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THERAPEUTIC PROPERTIES OF MEDICINAL PLANTS: A REVIEW OF PLANTS WITH ANTICANCER ACTIVITY (PART 1)

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ABSTRACT

Many previous studies showed that a wide range of medicinal plants exerted cytotoxic and anticancer activity. These plants included: *Adonis aestivalis*, *Ailanthus altissima*, *Alhagi maurorum*, *Allium cepa*, *Allium porrum*, *Allium sativum*, *Allium schoenoprasum*, *Althaea officinalis*, *Althaea rosea*, *Ammannia baccifera*, *Anagyris foetida*, *Anchusa italica*, *Antirrhinum majus*, *Aristolochiamaurorum*, *Apium graveolens*, *Arctium Lappa*, *Aristolochia maurorum*, *Artemisiacampestris*, *Arundo donax*, *Asclepias curassavica*, *Asparagus officinalis*, *Astragalus hamosus*, *Bauhinia variegate*, *Bellis perennis*, *Betula alba*, *Bidens tripartite*, *Brassica rapa*, *Bryonia dioica*, *Bryophyllum calycinum*, *Caccinia crassifolia*, *Caesalpinia crista*, *Calendula officinalis*, *Calotropis procera*, *Canna indica*, *Capparis spinosa*, *Capsella bursa-pastoris*, *Capsicum annuum*, *Capsicum frutescens*, *Carthamus tinctorius*, *Casuarina equisetifolia*, *Celosia cristata*, *Chenopodium album* and *Chrozophora tinctoria*. This review was designed to highlight the anticancer effects of the medicinal plants as asource of pharmaceutical research and therapeutic uses.

Key words: Medicinal plants, Cytotoxicity, anticancer, Pharmacognosy, Pharmacology, Therapeutics.

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INTRODUCTION

Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. Plants have been used as drugs by humans since thousands of years ago. As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Traditional medicine is based on beliefs and practices that existed before the development of so-called modern medicine or scientific drug therapy. However, The recent pharmacological studies showed that the medicinal plants exerted many pharmacological effects [1-53], among these the anticancer and cytotoxic effects. This review was designed to highlight the anticancer effects of the medicinal plants.

Adonis aestivalis

Cardenolide compounds, isolated from the seeds of *Adonis aestivalis*, were examined for their cytotoxic activity against neoplastic HSC-2, HSC-3, HSC-4, and HL-60 cells, as well as HGF, HPLF, and HPC normal cell lines. Three of five cardenolide compounds isolated from the seeds of *Adonis aestivalis* were found to display selective cytotoxicity toward malignant tumor cell lines. Although the morphological observations of HL-60 and HSC-2 cell deaths revealed changes characteristic of apoptosis, neither DNA degradation nor activation of caspase-3 was observed. The findings demonstrated that these compounds may trigger caspase-3-independent apoptotic cell death in HL-60 and HSC-2 cells[54].

Ailanthus altissima

The cytotoxic activities of quassinoids were

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evaluated on the tumor cell lines HeLa, MCF-7, MDA-MB-231, HepG2 and A549 cells, as well as the normal HUVEC line *in vitro*. They exhibited different levels of inhibitory activity against tumor cell lines [33, 66]. However, MTT assay was carried out to investigate the cytotoxic effect of *Ailanthus altissima* extract on PAE cells. It didn't exert significant toxic effect on PAE cells at 40-100 (mu)g/ml compared to control [55].

The cytotoxicities of canthin-6-one, 1-methoxycanthin-6-one, 5-methoxycanthin-6-one, and canthin-6-one-3-N-oxide to guinea pig ear keratinocytes were studied, they showed cytotoxicity with IC_{50} values range from 1.11 to 5.76 micrograms/ml. There is no significant difference in activity among these four cytotoxic alkaloids [56].

The anti-tumor constituents of fruits of *Ailanthus altissima* (Mill) Swingle was investigated. Four compounds were isolated and identified as shinjulactone A, shinjuglycoside B, 5-hydroxymethylfuraldehyde and protocatechuic acid. The anti-tumor activities of two of them and the extracts of the fruits of *Ailanthus altissima* (Mill) Swingle were evaluated by MTT. The anti-tumor results demonstrate that shinjulactone A, shinjuglycoside B, 5-hydroxy methyl furaldehyde, together with extracts Ⅰ (the extract with water of fruits of *Ailanthus altissima* chromatographed on HPD-100 resin and eluted 60% ethanol) and Ⅱ (the EtOAc extract of ethanolic extract of fruits of *Ailanthus altissima*), exhibit moderate antiproliferative activity [57].

Ailantinol E, ailantinol F, and ailantinol G, and related compounds isolated from *Ailanthus altissima*grown in Taiwan, were evaluated for its antitumor promoting effects against Epstein-Barr virus early antigen activation introduced by 12-O-tetradecanoylphorbol-13-acetate in Raji cells. Quassinoids were found to show potent activity [58]. Short-term *in vitro* assays for tumor promoters and antitumor promoters (Epstein-Barr virus activation test) were carried out for 14 quassinoids isolated from *Ailanthus altissima*. Some quassinoids, including ailantinol B, ailantinol C, ailanthone, and shinjulactone A, showed moderate activity at a molar ratio of 1:100 [59].

The cytotoxic potential of the extracted quassinoids, altissinol A and B, together with 12 known quassinoids were evaluated *in vitro* against three human hepatoma cell lines. Seven quassinoids displayed potent cytotoxic activities against human hepatoma Hep3B and HepG2 cell lines. Interestingly, 3 compounds exhibited cytotoxic activity against multidrug resistance HepG2/ADM cell line with IC_{50} value 4.3-fold more sensitive to Doxorubicin [(60)].

*Ailanthus altissima*Swingle was evaluated for its cytotoxic and antiproliferative activities by a bioassay-oriented study. Cytotoxicity observed in HeLa cells was time-dependent; the treatment with 10 microg/ml of the root chloroform extract reduced cell viability by 56% at 24h and 29% at 48 h of exposure. Significant effects were observed also for chromatographic fractions and the pure isolated alkaloid 1-methoxy-canthin-6-one. After 72h of incubation cell viability was less than 10% for all treatments. A possible apoptotic effect was evaluated by monitoring the presence of hypodiploid elements in HeLa cells as well as in SAOS, U87MG and U-937 tumor cell lines. The cells incubated for different times with the active extract, fraction and pure alkaloid isolated from *Ailanthus altissima*showed a remarkable increase in the apoptosis [61, 62].

The effect of 1-methoxy-canthin-6-one, isolated from *Ailanthus altissima*Swingle was studied on apoptosis in human leukemia (Jurkat), thyroid carcinoma (ARO and NPA), and hepatocellular carcinoma (HuH7) cell lines. Cultures incubated with the compound showed >50% of sub-G1 (hypodiploid) elements in flow cytometry analysis; the apoptosis-inducing activity was evident at <10 micromol/l and half-maximal at about 40 micromol/l 1-methoxy-canthin-6-one. The appearance of hypodiploid elements was preceded by mitochondrial membrane depolarization, mitochondrial release of cytochrome c, and Smac/DIABLO and procaspase-3 cleavage. The effect of 1-methoxy-canthin-6-one was investigated in combination with human recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in the four cell lines. Suboptimal concentrations (10 micromol/l 1-methoxy-canthin-6-one and 0.25 ng/m TRAIL, respectively) of the two agents, unable to elicit apoptosis when used alone, induced mitochondrial depolarization, activation of caspase-3, and 45% to 85% of sub-G1 elements when added together to the cells. The synergism seemed to rely partly on the enhanced expression of TRAIL receptor 1 (TRAIL-R1; DR4), by 1-methoxy-canthin-6-one. Cell incubation with 1-methoxy-canthin-6-one resulted in activating c-Jun NH2-terminal kinase (JNK), as revealed by Western blotting; induction of apoptosis and TRAIL-R1 up-regulation by 1-methoxy-canthin-6-one were >80% prevented by the addition of the JNK inhibitor (JNKI) SP600125JNKI, indicating that both effects were almost completely mediated by JNK activity. On the other hand, synergism with TRAIL was reduced by about 50%, suggesting that besides up-regulating TRAIL-R1, 1-methoxy-canthin-6-one could influence other factor(s) that participated in TRAIL-induced apoptosis [63].

Alhagi maurorum

Cytoxicity test was carried out using methyl thiazolyl tetrazolium (MTT) on the human leukemia cell line (HL-60). Leaves and flowers extract induced inhibitory effect against the proliferation of HL-60 cells and IC_{50} was 16.0 and 22.0 µg/ ml respectively [64].

Allium cepa

In vivo and *in vitro* studies showed that the constituents of *Allium cepa* such as Allylsulfides (ajoene, allicin, diallylsulfide, dialyldisulfide, diallyltrisulfide, S-

allyl cysteine, and sallylmercaptocysteine) exerted anticarcinogenic and antitumor activities [65-75]. The aqueous extracts of *Allium cepa* exerted antiproliferative effects. The protein fraction of onion extract also exhibited antimitotic activity [76-77]. The beneficial effects of red, yellow and white onion extracts, particularly their antioxidant and antimutagenic activities were related to their phenols and flavonoids [78]. Many mechanisms proposed for anticancer activity of *Allium cepa* included, inhibition of cell proliferation , inhibition of protein tyrosine kinase, inhibition of carcinogens activation, and modulation of phase II enzyme activity [79].

All the eight saponins isolated from leek were tested for their cytotoxic activity against two different cell lines *in vitro*. Three of them showed cytotoxic activity [80].

Allium sativum

Diallyl disulfide from garlic (*Allium sativum*) has been shown to have an antiproliferative effect on human tumor cells including those of colon, lung, skin, breast and liver origins [81-86]. The consumption of garlic and related sulfur compounds has been reported to inhibits N-methyl-N-nitrosourea induced mammary cancer, dimethylhydrazine induced colon cancer, 4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone induced lung cancer, 1,2-dimethylhydrazine induced hepatic cancer, 7,12-dimethyl benz[*a*]anthracene and benzo[*a*]pyrene-induced skin cancer and carcinogen-induced stomach cancers in experimental animals [87-92]. Many studies showed a low incidence of stomach, colorectal, prostate, esophagus cancers and female breast carcinoma in societies with high Allium vegetables consumption [90, 93-99].

Garlic oil increased glutathione (GSH) peroxidase activity in isolated epidermal cells incubated in the presence or absence of the potent tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), and inhibited the sharp decline in the intracellular ratio of reduced (GSH)/oxidized (GSSG) glutathione caused by TPA. According to these findings, it was postulated that the inhibitory effects of garlic oil on skin tumor promotion may result from their enhancement of the natural GSH-dependent antioxidant protective system of the epidermal cells[100]

On the other hand, garlic and some of its constituents inhibited the nuclear factor kappa B ($NF\text{-}_kB$) activation induced by various receptor agonists, including lipopolysaccharide and tumor necrosis factor a (TNFa) [101, 102]. In addition, garlic extract can directly inhibit the Toll-like receptors (TLRs)-mediated signaling pathway at the receptor level. Garlic extract and its sulfur-containing compounds inhibited nuclear factor kappa B ($NF\text{-}_kB$) activation induced by various receptor agonists including lipopolysaccharide (LPS)[103].

Allium schoenoprasum

The antiproliferative and tumour arresting effects of phenolic compounds (PhC) in flowers of *Allium schoenoprasum* were investigated. The effects on proliferation of HaCaT cells were evaluated *in vitro* using phenolic compounds in cultivation medium (100, 75, 50 and 25 µg/mL). It appeared that even low concentrations of these flowers' phenolic compounds inhibited cell proliferation significantly [104].

DNA polymerase inhibitory activity and antiproliferative activity of chive glycolipids toward human cancer cells was investigated, chive had an inhibitory effect on pol alpha activity and human cancer cell proliferation[105].

The chemopreventive effects of Allium vegetables (onions, garlic, shallots, leeks, chives, and so forth) have been studied extensively, consumption of large amounts of Allium vegetables reduced the risk for gastric cancer (odds ratio, 0.54; 95% confidence interval, 0.43-0.65). Specific analyses for onion, garlic, leek, Chinese chive, scallion, garlic stalk, and Welsh onion yielded similar results, except for onion leaf. The estimated summary odds ratio for an increment of 20 g/day of Allium vegetables consumed (approximately the average weight of 1 garlic bulb) was 0.91 (95% confidence interval, 0.88-0.94), based on case-control studies from the dose-response meta-analysis[106].

Althaea officinalis

Scopoletin produced dual action on tumoral lymphocytes exhibiting both a cytostatic and a cytotoxic effect on the cell , and also exert apoptosis. Proliferation of normal T lymphocytes was found due to the interaction with kinase C (PKC) protein. It indicates that scopoletin may be a potential anti-tumoral compound [107].

Althaea rosea

The cytotoxic activity of n-hexane, methanol, ethanol, ethyl acetate and water extracts of *Althaea rosea* L. was investigated by brine shrimp assay. Ethyl acetate extract showed cytotoxic activity against brine shrimp [108].

Ammannia baccifera

The methanolic extract of *A. baccifera* was cytotoxic to the HeLa cancer cell line but relatively non-toxic to the normal cell line NIH 3T3. Treatment of mice with *A. baccifera* extract resulted in significant decreases in tumor volume, viable cell count and tumor weight and enhanced the life span of DAL bearing mice. Hematological parameters such as RBC, hemoglobin and lymphocyte count reverted to normal level in *A. baccifera* treated mice [109].

A remedy containing five plants including *Ammannia baccifera* exerted anticancer activity in twoanimal models (mammary cancer in rats and cervical

cancer xenografted nude mice) without significant cytotoxic activity in vitro[27].The crude hexane extracts of *Ammanniabaccifera* showed very high cytotoxicity to brine shrimp ($LC_{50,}$ 6 hrs. =7.96 and 1.02 µg/ml). The cytotoxicity of 1,4-naphthoquinone , 4-hydroxy-1-tetralone and alkyl rans-4-hydroxycinnamte to brine shrimp was (LC_{50},6 hrs.=10.56, 17.88 and 166.74 µg/ml, respectively)[110].

Anagyris foetida

The alkaloids of *Anagyris foetida* showed cytotoxicity activity against two tumour cell lines [111].

Anchusa italica

The cytotoxic activity of *Anchusa italic*a against MCF-7, HepG2, WEHI and MDBK cell lines was evaluated.IC50 was more than 100 µg/ml against all evaluated cell lines[(112)]. *Anchusa italica* is one of the thirteen plantscontained in the Abnormal Savda Munziq of Traditional Uighur formula *(*ASMq), which used for the treatment and prevention of cancers. The effects of ethanol extract of ASMq on cultured human hepatoma cells (HepG2) was carried out to explore the mechanism of its putative anticancer properties by using many experimental methods including the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) bromide, neutral red and lactate dehydrogenase (LDH) leakage, the incorporation of ^{3}[H]-leucine and ^{3}[H]-nucleosides into protein, DNA and RNA, and quantifying the formation of malondialdehyde-thiobarbituric acid (MDA). ASMq ethanol extract significantly inhibited the growth of HepG2 and cell viability, increased the leakage of LDH after 48 hours or 72 hours treatment in a concentration and time dependent manner (P <.05). Cellular protein, DNA and RNA synthesis were inhibited in a concentration and time dependent manner (P <.05). No significant MDA release in culture medium and no lipid peroxidation in cells were observed. Accordind to the results, the cytotoxic effects of ASMq ethanol extract might be related to inhibition of cancer cell growth, alteration of cell membrane integrity and inhibition of cellular protein, DNA and RNA synthesis [113].

Antirrhinum majus

The cytotoxic effect of the plant extract and its fractions was studied by haemolytic activity against human red blood cells (RBCs) using Triton X-100 as positive control (99.78). The percentage lysis was evaluated by comparing the absorbance of sample with the Triton X-100 as positive control. The percent lysis red blood cells was observed after treatment with Snapdragon absolute methanol extract and its fractions as follows: absolute methanol extract (4.89 ± 0.04), *n*-butanol (4.14 ± 0.05), chloroform (3.18 ± 0.02), ethyl acetate (2.23 ± 0.03) and *n*-hexane extract (extracted by soxhlet) (2.45 ± 0.02). The study showed that the percent lysis of human erythrocytes resulted in less than 5.0 % for all samples, thus these findings indicate minor cytotoxicity of the plant [114].

Aristolochia maurorum

The crude aqueous extract of *Aristolochia maurorum* was examined for their cytotoxicity against Vero, BSC-1, Hep-II and RD cell lines by assays microculture neutral red dye absorption and microscopical follow up for cytopathic effects [115].

Apium graveolens

Apium graveolens seeds have been assessed for chemopreventive activity. The antiproliferative effect of the methanolic extract of *Apium graveolens* was evaluated *in vitro* on two human cell lines (DLA, Dalton's lymphoma ascites; L929, Mouse lung fibroblast). Typical morphological changes including cell shrinkage, chromatin condensation and characteristic DNA ladder formation were induced by *Apium graveolens*. Antitumor screening by the short-term cytotoxicity study with DLA cells showed that the *Apium graveolens* extracts exhibited a dose dependent inhibition of the growth. The extract was found to be cytotoxic towards L-929 cells in 72 hrs MTT assay and concentration required for 50% cell death was 3.85µg/ml [116]. In an *in vitro*study, sedanolide, a natural phthalide from celery seed oil, showed protective effects against hydrogen peroxide (H_2O_2) - and tert-butyl hydroperoxide (tBOOH)-induced toxicity in HepG2 and CaCo-2 cells[117].

Arctium Lappa

The cytotoxic and genotoxic effects of *A. lappa* root aqueous extract were examined on the root meristem cells of *Allium cepa.* Onion bulbs were exposed to 12, 62.5 and 125 mg/ml concentrations of the extracts of *A. lappa*. All the tested extracts have been observed to have cytotoxic effects on cell division in *A. cepa. A. lappa* root extract induced the total number of chromosomal aberrations and micronuclei (MNC) formations in *A. cepa* root tip cells significantly. Two of the tested concentrations were observed to have mitodepressive effects on cell division and induced mitotic spindle disturbance in *Allium cepa*[118].

Foldeak and Dombradi also confirmed the antitumor activity of *A. lappa* [118].Arctigenin, one of the major bioactive component of *Arctium lappa* L was reported to exhibit antioxidant, antitumor and anti-inflammatory activities [119].

The antiproliferative activity of the crude extract of *Arctium Lappa*, and semipurified fractions, and isolated compounds from the leaves of *A. lappa* was tested bybioassay-guided testing in Caco-2 cells. The crude extract was obtained with a 50% hydroethanolic extract and then partitioned with hexane, ethyl acetate, and *n*-

butanol. The ethyl-acetate fraction (EAF) showed antiproliferative activity [120].

Bioassay-guided cytotoxicity fractionation isolated the compounds lappaol A, C, and F, with cytotoxic activity , their IC_{50} values were 8, 16, and 40 ug/ml, respectively [121].

Onopordopicrin , a sesquiterpene lactone isolated from the leaves of *A. lappa* also inhibited the tumor necrosis factor and showed antitumor activity with IC_{50} of 15 umol/L by MTT and PTP assays against a cell line of promyelocytic leukemia (HL60) [122-124]**.**

Aristolochia maurorum

Its alkaloid compounds were evaluated as cytotoxic agents against the brine shrimp lethality test (BST), aristolochic acid I was found to be the most potent (LC50, 4.9 microg/mL) [125].

Artemisiacampestris

The essential oil of *Artemisia campestris* and the ethanol-water, hexane and water extracts of *A. campestris* collected in southern of Tunisia were investigated for their antioxidant (DPPH, ABTS and beta-carotene methods) and antitumor growth inhibition of human colon cancer HT-29 cells using MTT test activities. The essential oil and other extracts of *A. campestris* (100 μg/ml) showed cytotoxic activity against the HT-29 cells ranging from 19.5% for essential oil to 64.4% for infusion extract. The ethanol-water and infusion extracts of *A. campestris* showed high antioxidant activity[126]. The mutagenic and antimutagenic activities of *Artemisiacampestris* oils were investigated by the *Salmonella typhimurium*/microsome assay, with and without addition of an extrinsic metabolic activation system. The oils showed no mutagenicity when tested with *Salmonella typhimurium* strains TA98 and TA97. On the other hand, it had antimutagenic activity against the carcinogen Benzo (a) pyrene, when tested with *Salmonella typhimurium* strains TA98 and TA97 assay systems [127].

Arundo donax

Arundo donax was used incombination with *Spartium junceum* L. and *Cynodon dactylon* L. for the treatment of tumors (without specifying which kind of tumour)[128].

A lectin with antiproliferative activity towards human cancer cell lines and mitogenic towards human peripheral blood mononuclear cells was purified from the rhizomes of *Arundo donax*(Linn.). The molecular mass of native lectin was 32 kDa as determined by gel filtration chromatography. This showed the lectin to be a dimer, with subunits not held together by disulphide linkages. The *Arundo donax*lectin (ADL) was thermostable upto 55 °C and showed optimum activity in the range of pH 7.0–9.0 and comprised of 2.1% carbohydrate content [129].

A lectin (ADL) was isolated and purified from *Arundo donax*L. rhizomes. The purified lectin agglutinated native rabbit, pig erythrocytes and with lower intensity rat and human A, B and AB erythrocytes, and its hemagglutinating activity is independent of divalent cations, but it is decreased by denaturating and reducing agents. *Arundo donax*L. lectin displays cytotoxic effect on Dysdercus peruvianus and nematicide activity against *Meloidogyne incognita*. ADL decreases the germinability and delays the mean time for germinability of *Lactuca sativa* L. diasphores and also showed significant mitogenic and chemotactic effect. The lectin induce toxicity signals in mice by intraperitoneal injection with the dose of 300 mg/kg and 800 mg/kg caused 100 % death of the animals, 30 h after its administration. Seven isoforms of ADL were separated . ADL-III is rich in Glu/Gln, Gly and Asp/Asn and Cys residues, and its N-terminal a and b chains contain tryptophan residues. ADL-III showed significant mitogenic activity. ADL was able to bind to transformed cells from T-47D, HT-29 and T-24 lines in vitro. Immunohistochemical techniques allowed to localize ADL in the fiber cell walls and in some few cortical parenchyma cells of the rhizome [130].

Asclepias curassavica

The alcololic extract of *Asclepias curassavica* showed cytotoxic activity against nasopharynx human carcinoma cells. It was proved that calotropin (a cardiac glycoside) isolated from the plant, exerted cytotoxic activity. In addition, cardenoliedes extracted from the aerial parts and roots of *Asclepias curassavica* showed pronounced cytotoxicity (IC_{50} of 0.01 to 0.20 microgM/ml) against four cancer cell. Asclepin from the aerial part of *Asclepias curassavica* showed the strongest cytotoxic activity (IC_{50} of 0.02 microM), while 12 beta-hydroxycalotropin (a cardenolide) exerted significant cytotoxic activity (IC_{50} of 0.69 microM/ml) against HepG2 and (1.46 microM/ml) against Raji cell lines[130-132].

Asparagus officinalis

The plant exerted anticancer effects, the anticancer activity of *Asparagus officinalis* may be occurred via[133]: (1) an antimutagenic effect – preventing genetic mutations which can directly precede the earliest stages of cancer development.(2) the promotion of (cellular phase II detoxifying enzymes) which (facilitate the removal of drugs and xenobiotic compounds) that are carcinogenic and supporting overall liver function. (3) synergistically enhancing the antioxidant activity of other plant foods. (4) the inhibition of chronic inflammation (cycooxygenase-2 suppression) which is thought to play a role in tumor development. (5) the promotion of healthier digestion and immune function.

Asparagus saponins inhibited the growth of HepG2 cells in a dose-dependent manner. The median inhibitory concentration (IC_{50}) was 101.15 mg/l at 72

hours. The apoptosis morphology at 72 hours of treatment was obvious, showing cell protuberance, concentrated cytoplasm, and apoptotic bodies. The apoptotic rates at 72 hours were 30.9%, 51.7%, and 62.1% (for saponin concentrations of 50, 100 and 200 mg/l). Treatment with *Asparagus* saponins for 24 hours increased the intracellular level of reactive oxygen species and Ca^{2+}, lowered the pH, activated intracellular mitochondrial permeability transition pore, and decreased membrane potential in a dose-dependent manner. Treatment also increased the activity of caspase-9 and caspase-3, down-regulated the expression of Bcl2, up-regulated the expression of Bax, and induced release of CytC and activation of caspase-3 [134].

The crude saponins from the shoots (edible part) of asparagus were found to have antitumor activity. The asparagus crude saponins inhibited the growth of human leukemia HL-60 cells in culture and macromolecular synthesis in a dose and time dependent manner. The asparagus crude saponins at 75–100μg/ml range was cytostatic. Its concentrations greater than 200 μg/ml were cytocidal to HL-60 cells. The asparagus crude saponins at 6 μg/ml inhibited the synthesis of DNA, RNA and protein in HL-60 cells by 41, 5, and 4% respectively, and at 50 μg/ml by 84, 68 and 59% respectively. The inhibitory effect of asparagus crude saponins on DNA synthesis was irreversible[135].

Shao *et al*., isolated two oligofurostanosides from the seeds of *Asparagus officinalis* with cytotoxic activity. They inhibited the growth of human leukemia HL-60 cells in culture and macromolecular synthesis in a dose-dependent manner. The inhibitory effect on DNA synthesis was found to be irreversible[136].

Treatment of HepG2 human hepatoma cells with the leaf extract of *Asparagus officinalis* suppressed more than 70% of the intensity of hydrogen peroxide (1mM)-stimulated DCF fluorescence, a marker of reactive oxygen species .Cellular toxicities induced by treatment with hydrogen peroxide, ethanol, or tetrachloride carbon (CCl_4) were also significantly alleviated in response to treatment with the extracts of *A. officinalis* leaves and shoots. Additionally, the activities of 2 key enzymes that metabolize ethanol, alcohol dehydrogenase and aldehyde dehydrogenase, were upregulated by more than 2-fold in response to treatment with the leaf- and shoot extracts[137].

Saponins from old stems of asparagus (SSA) exerted potential inhibitory activity on tumour growth and metastasis. SSA suppressed cell viability of breast, colon and pancreatic cancers in a concentration-dependent manner, with half-maximum inhibitory concentrations ranging from 809.42 to 1829.96 μg/ml. However, SSA was more functional in blocking cell migration and invasion as compared with its cytotoxic effect, with an effective inhibitory concentration of 400 μg/ ml. A mechanistic study showed that SSA markedly increased the activities of Cdc42 and Rac1 and decreased the activity of RhoA in cancer cells [138].

One new (Sarsasapogenin O) and seven known steroids were isolated from the roots of *Asparagus officinalis* L. These compounds together with nine steroids which were previously isolated from this plant, were tested for cytotoxic activity. Among them, eight compounds displayed significant cytotoxicities against human A2780, HO-8910, Eca-109, MGC-803, CNE, LTEP-a-2, KB and mouse L1210 tumor cells [139].

Astragalus hamosus

The purified saponin mixture from *A. hamosus* cytotoxicity was evaluated against a panel of human tumor cell lines. The saponin mixture demonstrated significant antiproliferative effects against a multi-drug resistant cell line HL-60/Dox, with a collateral sensitivity phenomenon, i.e. the IC_{50} value was lower in the resistant sub-line in comparison withthe chemosensitive parent cell line HL-60 [140].

Evaluation of ant proliferative effect of a flavonol glycoside and saponins of *Astragalus hamosus* by MTT-dye reduction assay showed concentration-dependent inhibition of malignant cell proliferation by saponins, while the flavonoid exerted only marginal effects [141].

The anticancer activity of dinaline (histone deacetylase inhibitor), decitabine (DNA methylation inhibitor), erufosine (alkylphoshpcholine derivate), tamoxifen (estrogen modulator) were compared with the isolated mixture of two saponins,derived from *Astragalus hamosus*, L. (Fabaceae) in two breast carcinoma cell lines MCF-7 estrogen receptor (ER) positive and MDA-MB 231 - ER negative. The study confirmed the antineoplastic activity of the saponin mixture, derived from *Astragalus hamosus*, which were previously found to be active against human leukemia cells. Moreover, the saponin mixtureshowed dramatic decrease in the expression level of the mitochondrial protein BclxL, which outlines its special influence on the cell death signal transduction and suggests a probable mechanism of action [142].

Volatile compounds of this plant showed significant cytotoxic activity against human acute lymphoid leukemia in concentration dependent manner [143].

Bauhinia variegata

The ethanolic extract of *B. variegata* possessed antitumor effect in Dalton's ascitic lymphomas[144]; it was also protected liver from the cytotoxic effect of diethyl nitrosamine[145]. The ethanolic extract was also showed cytotoxicity on EAC mouse cell lines[146]. The methanolic extract of stem bark of *B. variegate* (at a dose of 500 and 1000 mg/kg bw) exerted anticancer effects in skin papilloma model against 7, 12- dimethylbenz (a) anthracene and croton oil induced skin carcinogenesis in mice. It was effective in decreasing the rate of tumor

incidence and the cumulative number of papillomas. Tumor yield and tumor burden were also found to be reduced. The depleted level of glutathione was restored in *B. variegata* bark extract treated groups[147].

Ethanolic extract of the stem of *B. variegata* showed chemoprevention and cytotoxic effect against N-nitrosodiethylamine induced experimental liver tumor in rats at a dose of 200mg/kg, and also on human cancer cell lines. Ethanolic extract suppressed liver tumor induced by N-nitrosodiethylamine as revealed by decrease in N-nitrosodiethylamine induced elevated level of serum glutamate pyruvate transaminase , serum glutamate oxaloacetate transaminase, alkaline phosphatase, total bilirubin, gamma glutamate transpeptidase, lipid peroxidase, glutathione peroxidase and glutathione-S-transferase [27]. Ethanolic extract was found to be cytotoxic against human epithelial larynx cancer and human breast cancer (HBL-100) cells [145].

Bellis perennis

Butanol extract of flowers of *Bellis perennis* showed antitumor activity when evaluated by potato disc tumor induction bioassay (93% inhibition). The active constituent is a saponin [3-*O*-α-rhamnopyranosyl polygalacic acid 28-*O*-{α-rhamnopyranosyl-(1→3)-β-Xylopyranosyl(1→4)-α-rhamnopyranosyl-(1→2)-[α-arabinofuranosyl -(1→3)-4-*O*-acetyl-β-fucopyranoside][(148)]. Antitumor activities of different fractions of *Bellis perennis* flowers at different concentrations were evaluated using potato Disc tumor induction bioassay. The most active fraction showed 99% tumor inhibition at 3000 mg/l [149].

Betula alba

A remarkable antiproliferative effect was recorded for betulinic acid in all tested tumor cell cultures including neuroblastoma, rabdomyosarcoma-medulloblastoma, glioma, thyroid, breast, lung and colon carcinoma, leukemia and multiple myeloma, as well as in primary cultures isolated from ovarian carcinoma, cervical carcinoma and glioblastoma multiforme. Furthermore, betulinic acid decreased cancer cell motility and induced apoptotic cell death. It also decrease bcl2 and cyclin D1 genes expression, and increased bax gene expression [150].

Betulin enriched birch extracts produced an in vitro antiproliferative effect on four malignant human cell lines: A431 (skin epidermoid carcinoma), A2780 (ovarian carcinoma), HeLa (cervix adenocarcinoma) and MCF7 (breast adenocarcinoma), by means of MTT assay. All of the bark extracts exerted a pronounced antiproliferative effect against human cancer cell lines[151].

Betulinic acid was tested for its cytotoxicity towards highly liver metastatic murine colon 26-L5 carcinoma cells. It showed cytotoxic effects with an $ED_{50}$of 75.4 μg/ml[152].

Betulinic acid inhibited the growth of three kinds of human cell lines, WI-38 fibroblast cells, VA-13 malignant tumor cells, and HepG2 human liver tumor cells, with IC_{50} values of 1.3, 11.6 and 21 μM, respectively [153].Betulinic acid also showed an inhibitory activity on the growth of K562 tumor cell line with IC_{50} value of 6.25 μg/ml and also induced 35% apoptosis at a concentration of 25 μg/ml[154].

Bidens tripartita

The methylene chloride extract of *Bidens tripartita* has demonstrated to have high activity in the inhibition of cancer L1210 (mouse leukemia) cells and against thrombin [155].

Brassica rapa

Anticancer activity of *Brassica rapa* was examined in the human lung cancer A-549 cell line (ATCC#CCL-185). It produced a considerable anticancer effect and moderate antioxidant effects [156- 157].

Crude *Brassica rapa* chinensis extracts were tested for mutagenic and/or anti-mutagenic properties as preliminary investigation for possible cancer chemopreventive potentials. Results from micronucleus assay involving human lymphocytes showed that the ratio between the normal cells and micronucleated cells or the mutated cells were low at cells cultured with crude *Brassica rapa* extract and Mitomycin-C. This suggests that glucosinolates in the crude *Brassica rapa* extract are potential antimutagenic compounds in human lymphocytes [158].

The cytotoxic effect of aqueous extract of *Brassica rapa*roots was studied in three types of cancer cell lines; Hep-2, AMN-3 and Hela in vitro. The results showed that the cytotoxic effect of the extract dependent on type of cells, amount of dose and exposure time. The concentration 1250 μg/ml gave higher growth inhibition (63 and 42%) against ANM-3 and Hep-2 respectively , the inhibition rate of 10000 μg/ml crud roots extract against Hela cells was 64% after 24 hours exposure [159].

A novel phenanthrene derivative, 6-methoxy-1-[10-methoxy-7-(3-methylbut-2- enyl)phenanthren-3-yl]undecane-2,4-dione, named brassica phenanthrene A along with two known diarylheptanoid compounds, 6-paradol and trans-6-shogaol, were exhibited high inhibitory activity against the growth of human cancer lines, HCT-116, MCF-7, and HeLa, with IC_{50} values ranging from 15.0 to 35.0 μM and against LDL-oxidation with IC_{50} values ranging from 2.9 to 7.1 μM [160].

An 9.4-kDa antifungal peptide designated as campesin was isolated from seeds of the plant. It inhibited proliferation of HepG2 and MCF cancer cells with an IC_{50} of 6.4 microM and 1.8 microM [161].

Bryonia dioica

The cytotoxic effects of *Bryonia dioica root* aqueous extract was evaluated in the Burkitt's lymphoma BL41 cell lines. Apoptosis induction was assessed by two corroborative assays; propidium iodide (PI) staining of cell DNA and flow cytometric. The *Bryonia dioica* aqueous extract induced cell death in a dose-dependent manner [162].The *Bryonia dioica* aqueous extract induced cell death in a dose-dependent manner. The IC_{50} of *Bryonia dioica* aqueous extract was estimated to be approximately 15, 63 µg/ml. This was accompanied by induction of apoptosis, activation of caspase-3 and -9, cleavage of PARP and loss of mitochondria membrane potential [162-163].

Bryophyllum calycinum

The antitumor effect of *Bryophyllum calycinum* Salisb.was evaluated against Ehrlich ascites carcinoma (EAC) bearing Swiss albino mice. The effect of methanol and aqueous extracts of *Bryophyllum calycinum* on tumor growth was evaluated by, the percentage inhibition of ascetic cells and percentage inhibition of tumor weight. Methanol and aqueous extracts were administered at doses of 100,200 and 400 mg/kg body weight intraperitonially once a day for 7 days, after 24h of tumor inoculation. Decreases in tumor cell count and tumor weight were observed in extract treated animals when compared to EAC treated animals. The results were dose dependent in case of methanol extract[164].Five bufadienolides isolated from the leaves of the plantwere examined for their inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation in Raji cells induced by the tumor promoter,12-Otetradecanoylphorbol-13-acetate. All bufadienolides showed inhibitory activity, and bryophyllin A exhibited the most marked inhibition among the tested compounds. Bryophyllin C and bersaldegenin-3-acetate were less active [165].

Caccinia crassifolia

The methanolic root extract of the plant was tested for its cytotoxic activities against three cancer cell lines (MCF7, HepG2, WEHI164) and one normal cell line (MDBK). IC_{50} of the plant root extract against all cancer cell lines and normal cell line, was >100 µg/ml [166].

Caesalpinia crista

The methanol extract of *Caesalpinia crista* leaves were evaluated for antitumor activity against Ehrlich ascites carcinoma (EAC)-bearing Swiss albino mice. The extract was administered at the doses of 50, 100, and 200 mg/kg body weight per day for 14 days after 24h of tumor inoculation. After the last dose and 18h fasting, the mice were sacrificed. The methanol extract caused significant ($P<0.01$) decrease in tumor volume, packed cell volume, and viable cell count; and it prolonged the life span of EAC-tumor bearing mice[167].

The fractions of methanolic extracts of *Caesalpinia crista* were subjected to a brine shrimp lethality test to evaluate their cytotoxicity. Moderate cytotoxicity was found for the methanol extract and its three fractions compared with the standard drug, vincristine sulfate. The LC_{50} values of the methanol crude extract and ethyl acetate, chloroform, petroleum ether fractions and vincristine sulfate were 223.87, 281.84, 112.20, 199.53, and 12.59mµg/ml, respectively. Ethyl acetate fraction showed maximum cytotoxicity, whereas minimum cytotoxicity was observed for the chloroform fraction [168].

A new cassane-type diterpene (1α-acetoxy-5α, 7β-dihydroxycassa-11,13(15)-diene-16,12-lactone) isolated from *Caesalpinia crista* was evaluated for antitumor activity against T47D, DU145, it showed significant inhibitory activities [169].

Three cassane diterpene (caesalpinolide-C, caesalpinolide-D and caesalpinolide-E) and one cassane furanoditerpene were tested for their antiproliferative activity against MCF-7 (breast adenocarcinoma), DU145 (prostate carcinoma), C33A (cervical carcinoma) and Vero (African green monkey kidney fibroblast) cells. They were found to exert low to moderate antiproliferative activity profile [170].

Calendula officinalis

*C. officinalis*tea exerted selective dose-dependent cytotoxic action against cancer cells. *C. officinalis* tea exerted highly selective antitumor effect especially to melanoma Fem-x cells [(124)]. *Calendula officinalis* saponins were antimutagenic for benzo(a)pyrene with a dose effect relationship *in vitro*. They also showed cytotoxic and antitumor activity against mouse Ehrlich carcinoma [171-172].

The cytotoxicity of *Calendula officinalis* was evaluated in L929 and HepG2 cells with the MTT assay. Cytoxicity experiments demonstrated that *Calendula officinalis* was not cytotoxic for L929 and HepG2 cells at concentrations less than or equal to of 15 mg/ml. However, in concentrations greater than or equal to 30 mg/ml, the toxic effects were observed [173].

Fifteen compounds isolated from *Calendula officinalis*were evaluated against the Epstein-Barr virus early antigen (EBV-EA) activation induced by TPA, ten compounds exhibited moderate inhibitory effects (IC_{50} values of 471-487 mol ratio/32 pmol TPA). Furthermore, upon evaluation of the cytotoxic activity against human cancer cell lines *in vitro*, two triterpene glycosides exhibited potent cytotoxic effects against colon cancer, leukemia, and melanoma cells [174].

Barajas *et al.*, evaluated the dual and opposite effect of *Calendula officinalis* flower extract as a chemoprotector and promoter in rat hepatocarcinogenesis model. It was reported that a protective activity of the plant extract was noted at low doses, while the doses above 10

mg/kg increased altered hepatocyte foci. Such a dual effect is an example of the phenomenon of hormesis [175].

Three extracts of *Calendula officinalis* (heptane, ethyl acetate and methanol) were introduced to a human skin fibroblast (HSF) and human breast cancer cells (T47D) cultures. The ethyl acetate but not the heptane and methanol extracts in concentrations above 25 microg/ml stimulated cell proliferation and cellular metabolism by increase of mitochondrial dehydrogenase activity. However, concentrations exceeding 75microg/ml have been found to be toxic for cells [176].

The anti-tumor and immunomodulatory activities of laser activated *Calendula officinalis* extract (LACE) was investigated *in vitro*. Tumor cell lines derived from leukemias, melanomas, fibrosarcomas and cancers of breast, prostate, cervix, lung, pancreas and colorectal were used. The tumor cell proliferation *in vitro* was measured by BrdU incorporation and viable cell count. Effect of (LACE) on human peripheral blood lymphocyte (PBL) proliferation *in vitro* was also analyzed. Studies of cell cycle and apoptosis were performed in LACE-treated cells. *In vivo* anti-tumor activity was evaluated in nude mice bearing subcutaneously human Ando-2 melanoma cells. The LACE extract showed a potent *in vitro* inhibition of tumor cell proliferation when tested on a wide variety of human and murine tumor cell lines. The inhibition ranged from 70 to 100%. Mechanisms of inhibition were identified as cell cycle arrest in G0/G1 phase and Caspase-3-induced apoptosis. The same extract showed an opposite effect when tested on PBLs and NKL cell line, in which *in vitro* induction of proliferation and activation of these cells was observed. The intraperitoneal injection or oral administration of LACE extract in nude mice inhibited *in vivo* tumor growth of Ando-2 melanoma cells and prolonged the survival day of the mice [177].

Calotropis procera

The *Allium cepa* root tip meristem model was used to evaluate the cytotoxic and anti-mitotic activities of latex of *Calotropis procera* (DL). Both DL and cyclophosphamide arrested the root growth. The mitotic cells were counted in the root meristems in at 0, 48 and 96h of incubation. The mitotic index ranged between 60.7±0.7 and 63.0±2.3 in the control group over a period of 96h. DL produced a significant decrease in mitotic index that was dose and time dependent. The mitotic index at 10 mg/ml concentration of DL was 32.7±0.8 at 48h as compared to 57.6±0.4 at 0h, while at 96h, the cellular morphology was lost[178].

The cytotoxic activity of methanolic extract of *Calotropis procera* flowers was studied by MTT assay using Hep2 and Vero cell lines. The extract showed maximum activity on Hep 2 cells than Vero cells at higher concentration, and it exhibited toxicity only on Hep 2 cells at lower concentration. Following treatment with the extracts for 24h, the cells lost their morphology and showed cell aggregation, cell roundening and finally the 100 % inhibition was observed at the concentration of 50, 25 and 12.5 mg [179].

Different extracts of *Calotropis procera* leaves were evaluated for *in-vitro* cytotoxic activity against the Hep-2 cell line. The *n*-butanol extract had most pronounced cytotoxicity against the Hep-2 [180].

Cardiotonic steroid UNBS1450 01 (derived from 2-oxovoruscharin) from *C. procera* exerted anti-cancer activity. UNBS1450 01 has been proven to be a potent sodium pump inhibitor, showing anti-proliferative and cell death-inducing activities. This anti-cancer potential of UNBS1450 01 was achieved by disorganization of the actin cytoskeleton after binding to the sodium pump at the cellular membrane, by inducing autophagy-related cell death, by repressing NF-kB activation as well as by down-regulating c-Myc in cancer cells [181].

The root extract of *C. procera* has been found to produce a strong cytotoxic effect on COLO 320 tumor cells [182].

The hemi synthetic derivative of a cardenolide isolated from the root barks of *C. procera* showed a strong cytotoxic effect on several human cancer lines, a high *in vivo* tolerance to tumor growth and prolonged survival in the human xenograft models of nude mice [183].

The cytotoxic potential of stem organic extracts from *Calotropis procera* was evaluated against cancer cell lines by MTT assay. Subsequently, samples with cytotoxic effects were tested for antimitotic activity on sea urchin egg development and for *in vivo* antiproliferative activity in mice bearing Sarcoma 180 tumor. Among the five extracts (hexane, dichloromethane, ethyl acetate, acetone and methanol), ethyl acetate and acetone extracts displayed higher cytotoxic potential against tumor cells, with IC_{50} ranging from 0.8 to 4.4 μg/ml, while methanolic extract was weakly cytotoxic. Cytotoxic extracts also exhibited cell division inhibition capacity by antimitotic assay, revealing IC_{50} values lower than 5 μg/ml. In the *in vivo* antitumor assessments, ethyl acetate- and acetone extract-treated animals showed tumor growth inhibition ratios of 64.3 and 53.1%, respectively, with reversible toxic effects on liver and kidneys[184].

Dry latex of*C. procera* has the potential for anti-cancer effect due to its differentiable targets and non-interference with regular pathway of apoptosis. Dry latex treatment of mice showed a complete protection against hepato carcinogenesis. No adverse effect was observed in these animals. The serum vascular endothelial growth factor (VEGF) level was significantly lowered in the treated mice as compared to control animals. Cell culture studies revealed that the methanolic extract of dry latex as well as its fraction 8 induced extensive cell death in both hepatoma (Huh7) and non-hepatoma (COS-1) cell lines, while nontransformed hepatocytes (AML12) were spared. This effect was accompanied by extensive fragmentation of DNA in Huh-7 and COS-1 cells. No change in the levels

of canonical markers of apoptosis such as Bcl2 and caspase 3 was observed[185].

The anti-tumor potential of the root extracts of *Calotropis procera* was investigated using the methanolic, hexane, aqueous and ethyl acetate extract against Hep2 cancer cells. Treatment with the extracts at different doses of 1, 5, 10 and 25 µg/ml revealed that methanolic, hexane and acetate extract possessed cytotoxicity, whereas aqueous extract had no cytotoxic effect. Acetate extract (10 µg/ml) showed strongest cytotoxic effect (96.3 %) on Hep2 at 48h exposure, whereas methanolic and hexane exhibited cytotoxicity of 72.7 and 60.5 %, respectively. The extract-treated cells exhibited typical morphological changes of apoptosis. The root extracts produced apoptosis of Hep2 cells through cell cycle arrest at the S phase, thus preventing cells from entering the G2/M phase [186].

The *in vitro* and *in vivo* antitumor activities of *Calotropis procera* protein (CP-P) isolated from root bark, was studied. CP-P protein inhibited the proliferation and induced apoptosis of breast cancer cells through the suppression of nuclear factor kappaB (NF-kB) activation. When CP-P was administered individually or in combination with cyclophosphamide (CYC, 0.2 mg/kg) to rats with 7, 12-dimethyl benz(a)anthracene (DMBA)-induced breast cancer, it decreased tumor volume significantly without affecting the body weight. SOD, CAT, GST, GSH, vitamin E and C levels were high in combination-treated groups (CP-P+CYC) versus the CYC alone-treated groups. Also, the combination was more effective in down-regulating the expression of NF-kB-regulated gene products (cyclin D1 and Bcl-2) in breast tumor tissues [187].

Normal human skin fibroblast (HEPK) cells were exposed to Calo-protein of *Calotropis procera* to assay for cytotoxicity. However, this protein did not exert any toxic effect on skin cells even at higher concentrations (1000µg/ml). Furthermore, the Calo-protein did not display any cytolytic effects at all the tested concentrations after 24h compared with control cells. Light microscopic images of human skin fibroblasts were exposed to the Calo-protein at varying doses (1000–0.001µg/ml). The dose of (100µg/ml) of protein did not affect the cell morphology, but the higher dose of protein (1000µg/ml) showed some changes on HEPK cells after 24h exposure [188].

Canna indica

The dichloromethane and ethanol extracts of the leaves of Canna indica.
Were evaluated for brine shrimp toxicity.Their LC50 val ues were 273.9(167.8-447.0) and >1000 µg/ml respectively [189].

Capparis spinosa

Onion bulbs were treated with three different concentrations (10, 20 and 30g/L) of *Capparis spinosa* flower buds aqueous extract for 24 h without ethyl methane sulfonate (EMS) treatment. Growth retardation, significant decrease in mitotic index and chromosome aberrations were observed in root-tip cells treated with aqueous extract before and after the (EMS) treatment when compared with the controls in all treatments. These effects were concentration-dependent and statistically significant ($p<0.05$). The results suggest that, *Capparis spinosa* buds aqueous extract is non-genotoxic. However, the study reveals that *Capparis spinosa* aqueous extract has antimutagenic potential against EMS induced chromosomal aberrations in *A. cepa* root meristem cells and the antimutagenic potential of *Capparis spinosa* flower buds extract is effective at 30 g/L concentration [190].

A novel dimeric 62-kDa lectin was also extracted from caper (*C. spinosa*) seeds, it inhibited the proliferation of both hepatoma HepG2 and breast cancer MCF-7 cells [191].The effect of the crude aqueous *Capparis spaniosa* leaf extract in a concentration of used (125، 250،500 and1000 µg/ml, for 48-72 hrs exposure time) was studied against two cellular cancer lines, human epidermoid larynx carcinoma Hep-2 and human cervix uteri epitheloid carcinoma Hela. The extracts induced significant inhibitory effect ($p<0.001$) on the cancer lines growth,Hep-2 and Hela with low concentration. The cellular Hep-2 density was (0.340%), whereas the density in Hela was (0.6545%) at the lowest concentration 125 µg / ml. The highest inhibitory effect of the extract was recorded at (1000) µg/ml. The effect appeared time dependent [192].

Capparis spinosa seeds contain a 38 kDa protein similar to imidazoleglycerol phosphate synthase that inhibited proliferation of hepatoma HepG2 cells, colon cancer HT29 cells and breast cancer MCF-7 cells with an IC_{50} of about 1, 40 and 60 mM, respectively [43]. On the other hand, Stachydrine was potent anti-metastatic agent, it markedly inhibit the malignancy and invasive capacity of malignant cancer cells. It inhibited the expression of chemokine receptors (CXCR3 and CXCR 4) in cancer cells. *Capparis spinosa* root bark extract also showed antitumor activity against Ehrlich Ascites carcinoma in albino mice. It significantly decreased the tumor volume, packed cell volume, and viable cell count and it prolonged the life span of EAC tumor-bearing mice [191, 194-195].

Chloroform extraction/fractions of *Capparis spinosa* L. also imposed inhibitory effects on SGC-7901 cells, while polar alkaloids showed mitochondrial apoptotic pathway and affected MPTP hole opening, membrane potential losing, cytochrome C releasing and showed IC_{50} value 33.437µg/·ml[196].

The cytotoxic effects of aqueous, methanolic crude extracts and secondary metabolites extracts (polyphenolic, rutin, and alkaloids) of mature fruit of C. spinosa was studied on human larynx carcinoma (Hep-2) and human cervix adenocarcinoma (HeLa) tumor cell lines *in vitro*. The study also included the investigation of the effect of polyphenol mature fruit extracts on mitotic index

(MI) of HeLa tumor cell line. The effect of (aqueous and methanol) crude extracts and secondary metabolites extracts (polyphenol, rutin, and alkaloids) of mature fruits of *C. spinosa* on Hep-2 and HeLa tumor cell lines have been showed highly significant difference ($P \leq 0.0001$) or ($P \leq 0.01$) among all types of extracts, and among all concentrations for each extract in two periods 24 and 48 hrs of the treatment. However, the study revealed that the effective extracts against the proliferation of tested cell line were polyphenol extracts with concentration of 10000 µg/ml in Hep-2 cells after 24 and 48 hrs, and with concentrations of 10000 and 5000 µg/ml in HeLa cell line after 48 hrs. The cytotoxic concentration 50% (CC50%) of polyphenolic extract was 6400 and 6800 µg/ml on Hep-2 tumor cell line after 24 and 48 hrs of treatment, respectively. The CC50% against HeLa cells was 7100µg/ml after 48 hrs. Other extracts, aqueous, methanolic crude extracts and secondary metabolites extracts (rutin and alkaloids) of mature fruit of *C. spinosa* caused less inhibition activity on the growth of Hep-2 and HeLa tumor cell lines. The CC50% for all these extracts were more than 10000 µg/ml [197].

Capsella bursa-pastoris

A neoplasm inhibitory substance has been identified as fumaric acid. An inhibitory effect of the extracts of the herb on Ehrlich solid tumour in mice was found to be due to the fumaric acid [10].The water, ethanol and methanol extracts of *C. bursa-pastoris* caused 42.9, 29.5 and 42.9% tumor inhibition [198].

The effects of methanol extracts of *Capsella bursa-pastoris* (MECB) was evaluated on the cell growth and apoptosis of HSC-2 human oral cancer cells. MECB caused growth inhibition and the induction of apoptosis in a concentration-dependent manner in HSC-2 cells. A marked reduction in specificity protein 1 (Sp1) expression following treatment with MECB was also observed. The down regulation of Sp1 by siRNA resulted in growth inhibition and a reduction of total poly (ADP-ribose) polymerase (PARP) expression. In addition MECB was significantly increased Bak expression levels and decreased Mcl-1 expression levels [199].

The treatment of ICR mice with ip injections (0.14 g/kg/ day) of the extract of *Capsella bursa-pastoris* herb caused 50 to 80% inhibition of the solid growth of Ehrlich tumor cells that had been inoculated into the sc tissue of the animals. The tumor lumps in the treated mice showed multifocal necroses and the infiltration of host fibrous tissue cells. An acidic substance was isolated in crystalline form from the herb extract as antitumor agent. This acidic substance was identified as fumanic acid and was effective in inhibiting the growth of Ehrlich Solid tumor at a dose of 10 mg/kg/day. The 50% lethal dose (ip) of this acid was 266 mg/kg [200].

Fumaric acid, isolated as the active component of *Capsella bursa-pastoris* was found to reduce markedly the growth and viability of Ehrlich, MH134, and L1210 mouse tumor cells in culture at concentration of 0.3 approximately 1.2 mg/ml. In contrast, fumaric acid at these concentrations in the culture medium had no deleterious effect on the monolayer development of mouse and chick embryo cells but exhibited activity to enhance the recovery of the cells from the toxic effects of mitomycin C, aflatoxin B1, N-methyl-N'-nitro-N-nitrosoguanidine, and potassium 1-methyl-7-[2-(5-nitro-2-furyl) vinyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate[201].

Capsicum annuum* and *Capsicum frutescens

Four types of chili (*Capsicum annuum*) extracts, categorized according to color (green and red), and size (small and large) were studied in Hep-G2 cells. Red small (RS) chili had an LC_{50} value of 0.378 ± 0.029 mg/ml compared to green big (GB) 1.034 ± 0.061 mg/ml and green small (GS) 1.070 ± 0.21 mg/ml. Red big (RB) was not cytotoxic. Capsaicin content was highest in RS and produced a greater percentage of sub-G1 cells ($6.47 \pm 1.8\%$) after 24 h exposure compared to GS ($2.96 \pm 1.3\%$) and control ($1.29 \pm 0.8\%$). G2/M phase was reduced by GS compared to RS and control cells. RS at the LC_{50} concentration contained 1.6 times the amount of pure capsaicin LC_{50} to achieve the same effect of capsaicin alone. GS and GB capsaicin content at the LC_{50} value was lower (0.2 and 0.66, respectively) compared to the amount of capsaicin to achieve a similar reduction in cell growth [202].

Capsicum annuum L. *var. angulosum* Mill. extracts showed relatively higher cytotoxic activity against two human oral tumor cell lines (HSC-2, HSG) than against normal human gingival fibroblasts (HGF), suggesting a tumor-specific cytotoxic activity [203].

The extracts of Indian spices like chili pepper, cloves, black pepper and black cumin were investigated for cytotoxic effect. In studying the *in vitro* anticancer activities of aqueous and ethanolic extracts against the TE-13 (esophageal squamous cell carcinoma) cell line, DAPI staining and DNA fragmentation assays showed maximum cell death and apoptotic cell demise (88%) to occur within 24 hours with an aqueous extract of chili pepper at 300 µl/ml [204].

By using an *in vitro* brine shrimp lethality bio-assay, the $LC_{50}$of *Capsicum frutescens* was 83.33 µg/ml [205].

Carthamus tinctorius

The *in vitro* effects of dichloromethane, methanol and hexane extracts of *Carthamus tinctorius* on caspase-dependent anti-tumor activity against human colon carcinoma SW620 cell lines were investigated. In addition, the immunomodulatory activity of each solvent extract was examined. Only dichloromethane extract of *C. tinctorius* exhibited inhibitory effect on growth of SW620 cells with IC_{50} of 0.15 mg/ml, in comparison to the Hep2 (0.5 mg/ml)

and control BHK cells (0.6 mg/ml). Moreover, it was associated with up-regulation of caspase 3, 7 and 9 and down regulation of Bcl2 transcripts in treated SW620 cell. The dichloromethane extract showed the highest stimulatory effect on the lymphocyte proliferation with an increase of 8±1.6 fold, followed by the methanol and hexane extract with increases of 12±1.1 and 14±1.6 fold, respectively[206].

The effects of *Carthamus tinctorius* (CT) on the dendritic cell (DC)-based vaccine in cancer treatment, cytokine secretion of mouse splenic T lymphocytes and the maturation of DCs in response to CT were analyzed. To assess the antitumor activity of CT extract on mouse CD117+ (c-kit)-derived DCs pulsed with JC mammal tumor antigens, the JC tumor was challenged by the CT-treated DC vaccine *in vivo*. CT stimulated IFN-γ and IL-10 secretion of splenic T lymphocytes and enhanced the maturation of DCs by enhancing immunological molecule expression. When DC vaccine was pulsed with tumor antigens along with CT extract, the levels of TNF-α and IL-1β were dramatically increased with a dose dependent response and more immunologic and co-stimulatory molecules were expressed on the DC surface. In addition, CT treated tumor lysate-pulsed DC vaccine reduced the tumor weight in tumor-bearing mice by 15.3% more than tumor lysate-pulsed DC vaccine without CT treatment. CT polarized cytokine secretion toward the Th1 pathway and also increased the population of cytotoxic T lymphocytes *ex vivo*[207].

The drug resistance index of the total extract of Carthami Flos (CF) and the dried flower of safflower, in MDR KB-V1 cells and its synergistic effects with other chemotherapeutic agents were studied. SRB cell viability assays were used to quantify growth inhibition after exposure to single drug and in combinations with other chemotherapeutic agents using the median effect principle. The combination indexes were then calculated according to the classic isobologram equation. The results revealed that CF showed a drug resistance index of 0.096. In combination with other chemotherapeutic agents, it enhanced their chemo-sensitivities by 2.8 to 4.0 folds and gave a general synergism in cytotoxic effect. The results indicate that CF could be a potential alternative adjuvant antitumour herbal medicine representing a promising approach to the treatment of some malignant and MDR cancers in the future [208].

A compound (Zhu-xiang) from herbal extracts containing ginseng and *Carthamus tinctorius* was used to treat the MDA-MB-231 breast cancer cell and normal human mammary gland cell lines. The Zhu-xiang showed significantly inhibition in cell proliferation and the inhibition was dose dependent. The inhibitory effect of Zhu-xiang was significantly greater than that of commonly used cytotoxic drugs. The inhibitory effect was a result of the induction of apoptosis, which was concentration- and time-dependent. DNA histograms indicate that the compound caused accumulation of cells mainly in the S phase. The viability of cells in breast solid tumours was measured by ATP bioluminescence assay to determine the drug-induced cytotoxicity of Zhu-xiang. The three different concentrations of Zhu-xiang all exhibited the ability to inhibit proliferation in solid tumour[209].

The mixture of erythro-alkane-6,8-diols from the flowers of *C. tinctorius* markedly suppressed the promoting effect of TPA (12-0-Tetradecanoylphorbol-13-acetate) on skin tumor formation in mice following initiation with 7,12-dimethylbenz [a]anthracene[(210)]. The anti-tumor activity of safflower polysaccharide (SPS) was examined *in vivo* and *in vitro*. The transplanted tumor model of LA795 lung cancer was established with T739 mouse and safflower polysaccharide (SPS) 40mg/kg was administered ip for 10 days and the tumor weight and the cytotoxicity of CTL cells, NK cells were detected. The Anti-tumor activity of SPS on three types of tumor cells *in vitro* was observed with trypan blue exclusion staining. SPS can significantly inhibit the growth of S180 Sarcoma in mice with an inhibitory rate of 51.33% ($P<0.01$). It can also inhibit the growth of LA795 lung cancer in mice and the tumor volume was reduced obviously for 3.29 mm^3 ($P<0.05$). It can remarkably enhance the cytotoxicity of splenic CTL cells, NK cells in tumor-bearing ($P<0.05$) [211].

Casuarina equisetifolia

Methanolic extracts of leaves of *Casuarina equisetifolia* showed moderate cytotoxic Activity in Brine Shrimp lethality bioassay test, where the $LC_{50}$was 95.87 µg/ml [212].

Celosia cristata

The cytotoxicity of water and organic solvent extracts was determined in the fibroblast cells Cos7 and in four cancer cell lines: HeLa, HepG2, SK-Hep1 and LS 174T**.** The aqueous extracts were also screened against BVDV and HBV, whereas organic solvent extracts were assayed on *T. brucei***.** IC_{50} of the water extracts against Cos7, HeLa, HepG2,SK-Hep1 and LS 174T were 263.9, 2773.5, 200, 180 and >200 µg/ml respectively. IC_{50} of CH2Cl2 extracts against HeLa and Cos 7 were 472.0 and 136.0 µg/ml,while IC_{50} of MeOH extracts against the same cell lines,were 499.8 and 77.2 respectively [213].

Chenopodium album

The effects of *Chenopodium album* (leaves) was evaluated on the growth of estrogen dependent (MCF-7) and estrogen independent (MDA-MB-468) human breast cancer cell lines. The different solvent extracts (petroleum ether, ethyl acetate and methanol) were assessed for their cytotoxicity using Trypan blue exclusion and MTT [3-(4, 5-dimethyl thiazol-2-yl)-2, 5-diphenyl tetrazolium] bioassay. Methanolic extract of *Chenopodium album* (leaves) exhibited maximum antibreast cancer activity

having IC_{50} value 27.31 mg/ml against MCF-7 cell line. Significant percent inhibition (94.06%) was recorded for MeOH extract of *Chenopodium album* (leaves) at 48 h of exposure and concentration 100 mg/ml ($p < 0.05$) against MCF-7 breast cancer cell line [214].

Chrozophora tinctoria

The cytotoxicity of the plant leaves , roots and stems extracts was studied using brine shrimp assay, antitumor activity using potato disc assay, and phytotoxicity activity using radish seed bioassay. Mortalities (%) of brine shrimps at concentrations of 1000,100 and 10 ppm of the plant leaves , roots and stems extracts were (80,30 and 20), (33.3, 26.6 and 20) and (36.6,20 and 20) respectively. In antitumor potato disc assay, the tumor inhibition (%) at concentrations of 1000,100 and 10 ppm of the plant leaves, roots and stems extracts were (55.43, 47.83 and 41.30), (58.82, 49.41 and 17.65) and (61.96, 45.65 and 35.87) respectively. In radish seed phytotoxicity assay, the percentage root growth inhibition or stimulation (%) at concentrations of 10000, 1000,100 and 10 ppm of the plant leaves, roots and stems extracts were (64.31, 13.02, 7.61 and 2.06), (56.93, 13.13, 2.80 and 1.75) and (53.49, 4.01, -3.93 and -8.60) respectively[215].

Effect of different concentrations of methanolic extracts of *Chrozophora tinctoria* against *Artemia salina* (a species of brine shrimp)(% mortality) showed 100 % mortality at concentration of 100, 300 and 1000 µl. However, n-hexaneextracts of *Chrozophora tinctoria* 100, 48.13 and 100% mortality at concentration of 100, 300 and 1000 µl.The LD_{50} of *Chrozophora tinctoria* against *Artemia salina* for methanol extract was 47.22 and n-hexane extract was 151.77 µg/ml [216].

The inhibitory effect of *Chrozophora tinctoria* on mouse skin tumors was studied in vivo, tumor initiation was achieved by a single topical application of 7, 12-Dimethylbenze (a) anthracene (DMBA) (40 µg/100 µl acetane/mouse). After 7 days, tumor promotion was begun by twice-weekly topical application of Benzoyl peroxide (BPO) (20 mg/300 µl acetone/mouse) for a period of 32 weeks. Also before 4 hours of DMBA application , animals received a single topical dose of *Chrozophora tinctoria* extract (10 mg/gr carbopol gel/mouse). Results showed that there were higher yields of tumors in those animals receiving both DMBA and BPO. However, the *Chrozophora tinctoria* pretreated group showed complete inhibition of tumor incidence. The authors suggested that the antitumor effect of the plant was mediated by its scavenging of free radicals which play an important role in skin cancer [217].

CONCLUSION

The paper reviewed the anticancer *effects* of the medicinal plants to open the door for their utilization in medical applications as a result of effectiveness and safety**.**

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