

Alkaloids as anticancer agents

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Abstract

Alkaloids are a class of naturally occurring organic nitrogen containing bases. Typical alkaloids are derived from plant sources, they are basic, they contain one or more nitrogen atoms (usually in a heterocyclic ring) and they usually have a marked physiological action on man or other animals. Alkaloids have potent anticancer activity against various cancers. In this review mainly discussed about alkaloids isolated and identified from plants that present anticancer activity. These substances have been classified by chemical groups and each provides the most relevant information of its pharmacological activity, action mechanism, chemical structure and other properties.

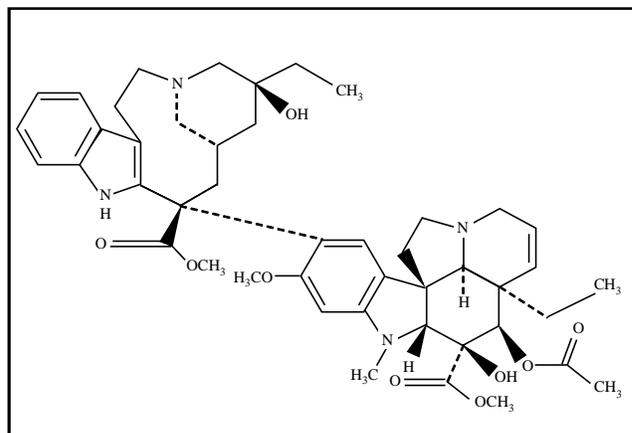
Key words: Chemopreventive, apoptotic, cytotoxicity, topoisomerase

Introduction

Plants are natural sources for drug discovery against various diseases. Cancer, a neoplastic disease, the natural course of it is fatal. Cancer cells exhibit the properties of invasion and metastasis and are highly anaplastic. Alkaloids an amazing group of phytoprinciples, isolated from medicinal plants, have a varied spectrum of effects such as analgesics to addictive. The structures of alkaloids are usually mimicked in synthesis of chemical drugs. Alkaloids have potent anticancer activity against various cancers. They are chemically heterogeneous group of approximately 2500 basic nitrogen containing substances, found in about 15 percent of all vascular land plants and in more than 150 plant families, widely distributed in higher plants particularly the dicotyledons (in abundance in the families *Apocynaceae*, *Papaveraceae*, *Papilionaceae*, *Ranunculaceae*, *Rubiaceae*, *Rutaceae* and *Solanaceae*), but less frequently in lower plants and fungi. Vinblastine and vincristine are the first significant anticancer alkaloid, isolated from the *Vinca rosea*; *Catharanthus roseus* (*Apocynaceae*) introduced new era in anticancer drug discovery.

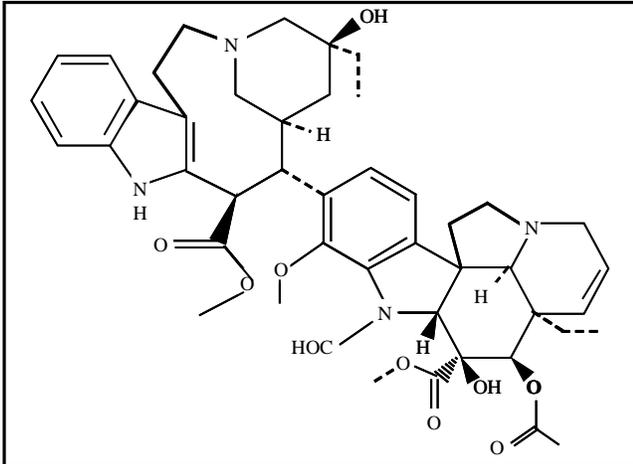
Efficacy of indole alkaloids in cancer prevention

There are various indole alkaloids isolated from medicinal plants. From periwinkle plant *Vinca rosea*; *Catharanthus roseus* (*Apocynaceae*), three compounds vinblastine, vincristine and vindesine introduced a new era of the use of plant material as anti cancer agents. Vinblastin and vincristine are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers including leukemias, lymphomas, advanced testicular cancer, breast and lung cancer and kaposi's sarcoma (Cragg and Newman, 2005).

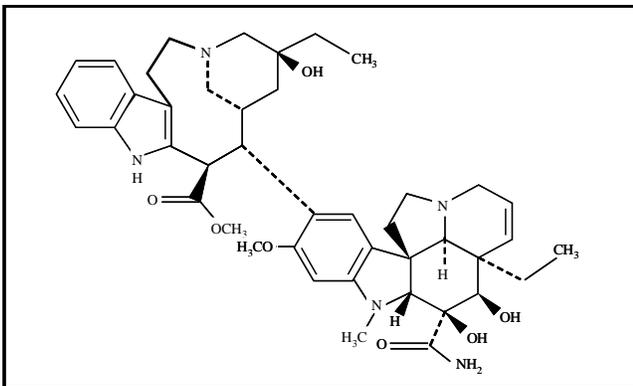


Vinblastine

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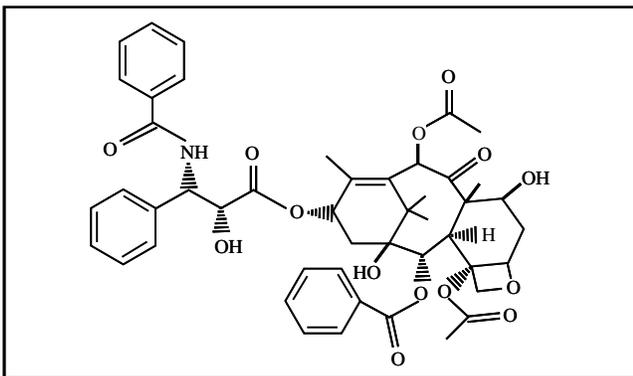


Vincristine

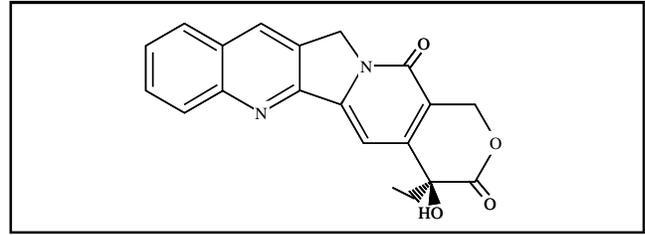


Vindesine

Vinca alkaloids and paclitaxel inhibits cell proliferation by altering the dynamics of tubulin addition and loss at the ends of mitotic spindle microtubules rather than by depolymerizing the microtubules (Mary *et al.*, 2010; Mary and Leslie, 2004). Taxol (a modified diterpene pseudo alkaloid) first isolated and identified by Wall and Wani from *Taxus brevifolia*, was found to inhibit cancer cell growth via the stabilization of microtubules (Nicholas *et al.*, 2004). It is significantly active against ovarian cancer, advanced breast cancer, and lung cancer (Rowinsky *et al.*, 1992).

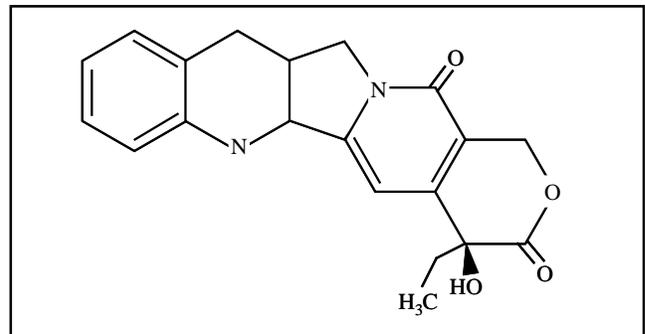


Taxol

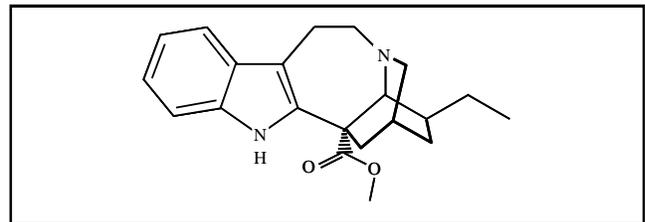


Camptothecin

There are 14 indole alkaloids and 3 triterpenoids were extracted from wood and stem bark of *Ervatamia heyneana* (Apocynaceae). From these camptothecin, 9-methoxy camptothecin coronaridine, pericalline, heyneatine and 10-methoxyeglandine- N-oxide displayed cytotoxic activity (Sarath *et al.*, 1980).

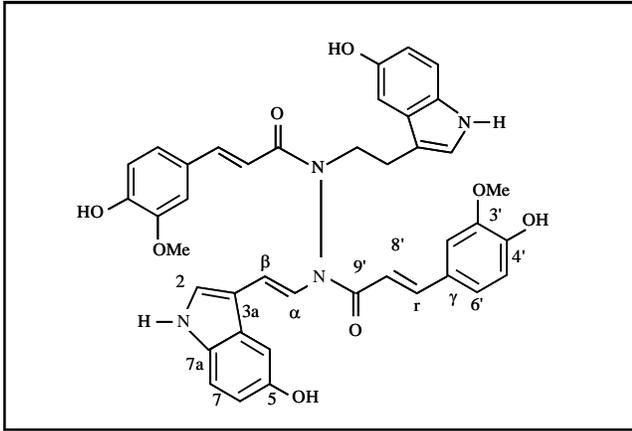
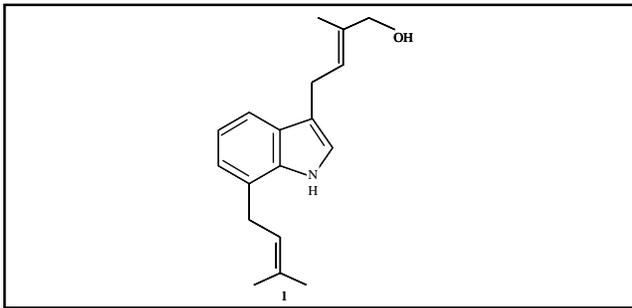


9-Methoxycamptothecin

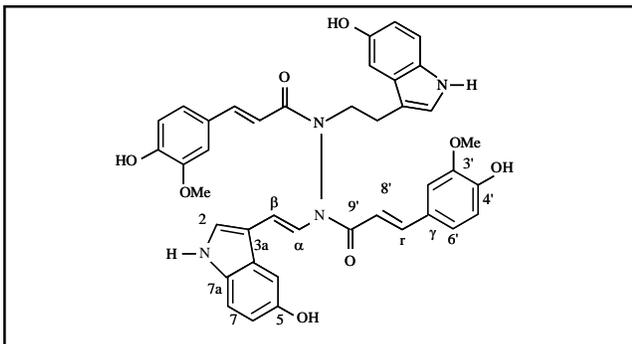
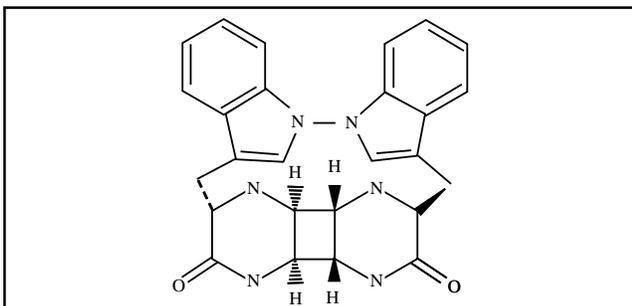


Coronaridine

Camptothecin, first isolated and identified from *Camptotheca acuminata* (Nyssaceae), have a wide spectrum of anticancer activity *in vitro* and *in vivo*. Presently, two first-generation analogues of camptothecin are used to treat ovarian, colorectal, and small-cell lung cancers, and several second-generation analogues are in clinical trials (Yu-Feng and Ruiwen, 1996). The clinical trials of Camptothecin by NCI in the 1970s but was dropped because of sever bladder toxicity (Potmeisel, 1995). Topotecan and irinotecan are semi synthetic derivatives of camptothecin and are used for the treatment of ovarian and small cell lung cancers and colorectal cancers, respectively (Creemers *et al.*, 1996; Bertino, 1997). Naucleorals A and B was a pair of new isomeric indole alkaloids isolated from the roots of *Nauclea orientalis*. It has cytotoxicity effect on HeLa and KB cells (Jirapast *et al.*, 2010).

**Naucleorals****Diprenylated indole alkaloid**

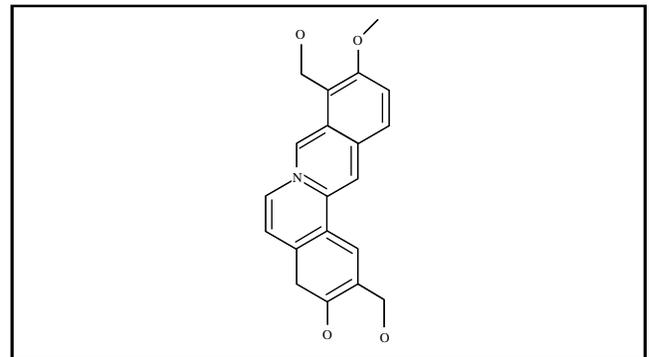
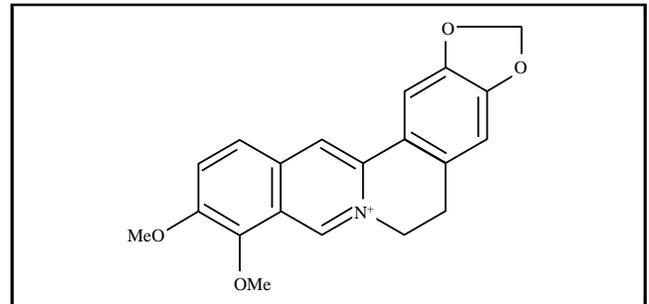
Montamine is a unique dimeric indole alkaloid, isolated from the seeds of *Centaurea montana* (Asteraceae) displayed significant *in vitro* anticancer activity in the MTT assay using the CaCO₂ colon cancer cell line (Mohammad *et al.*, 2006).

**Montamine****Schischkiniin**

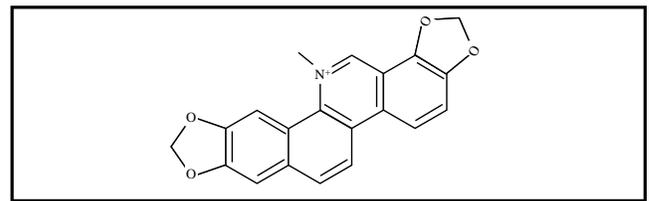
Schischkiniin, a unique indole alkaloid with anticancer and antioxidant properties, together with four known lignans arctiin, matairesinoside, matairesinol and arctigenin, have been isolated from the seeds of *C. schischkini* (Asteraceae). Schischkiniin and Arctigenin have cytotoxicity effect on CaCO₂ colon cancer cell lines. It was identified by brine shrimp lethality and MTT cytotoxicity assays (Mohammad, *et al.*, 2005).

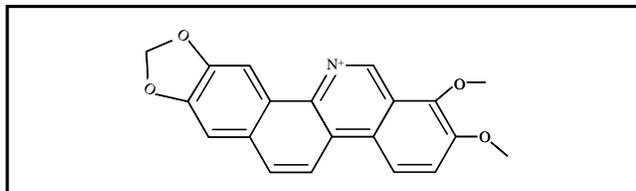
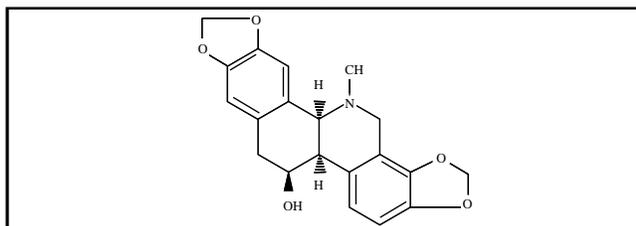
Antiproliferative activity of Isoquinoline alkaloids

Berberine was isolated from *Rhizoma coptidis*. It has potential chemopreventive property against colon tumor formation by inhibiting the enzyme cyclooxygenase-2 (COX-2) which abundantly expressed in colon cancer cells and plays a key role in colon tumorigenesis (Kazunori, 1999).

**Protoberberine****Berberine.**

Sanguinarine, chelerythrine and chelidonine are isoquinoline alkaloids derived from the greater *celandine*. It induces apoptosis in A549 human lung cancer cells, pancreatic carcinoma Asp-1 and Bxpc-3 cells (Haseeb *et al.*, 2007) and effective against melanoma skin cancer. It is also effective against multi-drug resistance in human cervical cells (Ilaria *et al.*, 2009; Byeong *et al.*, 2009; Zhihu *et al.*, 2002).

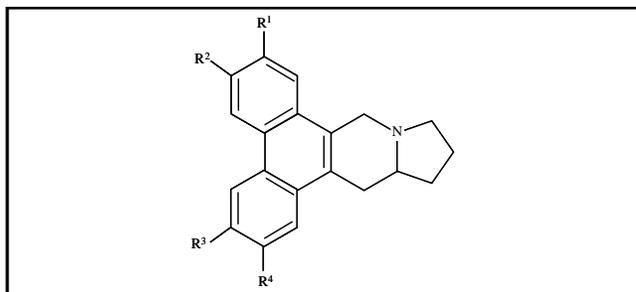
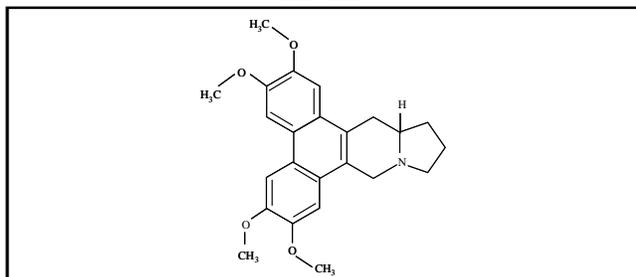
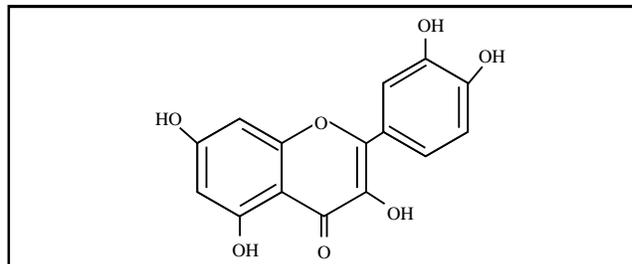
**Sanguinarine**

**Chelerythrine****Chelidoniumine**

Liriodenine isoquinoline alkaloid isolated from *Cananga odorata* (Annonaceae) have potent cytotoxic, anti proliferative and apoptosis inducing effects on human lung cancer cells and various types of human cancer cells (Hui *et al.*, 2004). It was found to be a potent inhibitor of topoisomerase II (EC 5.99.1.3) both *in vivo* and *in vitro* (Sung *et al.*, 1997).

Phenanthroindolizidine alkaloids in anti-inf-lammation

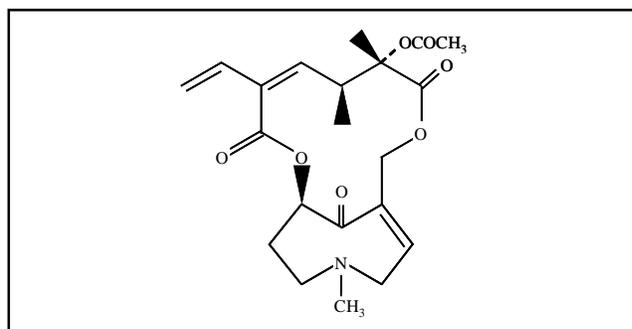
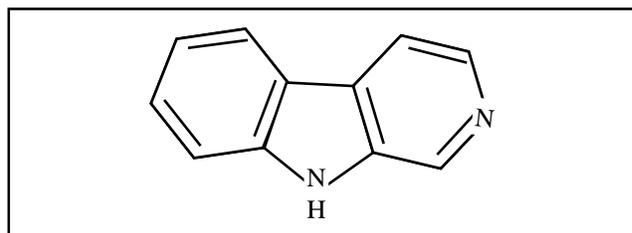
A phenanthroindolizidine alkaloid, Antofine derived from *Cynanchum paniculatum* (Asclepiadaceae) have antitumor and antiproliferative activity in several human cancer cells (Hye-young Min *et al.*, 2010). 6-methoxydihydrosan-guinarine (6ME) a benzophenanthridine alkaloid isolated from *Hylomecon* species is a potential chemotherapeutic agent. It inhibits the growth of hepato carcinoma HepG2 cells by apoptosis. In Col2 cells antofine induced arrest in the G2/M phase of the cell cycle (Sang *et al.*, 2003; Hu-Quan, 2005).

**Antofine****Tylophorine****Liriodenine**

Tylophorine, a representative phenanthroindolizidine alkaloid from *Tylophora indica* (Asclepiadaceae) plants, exhibits anti-inflammatory and anti-cancerous growth activities (Chia-Mao *et al.*, 2009; Linyi *et al.*, 2008). Pergularine (PGL) and tylophorinidine (TPD) are isolated from the Indian medicinal herb *Pergularia pallida* have potential anticancer activity (Narasimha and Venkatachalam, 2000).

Apoptotic induction of Pyrrolizidine alkaloids

Clivorine a pyrrolizidine alkaloids extracted from a Chinese medicinal plant *Ligularia hodgsonii* Hook, have anti-proliferative activity in human normal liver L-02 cells, by induce apoptosis (Li-Li *et al.*, 2005; Li-Li *et al.*, 2002).

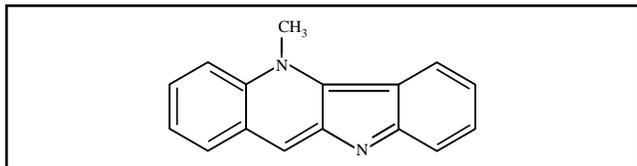
**Clivorine** **β -Carboline**

Inhibition of Topoisomerase by Benzo quinolizidine alkaloids

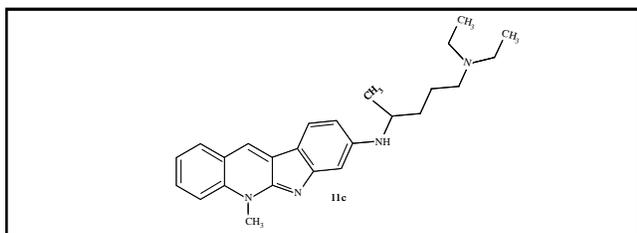
Beta carboline alkaloids of *Harmina harmane*, harmaline, harmalol and tryptoline isolated from *Peganum harmala* (Harmal) have antitumor activity by inhibiting the DNA topoisomerases and interfere with DNA synthesis. It was the most active compound, showing particular effectiveness on lung ($GI_{50} = 0.06 \mu M$), ovarian and renal cell lines (Shohreh, 2010; Anelise *et al.*, 2008; Kothapalli *et al.*, 1999).

Cytotoxicity of Indoquinoline alkaloids

Cryptolepine and neocryptolepine are two indoquinoline derivatives isolated from the roots of the African plant *Cryptolepis sanguinolenta*. They have potent cytotoxic activities against tumor cells. These two natural products intercalate into DNA and interfere with the catalytic activity of human topoisomerase II. Cryptolepine showed cytotoxicity in murine and human leukemia cells (Laurent *et al.*, 2000).



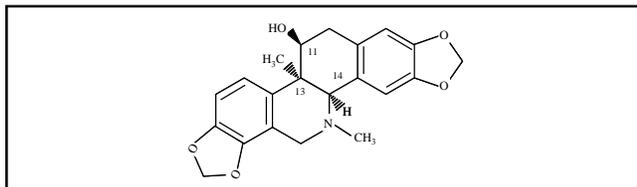
Cryptolepine



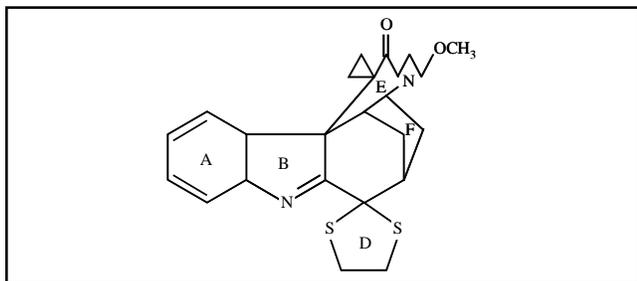
Neocryptolepine

Benzophenanthridine alkaloids as chemotherapeutic agents

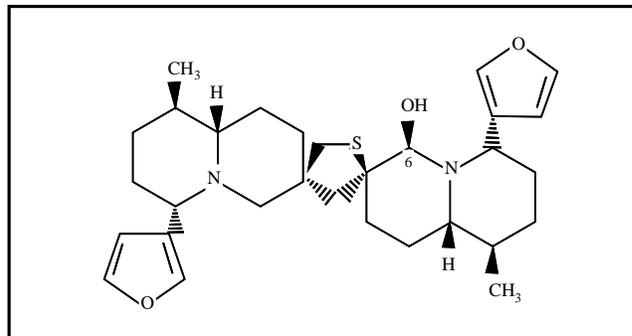
6-methoxydihydrosanguinarine (6ME), a benzophenanthridine alkaloid isolated from *Hylomecon* species, is a potential chemotherapeutic agent. It causes apoptotic cell death in HT29 colon carcinoma cells (Yong *et al.*, 2004). Corynoline, a hexahydrobenzo[*c*]phenanthridine-type alkaloid, exhibited potent inhibitory activity of the ICAM-1/LFA-1 adhesion and would be important on developing the clinically usable drugs for the inflammatory diseases (Miyoko *et al.*, 2005).



Corynoline



Carbazole



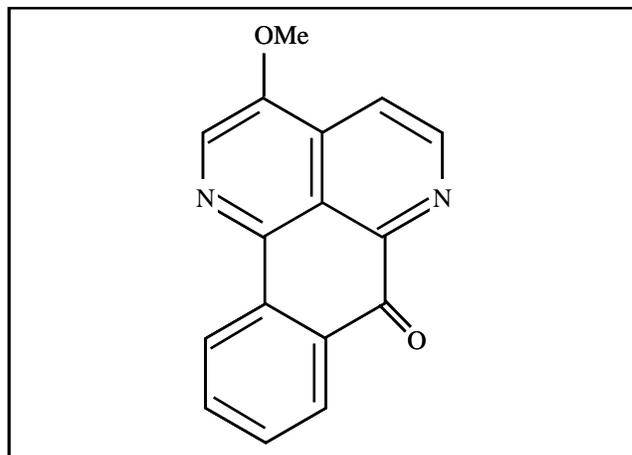
Alkaloids

Array of other alkaloid groups in cancer prevention

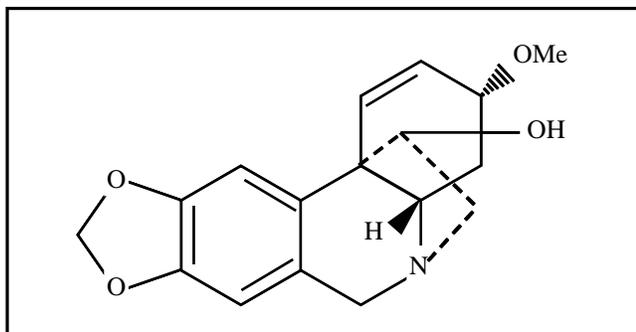
Carbazole alkaloids are isolated from the plant species *Murraya koenigii* (Rutaceae), they have effects on the growth of the human leukemia cell line HL-60. Three carbazole alkaloids, mahanine, pyrayafoline-D and murrifoline-I, showed significant cytotoxicity against HL-60 cells. (Ito *et al.*, 2006). 9-carbomethoxy-3-methylcarbazole, 9-formyl-3-methylcarbazole and 3-methylcarbazole were isolated from the roots of *Murraya koenigii* (Rutaceae). They have cytotoxicity against mouse melanoma B16 and adriamycin-resistant P388 mouse leukemia cell lines. (Manas *et al.*, 1997).

The alkaloid from the rhizomes of *Nuphar pumilum* showed cytotoxic effects on human leukemia cell (U937), mouse melanoma cell (B16F10), and human fibroblast (HT1080) (Hisashi *et al.*, 2006).

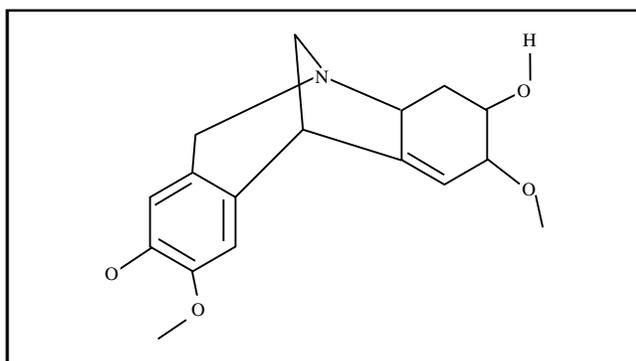
Sampangine is a plant-derived copyrine alkaloid extracted from the stem bark of *Cananga odorata* (Annonaceae). This azaoxaporphine alkaloid primarily exhibits antifungal and antimycobacterial activities but also displays *in vitro* antimalarial activity against *Plasmodium falciparum* and it is cytotoxic to human malignant melanoma cells. Sampangine have pro-apoptotic action against human HL-60 leukemia cells, leading to cell death (Jérôme *et al.*, 2005).



Sampangine



Crinamine



Montanine

The alkaloid Punarnavine isolated from the plant of *Boerhaavia diffusa* Linn. have antimetastatic activity using B16F-10 melanoma cells in C57BL/6 mice. Punarnavine could inhibit the metastatic progression of B16F-10 melanoma cells in mice (Manu and Girija, 2009).

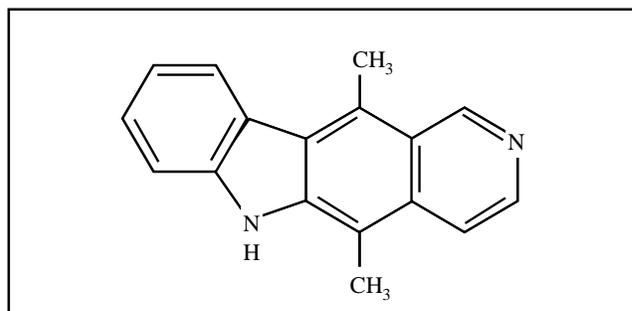
The alkaloid Bgugaine present in *Arisarum vulgareae*. It induces DNA damage in the HepG₂ cell line (Nafissa *et al.*, 1999). The 2-alkylpyrrolidine R-bgugaine, a natural alkaloid isolated from tubers of *Arisarum vulgare Targ. Tozz.* (Araceae). These two alkaloids exhibited an important cytotoxic activity on murine mastocytoma cell line P815 and the human laryngeal carcinoma cell line Hep (Benamar *et al.*, 2009).

Stemona alkaloids were isolated from the roots of *Stemona aphylla* and *S. burkillii*. They play an important role as a (P-glycoprotein) modulator as used *in vitro* and may be effective in the treatment of multidrug-resistant cancers. Stemofoline have synergistic growth inhibitory effect with cancer chemotherapeutic agents including vinblastine, paclitaxel and doxorubicin of KB-V1 cells (MDR human cervical carcinoma with P-gp expression), but not in KB-3-1 cells (drug sensitive human cervical carcinoma, which lack P-gp expression). Verapamil was employed as a comparative agent (Wisinee *et al.*, 2010).

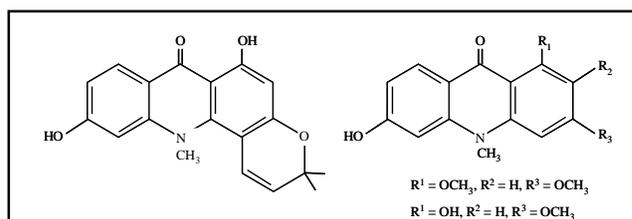
Alkaloids isolated from Amaryllidaceae, have inhibitory effect on P-glycoprotein (P-gp) and the apoptosis-inducing capacity. (Zupkó *et al.*, 2009). The selective apoptosis-inducing activity of Amaryllidaceae alkaloids belongs to the type of crinane. Crinamine and haemanthamine are potent inducers of apoptosis in tumour cells at micromolar concentrations. Structure-activity relationships demonstrated the requirement for both an alpha-C2 bridge and a free hydroxyl at the C-11 position as pharmacophoric requirements for this activity.

Lycorine, vittatine and montanine were isolated from the bulb of *Hippeastrum vittatum* (Amaryllidaceae) have cytotoxic activity against five human cell lines (HT29 colon adenocarcinoma, H460 non-small cell lung carcinoma, RXF393 renal cell carcinoma, MCF7 breast cancer, and OVCAR3 epithelial ovarian cancer) *in vitro*. Among three montanine have potential antiproliferative activity (Silva *et al.*, 2008).

Ellipticine (EPC), a natural alkaloid extracted from *Aspidosperma williansii* (Apocynaceae) has antitumor and cytotoxic activities on various tumors. The cytotoxic effect on lymphocytes was very strong (Elza *et al.*, 1988). The cytotoxic plant alkaloid of ellipticine inhibit topoisomerase II in human breast MCF-7 cancer cells (Canals *et al.*, 2005).



Ellipticine



Acridone alkaloids

Acridone alkaloids isolated from the Rutaceous plants have anticarcinogenic activity in mouse skin tumor *in vivo*. It expected that potentially valuable cancer chemo preventive agents (Masataka *et al.*, 2003). The acridone alkaloids of atalaphyllidine, 5-hydroxy-N-methylseverifoline, atalaphyllinine, and des-N-methylnoracronycine showed potent antiproliferative activity against tumor cell lines, whereas they have weak cytotoxicity on normal human cell lines. The structure activity revealed that a secondary amine,

hydroxyl groups at C-1 and C-5, and a prenyl group at C-2 played an important role for antiproliferative activities of the tetracyclic acridones (Satoru *et al.*, 1999).

Conclusion

Alkaloids play major role as anticancer agents by inhibiting the enzyme topoisomerase which is involved in DNA replication, inducing apoptosis and expression of p53 gene. Although they undoubtedly existed long before humans, some alkaloids have remarkable structural similarities with neurotransmitters in the central nervous system of humans, including dopamine, serotonin and acetylcholine. The amazing effect of these alkaloids on humans has led to the development of powerful pain-killer medications, spiritual drugs, and serious addictions by people who are ignorant of the properties of these powerful chemicals. Knowing the medicinal importance of alkaloids and research elucidating their mechanisms of action in uncontrolled proliferation of cells would help in formulating drugs and lead compounds in the era of modern drug discovery.

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