Indian Journal of Drugs, 2018, 6(1), 68-104 ISSN: 2348-1684

Review Article

NATURAL COMPOUNDS AS SOURCE OF ANTICANCER DRUG DISCOVERY

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Received: 26.10.2017
Accepted: 22.03.2018

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ABSTRACT

Cancer is the most severe health problem in the world and it causes the death of millions of people each year. Some of natural compounds identified from the fruits and vegetables such as curcumin, lycopene, genistein, diosgenin, beta carotene and ellagic acid are used in anticancer therapy. Also, some other natural compounds as vinca alkaloids, taxanes, podophyllotoxin and some derivatives of it were approved internationally as anticancer drugs from natural source. This review gives available information about different classes of natural compounds that have significant anticancer activity and can be as source of anticancer drug after further clinical evaluations.

KEY WORDS: Natural compounds, anticancer activity.

INTRODUCTION

Natural Products, especially plants, have been used for the treatment of various diseases for thousands of years. Plant secondary metabolites as flavonoids, alkaloids and others proved to be a good source of new medical compounds. Cancer is the second cause of death in the world and it can be described as a complex disease that is associated with a wide range of escalating effects both at the molecular and cellular levels. Since 1990, there is 22% increase in cancer cases where lung, stomach, liver, and colorectal cancers are the most deadly cancers (Parkin, 2001). Traditional medicines or herbal formulations can serve as the source of potential new drugs, so that initial research focuses on the active constituent of the plants. The development of novel plant derived natural products and their analogs for anticancer activity are going day by day. A number of promising agents of medicinal plants are used in clinical and preclinical development. Numerous types of bioactive compounds have been isolated from plant sources. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation (Kellard *et al*., 2000). In this review, the potent anti-cancer activity of some natural products is mentioned.

Natural compounds have potent anticancer activity

1. Flavonoids

Flavonoids are polyphenolic compounds and the main classes are flavones, flavonols, flavanones, isoflavones, and anthocyanidins, the plant which has potential health benefits is due to the high level of its flavonoidal content. There are many studies proved the protective effect of flavonoids against cancer. Most flavonoids are

present in nature as glycosides and as a fact quercetin glucosides can be absorbed more better than quercetin aglycone (Hollman and Katan 1998). Several flavonoids proved significant anticancer activity from that flavonols such as quercetin, kaempferol, and isoflavones as genistein.

Flavones

Luteolin has the ability to block the development of cancer cells *in vitro* and *in vivo* by inhibition of tumor cell proliferation, or by induction of cell cycle arrest and by induction of apoptosis via intrinsic and extrinsic signaling pathways. Moreover, luteolin was the most effective flavonoid that inhibited tumor cell proliferation with IC_{50} values between 3 and 50 µM *in vitro* (Seelinger *et al*. 2008). Luteolin has the ability to penetrate into human skin, and this may let to that luteolin be a candidate for the prevention and treatment of skin cancer (Seelinger *et al*., 2008). Luteolin 7-methyl ether which was isolated from *Blumea balsemifera* leaves proved a strong cytotoxic effect against human lung cancer cell lines with IC_{50} of 1.29 µg/ml and also it showed a moderate toxic effect against oral cavity cancer cell lines with IC_{50} of 17.83 µg/ml (Saewan *et al*. 2011). Apigenin can inhibit skin papillomas and also it proved the tendency to decrease conversion of papillomas to carcinomas (Wei *et al*., 1990).

Polymethylated flavones

A polymethoxy flavonoid, nobiletin has the ability to inhibit the tumor-invasive activity of human fibrosarcoma cells (Sato *et al.*, 2002).

Flavonols

Quercetin was reported that it prevents renal cell cancer (Wilson *et al*., 2009). Also quercetin, has the ability to reduce the risk of lung cancer (Wilson *et al*., 2009). Quercetin proved preventive effect on hepato carcinomas in rats, where a study indicated that quercitin indicated a preventive effect (Seufi *et al*., 2009). Kaempferol, a flavonol isolated from different plant species is very active in reducing vascular endothelial growth factor expression in ovarian cancer cells (Luo *et al*., 2010). Myricetin had a significant cytotoxic effect on leukemia cells (Romanouskaya and Grinev, 2009). Fisetin has the ability to inhibit the proliferation of bladder cancer cells and this is through blocking cell-cycle progression in the G0/G1 phase (Li *et al*., 2011).

Isoflavones

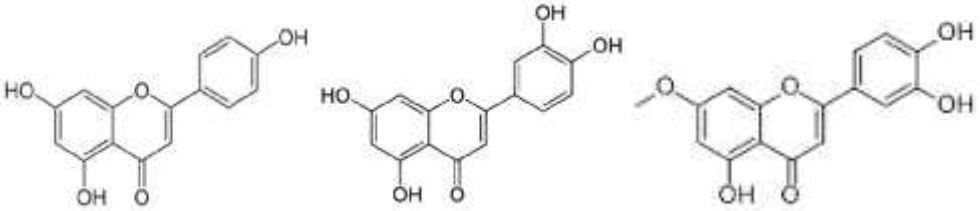
Genistein showed a concentration-dependent ability to inhibit both growth factor-stimulated and estrogen-stimulated cell proliferation of human breast cancer cells (So *et al*., 1997).

Anthocyanidins

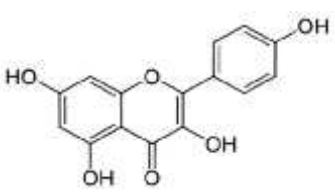
Some previous studies reported anti-cancer activity of anthocyanins as cyandin, cyanidin glycoside and malvidin where cyanidin-3-rutinoside identified of black raspberries has the ability to kill leukemia cells (Feng *et al*., 2007). Another study proved that cyanidin 3-O-β-glucoside and a bilberry extract reduced the formation of intestinal adenoma (Cooke *et al*., 2006). Some researchers reported that cyanidin 3-O-β-glucopyranoside may be considered as anticancer agent for the treatment of melanoma. Treatment of the cancer cells with cyanidin 3-O-β-glucopyranoside decreased cell proliferation without inducing apoptosis (Serafino *et al*., 2004). A study reported some reserachers found that blueberry anthocyanins proved anticancer activity by inhibiting cancer cell proliferation and can act as chemoinhibitors (Ana *et al*., 2010). Proanthocyanidins which are present in apples reduce the risk of pancreatic cancer by the percentage of 25 % (Rossi *et al*. 2010).

Other flavonoids

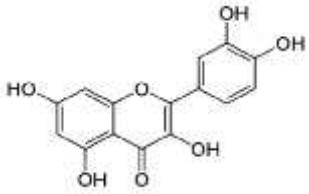
Some previous reports indicated that flavonoids such as hesperidin, naringin, neohesperidin, and rutin from *Citrus* species proved biological properties that include anti-carcinogenic, anti-oxidant andanti-inflammatory activities that promote and benefit human health (Lopez-Lazaro, 2002).



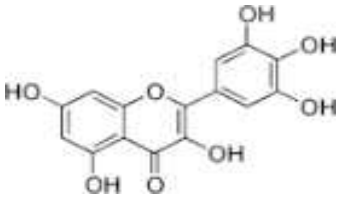
Apigenin **Luteolin** **Luteolin 7-methyl ether**



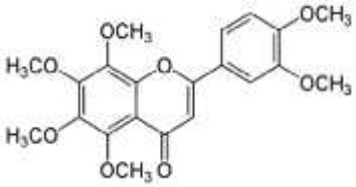
Kaempferol



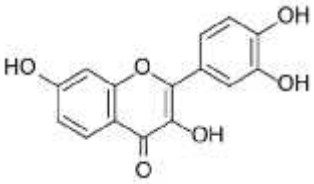
Quercetin



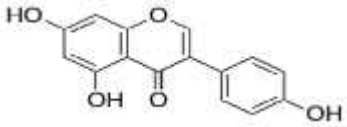
Myricetin



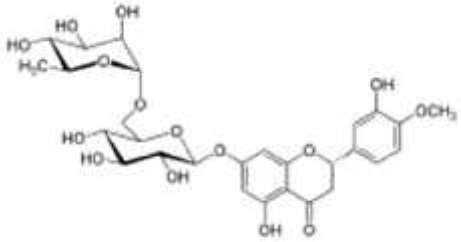
Nobiletin



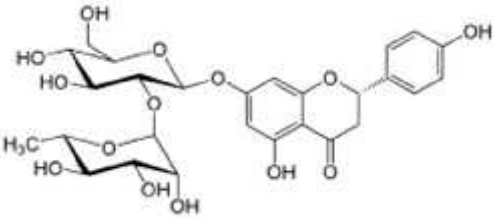
Fisetin



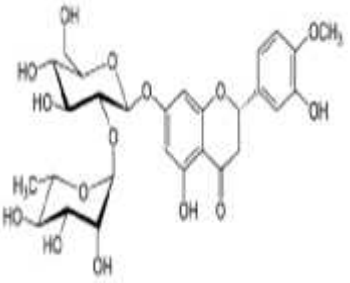
Genistein



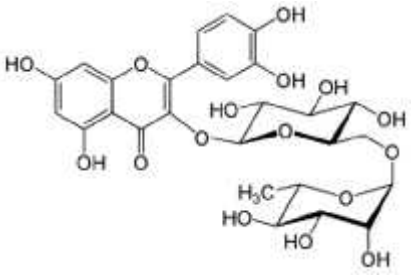
Naringin



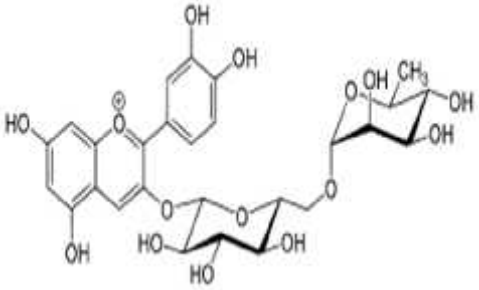
Hesperidin



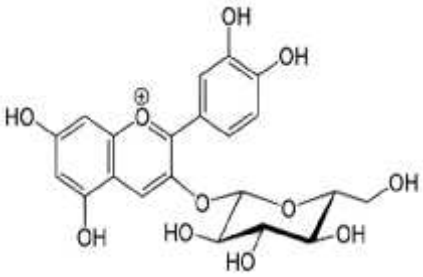
Neohesperidin



Rutin



Cyanidin-3-rutinoside



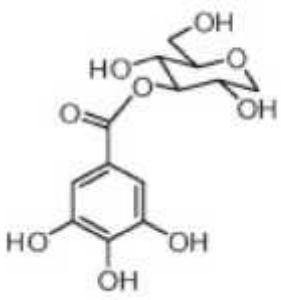
Cyanidin 3-O-β-glucopyranoside

Fig. 1. Chemical structure of some flavonoids have potent anticancer activity

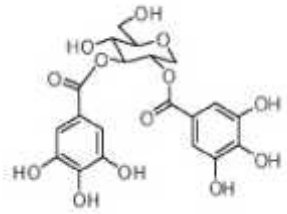
2. Tannins

Tannins are phenolic compounds with high molecular weight. They are acidic in reaction and this is due to the presence of phenolic or carboxylic groups. They form complexes with carbohydrates, and alkaloids (Kar, 2007). Some gallotannins as maplexins A-I which isolated from *Acer rubrum* species proved significant anticancer effects against human tumor cell lines as colon, and breast tumor cell lines (Gonzalez-Sarria *et al*., 2012). Tannins isolated from *Eugenia jambos* L. proved anticancer effect. These tannins have the ability to inhibit

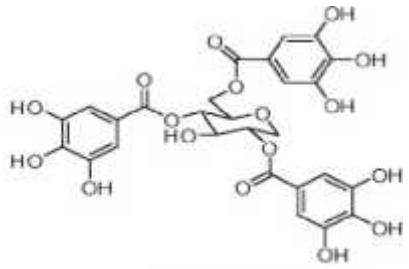
human promyelocytic leukemia cell line. Moreover, tannins can inhibit growth of human promyelocytic leukemia tumor cells (Yang *et al*., 2000). A study evaluated gallotannin can inhibit the proliferation and also can induce apoptosis in a human colon cancer cell line (Gali-Muhtasib *et al*., 2001). Hydrolyzable tannin's isolated of the *Limonium axaillere* exhibited inhibition of Ehrlish ascita carcinoma (Ahmed *et al*., 1999). *Punica granatum* fruits and its juice contained tannins (punicalagin, ellagic acid) in high content. Total tannin of *P. granatum* extract and its juice were tested for their anticancer potential *in vitro* on some tumor cell lines. The results indicated that they have the ability to induce apoptosis and decreased the viable cell number of human oral, prostate and colon tumor cells (Seeram *et al*., 2005). Corilagin is the tannin present in many plants. A study was carried out to test anticancer activity of corilagin against ovarian cancer cells. The results showed that corilagin can inhibit the growth of the ovarian cancer cell lines and corilagin isolated of *Phyllanthus niruri* plant can be used as therapeutic a agent against growth of ovarian cancer cells (Jia *et al*., 2013). Tannic acid has anti-carcinogenic effect against hepatic neoplasms and also this compound exhibited chemoprotective activity (Nepka *et al*., 1999). Hydrolyzable tannins indicated higher cytotoxic effect against human oral squamous cell carcinoma and salivary gland tumor cell lines (Sakagami *et al*., 2000).



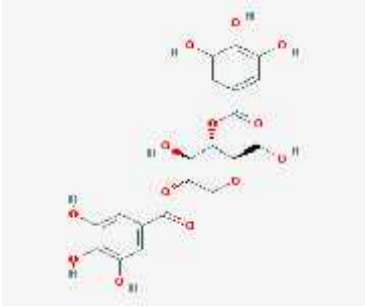
Maplexin A



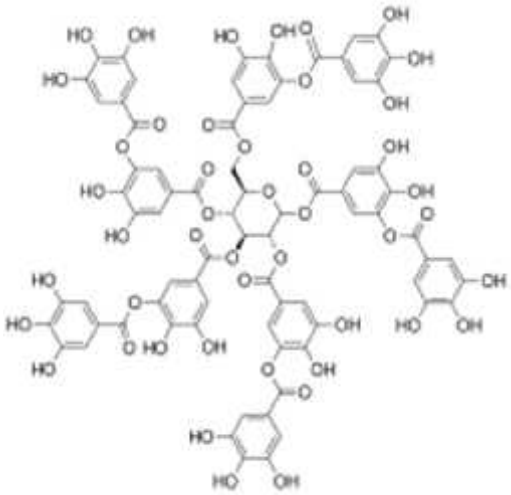
Maplexin C



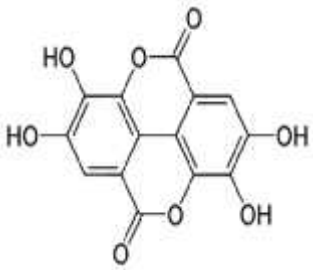
Maplexin E



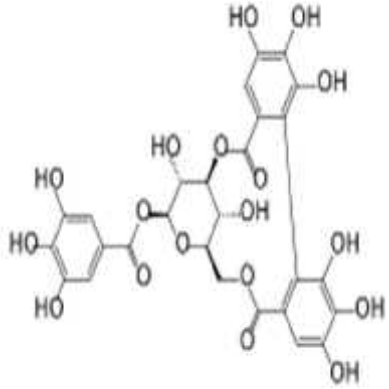
Maplexin D



Ellagic acid



Tannic acid



Punicalagin

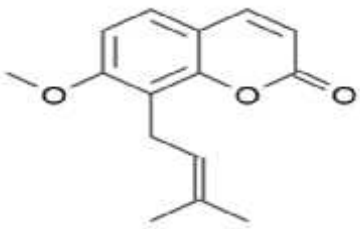
Corilagin

Fig. 2. Chemical structure of some tannins have potent anticancer activity

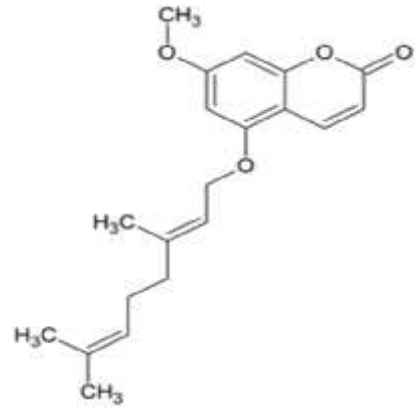
3. Coumarins

Coumarins are a type of benzopyrone class, where benzene ring is fused to pyrone ring. In the nature, coumarins are present in higher plants like *Rutaceae* and *Umbelliferae.* Also, coumarins were present in microorganisms as coumermycin from *Streptomyces* and aflatoxins from *Aspergillus* species (Lacy and Kennedy, 2004; Jain and Joshi, 2012). Coumarins as anticancer agents based on the chemical structure. They can inhibit telomerase enzyme, protein kinase activity and also down regulating oncogene expression or induce the caspase-9-mediated apoptosis (Amin *et al*., 2013; Nasr *et al*., 2014). Osthole compound which was isolated of several medicinal plants inhibited the growth of human lung cancer by inducing G2/M arrest and apoptosis (Xiaoman *et al*., 2011). Another coumarin, umbelliprenin, which was isolated of some *Ferula* species, induced the apoptosis in large cell lung cancer and adenocarcinoma cell line, at the different doses (Khaghanzadeh et al., 2012). Daphnetin inhibited the proliferation of human lung adenocarcinoma cells by suppression Akt/NF-κ B signalling pathways (Wang *et al*., 2013). A coumarin named, monastrol, indicated the most potent selective effect against breast cancer cell lines. Scopoletin which is present in many plants proved anticancer activity against prostate cancer cells by inhibition of expression of cyclin D1 which caused cell cycle arrest at G2/M phase (Li. *et al*., 2015). A coumarin named, 7-isopentenyloxycoumarin was tested for its anticancer activity against bladder cancer cells. The results indicated that the compound has selective cytotoxic effect on bladder cancer (Haghighi *et al*., 2014). Diversin, a terpenoid coumarin compound which was

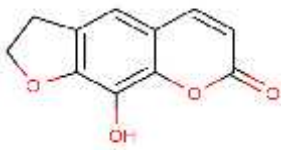
isolated of *Ferula diversivittata* has a cytotoxic effect against bladder cancer causing arrest of the cells in the G2/M phase (Haghighitalab *et al*., 2014). Pyranocoumarin, decursin compound which was isolated from *Angelica gigas* root inhibited proliferation in bladder and colon cancer cells (Kim *et al*., 2010). Cisplatin (methyl umbelliferone) is used to treat different kind of cancers including bladder cancer (Haghighitalab *et al*., 2014). Esculetin which is presented in many plants such as *Fraxinus rhynchophylla* and *Artemisia capillaries*. This compound can significantly inhibit proliferation of hepatocellular carcinoma cells by causing cell cycle arrest at S phase and inducing apoptosis (Wang *et al*., 2015). A coumarin named, 8-hydroxypsoralen isolated from peels of *Clausena lansium* (Lour.) Skeels. This compound indicated a significant anti-proliferative effect against human hepatocellular liver, lung and cervical carcinoma cell lines (Prasad *et al*., 2010). A coumarin named, 5-geranyloxy-7-methoxycoumarin which was isolated from *Citrus aurantifolia* L. Osbeck. This compound inhibited proliferation of human colon cancer by induction of apoptosis (Patil *et al*., 2012).



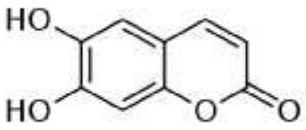
Osthole



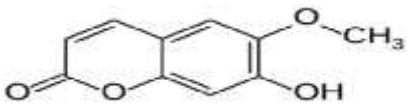
5-Geranyloxy-7-methoxycoumarin



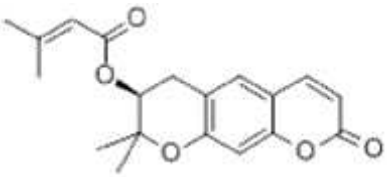
8-hydroxypsoralen



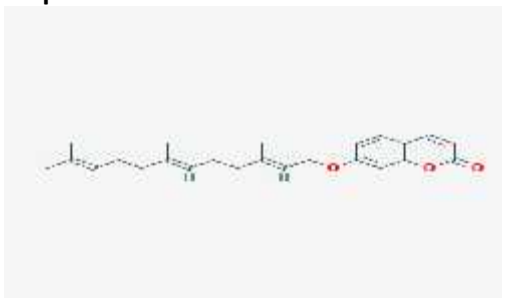
Esculetin



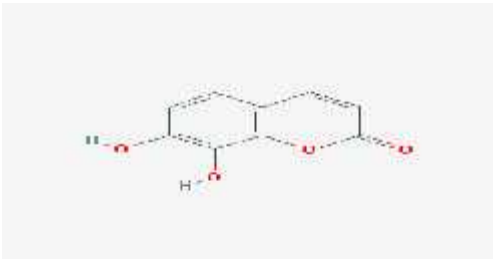
Scopoletin



Decursin



Umbelliprenin



Daphnetin

Fig. 3. Chemical structure of some coumarins have potent anticancer activity

4. Alkaloids

Alkaloids are natural compounds have organic nitrogen containing bases. Alkaloids derived from plant source are basic and they contain one or more nitrogen atoms in a heterocyclic ring. Alkaloids have potent anticancer activity against different types of cancers and they play a major role as anticancer agents by inhibiting the enzyme topoisomerase which is involved in DNA replication. Alkaloids have different types as:

Indole alkaloids

The first potent anticancer alkaloids are vinblastine and vincristine isolated from *Vinca rosea.* Vinblastine was used for the treatment of leukemia, breast, and lung cancers, while vincristine proved a good efficacy against leukemia, particularly acute lymphocytic leukemia in childhood (Gueritte and Fahy, 2005). These two alkaloids were used in combination with other cancer chemotherapeutic drugs for the treatment of different types of cancers as breast and lung cancers (Cragg and Newman, 2005). Taxol (modified diterpene pseudo alkaloid) which was isolated from *Taxus brevifolia*. This compound has the ability to inhibit cancer cell growth through the stabilization of microtubules (Nicholas and David, 2004). Moreover, it is very active against ovarian, advanced breast, and lung cancers (Rowinsky *et al.,* 1992). Camptothecin, which was identified of *Camptotheca acuminata* has anticancer activity. This compound is used to treat ovarian, colorectal, and lung cancers (Yu-Feng and Ruiwen, 1996). Schischkiniin isolated from *C. schischkinii* seeds has anticancer, antioxidant properties, and cytotoxicity effect against colon cancer cell line. It was identified by brine shrimp lethality and MTT cytotoxicity assays (Mohammad *et al*., 2005). Montamine which is dimeric indole alkaloid, isolated of *Centaurea montana* seeds showed a potent anticancer activity against colon cancer cell line (Mohammad *et al*., 2006).

Isoquinoline alkaloids

Berberine which was isolated of *Rhizoma coptidis*. This compound has a potent chemopreventive effect against colon tumor formation (Kazunori, 1999). The three alkaloids, Sanguinarine, chelerythrine and chelidonine have the ability to induce apoptosis in human lung cancer cells, pancreatic carcinoma and also the compounds are very effective against melanoma skin cancer (Haseeb *et al.*, 2007). Liriodenine isolated of *Cananga odorata* has a potent cytotoxic, antiproliferative and apoptosis inducing effects on human lung cancer cells and different types of human cancer cells (Chang *et al.,* 2004). It also a good inhibitor of topoisomerase both *in vivo* and *in vitro* (Sung *et al*., 1997).

Phenanthroindolizidine alkaloids

Antofine, the alkaloidal compound isolated of *Cynanchum paniculatum* has antitumor and antiproliferative activities in several human cancer cells (Hye-young *et al.,* 2010). Another alkaloid named, tylophorine isolated of *Tylophora indica* showed anti-inflammatory and anti-cancer activities (Chia-Mao *et al.*, 2009; Linyi *et al.,* 2008).

Pyrrolizidine alkaloids

Clivorine identified of *Ligularia hodgsonii* Hook, showed a potent antiproliferative effect in human normal liver cells by inducing apoptosis (Li-Li *et al*., 2005; Li-Li *et al*., 2002).

Benzo quinolizidine alkaloids

Beta carboline, the alkaloidal compound identified of *Harmina harmane*, and the three alkaloidal compounds named, harmaline, harmalol and tryptoline were isolated from *Peganum harmala* proved antitumor activity by inhibiting the DNA topoisomerases and interfere with DNA synthesis. It was very active compound against lung, ovarian and renal cell lines (Shohreh, 2010: Kothapalli and Sekharipuram 1999).

Indoquinoline alkaloids

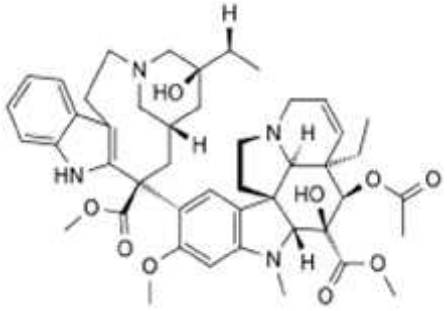
Cryptolepine and neocryptolepine compounds isolated from *Cryptolepis sanguinolenta* roots. Both compounds have potent cytotoxic effects against some tumor cells. These compounds intercalate into DNA and interfere with the catalytic activity of human topoisomerase II. (Laurent *et al*., 2000).

Benzophenanthridine alkaloids

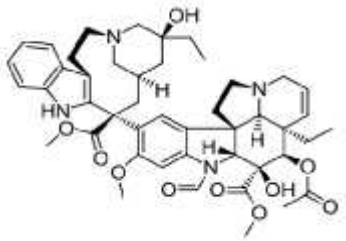
An alkaloid compound, 6-methoxydihydrosanguinarine isolated from *Hylomecon* species, may be considered as a potential chemotherapeutic agent where it caused apoptotic cell death in colon carcinoma cells (Yong *et al*., 2004).

Other alkaloids groups

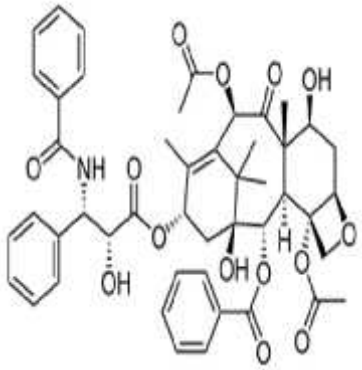
Carbazole alkaloids which are isolated from *Murraya koenigii* species. These alkaloids showed significant effects on the growth of human leukemia cell line. Mahanine, pyrayafoline-D and murrafoline-I, proved potent cytotoxic effect against human leukemia cell line (Ito *et al*., 2006). Sampangine, and azaoxoaporphine alkaloids isolated of *Cananga odorata* stem bark. They are cytotoxic to human malignant melanoma cells and also, they have pro-apoptotic action against human leukemia cells leading to cell death (Jérôme *et al*., 2005). Other alkaloids as lycorine, vittatine and montanine which were isolated of the of *Hippeastrum vittatum* bulb indicated a cytotoxic effect against some human cell lines colon adenocarcinoma, renal cell carcinoma, breast cancer, and epithelial ovarian cancer. The compound montanine proved a potent antiproliferative effect (Silva *et al*., 2008). Ellipticine, a natural alkaloid identified from *Aspidosperma williansii* has antitumor and cytotoxic activities on different types of tumors. The cytotoxic effect of that compound on lymphocytes was very strong (Elza *et al*., 1988). It inhibited topoisomerase II in human breast cancer cells (Canals *et al*., 2005). Some alkaloids named, stemona alkaloids isolated from *Stemona aphylla* roots. These compounds play a significant role as P-glycoprotein modulator and also, they are very effective in the treatment of multidrug-resistant cancers. Stemofoline has synergistic growth inhibitory effect with cancer chemotherapeutic agents as vinblastine, paclitaxel and doxorubicin of KB-V1 cells (Wisinee *et al*., 2010). Acridone alkaloids as 5-hydroxy-N-methylseverifoline which is isolated from Rutaceous plants proved anticarcinogenic activity in mouse skin tumor *in vivo*. It expected to be potentially valuable cancer chemopreventive agent (Masataka *et al*., 2003).



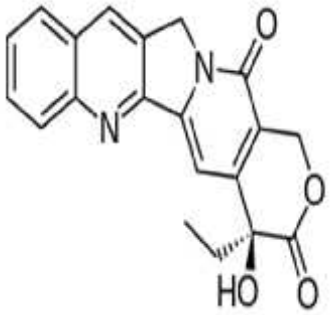
Vinblastine



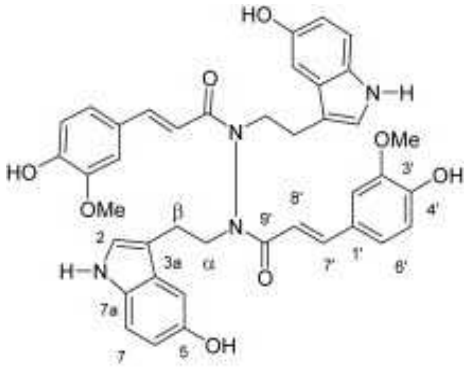
Vincristine



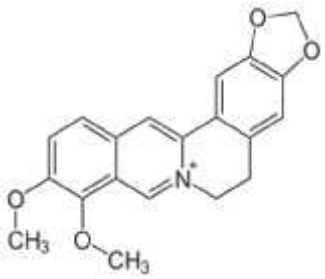
Taxol



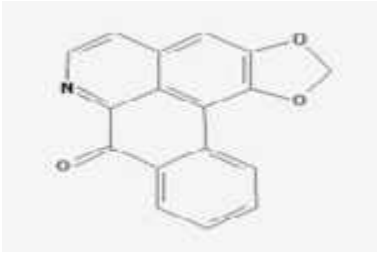
Camptothecin



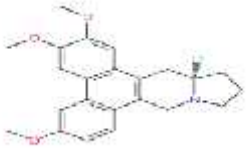
Berberine



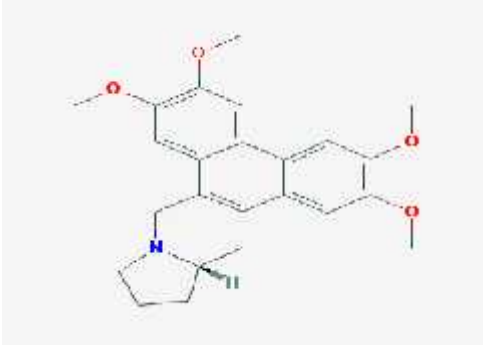
Montamine



Antofine

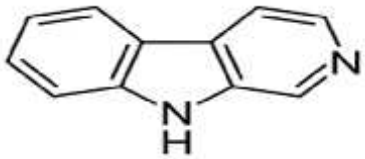


Liriodenine

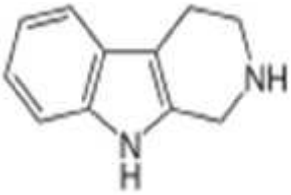


Tylophorine

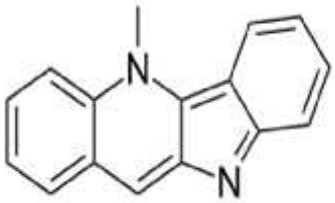
Clivorine



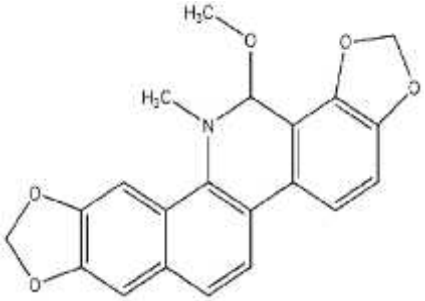
Beta carboline



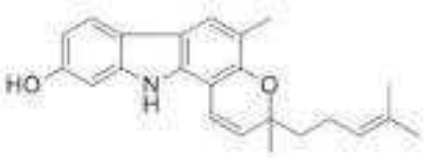
Tryptoline



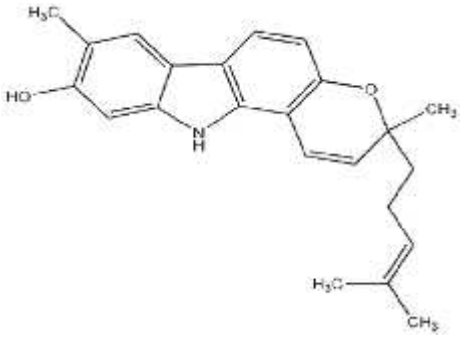
Cryptolepine



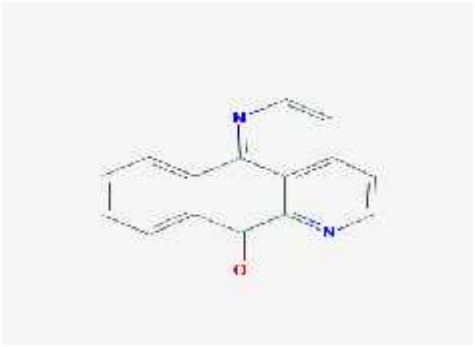
6-methoxydihydrosanguinarine



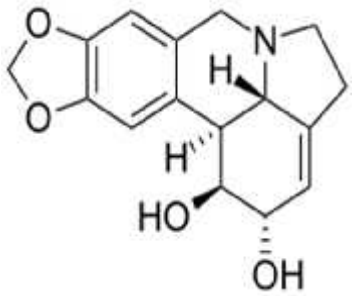
Mahanine



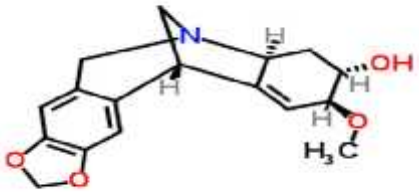
Pyrayafoline-D



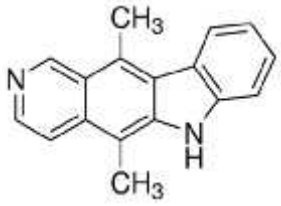
Sampangine



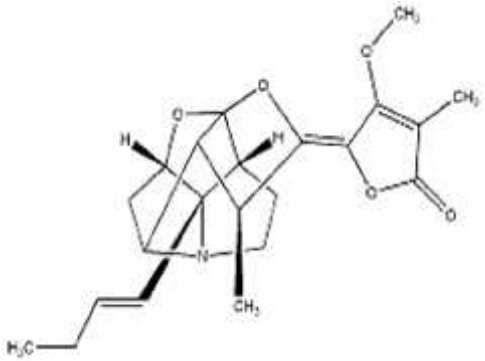
Lycorine



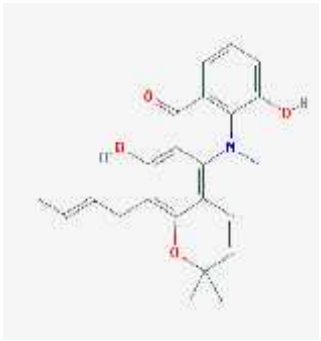
Ellipticine



Montanine



Stemofoline



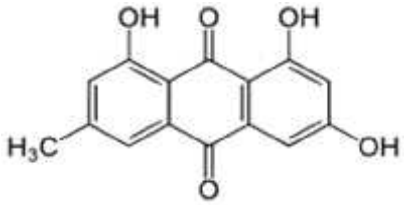
5-hydroxy-N-methylseverifoline

Fig. 4. Chemical structure of some alkaloids have potent anticancer activity

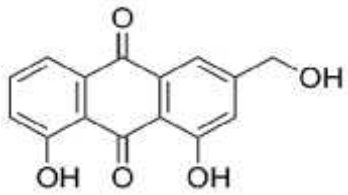
5. Anthraquinones

Anthraquinones are aromatic organic compounds. The term anthraquinone, may refer to one specific isomer, 9, 10-anthraquinone where keto groups are located on the central ring. Some plants have high levels of the anthraquinones as *Cascara sagrada* Frangula, Rhubarb and Senna. Some anthraquinones as emodin, aloe emodin, and rhein, can inhibit growth and proliferation of different types of cancer cells. Emodin was reported to inhibit proliferation in breast, lung, cervical, colorectal, and prostate cancers cells (Chang *et al*.,

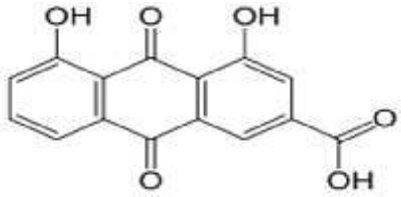
1996; Zhang *et al*., 1995; Cha *et al*., 2005; Kuo *et al*., 1997; Chan *et al*., 1993). Aloe-emodin has the ability to inhibit cell growth in different types of tumor cells, including human lung carcinoma (Lee *et al*., 2001), hepatoma (Kuo *et al*., 2002) and leukemia cell lines (Chen *et al*., 2004), and also, aloe-emodin proved a significant effect for neuroecto dermal tumor cells (Pecere *et al*., 2003). Rhein, another anthraquinone compound was reported that it indicated inhibitory effect on the proliferation of human breast, colon, lung, and glioma cancer cells. (Cichewicz *et al*., 2004; Floridi *et al*., 1991).



Emodin



Aloe emodin



Rhein

Fig. 5. Chemical structure of some anthraquinones have potent anticancer activity

6. Terpenoids

Terpenoids represent the largest class of natural products and also they are good candidate compounds for drug discovery. There are different types of terpenoids that inhibit cancer cell proliferation and metastasis via various mechanisms. There are classified into main five categories according to the chemical structures, namely monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids and tetraterpenoids. Terpenoids consist of nearly 25,000 structures that have potential practical applications in the pharmaceutical and chemical industries**.**

Monoterpenoids

Limonene is a member of monoterpene which is a class of terpenoid derivatives. It is present in citrus fruits essential oils and other several plants. It can be in two optically active figures, L-limonene and D-limonene. D-limonene is a major constituent of several citrus oils as lemon, orange, and grapefruit. D-limonene is well known as chemopreventive agent against different types of cancer. It has anticancer effect against liver cancer by increasing the levels of hepatic enzymes that can detoxify carcinogens (Sun, 2007). It can suppress the growth of pancreas, stomach, colon, skin, and liver cancers in animal models. D-limonene can inhibit tumor growth and metastasis, and this can be through it has antiangiogenic, and anti-oxidant effects. The combination of D-limonene and some known cytotoxic agents, as fluorouracil (5-FU) and docetaxel, resulted in a significant anticancer effect than either single treatment via a mechanism involving reactive oxygen species (ROS) generation (Rabi and Bishayee, 2009).

Cantharidin

This compound was isolated from *Mylabris phalerata*. It was reported that it was used as an anti-cancer agent for the treatment of hepatoma and esophageal carcinoma (Liu and Chen, 2009). It is a natural defensive toxin produced by several species of blister beetles (McCluskey *et al*., 2000). Anti-cancer activity of cantharidin was experimentally demonstrated where it showed a strong *in vitro* anticancer activity against a broad spectrum of cancer cells, as leukemia, colorectal carcinoma, hepatoma, bladder carcinoma, and breast cancer (Chen *et al*., 2002; Huan *et al*., 2006; Huh *et al*., 2004).

Sesquiterpenoid

Artemisinin is bioactive terpenoid which was isolated of the Chinese medicinal herb *Artemisia annua*. Artemisinin has been implicated in cancer treatment (Firestone and Sundar, 2009; Tan *et al*., 2011). Artemisinin is a sesquiterpene trioxane lactone has a peroxide bridge, which is very necessary for its bioactivity. Anti-cancer effect of dihydroartemisinin has been studied where it inhibits the proliferation of different types of cancer cells, as leukemia, breast, ovarian, prostate, colon, hepatoma, gastric cancer, melanoma, and lung cancers (Jiao *et al.*, 2007; Lu *et al*., 2008; Chen *et al*., 2009; Lu *et al.*, 2011; Wang *et al*., 2010).

Diterpenoids

Tanshinone IIA

Tanshinone IIA is the major diterpenoid compound from *Salvia miltiorrhiza* plant. Anti-cancer effects of tanshinone IIA were studied in different human carcinoma cells, as hepatocellular carcinoma, leukemia, breast, and colon cancers. The results proved that tanshinone IIA has a cytotoxic effect against multiple human cancer cell lines (Sung *et al*., 1999).

Triptolide

Triptolide is a diterpene which was isolated from *Tripterygium wilfordii* plant. It has immunosuppressive and anti-inflammatory effects, moreover triptolide was reported that it exhibited potent anti-proliferative effects. It inhibited the proliferation of several cancer cell lines, with IC_{50} values at nanomolar levels. *In vivo* anti-cancer effect of that compound was confirmed in xenograft animal models, and so this compound was entered clinical trials for cancer treatment (Liu, 2011).

Pseudolaric acid B

It is isolated from *Pseudolarix kaempferi*. Anti-cancer effect of that compound was studied. A significant cytotoxic effect of this compound on a broad-spectrum cancer cell lines as lung, colon, breast, brain, and renal origins was observed (Pan *et al*., 1990). Further evaluations proved a potent cytotoxic activity via targeting and destabilization of microtubules. Pseudolaric acid B has the ability to inhibit angiogenesis at a non-cytotoxic dosage (Wong *et al*., 2005).

Andrographolide

Andrographolide is a labdane diterpenoid which represent the major and bioactive compound of *Andrographis paniculata*. This compound displayed a significant anti-inflammatory and anti-cancer effects in both *in vitro* and *in vivo* experimental models of inflammation and cancer (Lim *et al*., 2011).

Oridonin

Oridonin is a bioactive compound which is isolated from *Rabdosia rubescens*. This compound proved a therapeutic effect on different types of solid tumors, that include skin carcinoma, liver, osteoma, and colorectal cancers. Oridonin can inhibit the growth of acute lymphoblastic leukemia, and chronic lymphocytic leukemia (Ikezoe *et al*., 2005). *In vivo* anti-cancer effect was reported in a colorectal cancer colostomy implantation model (Jin *et al*., 2011).

Triterpenoids

Celastrol

Celastrol, has another name as tripterine, and it is a bioactive terpenoid from *Tripterygium wilfordii*. This compound has anti-oxidant, anti-cancer, and anti-inflammatory activities (Calixto *et al*., 2004). Anti-cancer activity of celastrol is well known where different signaling pathways appear to be affected by celastrol treatment and this may due to its anti-cancer effects. Celastrol can inhibit the function of proteasomes (Pang *et al*., 2010; Yang *et al*., 2006).

Cucurbitacins

Cucurbitacin and its derivatives are widely distributed in the plants. Some previous studies reported that cucurbitacins have strong bioactivities in humans as anti-cancer, anti-inflammatory, and hepatoprotective effects (Miro, 1995; Lee *et al*., 2010).

Some reports showed that most cucurbitacins significantly inhibit the proliferation of multiple tumor line cells of IC_{50} at nanomolar levels *in vitro*. A more recent study showed that cucurbitacin B inhibited the growth of different types of human cancer cells lines. Cucurbitacin B showed a strong antiproliferative activity against breast cancer cells (Suwit *et al*., 2012).

Alisol

Alisol compounds are type of triterpenoids which are isolated from the rhizome of *Alisma orientalis* (Sam.) In these years, these compounds gained an increasing attention due to their potent anticancer effects (Lee *et al*., 2001). Alisol B induces endoplasmic reticulum stress, autophagy, and apoptosis in several cancer cell lines, with the sarcoplasmic/endoplasmic reticulum Ca2+ ATPase as its potential molecular target (Law *et al*., 2010). Moreover, alisol B 23-acetate is considered as a potent multiple drug resistance-reversing agent that restores the sensitivity of multiple drug resistance cell lines (Wang *et al*., 2004).

Pachymic acid

Pachymic acid, is a triterpenoid compound isolated from *Poria cocos*. It has anti-cancer activity (Ling *et al*., 2011; Ling *et al*., 2010; Gapter *et al*., 2005; Zhou *et al*., 2008; Li *et al*., 2004). It showed cytotoxic effect against human lung, prostate, and colon carcinoma cells (Zhou *et al*., 2008; Li *et al*., 2004). Also, It also showed inhibitory effect on both DNA topoisomerase I and II (Li *et al*., 2004).

Tetraterpenoids

The most known tetraterpenoids are carotenoids**.** The intake of these compounds reduces the risk of different types of cancers, and thus this suggests the preventive role of carotenoids in cancer disease.

Some previous reclinical studies indicated the therapeutic role of some carotenoids, as beta-carotene, alpha-carotene, lycopene, lutein, and astaxanthin and all of these compounds have proved anti-carcinogenic activity (Tanaka *et al*., 2012).

Lycopene

Lycopene is a tetraterpenoid compound isolated from tomatoes. Lycopene and soy isoflavones delayed progression of both hormone refractory and hormone-sensitive prostate cancer (Vaishampayan *et al*., 2007). Moreover, Lycopene exhibited anti-oxidant effects through scavenging ROS, which allows lycopene to prevent lipid peroxidation and DNA damage (Kelkel *et al*., 2011).

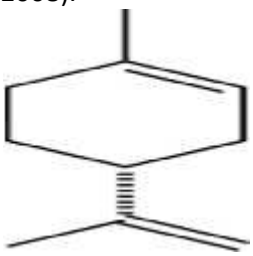
Some other compounds

Ursolic acid

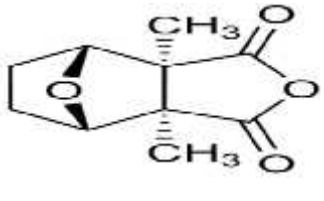
Some reports indicated anticancer activity of ursolic acid where it proved anti-cancer effect against lung cancer. It can inhibit the catalytic activity of vaccinia-related kinase 1 through direct binding to the catalytic domain of vaccinia-related kinase 1 (Kim *et al*., 2015).

Betulinic acid

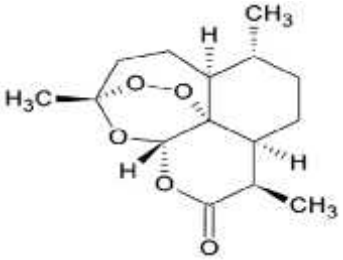
Betulinic acid is a good candidate for cancer therapy where it has the ability to exhibit antitumor effect without any cytotoxicity. The cytotoxic research on betulinic acid indicated that it had a selective cytotoxicity on tumor cell lines but not on the normal cells and thus this suggests that it may act as a therapeutic agent (Rabi et al., 2008).

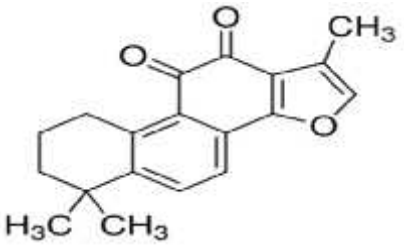


Limonene

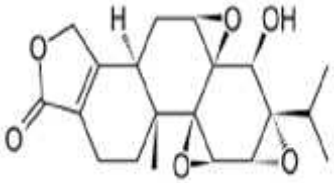


Cantharidin

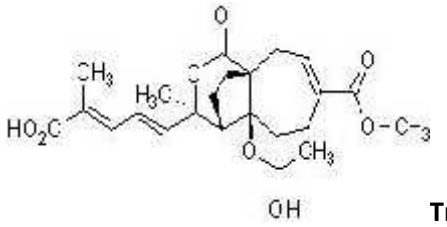




Artemisinin

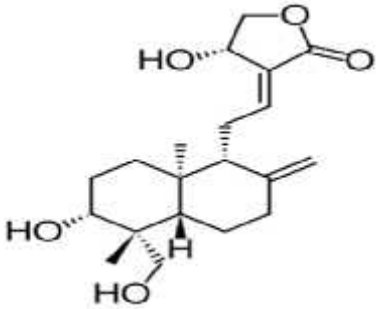


Tanshinone IIA

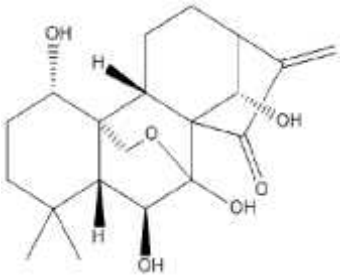


Triptolide

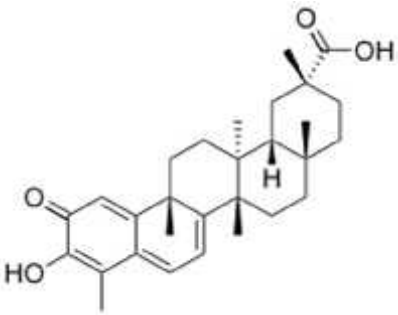
Pseudolaric acid B



Andrographolide

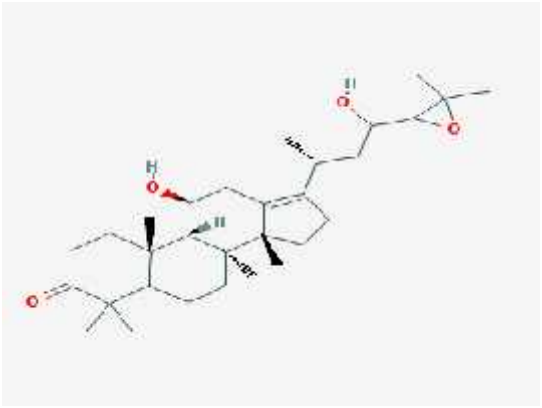


Oridonin

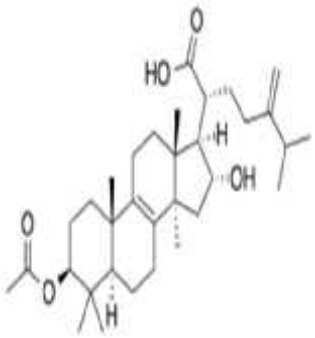


Cucurbitacin

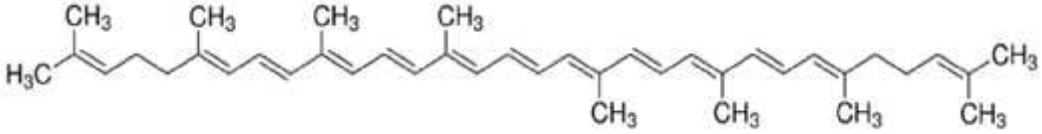
Celastrol



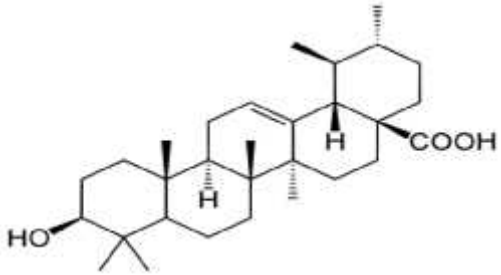
Alisol B



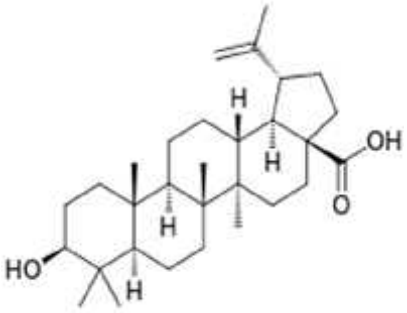
Pachymic acid



Lycopene



Ursolic acid



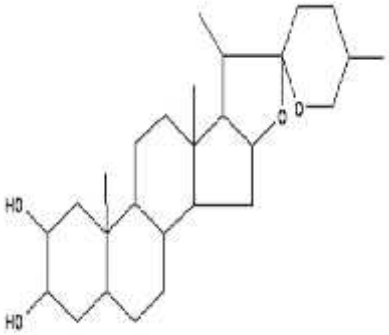
Betulinic acid

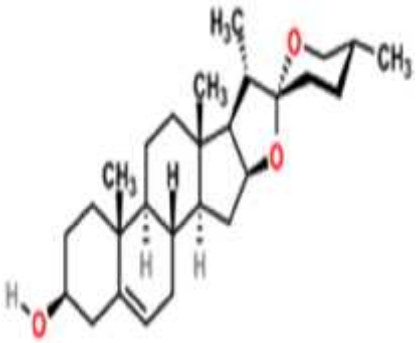
Fig. 6. Chemical structure of some terpenoids have potent anticancer activity

7. Saponins

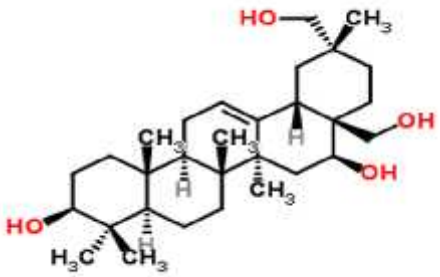
Saponins are steroidal or triterpenoid aglycones with one or more sugar moities (Kensil, 1996). They have antioxidant and anticancer activities (Vuong *et al*., 2014). Saponins have immunomodulatory potential through cytokine interplay (Sun *et al*., 2009), cytostatic and cytotoxic activities on malignant tumor cells (Bachran *et al*., 2008).

The plant *Agave scottii* from Asparagaceae family has major constituent as gitogenin. This component was reported that it can inhibit walker 256 carcinoma (Bianchi and Cole, 1969). Previous reports indicated that saponins from *Astragalus* species have antitumor potentials in human colon cancer cells and tumor xenografts (Tin *et al*., 2007). A study reported that cytotoxic effect of triterpene saponins from *Aralia elata* leaves from Araliaceae family was studied. These compounds proved a significant cytotoxic effect against human promyelocytic leukemia cells and lung cancer cancer cells (Zhang *et al*., 2012). The plant *Yucca schidigera* has steroidal saponin and furostanol saponins. Steroid saponin proved mutagenesis-inhibitory effect (Man *et al*., 2009). These compounds can inhibit growth of human oral epidermoid carcinoma cells (Kaminobe *et al*., 2002). Some steroidal saponins and its aglycone diosgenin were studied for their antitumor activity (Man *et al*., 2010). The saponins, gymnemagenol and dayscyphin C proved a potent anticancer effect on hela cells under *in vitro* conditions (Khanna and Kannabiran, 2009). Saponins named, sorbifoside C and D which were identified from *Xanthoceras sorbifolia* Bunge from Sapindaceae were tested for their anticancer activity. The results indicated that these saponins were very active against many of cancer cells as bladder, cervix, prostate, lung, breast, colon, liver, bone, skin, brain, and ovary (Chan, 2007). Previous reports indicated that saponin fractions of *Panax notoginseng* leaves from Araliaceae family were determined for their cytotoxic effects against human pancreatic, lung, hepatocellular cancers and gastric adenocarcinoma. This saponin fraction can be considered as a new alternative source of anticancer activity (Qian *et al*., 2014). A study reported cytotoxic effect of saponin fraction isolated of *Solanum trilobatum* of Solanaceae family against larynx cancer cell lines. The results indicated that the saponin fraction in a dose dependent mannar has the ability to suppress the cell proliferation (Kanchana and Balakrishna, 2011).

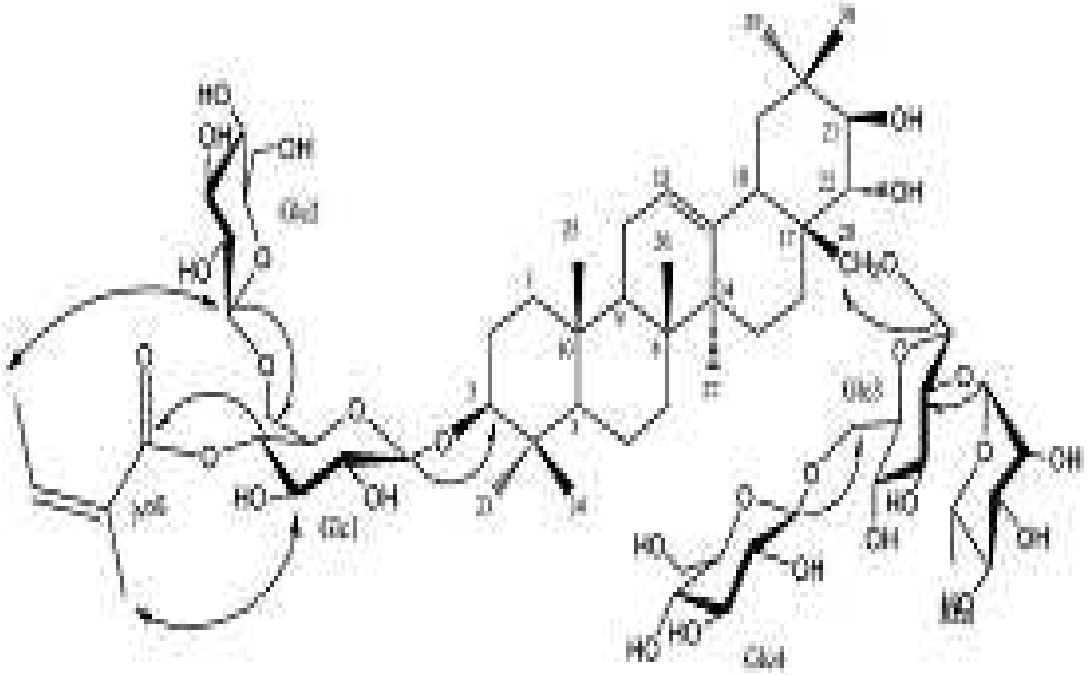




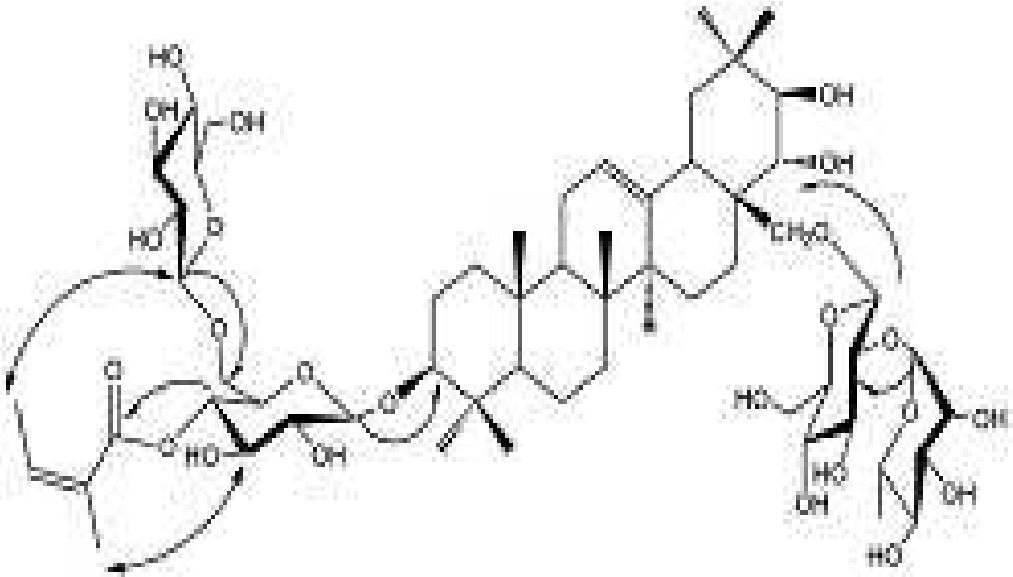
Gitogenin **Diosgenin**



Gymnemagenol



Sorbifoside C



Sorbifoside D

Fig. 7. Chemical structure of some saponins have potent anticancer activity

CONCLUSION

Plants are widely used as medicines since centuries for the treatment of different types of diseases. People since a long time have relied on traditional herbal agents to meet their health care requirements. Although the presence of conventional drugs, herbal medicines are still having a place in treatment due to their wide range of healing properties. Natural products are considered as a wonderful source for the development of anti-cancer drugs. Secondary metabolites as flavonoids, alkaloids, saponins and others, obtained from different plants are mainly responsible for their several medicinal properties. Further and deep research is going on for the development of new anti-cancer drugs where recent medications for the treatment of cancer show various adverse side effects which may be overcome by replacing that with plant derived compounds. The immense potential of plants in cancer therapy still remains unexplored and need more deep research studies. It is necessary to develop newer anti-cancer drugs from plant materials which may be a good way to a non-toxic mode of cancer control and also it is importance to make people aware of the health benefits of different plant products and its potent role in cancer prevention and treatment as it might provide a unique means of cancer therapy and management.

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