoid compound is predominantly obtained from the Cucurbitaceae plants. They possess antiproliferative behavior against various cancer cell lines. Reports show that Cucurbitacin- I and B selectively inhibit both signal transducer/Janus Kinase 2 (JAK2) activity and activator of transcription 3 (STAT3) pathways. STAT3 is activated in many cancer cell types like prostate cancer, breast cancer and also carcinoma of the head, neck and nasopharynx. Reports show that inhibition of this oncogenic signaling pathway, STAT3, causes tumor cell growth inhibition and leads to apoptosis of cancer cells. Polymeric miscelles are used in delivering this compound because of its water insolubility and non-specific toxicity (Molavi et al., 2008; Bernard and Olayinka et al., 2010).

13. Curcumin

Curcumin (diferuloylmethane), a polyphenolic compound is isolated from the Indian plant spices, *Curcuma longa* (commonly called turmeric), now finds its application as potential anti-cancer compound. About 3–5% of this yellow pigment of turmeric contains curcuminoids. Curcumin is involved in modulating the cell cycle pathway and induces apoptosis of various cancer cells. But the exact mechanism of action is yet to be studied clearly. Phase I/II trials are ongoing on the effects of curcumin on colorectal cancer, multiple myeloma and pancreatic cancer. Curcumin used at a high dosage level is reported to be safe by phase I clinical trials (Sa et al., 2010; Goel et al., 2008).

14. Daphnoretin

Daphnoretin, a bis-coumarin derivative, extracted in good amounts from the root bark of *Wikstroemia indica* (Thymelaeaceae) was found to have good anti-cancer activity (Lu et al., 2011). Daphnoretin causes suppression of protein and DNA synthesis in Ehrlich ascites carcinomas. It is also seen to suppress the hepatitis B surface antigen expression on human hepatoma Hep3B cells (Diogo et al., 2009).

15. Diadzein and Genistein

Diadzein (4', 7- Dihydroxyisoflavone) and Genistein (4', 5, 7-Trihydroxyisoflavone) are the two aglycones present abundantly in the Soy Isoflavones. Major sources include important legumes like lupine (Lupinus spp.), fava bean, (Vicia faba), soybeans (Glycine max), kudzu (Pueraria lobata), and psoralea (Psoralea corylifolia) (Kaufman et al., 1997). These phytochemicals work by inhibiting 3A4-mediated metabolism. Reports show that they are capable of inhibiting oxidative metabolism also (Moon et al., 2006). Genistein is found to inhibit cell proliferation in both ovarian and breast cancers. They also inhibit chemically induced cancers in stomach, bladder, lung, prostate, colon and blood (Dixon and Ferreira et al., 2002).

16. Ellipticine

A plant alkaloid, Ellipticine (5, 11-dimethyl-6H-pyrido [4, 3-b] carbazole) and its derivatives were isolated from Apocynaceae

plant species (eg. *Ochrosia borbonica, Excavatia coccinea*, *Ochrosia elliptica*). They exhibit significant anti-tumor properties against various cancer cell types. The primary function of this drug is that it intercalates with DNA and also causes inhibition of Topoisomerase II activity. It is also reported that this drug, inhibits cell growth and causes apoptosis of human hepatocellular carcinoma HepG2 cells (Kao et al., 2006).

Table 1. List of plant derivatives used in cancer therapy

S. No	Semisynthetic analogs of plant derivatives	Species and Genus name	Experiments on various cancer cells	Mechanism of action	Reference
1	Vindesine and Vinorelbine	*Catharanthus roseus*	Leukemias, lymphomas, advanced testicular cancer, breast cancer, lung cancer and Kaposi's sarcoma.	mitotic block	Cragg and Newman, 2005
2	Vinflunine	*Catharanthus roseus*	Reduced toxicity in animal models	mitotic block	Okouneva et al., 2003; Simeons et al., 2008
3	Etoposide and Teniposide	*Podophyllum peltatum* and *Podophyllum emodi*	Lymphomas, bronchial and testicular cancers.	-	Shoeb, 2006
4	Taxol®	*Taxus brevifolia* Nutt, *Taxus baccata*	Metastatic, breast, ovarian, lung, prostate cancer and lymphoid malignancies	Anti-mitotic	Kingston, 2007
5	Taxotere®	*Taxus brevifolia* Nutt, *Taxus baccata*	Used in patients resistant to Paclitaxel	Anti-mitotic	Hait et al., 2007
6	Topotecan	*Camptotheca acuminate*	Epithelial ovarian cancer and small cell lung cancer	DNA topoisomerase I inhibition	Creemers et al., 1996
7	Irinotecan	*Camptotheca acuminate*	Metastatic and colorectal cancer	DNA topoisomerase I inhibition	Fuchs et al., 2006
8	Exatecan	*Camptotheca acuminate*	Potential anti-tumor activity both *in vitro and in vivo*	DNA topoisomerase I inhibition	Mineko et al., 2000
9	LE-SN-38	*Camptotheca acuminate*	Various cancer cell lines	DNA topoisomerase I inhibition	Zhang et al., 2004
10	Berbamine	*Berberis amarensis*	Chronic myeloid leukemia	Caspase-3-dependent apoptosis	Xie et al., 2009; Xu et al., 2006
11	Berberine	*Hydrastis canadensis* L., *Berberineeris* sp& *Arcungelisia* flaw	Osteosarcoma, lung, liver, prostate and breast cancer	Not known	Wang et al., 2011; Patil et al., 2010
12	Beta-lapachone	*Tabebuia avellanedae*	breast cancer, prostate cancer, lung cancer, pancreatic cancer and promyelocytic leukemia.	Inhibition of topoisomerase I and II	Li et al., 2000; De Almeida, 2009

13	Betulinic acid	*Betula alba*	Exhibits anti-cancer activity in humans	Triggers mitochondrial pathway of apoptosis	Fulda, 2008
14	Colchicine	*Colchicum autumnale* and *Gloriosa superba* L.	Leukemic and solid tumors	Anti-mitotic	Dubey et al., 2008
15	Combretastatin A-4	*Combretum caffrum* Kuntze	Phase II clinical trials	Tubulin structure disruption	Thomson et al., 2006; Ley et al., 2007
16	Cucurbitacin	Cucurbitaceae species	Various cancer cell lines	Inhibits signal transducer/JAK 2 activity and activates STAT3 pathway	Molavi et al., 2008; Bernard and Olayinka et al., 2010
17	Curcumin	*Curcuma longa*	colorectal cancer, multiple myeloma and pancreatic cancer.	Exact mechanism of action is still unknown	Sa et al., 2010; Goel et al., 2008
18	Daphnoretin	*Wikstroemia indica*	a) Ehrlich ascites carcinomas and b) human hepatoma Hep3B cells.	a) suppression of protein and DNA synthesis b) suppresses Hepatitis B surface antigen expression	Lu et al. 2011; Diogo et al., 2009
19	Diadzein and Genistein	*Lupinus* species, *Vicia faba, Glycine max, Psoralea corylifolia*	Genistein inhibits ovarian and breast cancers and also chemically induced cancers of stomach, bladder, lung, prostate, colon and blood.	Inhibits 3A 4-mediated metabolism and oxidative metabolism	Kaufman et al., 1997; Moon et al., 2006; Dixon and Ferreira et al., 2002
20	Ellipticine	*Ochrosia borbonica, Excavatia coccinea, Ochrosia elliptica*	Various cancer cell types	DNA intercalation and inhibition of topoisomerase II	Kao et al., 2006
21	Emodin	Rhizome of rhubarb	lung, liver, ovarian and blood cancer	Apoptosis of cancer cells by several pathways	Huang et al., 2009
22	Flavopiridol	*Amoora rohituka* and *Dysoxylum binectariferum*	colorectal, non-small cell lung cancer, renal cell carcinoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and also solid tumors	Inhibits cell cycle progression at G1 or G2 phase	Mans et al., 2000
23	Harringtonine and Homoharring-tonine	*Cephalotaxus harrintonia*, *C. hainanensis* and *C. qinensis*	Acute myeloid leukemia and chronic myeloid leukemia.	Inhibition of protein synthesis and chain elongation during translation	Cragg and Newman, 2005; Efferth et al., 2007
24	Indirubin	Chinese herb, Danggui Longhui Wan	Chronic myeloid leukemia	Inhibits cyclin-dependent kinases	Nam et al., 2005

25	Ingenol 3-o-angelate	*Euphorbia peplus* L.	actinic keratosis and basal cell carcinoma	Causes necrosis of tumor by the activation of PKC	Hampson et al., 2005
26	4-Ipomeanol	*Ipomoeca batatas*	Lung specific cancer in animal models	cytochrome P-450-mediated conversion into DNA-binding metabolites	Ancuceanu and Istudor, 2004
27	Irisquinone	*Iridaceaelatea pallasii* and *Iris kumaoensis*	Good activity in transplantable rodent tumors	Acts as a chemosensitizer	Hazra et al., 2004
28	Phenoxodiol	plant isoflavone, genistein	Ovarian, prostate and cervical cancer	inhibit plasma membrane electron transport and cell proliferation	Herst et al., 2009
29	Pandimex™	saponins of ginseng	Advanced cancers of breast, colon-rectum, lung, pancreas and solid tumors	Cell cycle arrest and acts as P-glycoprotein blocker	Pan et al., 2010
30	Perillyl alcohol	Many plant species like mints, cherries, lavenders and many others	Non small cell lung cancer, prostate cancer, colon cancer and breast cancer.	Exact mechanism is yet to be identified	Pan et al., 2010; Bardona et al., 2002; Yeruva et al., 2007
31	Pervilleines	*Erythroxylum pervillei*	Yet to be done	Inhibitors of P-glycoprotein	Mi et al., 2001; Mi et al., 2002; Mi et al., 2003
32	Salvicine	*Salvia prionitis* Hance	Malignant tumors	Inhibition of topoisomerase II	Deng et al., 2011
33	Schischkinnin	*Centaurea schischkinii*	Colon cancer lines *in vitro*	Not known	Shoeb et al., 2005
34	Montamine	*Centaurea Montana*	$CaCo_2$ colon cancer cell line *in vitro*	Not known	Shoeb et al., 2006
35	Silvestrol	*Aglaia foveolata* Panell	Prostate, breast and lung cancers.	apoptosome/mitochondrial pathway was involved in triggering extrinsic pathway of programmed cell death of tumor cells	Kinghom et al., 2009; Kim et al., 2007
36	PG490-88	*Tripterygium wilfordii* Hook F	Prostate cancer	Enhances the anti-tumor effects of cytotoxic and chemotherapeutic agents, thereby induces apoptosis.	Liu, 2011

17. Emodin

Emodin (1, 3, 8-trihydroxy-6-methyl-anthraquinone) is one of the active component isolated from the rhizome of rhubarb. Rhubarb is used as a traditional Chinese medicine for treating various

diseases. This anthraquinone compound causes apoptosis in many types of cancers including lung cancer, liver cancer, ovarian cancer and blood cancer by several pathways (Huang et al., 2009).

18. Flavopiridol

Flavopiridol, a semisynthetic flavone derivative of the plant alkaloid rohitukine is isolated from the leaves and stems of *Amoora rohituka* and also from *Dysoxylum binectariferum* (Maliaceae). This anti-cancer agent works by inhibiting cell cycle progression at G1 or G2 phase by interfering with the phophorylation activity of cyclin-dependent kinases. Flavopiridol is under phase I trials for treating solid tumors and is also undergoing phase II clinical trials for the treatment of wide range cancers like colorectal, non-small cell lung, and renal cell carcinoma, non-Hodgkin's lymphoma and also chronic lymphocytic leukemia (Mans et al., 2000). It is also found effective against rhabdoid tumors, a pediatric malignancy (Smith et al., 2008).

19. Harringtonine and Homoharringtonine

Harringtonine and Homoharringtonine are the two alkaloid esters of cephalotaxine. They were originally used as the traditional Chinese medicine to cure cancer. These compounds were isolated from the evergreen coniferous shrubs of Cephalotaxus species, like *C. harrintonia*, *C. hainanensis* and *C. qinensis*. Homoharringtonine is found effective against various leukaemic cells. They work by inhibiting protein synthesis and also cause inhibition of chain elongation during translation. It is found that, a mixture of harringtonine and homoharringtonine can be used in treating both acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) (Cragg and Newman, 2005; Efferth et al., 2007).

20. Indirubin and Meisoindigo

Indirubin is an important active compound of the traditional Chinese herbal medicine, Danggui Longhui Wan. Indirubin works by inhibiting cyclin-dependent kinases, which causes cell cycle arrest and also inhibits the proliferation of tumor cells. This active agent was used in the treatment of chronic myeloid leukemia (Nam et al., 2005). But due to various disadvantages of indirubin like poor solubility and absorption, methylisoindigotin (abbreviated as meisoindigo) has been derived. Meisoindigo, a second generation derivative of indirubin, showed good efficiency with lower toxicity effects. Their mode of action is still not fully understood. Yet it has been reported that they cause inhibition of DNA and RNA biosynthesis in W256 cells and also inhibits the microtubular assembly. This anti-cancer agent is clinically effective against chronic myeloid leukemia (CML) (Liu et al., 1996).

21. Ingenol 3-o-angelate

Ingenol 3-angelate (PEP-005), a derivative of ingenol was originally obtained from the plant species, *Euphorbia peplus* L. This diterpene ester initially causes necrosis of tumor cells by the activation of PKC leading to tumor cell death. This compound is under phase II clinical trials for treating actinic keratosis and basal cell carcinoma (Hampson et al., 2005).

22. 4-Ipomeanol

4-Ipomeanol is a pneumotoxic furan derivative. It is obtained from the sweet potato *Ipomoeca batatas* (Convolvulaceae) which has been affected by *Fusarium solani*. The mechanism of action is that it causes cytochrome P-450-mediated conversion into DNA-binding metabolites. This monoterpene, cytotoxic agent showed promising result for lung-specific cancer in pre-clinical studies with animal models. But, unexpectedly, poor results were obtained in a

clinical setting (Ancuceanu and Istudor, 2004).

23. Irisquinone

Irisquinone, a benzoquinone with anti-tumor activity is obtained from plant species like *Iridaceaelatea pallasii* and *Iris kumaoensis* (Iridaceae). Irisquinone showed good activity against transplantable rodent tumors and also acts as a chemosensitizer (Hazra et al., 2004).

24. Phenoxodiol and Protopanaxadiol

Phenoxodiol (2H-1-benzopyran-7-0, 1, 3-[4-hydroxyphenyl], PXD) is a synthetic analog of naturally occurring plant isoflavone, genistein. Reports of phenoxodiol demonstrated that they inhibit plasma membrane electron transport and cell proliferation and leads to apoptosis of many cancer cell lines. This anti-cancer drug is being developed as a "chemosensitizer" and is currently under Phase III clinical trials for treating ovarian cancer and also in the initial stages of clinical trial for treating prostate and cervical cancer (Herst et al., 2009).

Protopanaxadiol (Pandimex™) is a triterpene aglycone obtained from saponins of ginseng. This compound arrests cell cycle through various signaling mechanisms leading to cancer cell death. Protopanaxadiol, an efficient P-glycoprotein blocker, shows cytotoxicity against multi-drug resistant tumors. It is used in treating advanced cancers of breast, colon-rectum, lung and pancreas. Protopanaxadiol is under Phase I clinical trial for the treatment of lung cancer and solid tumors (Pan et al., 2010).

25. Perillyl alcohol

Perillyl alcohol, a monocyclic monoterpene is found naturally in many plant species like mints, cherries, lavenders, lemongrass, sage, cranberries, perilla, wild bergamot, ginger grass, savin, caraway and celery seeds. Perillyl alcohol induces apoptosis, differentiation and cell cycle arrest in the G_1 phase and causes inhibition of cancerous cell growth. But the exact mechanism of action is yet to be identified. Investigation is still being done on the effectiveness of chemotherapeutic activity against human cancers like non small cell lung cancer, prostate cancer and colon cancer. Combination therapies were used in treating breast cancer cells (Pan et al., 2010; Bardona et al., 2002; Yeruva et al., 2007).

26. Pervilleines

Pervilleines A, B, C, and F are obtained from the roots of *Erythroxylum pervillei*. They act as good inhibitors of P-glycoprotein which causes a multidrug resistance related to low response for cancer therapy. Further investigation on clinical trials is yet to be done (Mi et al., 2001; Mi et al., 2002; Mi et al., 2003).

27. Salvicine

Salvicine, a diterpenoid quinone is obtained as a derivative of the naturally occurring lead saprorthoquinone compound. This lead product is isolated from a Chinese medicinal plant species, *Salvia prionitis* Hance (Labiatae). Salvicine reported significant in-vitro and in-vivo activity against malignant tumors by inhibiting the activity of Topoisomerase II (Deng et al., 2011).

28. Schischkinnin and Montamine

Schischkinnin, an indole alkaloid is obtained from the seeds of *Centaurea schischkinii*. They showed moderate in-vitro anti-cancer activity. Certain flavanoids and lignans were also isolated from *C. schischkinii* which exhibited low cytotoxicity. Most of these compounds are found effective against colon cancer cell lines in-vitro (Shoeb et al., 2005). Montamine, a dimeric indole alkaloid is obtained from the seeds of *Centaurea Montana* (Asteraceae). Among various compounds isolated from *C. Montana*, montamine demonstrated significant in-vitro anti-cancer

potential against $CaCo_2$ colon cancer cells (Shoeb et al., 2006).

29. Silvestrol

Silvestrol, a cytotoxic rocaglate derivative is obtained from the fruits and twigs of *Aglaia foveolata* Pannell (Meliaceae). They are found effective against prostrate, breast and lung cancers. The mechanism of action of silvestrol on LNCaP, hormone-dependent human prostate cancer cell line was studied. It revealed that an apoptosome / mitochondrial pathway was involved which triggers extrinsic pathway of programmed cell death of tumor cells. Another derivative, Episilvestrol, an epimer of silvestrol, was found less effective as a cytotoxic agent when compared to silvestrol (Kinghom et al., 2009; Kim et al., 2007).

30. Triptolide

Triptolide is a traditional Chinese medicine obtained as a purified extract from a shrub-like vine named *Tripterygium wilfordii* Hook F. This diterpenoid triepoxide enhances the anti-tumor effects of cytotoxic and chemotherapeutic agents and thereby induces apoptosis of tumor cells. Because of its severe toxicity and water insolubility, new triptolide derivatives like PG490-88 or F60008 have been synthesized which are water-soluble and proved to be very safe and effective. PG490-88 (14-succinyl triptolide sodium salt) is under Phase I clinical trial for treatment of prostate cancer (Liu, 2011).

The semi-synthetic analogs of plant derivatives reported by various scientists have been compiled and given in Table I.

Conclusion

From the preceding review, it can be concluded that Etoposide and Teniposide are active against lymphomas, bronchial and testicular cancer; Topotecan was found active against epithelial ovarian cancer and small cell lung cancer; Irinotecan was found effective against metastatic colorectal cancer; Homoharringtonine showed potential activity against various leukemic cells; Ingenol 3-o-angelate was active against actinic keratosis and basal cell carcinoma; PG-490-88 was found active against prostate cancer; Meisoindigo was effective in patients with chronic myeloid leukemia; Berberine was active against osteocarcoma, lung, liver, prostate and breast cancer; Phenoxodiol was found active against ovarian cancer. Protopanaxadiol (Pandimex™) was effective in treating advanced cancer of the breast, colo-rectal, lung and pancreatic cancer. Paclitaxel (Taxol®) and docetaxel (Taxotere®) was considered to be the most efficient drug introduced in the last decade which was found active against broad spectrum of cancer cells. Hence there is hope in the pharmaceutical industry, that even more powerful commercial drugs can be developed sooner, using plant derivatives, to effectively treat cancer and save mankind.

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