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New Anticancer Agents: Recent Developments in Tumour Therapy

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ABSTRACT

Cancer is the second leading cause of death worldwide. Conventional cancer therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Cancer control may therefore benefit from the potential that resides in alternative therapies. The demand to utilize alternative concepts or approaches to the treatment of cancer is therefore escalating. There is compelling evidence from epidemiological and experimental studies that highlight the importance of compounds derived from plants "phytochemicals" to reduce the risk of colon cancer and inhibit the development and spread of tumors in experimental animals. More than 25% of drugs used during the last 20 years are directly derived from plants, while the other 25% are chemically altered natural products. Still, only 5-15% of the approximately 250,000 higher plants have ever been investigated for bioactive compounds. The advantage of using such compounds for cancer treatment is their relatively non-toxic nature and availability in an ingestive form. An ideal phytochemical is one that possesses anti-tumor properties with minimal toxicity and has a defined mechanism of action. As compounds that target specific signaling pathways are identified, researchers can envisage novel therapeutic approaches as well as a better understanding of the pathways involved in disease progression. Plant derived compounds have played an important role in the development of several clinically useful anticancer agents. Several anticancer agents including taxol, vinblastine, vincristine and topotecan are in clinical use all over the world. A number of promising agents such as combrestatin, betulinic acid and silvesterol are in clinical or preclinical development.An attempt has been made to review some medicinal plants used for the prevention and treatment of cancer and recent state of development of anticancer drugs regarding Natural Products.

INTRODUCTION

NATURAL DRUGS HAVING ANTI-CANCER ACTVITY

The anticancer properties of plants have been recognized for centuries. Isolation of podophyllotoxin and several other compounds (known as lignans) from the common mayapple (Podophyllumpeltatum) ultimately led to the development of drugs used to treat testicular and small cell lung cancer [1]. The National Cancer Institute (NCI) has screened approximately 35,000 plant species for potential anticancer activities. Among them, about 3,000 plant species have demonstrated reproducible anticancer activity[2]. Many studies have focused on the chemoprotective properties of plants such as anticarcinogenic properties of Abrusprecatorius on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumor cells[3] . Similarly, Dharet al. have examined the anticancer properties of Albizzialebbeck on sarcoma in mice and Alstoniascholaries on benzo[a]pyrene-induced forestomach carcinoma in humans. Other plants that have shown anticarcinogenic properties include Anacardiumoccidentale in hepatoma, Asparagus racemosa in human epidermoid carcinoma, Boswelliaserrata in human epidermal carcinoma of the nasopharynx, Erthyrinasuberosa in sarcoma[4], Euphorbia hirta in Freund virus leukemia, Gynandropispentaphylla in hepatoma, Nigella sativa in Lewis lung carcinoma, Peaderia foetida in human epidermoid carcinoma of the nasopharynx, Picrorrhiza kurroa in hepatic cancers, and Withania somnifera in various tumors[5]. The chemopreventive potential of an 80% hydroalcoholic extract (50 and 180 mg/kg/day for 14 days) of Andrographis paniculata has been reported against

chemotoxicity, including carcinogenicity[6]. The authors observed the modulatory influence of A. paniculata on hepatic and extrahepatic carcinogen metabolizing enzymes (viz. cytochrome P450), antioxidant enzymes, glutathione (GST) content, lactate dehydrogenase (LDH) and lipid peroxidation in Swiss albino mice. Some other workers also reported the anticancer and immunostimulatory activities of A. paniculata. Azadirachta indica (Neem) has been used in buccal carcinogenesis, skin carcinogenesis, prostate cancer, mammary carcinogenesis, gastric carcinogenesis Ehrlich carcinoma and B16 melanoma. Dietary neem flowers caused a marked increase in glutathione S-transferase (GST) activity in the liver, while resulting in a significant reduction in the activities of some hepatic P450-dependent monooxygenases.[6]

These results strongly indicate that neem flowers may have chemopreventive potential. Young animals were fed with AIN-76 purified diets containing either 10-12.5% ground freeze-dried neem flowers for 1 week prior to, during, and for 1 week after the administration of each carcinogen[8]. Interestingly, it was found that neem flowers resulted in a marked reduction of the incidence of mammary gland (about 35.2%) and liver tumours (61.7% and 80.1% for benign and malignant tumours, respectively).[7] Furthermore, the multiplicity of tumours per rat was also lower in the neem flower groups, i.e. those for mammary gland tumours and benign and malignant liver tumours were reduced to 44.0%, 87.9% and 88.9%, respectively. These results clearly demonstrated that neem flowers contain some chemopreventive agents capable of inhibiting liver andch mammary gland carcinogenesis in rats. Administration of ethanolic neem leaf extract (ENLE) inhibited DMBAinduced hamster buccal pouch carcinogenesis, as revealed by the absence of neoplasm. These results suggest that the chemopreventive effect of ENLE may be mediated by induction of apoptosis.[9]

The modulatory effect of neem leaf with garlic on hepatic and blood oxidant-antioxidant status may play a key role in preventing cancer development at extrahepatic sites. The ethanolic extract of neem has been shown to cause cell death of prostate cancer cells (PC3) by inducing apoptosis, as evidenced by a dose-dependent increase in DNA fragmentation and a decrease in cell viability. Camellia sinensis (Tea) is one of the most popular beverages in the world. The consumption of tea has been associated with a decreased risk of developing cancers of the ovary, oral cavity, colon, stomach and prostate. This beneficial health effect has been attributed to the catechins (flavonoids) in tea. Their biological benefits are due to their strong antioxidant and antiangiogenic activity as well as their potential to inhibit cell proliferation and modulate carcinogen metabolism. Citrus limon (Nibu) fruit contains flavonoid, flavone, limonoid, limonene, nobiletin and tangeretin.

The flavonoid, tangeretin and nobiletin are potent inhibitors of tumor cell growth and can activate the detoxifying P450 enzyme system. Limonoids inhibit tumour formation by stimulating the GST enzyme. Compounds including sulforaphane, isothiocyanates, isoflavones and pomiferin are considered to be HDAC inhibitors. They inhibit the activity of carcinogenic proteins. For example, sulforaphane has shown to inhibit important targets in breast cancer proliferation. Decreased expression of ER, EGFR and HER-2 resulted from HDAC inhibition by sulforaphane treatment in breast The limonene (a terpenoid) also possesses anticancer activity. Nibu fruit is used for inhibition of human breast cancer cell proliferation and delaying of mammary tumorigenesis. It is also used in metastasis and leukemia. The derivatives (viz. chlorogenic, dicaffeoylquinic and tricaffeoylquinic acids) of caffeoylquinic acid contained in Ipomoea batatas tubers (Shakarkand) have potential cancer chemoprotective effect. 4-Ipomeanol (a furanoterpenoid) isolated from I. batatas has been found to exhibit anticancer activity against non-small cell lung cancer lines. Further, leaves of Martyniaannusa, bark of Prunus spp., and stem of Rhaphidophorapertusa have been used against neck, lung and abdominal cancers, respectively.

It has been reported that medicinal plants may promote host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues. Several reports describe that the anticancer activity of these plants is due to antioxidants such as vitamins (A, C, E), carotene, enzymes (e.g., superoxide dismutase, catalase and glutathion peroxidase), minerals (e.g., Cu, Mn, Se and Zn), polysaccharides, polyphenols (e.g., ellagic acid, gallic acid and tannins), flavonoids (e.g., quercetin, anthocyanins, catechins, flavones, flavonones and isoflavones), lignins, xanthones, etc. cancer cell lines. In cancer cells, epigenetically-silenced genes which are functional for chromatin acetylation are reactivated by HDAC inhibitors and cancer cells are then able to enter programmed cell death (apoptosis). Plant-derived compounds which show inhibition of HDAC can enhance chemotherapeutic sensitivity in human cancers. Derivatives of vinca alkaloids, vincristine, vinblastine, vinorelbine, vindesine and vinflunine are drugs which will inhibit the dynamics of microtubules by binding to β-tubulin.

Taxanes such as paclitaxel and its analogue docetaxel are also microtubule disruptors. These compounds inhibit cell cycle phase transitions from metaphase to anaphase causing cell cycle arrest and apoptosis. Replication of cancer cells is reduced by paclitaxel as it stabilizes or polymerizes microtubules in the cells. Paclitaxel was one of the first drugs to have a huge impact on cancer treatment and vincristine and vinblastine were two of the initial drugs to be isolated.Combinations of drugs derived from vinca alkaloids, Taxus diterpenes, Podophyllum lignans and Camptotheca alkaloids in plant extracts may enhance their anticancer effects and improve their efficacy as therapeutic agents . Extracts from Urticamembranaceae, Artemesiamonosperma and Origanumdayi Post in Solowely et al., 2014 were investigated to test their effects on a wide range of cancer cell lines from lung, breast, colon and prostate cancers.

The investigation showed the plant extracts with a combination of anticancer compounds were able to have killing activity which was specific to cancer cells and showed no effect on normal human lymphocytes and fibroblasts. This makes plant extracts more desirable as therapeutic agents than those that are chemically derived which cause toxic complications in cancer treatment. The plant extracts induced

apoptosis which was demonstrated by an increased sub-G1 phase population of cells with lower DNA content and condensation of chromatin. Also an increase in caspase 3 activation was seen after extract treatment which is a key stage in apoptotic cell death. The anticancer characteristics of a number of plants are still being actively researched and some have shown promising results. Some plants and plant products that have shown promise as anticancer agents are discussed in detail in the following sections.

Actaea crenata

belonging to the family Ranunculaceae is commonly known as black cohosh and black snakeroot. It contains cycloartenol type triterpenoids, cinnamic acid derivates and cimicifugoside. This plant is also well known for its role in amenorrhea and ovaritis. The main compound of this plant is actein and it shows inhibition of human HepG2 liver cancer cells growth by reducing the cholesterol and free fatty acid levels in liver.

Ardisia crenata

belongs to the Myrsinaceae family and commonly known as coral bush, spice berry, red berries and coralberry. It is commonly found in warm climate of tropical and sub-tropical regions. It contains cyclic depsopeptide, triterpenoidsaponins and alkenylphenol. Anticancer activity of this plant is due to the presence of ardisiacrispin, which is a mixture of two triterpenoidsaponins i.e. ardisiacrispin A and B. One study showed that the ardisiacrispin inhibits proliferation of uncontrolled liver cancer cell line (Bel-7402) by microtubule disruption and induction of proapoptotic activities.

Bacopa monnieri

belongs to the Scrophulariaceae family and found throughout the plains in India. It is reported to contain tetracyclic triterpenoidsaponins, bacosides A and B, herpestine, brahmine, flavonoids, stigmasterol. Stigmasterol is known to possess anticancer activity by inducing apoptosis mediated by the activation of protein phosphatase 2A by ceramide. Study conducted by Ghosh evaluated the antitumor activity of stigmasterol isolated from BacopaMonnieri on Ehrlich Ascites Carcinoma in swiss albino mice and found that stigmasterol enhanced the life span of tumor bearing mice by decreasing the tumor volume and viable cell count.

Berberis vulgaris

root contains berberine, berbamine, chelidonic acid, citric acid, columbamine, hydrastine, isotetrandrine, jacaranone, magnoflorine, oxycanthine and palmatine. Berberine (an isoquinoline alkaloid), possesses anticancer, immunoenhancing, antioxidant and anti-inflammatory properties. Berberine arrests cancer cell cycle in G1-phase and induces apoptosis. Berberine possesses strong anticancer activity against prostate cancer, liver cancer and leukaemia. Berberine interferes with P-glycoprotein in chemotherapy-resistant cancers. Berberine also increases the penetration of some chemotherapy drugs through the blood-brain barrier, thereby enhancing their effect on intracranial tumours. Berberis vulgaris root bark contains three phenolic compounds, tyramine, cannabisin-G and lyoniresinol. Cannabisin-G and lyoniresinol exhibit strong antioxidant activity. Cannabisin-G protects against breast cancer. Berberis vulgaris also inhibits growth of stomach and oral cavity cancers.

Bidens pilosa

belongs to the Asteraceae family and native to the America. It contains polyacetylenes, flavonoids, phenylpropanoidsterpenoids, and others compounds. Phenyl-1, 3, 5-heptatriyn possesses toxicity profile on normal blood cells in erythrocyte osmotic fragility experiments along with other extracts. Hexane, methanol and chloroform extracts of Bidenspilosa and their fractions were tested on various cancer cell lines. Results showed the antitumor activity of extracts among which hexane extract showed maximum activity.

Catharanthus roseus

belongs to the Apocynaceae family and commonly known as rosyperiwinkle or Madagascar periwinkle. Its main compound is alkaloids, and used for the circulatory diseases treatment and provide relief to the normal cerebral blood flow obstruction. Vinblastin and vincristine are the two well-known compounds which significantly effects against the human neoplasm. Vincristinsulfate arrest mitosis and utilized for the treatment of acute leukemia in children and vinblastinsulfate is utilized for the treatment of choriocarcinoma, lymphosarcoma, neuroblastoma and carcinoma of lung, breast and other organs.

Cedrus deodara

belongs to the Pinaceae family and found in the Western Himalaya, northern Pakistan, north central India, eastern Afghanistan, western Nepal and south-western Tibet. It is known as deodar in Hindi and devdar in Sanskrit. It contains taxifolin, cedrinoside, cedrin, cedeodarin and deodarin. Stem wood extract of C. deodara which contains lignin composition exhibits cytotoxicity to the human cancer cell lines and also induce tumor regression in murine models. Bark of this plant shows potential in the rheumatoid arthritis inflammation, fever, cancer, dysentery, diarrhea and ulcer.

Centella asiatica

belongs to the Apiaceae family and commonly known as brahmamanduki in Hindi, mandukaparni in Sanskrit and pennywort in English. It is commonly found in India, Australia, Pacific Islands, New Guinea, Iran and Malaysia. It contains numerous compounds such as asiaticoside, pectic acid, hydrocotyline, sterol, flavonoid, vallerine, ascorbic acid and thankunosides. Partially purified fraction of Centellaasiatica suppressed mouse lung fibroblast cell proliferation and oral administration slowed the solid development and ascites tumours. Pre-treatment with this plant increase the survival time of irradiated animals and show protection against radiation induces damage in liver. This plant shows inhibition in lipid peroxidation in various organs like lungs, liver, heart, brain, spleen and kidney and shows potential towards the cancer inhibition.[10]

Citrus

fruits belong to the family, Rutaceae found all over the world and top the world fruit market. There are four important

species in citrus fruit with a wide variety of hybrid species as well. Several reports show citrus as a potent anti-tumor agent. Citrus peels are a rich source of phytochemicals such as phenols, limonoids, flavonoids and polysaccharides. Zhao et al. extracted and purified an acidic polysaccharide from the peels of Citrus aurantifolia. The main components of the acidic polysaccharides (CA) are rhamnose (Rha), arabinose (Ara), galactose (Gal), glucose (Glu), mannose (Man) and galacturonic acid (GalA). The antitumor activity of CAs was evaluated in mice transplanted H22 hepatoma cells. CA restricted the tumor cell cycle in S phase and stimulated the expression of proapoptotic factor caspase 3. CA enhances immune response against cancer cells by increasing the levels of tumor infiltrating CD8+ T lymphocytes. It inhibits the expression of anti-apoptotic protein BclxL and Mcl-1. The results conclude that acidic polysaccharides from citrus peels could be used as an adjuvant in treating hepatocellular carcinoma. Park et al. characterized a pectic polysaccharide, rhamnogalacturonan II (CPE-II) from peels of Citrus unshiu. Citrus peels are an abundant source of polyhydroxyl flavonoids (PHFs) such as hesperidin, neohesperidin and naringin; and polymethoxyflavones (PMFs), most of these components act as potent antitumor compounds. PMFs are reported to significantly inhibit metastasis by restricting cell adhesion and its invasion. It enhances cytolysis by increasing the expression of NK cells. Cell cycle is arrested in G1 phase by inhibiting cyclin-dependent kinases (Cdk) and enhancing Cdk inhibitor proteins. The efficacy of citrus peels against skin cancer has been studied in a two stage skin carcinogenesis model.

Curcuma longa -

Curcumin (Di-feruloyl-methane) and curcuminoids isolated from Curcuma longa suppress cancer at every step, i.e. initiation, growth and metastasis. Curcumin arrests the cancer cells proliferation in G2/S phase and induces apoptosis (programmed cell death). It inhibits angiogenesis, a crucial step in the growth and metastasis of cancer. Curcumin and Genistein (isolated from Glycine max) act synergistically to inhibit growth & spread of oestrogen-positive breast cancer. Curcumin works even in multidrug-resistant breast cancers. Curcumin suppresses adhesion of cancer cells, thus preventing metastasis. Curcumin inhibits growth & spread of various cancers including that of breast, lung, oesophagus, liver, colon, prostate, head & neck and skin. Curcumin is particularly effective in radiotherapy-resistant prostate cancer. Curcumin is effective even in advanced stages of cancer. Curcumin also protects from stomach cancer and colon cancer.Curcuma longa also possesses antimutagenic, antioxidant, immunostimulant, anti-inflammatory, hepatoprotective and radioprotective properties.

Emblica officinalis

contains ellagic acid, gallic acid, quercetin, kaempferol, emblicanin, flavonoids, glycosides and proanthocyanidins. Emblica officinalisis valued for its unique tannins and flavanoids, which possess powerful antioxidant and anticancer properties. Ellagic acid isolated from Emblica officinalis is a powerful antioxidant and has the ability to inhibit mutations in genes. Ellagic acid also repairs chromosomal abnormalities. Quercetin, isolated from Emblica officinalis has hepatoprotective effect. Emblicanin A & B (tannins) possess strong antioxidant and anticancer properties. Emblica officinalis inhibits growth & spread of various cancers including that of the breast, uterus, pancreas, stomach, liver and malignant ascites. Emblica officinalis is an excellent rejuvenator and antioxidant herb. It is highly nutritious and an important source of Vitamin C, minerals and amino acids.Emblica officinalis protects against much cancer particularly the liver cancer. Emblica officinalis reduces side effects of chemotherapy & radiotherapy.

PLANT COMPOUNDS WITH ANTICANCER PROPERTIES

Medicinal plants have been used for thousands of years in folk medicines in Asian and African populations and many plants are consumed for their health benefits in developed nations. According to the World Health Organisation (WHO) some nations still reply of plant-based treatment as their main source of medicine and developing nations are utilising the benefits of naturally sourced compounds for therapeutic purposes. Compounds which have been identified and extracted from terrestrial plants for their anticancer properties include polyphenols, brassinosteroids and taxols.

POLYPHENOLS

Polyphenolic compounds include flavonoids, tannins, curcumin, resveratrol and gallacatechins and are all considered to be anticancer compounds. Resveratrol can be found in foods including peanuts and grapes and red wine. Gallacatechins are present in green tea. It is thought including polyphenols in a person's diet can improve health and reduce risk of cancers by being natural antioxidants. The cytotoxicity of polyphenols on a range of cancer cells has been demonstrated and their antioxidant properties determined. Polyphenols are thought to have apoptosis inducing properties showing anticancer properties which can be utilized. The mechanism in which polyphenols are thought to carry out apoptosis initiation is through regulating the mobilization of copper ions which are bound to chromatin inducing DNA fragmentation. In the presence of Cu(II), resveratrol was seen to be capable of DNA degradation. Other properties plant polyphenols show is their ability to interfere with proteins which are present in cancer cells and promoting their growth. Cancer agents may be altered through the polyphenol regulating acetylation, methylation or phosphorylation by direct bonding. For example, curcumin treated cancer cells in various cells lines have shown suppression of the Tumour Necrosis Factor (TNF) expression through interaction with various stimuli.

FLAVANOIDS

Flavonoids are different from the polyphenolic compounds and constitute a large family of plant secondary metabolites with 10,000 known structures. They are physiologically active agents in plants and becoming of high interest scientifically for their health benefits. Various plants have been investigated for their flavonoid content and how these compounds affect cancer cells, such as fern species and plants used in traditional Chinese medicines like the litchi leaf. There is a high content of flavonoid compounds such as anthocyanins, flavones,

flavonols, chalcones and many more which can be found in just one structure of the plant like its seed. Coa et al., 2013, identified and looked at the anticancer effects of flavonoids on human lung cancer cells (A456 cell line) from the fern species Dryopteriserythrosora.

They found flavonoids to demonstrate cytotoxicity on cancer cells and to have high free radical scavenging activity. Purified flavonoids have also shown anticancer activities against other human cancers including; hepatoma (Hep-G2), cervical carcinoma (Hela) and breast cancer (MCF-7). The flavonoids extracted from Erythrinasuberosa stem bark (4'-Methoxy licoflavanone (MLF) and Alpinumisoflavone (AIF)) were shown to have cytotoxic effects in HL-60 cells (human leukaemia). MLF and AIF induced apoptosis through intrinsic and extrinsic signalling pathways. The mitochondrial membrane potential is significantly reduced due to the induction of apoptotic proteins. With mitochondria damage to cells the cancer cells cannot survive.

Other studies have looked at flavonoid extracts from fern species and found that even in low concentrations they still demonstrate high percentage of anticancer activity.As previously mentioned polyphenols can inhibit or alter the regulation of proteins and other agents which may be contributing to the survival of cancer cells. Signal Transducer and Activator of Transcription (STAT) proteins are anti-apoptotic and contribute to cancer cell growth. MLF and AIF inhibit members of this family of proteins by preventing their phosphorylation needed for the cancer cells survival. Also, these flavonoids inhibit the expression of NF-κB which is needed for cancer cell survival and angiogenesis and proliferation.

c. BRASSINOSTEROIDS

Brassinosteroids (BRs) are naturally occurring compounds found in plants which play roles in hormone signalling to regulate growth and differentiation of cells, elongation of stem and root cells and other roles such as resistance and tolerance against disease and stress. Also, BRs are used for regulation of plant senescence. They are essential for plant growth and development. BRs are another naturally occurring compounds which have demonstrated therapeutic significance in the cause against cancer.

Two natural BRs have been used in investigations with cancerous cells to demonstrate anticancer properties that these compounds possess. 28-homocastasterone (28-homoCS) and 24-epibrassinolide (24-epiBL) have demonstrated anticancer effects on various cancer cell lines and proven to be effective at micromolar concentrations. A characteristic of cancer cells is that they do not naturally undergo apoptosis and proliferate indefinitely. BRs can induce responses necessary for growth inhibition and induce apoptosis by interacting with the cell cycle. BRs have been used in investigations to treat a range of cancer cell lines which include; T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226, cervical carcinoma HeLa, lung carcinoma A-549 and osteosarcoma HOS cell lines. Also included are cell lines in breast cancer and prostate cancer.

Estrogen receptor (ER), epidermal growth factor receptor (EGFR) and human EGFR-2 (HER-2) are some of the critical proteins which are targeted in treatment of breast cancer as they are abundant in breast cancer cells such as MCF-7, MDA-MB-468, T47D and MDA-MB-231. In prostate cancer cells (LNCaP and DU-145 cell lines) the androgen receptor (AR) is a critical protein involved in its development and shares a similar structure to ER. BRs will interact or bind to receptors of these proteins and inhibit the growth of both hormone sensitive and hormone insensitive cancer cells. Also, BRs can induce cell cycle blockage. Treatment of breast cancer cell lines with 28-homoCS and 24-epiBL showed reduction in cyclin proteins which are involved in G1 cell cycle phase. At this phase in the cell cycle cells will either under repair or enter apoptosis, treatment with BRs induces apoptosis at this stage which cancer cells would not be able to do naturally without treatment. In prostate cancer cell lines, LNCaP and DU-145, the balance of apoptotic proteins which promote cell survival and those which induce programmed cell death changes with BRs treatment. The levels of the Bax pro-apoptotic protein increase after BRs treatment and anti-apoptotic proteins such as Bcl-2 are reduced. Along with their anticancer properties BRs generate different responses in normal and cancer cells. A key specification in anticancer treatment is for the agent not to be cytotoxic to normal cells and be cell specific to cancer cells; this is where agents of BRs origin are of interest for therapeutic properties.

NEW ANTICANCER AGENTS: RECENT DEVELOPMENTS IN TUMOUR THERAPY

Some rare compounds have also been exploited for their anticancer property. Nordihydroguaiaretic acid, a naturally occurring lignin from creosote bush (Larrea divaricata Cav. or Corillea tridentate), and its synthetic analogues are potentially useful in treating cancer. Remarkably, terameprocol, a tetra-O-methyl derivative of nordihydroguaiaretic acid, is in phase I/II clinical trials as an anticancer agent. Thymol, piperitone, and methyleugenol, essential oils from the root of Anemopsis californica inhibited the growth of human endometrial cancer cell-line AN3CA and of the cervical cancer cell line HeLa. Iridoids, bioactive compounds in the roots and rhizomes of plants belonging to the genus Valeriana (Valerianaceae), are known to be inhibitors of cell migration. Ammopiptanthus mongolicus and an Ammopiptanthus mongolicus lipid, traditionally used in China have been shown to inhibit liver cancer.

Ethyl acetate fractionated extracts of Calligonum comosum (Polygonaceae) demonstrated anticancer properties. Two compounds, terrequinone A and terrefuranose derived from rhizosphere fungi, displayed selective cytotoxicity against cancer cell lines compared with the normal fibroblast cells. Pituranthos tortuosus extracts have been reported to demonstrate antiproliferative and apoptotic properties using leukemia cell lines . Terpinen-4-ol, sabinene, α-terpinene, and β-myrcene isolated from P. tortuosus, exhibited significant cytotoxicity towards against human cancer cell lines, namely, human hepatocellular liver carcinoma cell line HepG2, colon cancer cell line HCT116, and breast cancer cell line MCF7.

A cycloartane-type triterpenoid, an aliphatic alcohol glycoside, eudesmane-type sesquiterpenoid, and a guaiane-type sesquiterpenoid, isolated from the resinous exudates of Conmmiphora opobalsamum, showed moderate antiproliferative effects on human prostate cancer cell lines and inhibited the expression of androgen receptor in LNCaP cells. It was found that extracts derived from Varthemia iphionoides, exhibited cytotoxicity against leukemia cell proliferation. Polyphenols and sterols of virgin argan oil exhibited dose-dependent cytotoxic effects and antiproliferative actions on three human prostatic cell lines (DU145, LNCaP, and PC-3). Teucrium polium plant extract inhibited cell proliferation and induced cell cycle arrest and reduction of the G0-G1 phase, suggesting therapeutic potential against metastatic disease. Many cytotoxic compounds have been isolated from tunicates, also known as urochordates, which belong to the subphylum protochordate. Compounds derived from the Didemnidae family are structurally unique, and include alkaloids and various peptides. For example, fascaplysin is an alkaloid isolated from two Didemnum tunicates and four other distinct types of sponges. Didemnid ascidians hosting the symbionts Prochloron sp. have yielded distinctively related cyclic peptides with cytotoxic activity. Some other antitumor compounds, isolated from Ascidian lissoclinum are haterumaimides F–I, J–K and N–Q, showing different levels of cytotoxic potential against P388 leukemia cells.

Haterumaimide J and K obtained from Lissoclinum sp. exhibited cytotoxicity against murine leukemia P388 cells. Dichlorolissoclimide, chlorolissoclimide from Lissoclinum sp. showed an antiproliferative effect due to blockage of G1 phase cells against the non-small cell bronchopulmonary carcinoma line NSCLC-N6. Cyclopentenones from Lissoclinum sp. also showed significant cytotoxicity towards human colon carcinoma HCT116, epidermal cancer line A431 and the human alveolar basal epithelial adenocarcinoma line A549. Lissoclibadin and lissoclinotoxin, obtained from Lissoclinum cf. badium showed a wide range of inhibitory effects against the human colon cancer lines DLD-1 and HCT116, the breast cancer line MDA-MB-231, the renal cancer line ACHN and the NSCLC line NCI-H460.Tuberatolide A, tuberatolide B and 2'-epi-tuberatolideB, obtained from Botryllus tuberatus inhibited the chenodeoxycholic acid -activated human farnesoid X receptor (hFXR) without significant effect on steroid receptors. Some of the compounds obtained from Sidnyum turbinatum showed in vitro antiproliferative activity against the mice fibrosarcoma cell line (WEHI164). Moreover, haouamine A and haouamine B from Aplidium haouarianum exhibit selective cytotoxic activity towards the HT-29 human colon carcinoma cell line.

CONCLUSION

This review article explains potential anticancer active ingredients from natural source. They would be least toxic and more effective than rest synthetic molecules. Hence millions of patients will be benefitted. These plants may promote host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues. Several reports describe that the anticancer activity of these plants is due to presence of antioxidants (viz., vitamins, carotene, enzymes, minerals, polysaccharides, polyphenols, flavonoids, lignins, xanthones, etc.). Many medicinal plants described in this article contain several of these antioxidants.Thus, the various combinations of the active components of these plants after isolation and identification can be made and have to be further assessed for their synergistic effects. Preparation of standardized dose and dosage regimen may play a critical role in the remedy of cancer. The rate with which cancer is progressing, it seems to have an urgent and effective effort for making good health of humans as well as animals. There is a broad scope to derive the potent anticancer agents from medicinal plants, which need thorough research

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