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Review Article

Medicinal plants with anticancer effects (part 2)- plant based review

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Abstract: Herbal medicine is the oldest form of medicine known to mankind. It was the mainstay of many early civilizations and still the most widely practiced form of medicine in the world today. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many pharmaceutical drugs. This paper represented the second part of our previous review to highlight the anticancer effects of the medicinal plants as a source of pharmaceutical research and therapeutic uses.
Keywords: medicinal plants, herbs, anticancer, cytotoxic**,** antitumor.

Introduction:

The previous studies showed that many medicinal plants exerted cytotoxic and anticancer activity [1-2]. These plants included: *Adonis aestivalis* [3], *Ailanthus altissima* [4], *Alhagi maurorum* [5], *Allium species* [6], *Althaea species* [7], *Ammannia baccifera* [8], *Anagyris foetida* [1], *Anchusa italic* [9], *Antirrhinum majus* [10], *Aristolochia maurorum* [1], *Apium graveolens* [11], *Arctium Lappa* [12], *Aristolochia maurorum* [1], *Artemisia campestris* [13], *Arundo donax* [14], *Asclepias curassavica* [15], *Asparagus officinalis* [16], *Astragalus hamosus* [17], *Bauhinia variegate* [18], *Bellis perennis* [19], *Betula alba* [20], *Bidens tripartite* [21], *Brassica rapa* [22], *Bryonia dioica* [1], *Bryophyllum calycinum* [23], *Caccinia crassifolia* [1], *Caesalpinia crista* [24], *Calendula officinalis* [25], *Calotropis procera* [26], *Canna indica* [27], *Capparis spinosa* [28], *Capsella bursa-pastoris* [29], *Capsicum annuum* [30], *Capsicum frutescens* [30], *Carthamus tinctorius* [31], *Casuarina equisetifolia* [32], *Celosia cristata* [33], *Chenopodium album* [34] and *Chrozophora tinctoria* [35]. This paper represented the second part of the review to highlight the anticancer effects of the medicinal plants as a source of pharmaceutical research and therapeutic uses.

Plant with anticancer activities

Cicer arietinum

Cytotoxic activity of C-25 protein isolated from *Cicer arietinum* was studied on oral cancer cells and normal cells. It reduced the cell proliferation of human oral carcinoma cells with IC_{50} of 37.5 µg/ml and no toxic effect was found on normal human peripheral blood mononuclear cells even at higher concentration of 600 µg/ml[59]. Results of the cytotoxicity evaluation of isoflavones isolated from *Cicer arietinum* (10, 20, 40, 80, 160 and 360 µg/ml) against MCF-7 breast cancer cell line showed a dose dependent inhibition of cell growth [36-37].

Cichorium intybus

Ethanolic extract of chicory root showed a tumour-inhibitory effect against Ehrlich ascites carcinoma in mice. A 70% increase in the life span was observed with a 500 mg/kg/day intraperitoneal divided over 8 doses [38-39].

Magnolialide, a 1β-hydroxyeudesmanolide isolated from the roots of Cichorium intybus, inhibited several tumor cell lines and induced the differentiation of human leukemia HL-60 and U-937 cells to monocyte or macrophage-like cells [40].

The aqueous-alcoholic macerate of the leaves of Cichorium intybus exerted an antiproliferative effect on amelanotic melanoma C32 cell lines [41].

The anticancer properties of aqueous extracts of *Cichorium intybus* was studied against cell lines including human prostate cancer PC-3 cells, human breast carcinoma T47D cells and colon cancer RKO cells. Extract of *Cichorium intybus* demonstrated a modest cell growth inhibition in all three cancer cell lines. *Cichorium intybus* (seeds) exhibited 5-24% inhibition in cell viability at 1.0 to10% concentration for 24 hours [42].

Chicory contained photosensitive compounds such as cichoriin, anthocyanins, lactucin, and lactucopicrin. The protective effect of sun light-activated chicory against dimethylbenz[a]anthracene (DMBA) induced benign breast tumors was

investigated in female Sprague-Dawley rats. Chicory's extract was significantly increased P. carbonyl (PC) and malondialdehyde (MDA) and decreased the hepatic levels of total antioxidant capacity (TAC) and superoxide dismutase (SOD) in benign breast tumors-induced group compared to control. It also significantly decreased the number of estrogen receptors ER-positive cells in tumor masses [43].

Cistanche tubulosa

The extract of the aerial parts of the plant was screened for toxicity with larvae (nauplii) of *Artemia salina* (brine shrimp). LD_{50} of the plant extract on *Artemia salina* was 62.95 (49.26-79.05) ppm. *Cistanche tubulosa* extract showed the highest toxicity among 8 plants, a trait which introduce *Cistanche tubulosa* as a potentional anticancer plant [44].

Citrullus colocynthis

The antiproliferative effect of cucurbitacin glycosides extracted from *Citrullus colocynthis* leaves was studied in human breast cancer cell growth. Leaves were extracted and cucurbitacin B/E glycosides were isolated from the extract. The Cucurbitacin glycoside combination (1:1) inhibited growth of ER+ MCF-7 and ER- MDA-MB-231 human breast cancer cell lines. Cell-cycle analysis showed that treatment with isolated cucurbitacin glycoside combination resulted in accumulation of cells at the G2/M phase of the cell cycle. Treated cells showed rapid reduction in the level of the key protein complex necessary to the regulation of G2 exit and initiation of mitosis, namely the p34CDC2/cyclin B1 complex. cucurbitacin glycoside treatment also caused changes in the overall cell morphology from an elongated form to a round-shaped cell, which indicates that Cucurbitacin treatment caused impairment of actin filament organization. This profound morphological change might also influence intracellular signaling by molecules such as protein kinase B (PKB), resulting in inhibition in the transmission of survival signals. Reduction in PKB phosphorylation and inhibition of survivin, an antiapoptosis family member, was observed. The treatment caused elevation in p-STAT3 and in p21WAF, proven to be a STAT3 positive target in absence of survival signals. Cucurbitacin glycoside treatment also induced apoptosis, as measured by Annexin V/propidium iodide staining and by changes in mitochondrial membrane potential (DC) using a fluorescent dye, JC-1. The results revealed that cucurbitacin glycosides exhibit pleiotropic effects on cells, causing both cell cycle arrest and apoptosis. These results suggest that cucurbitacin glycosides might have therapeutic value against breast cancer cells [45-46].

Citrus species

Epidemiological studies have shown that the consumption of fruits is associated with a decreased risk of cancer. The ingestion of citrus fruit has been reported to be beneficial for the reduction of certain types of human cancer [47].

The *in vitro* effects of concentrated lime juice (CLJ) extract was evaluated on the spontaneous proliferation of human breast carcinoma cell line (MDA-MB-453) and a human lymphoblastoid B cell line (RPMI-8866). CLJ extract was prepared by freeze-drying fresh fruit juice and dialyzing the concentrated extract against phosphate buffered saline in orderto deplete low molecular weight micronutrients such as flavonoids as well as adjusting the pH of the extract to the physiological range. The effects of different concentrations of the CLJ extract on the spontaneous proliferative responses of the cell lines were determined by 3 H-thymidine incorporation after24 hrs of incubation. CLJ extract had no significant effect on MDA-MB-453 cell line, however, using the concentrations of 125, 250, and 500 µg/ml of CLJ extract a significant inhibition of the spontaneous proliferation of RPMI-8866 cell line was detected ($P<0.05$) [48].

The bioactive compounds isolated from of seeds of *Citrus aurantifolia* were found to posses the potential of inhibiting human pancreatic cancer cells. While, the compounds purified from peel had the potential of suppressing the colon cancer cells. The purified compounds from seeds exhibited significant inhibition of Panc-28 cells with IC_{50} values in the range of 18.1-100 µM, which was confirmed by viable cell count. DNA fragmentation and expression of proteins in cells treated with compounds showed the induction of apoptosis through p53 and caspase-3 mediated pathway. The volatile oil showed 78 per cent inhibition of human colon cancer cells (SW-480) with 100 µg/ml concentration at 48 h. Lime volatile oil showed DNA fragmentation and induction of caspase-3 up to 1.8 and two folds after 24 and 48 h, respectively [49].

Citrus aurantifolia fruit volatile oil showed 78% inhibition of human colon cancer cells (SW-480) with 100 µg/ml concentration at 48 h. Lime volatile oil showed DNA fragmentation and induction of caspase-3 up to 1.8 and 2- folds after 24 h and 48 h, respectively. Analysis of apoptosis-related protein expression further confirmed apoptosis induction by lime volatile oil [50].

The genotoxic effect of the crude volatile oils (0.005, 0.010, 0.025, 0.050, 0.075, 0.1 ppm) of *Citrus limon* fruit peels was investigated through estimation of mitotic index (MI) and blast index (BI) in human lymphocytes after treatment with prepared concentrations. The results showed that volatile oils from maturated and non maturated lemon peels possessed genetic effect by increasing MI and BI value of treated lymphocytes. It also appeared that volatile oils stimulated increasing the production of lymphocytes but with more than synergistic treatment with (PHA). Otherwise, It was also found that volatile

oils exerted toxic effects against lymphocytes viability [51].

The antimutagenicity and anticancer effect of *Citrus medica* fruit juice were evaluated on human astrocytoma cancer cells cultured in DMEM (Gibco), cancer cell line were treated by half-ripe and ripe *Citrus medica* fruit juice and cellular vital capacity was determined by MTT. The *Citrus medica* fruit juice was subsequenthy evaluated in terms of antimutagenicity and anticancer properties by a standard reverse mutation assay (Ames Test) which was performed with histidine auxotroph strain of *Salmonella typhimurium* (TA100). By MTT, human astrocytoma cell line revealed a meaningful cell death when compared with controls ($P<0.01$). In Ames Test, the fruit juice prevented the reverted mutations and the hindrance percent of half-ripe *Citrus medica* was 71.7% and ripe *Citrus Medica* was 34.4% in antimutagenicity test and this value in anticancer test was 83.3% and 50% in half-ripe *Citrus medica* and ripe *Citrus medica* respectively [52-53].

C. limetta root extract at the concentration of 500 µg/ml was found to be lethal towards the larvae of brine shrimp (*Artemia franciscana*) in a study conducted in the Amazonas state of Brazil, which can serves as a pre-screen to existing cytotoxicity and antitumor assays [54].

The antitumor activity of methanol extract of peel of *Citrus limetta* fruits (MECL) was evaluated against Ehrlich ascites carcinoma (EAC) cell line in Swiss albino mice. Twenty-four hours after intraperitoneal inoculation of tumor EAC cells in mice, MECL was administered at 200 and 400 mg/kg bw, ip daily for nine consecutive days. On the 10^{th} day, half of the mice were sacrificed for the estimation of tumor growth (tumor volume, viable and non-viable tumor cell counts), and hematologic parameters (red blood cells, white blood cells and hemoglobin). The rest animals were kept alive for assessment of survival parameters (median survival time and percentage increase in life span of EAC bearing mice). Intraperitoneal administration of MECL at the doses of 200 and 400 mg/kg for nine days to the carcinoma induced mice demonstrated a significant ($P<0.001$) decrease in tumor volume, viable tumor cell count, tumor weight and a significant ($P<0.001$) improvement in hematologica parameters and life span as compared to the EAC control mice. The results establishes marked and dose dependant antitumor effect of *Citrus limetta* fruit peel against Ehrlich ascites carcinoma bearing Swiss mice [55].

Limonene, one of the main constituents of citrus species fruit, reduces the risk of mouth, skin, lung, breast, stomach and colon cancer. Hesperidin, and its flavone analogue, diosmin, also exerted anti-carcinogenic activities in various *in vivo* studies. The polymethoxylated flavones have shown strong anti-proliferative action against cancer cells and antigen activated T-lymphocytes. Beta-cryptoxanthin (an orange-red carotenoid) inhibited development of lung cancer [56-57].

A study of the inhibitory effects of two limonoid aglycones (limonin and nomilin) on the formation of benzo[a]pyrene induced neoplasia in the fore stomach of ICR/Ha mice showed that incidence of tumors was reduced by more than 50% at 10mg/dose [58].

The cytotoxicity of hesperidin from the peel of *Citrus sinensis* was evaluated gainst different human carcinoma cell lines (larynx, cervix, breast and liver carcinoma cell lines). The results revealed that hesperidin exhibited pronounced anticancer activity against the selected cell lines. IC_{50} were 1.67, 3.33, 4.17, 4.58 µg/ml, respectively [59].

Clerodendron inerme

The modifying effects of ethanolic extract of *Clerodendron inerme* leaves on membrane integrity was investigated by measuring the levels of plasma and erythrocyte membrane glycoconjugates and red blood cell osmotic fragility during 7,12-dimethylbenz(a)anthracene (DMBA) induced skin carcinogenesis in Swiss albino mice. The skin squamous cell carcinoma was induced in the shaved back of mice, by painting with DMBA (25 µg/0.1 ml acetone) twice weekly for 8 weeks. 100% tumor formation was recorded in the fifteenth week of experimental period. The status of glycoconjugates in plasma and erythrocyte membrane and red blood cell osmotic fragility was assayed by using specific colorimetric methods. The levels of glycoconjugates were increased in plasma whereas decreased in erythrocyte membrane of DMBA treated animals as compared to control animals. Red blood cells from tumor bearing animals were more fragile than those from control animals. Oral administration of ethanolic leaf extract of *Clerodendron inerme* (CILEE) 300 mg/kg significantly prevented the tumor formation as well as restored the status of glycoconjugates and red blood cell osmotic fragility in DMBA treated animals [60-61].

The chemopreventive and anti-lipidperoxidative effect of the ethanolic extract of *Clerodendron inerme* leaves were studied in 7,12-dimethylbenz(a) anthracene (DMBA) induced skin carcinogenesis in Swiss albino mice. The skin squamous cell carcinoma was induced in the shaved back of mice by painting with DMBA (25 µg/0.1 ml acetone) twice weekly for 8 weeks. 100% tumor formation was recorded in the fifteenth week of experimental period. Elevated lipid peroxidation and decline enzymatic and non-enzymatic antioxidant status was observed in tumor bearing mice. Oral

administration of the ethanolic extract of *Clerodendron inerme* leaves (300 mg/ kg bw) for 25 weeks significantly prevented the tumor incidence, volume and burden of tumor. The ethanolic extract of *Clerodendron inerme* leaves also showed potent antilipidperoxidative effect as well as enhanced the antioxidant defense mechanisms in DMBA painted mice [62].

The chemopreventive potential of the aqueous leaf extract of *Clerodendron inerme* (CiAet) was investigated in 7,12-dimethylbenz(a) anthracene (DMBA)-induced hamster buccal pouch carcinogenesis. Oral squamous cell carcinoma was develop in the buccal pouch of male Syrian golden hamsters by painting them with 0.5% DMBA in liquid paraffin thrice a week for 14 weeks. The tumour incidence, tumour volume and tumour burden that were formed in the hamster buccal pouches were determined. Oral administration of CiAet at a dose of 500 mg/kg body weight to DMBA-painted animals on days alternate to DMBA painting for 14 weeks significantly prevented the tumour incidence, and decreased tumour volume and tumour burden. CiAet also exerts potent antilipidperoxidative effect and improved the antioxidant defence system in DMBA-painted animals. The chemopreventive efficacy of CiAet was evident by inhibition of tumour formation (80%) in DMBA-painted animals [63].

Clitoria ternatea

The *in vitro* cytotoxic effect of petroleum ether and ethanolic flower extracts (10, 50, 100, 200, 500 µg/ml) of *Clitoria ternatea* was studied using trypan blue dye exclusion method. Both extracts exhibited significant dose dependent cell cytotoxic activity. For petroleum ether extract the concentration 10 µg/ml showed 8% reduction in cell count, however, 100% reduction was observed at 500µg/ml. In case of ethanolic extract, 10 µg/ml concentration possessed 1.33 % reduction in cell count, while, at 500µg/ml 80 % reduction in cell count was observed [64-65].

The cytotoxicity of the aqueous and methanol extracts of the flowers of *Clitoria ternatea* was evaluated on six types of normal and cancer-origin cell lines. These included the hormone-dependent breast cancer cell line (MCF-7), non-hormone-dependent breast cancer cell line (MDA-MB-231), human ovary cancer cell line (Caov-3), human cervical cancer cell line (Hela), human liver cancer cell line (HepG2) and human foreskin fibroblast cell line (Hs27). The anti-proliferation activities of the extracts were examined by employing colorimetric MTT (3-(4,5-dimethylthiazol-2-yl) 2,5 diphenyltetrazolium bromide) assay through time periods of 24, 48 and 72 hours. Results showed that the water extracted of *Clitoria ternatea* had significant effects ($p<0.05$) against MCF-7 with an IC_{50} value of 175.35 µg/ml [66].

The crude methanol extract of leaves, seeds and stem-bark of *Clitoria ternatea* demonstrated a significant cytotoxic activity in a brine shrimp lethality bioassay test. The LC_{50} values of the crude methanol extract of leaves, seeds and stem-bark were 25.82, 110.92 and 179.89 µgm/ml respectively. Crude methanol extract and methanol fraction of leaves showed a very promising cytotoxic activity [67].

The ethanolic extract of *Clitoria ternatea* . was evaluated for its *in vitro* cytotoxic and antioxidant activities. The extract showed potent cytotoxic activity in trypan blue dye exclusion method using DLA cell lines with EC_{50} value of 305µg/ml and exhibited a dose dependent decrease in cell count for all the concentrations tested (0.0196-10 µg/ml) [68].

The anticancer activity of *Clitoria ternatea* was evaluated in Dalton's lymphoma (DLA) bearing mice. Tumour was induced in mice by the intraperitoneal injection of DLA cells. After 24 hours of tumour inoculation, methanol extract of *Clitoria ternatea* (MECT) was administered at doses of 100 and 200mg/kg body weight for 14 consecutive days. The effect of MECT was assessed using *in vitro* cytotoxicity, survival time, peritoneal cell count, hematological studies and antioxidant parameters. Treatment with MECT decreased tumour volume, packed cell volume and viable count. It also increased the non-viable cell count and mean survival time, thereby increasing the life span of EAC bearing mice. Hematological profile reverted to more or less normal levels in the treated group [69].

Convolvulus arvensis

A purified bindweed extract was used to inhibit the growth of tumour cells and to inhibt the growth of blood vessels and enhance immune function. The high molecular weight extract inhibited angiogenesis in chicken chorioallantoin membranes by 73% and at the dose of 14 mg inhibited tumour growth in mice by 77% [70-71].

The cytotoxic effects of chloroform, ethyl acetate and hydroalcoholic extracts of arial parts of *Convolvulus arvensis* were evaluated in human tumor cell line (Hela). Different concentrations of the extracts were added to the cultured cells and incubated for 72 h. Cell survival was evaluated using MTT assay. Chloroform extract showed the highest cytotoxic effect among the extracts (IC_{50} 15 µg/ml), whereas ethyl acetate and hydroalcoholic extracts were less cytotoxic against Hela cells (IC_{50} was 25 and 65µg/ml, respectively) [72].

PGM protein isolated from the water extract inhibited the tumor growth and angiogenesis in chick embryo and improved lymphocyte [70-73].

The aerial parts of *Convolvulus arvensis* were extracted with 80% aqueous ethanol and fractionated using petroleum ether, chloroform, ethyl acetate and *n*-butanol which were then examined on bone marrow of mice by measuring the mitotic index (MI) and chromosomal aberrations (CA) in addition to the total white blood cells counts (WBCs) for two doses of the each fraction, 200 and 400mg/kg. The *in vitro* tests included assessment of cultured cell viability of human rabdomyosarcoma RD and human normal lymphocytes with measurement of tumor necrosis factor alpha TNF-α in cultured media using three concentrations 25µg/ml, 50µg/ml and 100µg/ml for each fraction. Results revealed that the chloroform and *n*-butanol fractions significantly decreased MI and increased CA in a dose of 200 and 400mg/kg. The petroleum ether only in high doses gave significant effects. The ethyl acetate fraction of low dose increased MI and decreased CA, while the high dose gave the inverse action. The *in vitro* study showed inhibition the viability of the cultured cell as the concentrations increased, for all the fractions accompanied with decreased the level of TNF-α [74].

The cytotoxic effect of ethanol extract of aerial parts of *Convolvulus arvensis* was evaluated against lymphoblastic leukemia, Jurkat cells. The cells were exposed to different concentrations (10, 25, 50, 75 and 100 µg/ml) of the extract to determine cell viability, cell proliferation and apoptosis using trypan blue exclusion assay, 3-(4,5- dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) and fluorescent activated cell sorter (FACS) analysis. Trypan blue exclusion assay and MTS assay results indicated that the ethanol extract decreased the number of living cells in a concentration-dependent fashion. The results of FACS analysis showed that the lowest concentration of the extract (10 µg/ml) was most effective for the induction of apoptosis as it induced maximum apoptosis (85.34 %) and the highest concentration (100 µg/ml) was less effective as it induced less apoptosis (53.70 %) in Jurkat cells ($p<0.05$) [75].

The ability of crude alkaloids extracted from the leaves of *Convolvulus arvnsis* to distract the microtubule network of mice cell line (CHO) (an invasive metastasis cell line) was evaluated. The assessment was carried out using the immunostaining technique. The extract was able to distract the microtubules of the cells line after 60 min of exposure in a concentration as little as 20 µg/ml. In DAPI staining, the cells apoptosis was not detected in this concentration. The apoptotic cell have been observed when the concentration of the alkaloid extract elevated up to 80 and 100 µg/ml. The cells were capable of recovering there native microtubules constriction after 12 hr of the alkaloid removal from the media. The extract concentration of 1mg/Kg/bw efficiently inhibited CHO cell line tumor growth to 97.14% in mice after three weeks treatment compared to untreated control animals [76].

The cytotoxicity of (aqueous and methanol) crude leaves, stems and roots extracts as well as proteoglycan and glycoside fraction I (FI) of *Convolvulus arvensis* was evaluated against human Rhabdomyosarcoma (RD) tumor cell line *in vitro*. The effect of glycoside FI fraction on mitotic index (MI) of RD cell line was investigated as well. Aqueous and methanol leaves extracts and glycoside FI had more cytotoxic effects at 10 mg/ml after 24 h. After 48 h, proteoglycan and glycoside FI at 10 mg/ml revealed very high cytotoxic activity compared with other concentrations. After 72 h, glycoside FI at 10 mg/ml showed more cytotoxic inhibition compared with other extracts. The cytotoxic concentration 50% (CC_{50}%) of Glycoside FI was 1.775, 0.870 and 0.706 mg/ml after 24, 48, and 72 h, respectively. The root aqueous extract had less cytotoxic effect after 72 h than other extracts; the CC_{50}% was 7.437 mg/ml. Cytotoxicity of root aqueous extract was more pronounced at high concentration, 10 mg/ml. The effect of glycoside FI on MI of RD tumor cell line was concentration dependant [77].

The cytotoxic effect of *Convolvulus arvensis* (methanolic extract) was evaluated against 2 stage skin carcinogenesis protocol, by tumor initiator, 7-12-dimethyl benz(a)antheracene (DMBA) and tumor promoter, croton oil in Swiss albino mice. They induced 100% skin ulceration in carcinogen control, and cumulative number of papilloma (CP), tumor yield (TY) and tumor burden (TB) were calculated as 18.20 ± 1.643, 3.640 ± 0.3286 and 3.640 ± 0.3286, respectively. Local application of the extract at 300 mg/kg/day inhibited the tumor incidence up to 20% in 16 weeks and showed a significant decline in continuous group in CP 4.800 ± 6.611 and TY 0.9600 ± 1.322 compared to carcinogen group. For assistance of morphological alteration, biochemical investigations were performed. Extract increased the reduced glutathione from 3.286 ± 0.207 to 7.1260 ± 0.4953 µmol/g, superoxide dismutase from 1.722 ± 0.1262 to 6.5160 ± 0.3710 µmol/g, catalase from 13.624 ± 0.813 to 18.792 ± 0.714 of H_2O_2 reduction/mg protein/min, and decreased lipid peroxidation from 7.652 ± 0.1863 to 4.2340 ± 0.5928 nmol/mg compared to carcinogen group. Histopathological changes showed papilomatosis and ulceration in carcinogen while acanthosis with normal psychological features in the continuous group [78].

Convolvulus scammonia

The effect of aqueous and alkaloid crude extracts of *Convolvulus scammonia* on bone marrow cells multiplication was studied in mice implanted with hepatic cancer cells (hepatic cell H22). The inhibitory effect of crude aqueous extract of *Convolvulus scammonia* dried extracts was compared with crude alkaloidal extract, on the bone marrow

cells multiplication in mice at doses of 10, 20, 40, 80 160 mg/kg. The inhibitory effects of each extract was compared with colchicine. The crude alkaloid extract showed arresting percent of metaphase more than aqueous extract in the small doses, in high doses (160 mglkg), both achieved 70% of the inhibitory effect of cholchicine. Furthermore, the study also showed that both extracts were active in reducing tumor size in dose dependent manner. The high therapeutic doses of aqueous and alkaloids extracts were 1.2 and 1 mg/kg which reduce the tumor size by 87.1 and 87.9% respectively [79].

The ability of crude alkaloids extracted from the leaves of *Convolvulus scammonia* was evaluated in mice hepatocarcinoma cell line (H22), which is an invasive metastasis cell line. The assessment was carried out using the immunostaining technique. The extract was able to distract the microtubules of the cells under investigation after 60 min of exposure in a concentration as little as 20 µg/ml. In using of DAPI staining, the cells apoptosis was not detected in this concentration and time. The apoptotic cell have been observed when the concentration of the alkaloid extract elevated up to 80 and 100 µg/ml during the mentioned exposure time. The cells were capable of recovering their native microtubules constriction after 12 hr of the alkaloid removal from the media. The extract concentration of 1mg/Kg bw efficiently inhibited H22 cell line tumor growth *in vivo* to 97.14% in mice after three weeks treatment compared to untreated control animals [80].

The effect of crude alkaloid and aqueous extraction from roots of *Convolvulus scammonia* was studied on the microtubule network of CHO cell line (China hamster). Computer-assisted image analysis model was used for demonstration the microtubule network changes induced by crude alkaloids. Cells were treated with alkaloid and aqueous extraction from roots of *Convolvulus scammonia* at various concentrations 2 µg/l to 800 µg/l for 60 min, or with crude alkaloid at a concentration of 4615 µg/l and 9230 µg/l for 60 min. Microtubules were detected by means of indirect Immunofluorescence. The damage was examined in a fluorescence microscope. On the other hand, cells were treated for 60 min with alkaloid at concentrations of 20 µg/l or 800 µg/l and the recovery process was studied in time intervals of 6, 7, 8, 9, 10 hours, or 8 and 12 hours, respectively. Differences in the arrangement of microtubules were assessed by means of quantification of the cytoskeleton changes in cells treated with alkaloid at a concentration of 20 µg/l and in untreated control cells. Untreated control cells showed a microtubule network distribution along the whole cell content. Cells exposed to alkaloid and aqueous extraction from roots of *Convolvulus scammonia* at concentrations of 2 µg/l for 60 min did not show considerable changes in the regularity of microtubules. Cells exposed to concentrations of 10 , 20, 30,40, 80, 100, 200, 400, and 800 µg/l for 60 min showed changes in the arrangement of the microtubular network. The network of cytoplasmatic microtubules at concentrations of 10, 20 µg/l was thinned down, and individual fibres had a wavelike shape. The network damage increased with the increasing concentration of extracts. The microtubules appeared more thinned down with fragmentation of fibers. At a higher concentration of 400 µg/l, sometimes blebs were formed. Cells exposed to alkaloids at concentrations of 4615 µg/l and 9230 µg/l formed paracrystals. No significant difference was detected between alkaloid and aqueous extract treated cells. When cells were exposed to alkaloid at a concentration of 20 µg/l for 2, 5, or 10 minutes, no noticeable changes occurred in the microtubule network. The 20min treatment at a concentration of 20 µg/l caused disruption of microtubules. The network was thinned down, and individual fibers had a wavelike shape. The cells exposed to alkaloid at a concentration of 800 µg/l for 5 minutes showed a severely defective microtubular network [81].

Corchorus aestuans

The alcoholic extract of the entire plant was found to have anticancer activity against epidermal carcinoma of nasopharynx in tissue culture [82-83]. The effects of Saikosaponin-A on human breast cancer cell lines (MDA-MB-231 and MCF-7) were investigated. Results demonstrated that Saikosaponin-A inhibited the proliferation or viability of the MDA-MB-231 and MCF-7 cells in a dose-dependent manner. Saikosaponin-A treatment of MDA-MB-231 for 3 hours and of MCF-7 cells for 2 hours, respectively caused an obvious increase in the sub-G1 population of cell cycles. Apoptosis in MDA-MB-231 cells was independent of the P53/p21 pathway mechanism and was accompanied by an increased ratio of Bax to Bcl-2 and c-myc levels and activation of caspase-3. In contrast, apoptosis of MCF-7 cells was initiated by the Bcl-2 family of proteins and involved p53/p21 dependent pathway mechanism, and was accompanied by an increased level of c-myc protein [84].

The *in vitro* anti-cancer activity of Corchorusin-D (COR-D) was evaluated on melanoma cells (B16F10, SK-MEL-28, and A375). The results demonstrate that COR-D showed maximum inhibition of B16F10 cells *in vitro*. COR-D induced mitochondrial dysfunction and altered the Bax/Bcl-2 ratio with down regulation of pro-caspases 9 and activation of caspase 3 in B16F10 cells, triggering intrinsic pathway of apoptosis. Moreover, it inhibited the *in vivo* B16F10 tumor growth and increased the survival rate of mice. Greater number of Annexin V-FITC and propidium iodide (PI)-positive tumor cells signified that COR-D induced apoptosis *in vivo* also. The reduction in tumor growth was well correlated with decreased microvascular density of the tumor cells in treated mice. The authors concluded that COR-D-induced

mitochondrial dysfunction was responsible for the induction of apoptotic cell death [85].

The anti-leukemic activity of the methanol extract of aerial parts (ME) of *C.* acutangulus has been investigated, with studying the active ingredient responsible for this activity. The anti-leukemic activity of ME, its fractions and corchorusin-D (COR-D), the active ingredient, was investigated in leukemic cell lines U937 and HL-60 using cell viability and MTT assays. The molecular pathways leading to the activity of COR-D were examined by confocal microscopy, flow-cytometry, caspase and Western blot assays. ME, its n-butanolic fraction and COR-D inhibited cell growth and produced significant cytotoxicity in leukemic cell lines U937 and HL-60. COR-D produced apoptotic cell death via mitochondrial disfunction and was found to pursue the intrinsic pathway by inciting the release of apoptosis-inducing factors (AIFs) from mitochondria. COR-D-induced translocation of Bax from cytosol to mitochondria facilitating caspase-9 activation and up regulation of downstream pathways leading to caspase-3 activation and PARP cleavage, which resulted in the subsequent accumulation of cells in the sub-G0 phase followed by DNA fragmentation [86].

The anticancer effect of corchorusin-D (COR-D), was studied in the chronic myelogenous leukemic cell line K562, using MTT assay, phase contrast and confocal microscopy, annexin V binding, cell cycle analysis and western blotting. COR-D inhibited cell growth in K562 cells and showed increasing number of Annexin V FITC binding cells. Characteristic apoptotic changes were recorded under phase contrast and confocal microscopes with accumulation of cells in the sub-G0 phase. The apoptosis involved drop in Bcl-2/Bax ratio, loss of mitochondrial membrane potential, release of cytochrome c in cytosol followed by activation of caspases 9 and 3, and cleavage of PARP. Down-regulation of pro-caspase 10 was observed along with formation of death-inducing signaling complex between TNF-R1 and TRADD. COR-D suppressed PDK1 and AKT with activation of MAP kinase family members ERK1/2, JNK1/2 and p38. Accordingly, it induced apoptosis by activating mitochondrial and death receptor pathways and suppressing AKT/PKB rather than MAP kinase pathway. Significant enhancement of apoptosis, noted using specific inhibitors of ERK1/2, p38 and JNK1/2, suggests that COR-D can enhance apoptosis in K562 cells in combination with MAP kinase inhibitors [87].

Corchorus capsularis

Two antitumor against tumor promoter-induced Epstein-Barr virus activation were isolated from the leaves of jute (*Corchorus capsularis*). The antitumor-promoting activity was examined by an immuno blotting analysis. Their active components were identified as phytol (3,7,11,15-tetramethyl-2-hexadecen-1-ol) and mono-galactosyldiacylglycerol (1,2-di-*O*-α-linolenoyl-3-*O*-β-D-galactopyranosyl-*sn*-glycerol)**.** The content of the latter was found to vary among cultivars. The detectable amount of each active component increased by treatment of the leaves with hot water [88-89].

Brine shrimp lethality bioassay was carried out to determine the cytotoxicity of the crude methanolic extract of *Corchorus capsularis* (leaves) and its fructions. Butanol extract was the most potent extract (71.14% inhibition at a concentration of 1.25 mg/ml), followed by ethyl acetale (28.57% inhibition at a concentration of 1.25 mg/ml) and methanol extract (14.28% inhibition at a concentration of 1.25 mg/ml) [90].

Coriandrum sativum

Brine shrimp lethality bioassay revealed that coriander LC_{50} was 2.25 mg/ml [91]. The anticancer activities of *Coriandrum sativum* root, leaf and stem, as well as its effect on cancer cell migration, and its protection against DNA damage, with special focus on the roots was evaluated. The ethyl acetate extract of *Coriandrum sativum* roots showed the highest antiproliferative activity on MCF-7 cells ($IC_{50} = 200.0 \pm 2.6$ µg/ml), had the highest phenolic content and FRAP and DPPH scavenging activities among the extracts. Ethyl acetate extract of *Coriandrum sativum* root inhibited DNA damage and prevented MCF-7 cell migration induced by H_2O_2, suggesting its potential in cancer prevention and metastasis inhibition. The extract exhibited anticancer activity in MCF-7 cells by affecting antioxidant enzymes possibly leading to H_2O_2 accumulation, cell cycle arrest at the G2/M phase and apoptotic cell death by the death receptor and mitochondrial apoptotic pathways [92].

The antitumor and immunomodulating activities of aqueous and methanol extracts of *Coriandrum sativum* (leaf and seed) was investigated *in vitro*. The aqueous extract of *Coriandrum sativum* (leaf), caused significant ($P<0.05$) 24, 39 percent L5178Y-R lymphoma cells toxicity at 31.2 µg/ml (MIC), whereas the methanol extract of *Coriandrum sativum* (seed and leaf) caused 40 and 31 percent cytotoxicity at 7.8, 62.5 µg/ml (MICs), respectively. In addition, *Coriandrum sativum* leaf aqueous extract stimulated significant ($P<0.01$) 14 to 45 percent splenic cells lymphoproliferation at 7.8 to 125 µg/ml respectively. The methanol extracts of *Coriandrum sativum* leaf extract caused significant ($P<0.01$) 43 to 59 percent lymphoproliferation at the tested concentrations. Furthermore, *Coriandrum sativum* aqueous extracts were significantly ($P<0.01$) reduce up to 100% nitric oxide production by LPS-stimulated macrophages [93].

Three different cell lines BMK (kidney), KHOS-2405 (bone), and WRL-68 (liver) were used to

determine cytotoxicity. Cells were treated with different *Coriandrum sativum* (Cilantro) concentrations (0.125%, 0.25%, 0.5%, 1%, 1.5%, 2% and 2.5%), for 24 hours. After this time, cytotoxic studies were performed. An embryo-toxicity study was done using fertile chicken eggs (Gallus gallus) inoculating with *Coriandrum sativum* concentrations (0.125%, 0.25%, 0.5%, 1%, 1.5%, 2% and 2.5%); incubated for 48 hours and observe them using an electronic microscope to check the effects. The three lines showed decreased proliferation and number of cells proportional to the concentrations. The cell cycle analysis showed that *Coriandrum sativum* arrested the WRL-68 cells in the (S) phase; the BMK cells were arrested in the G2 and M phase, and the KHOS cells in the G1 phase. *Coriandrum sativum* produced important morphologic effects on chicken embryos. The use of *Coriandrum sativum* produces toxicological effects on the embryos only in high doses [94].

Coronilla scorpioides

The cytotoxic study of the cardiac glycosides which were isolated from *Coronilla scorpioides* and other plants, were examined by brine shrimp. Their lethal concentration 50 (LC_{50}) was 18.84ppm. The antitumor activity potato disk assays of the cardiac glycosides had shown good activity − 30.8% [95].

Coronilla varia

Antitumour activity of *Coronilla varia* aerial parts extracts was assessed with the potato disc method. *Coronilla varia* extracts caused 66.7% growth inhibition and significantly decreased the mean number of tumours to 11.92 ± 2.15 in comparison with the negative control (water) 35.75 ± 4.54 [96].

The cytotoxic effect of extracts from *Cornilla varia* was investigated on MCF7 cancer cell line by MTT assay. *Corohilla varia* ethanol extract inhibited the proliferation of MCF7 cell line in RPMI 1640 medium. 5mg/ml was the optimum concentration of extract of *Coronilla varia* which inhibited cell line growth [97-98].

An alcoholic extract of the seeds of *Coronilla varia* showed inhibitory activity against KB cells in culture and was fractionated through a series of partitions, column chromatography, and preparative layer chromatography to yield hyrcanoside, daphnoretin, scopoletin, and umbelliferone. Hyrcanoside, extract from the seeds of *Coronilla varia* showed inhibitory activity against KB cells in culture [96, 99].

Cotoneaster racemiflora

The methanolic extract of *Cotoneaster racemiflora* showed strong toxicity in the shrimp lethality test [100]. The methanolic extract was subsequently divided into n-hexane, ethylacetate, n-butanol, and water soluble extracts. Out of these extracts, ethylacetate soluble fraction showed strong toxicity in brine shrimp lethality test [101].

The mutagenic and antimutagenic activities of the water extract of *Cotoneaster racemiflora* (with doses of 10000 mg/plate and lower) were investigated. The Ames test was performed as a standard plate incorporation assay with *S. typhimurium* strains TA98 and TA100 in the presence or absence of S9 (metabolic activation enzymes) mix. The assays were performed using the standard plaque incorporation method. The strains were tested on the basis of associated genetic markers. For each tester strain, a specific positive control was always used to test the experimental flaws, if any. While 4-nitro-O-phenylenediamine (4- NPDA, 20 mg/plate) for TA 98 and sodium azide (SA, 5 mg/plate) for TA100 were used as positive controls without S9 mix. Spontaneous revertants were within normal values in all strains examined. The average revertant colony numbers in negative control were 40±8 for TA98 and 115±6 for TA100 with S9 and 22±1 and 118±6 without S9, respectively ($p>0.05$). While application of S9 in TA98 was increased revertant colony numbers, application of S9 in TA100 was decreased revertant colony numbers ($p>0.05$). On the contrary, the plates with the positive control mutagens (SA, 2-AF, 2-AA and 4-NPDA) showed significant increases relative to the spontaneous mutation rate in the two tested strains. Most of the results, increasing or decreasing relative to negative control group, were not statistically significant at ($p <0.05$) in examined strains. In order to establish a dose-response relationship, 5 different concentrations of cotoneaster extract were tested, and no induced revertants were observed along the dose range tested in either with or without S9 with two strains. According to the results, all tested doses of cotoneaster extract were not mutagenic for *S. typhimurium* TA98 and TA100 in the presence and absence of S9 mix. Cotoneaster extract exhibited moderate antimutagenic activities at doses of 10000, 5000 and 1000 mg (32%, 33%, and 31%, respectively) against 4-NPDA in the absence of S9 mix in *S. typhimurium* TA98. It was appeared that there was dose-response relationships between the tested concentrations ($p<0.05$). Induced inhibition ratios were observed along the dose range tested in the absence of S9 mix. On the other hand, 100 and 10 mg doses of the extract were found to be weak antimutagenic with a ratio of 19% and 20%, respectively. While, cotoneaster extracts showed strong antimutagenicity at doses of 10000 (50%) and 5000 mg (49%) against 2-AF. 1000, 100 and 10 mg doses of the extract exhibited moderate antimutagenic activities in the presence of S9 mix in TA98 strain with a ratio of 40%, 29%, and 25%, respectively ($p<0.05$). It was appeared that metabolic activation enzymes (S9 mix) induced the inhibition ratios of the extract compared to those of extracts in the absence of S9, and a dose response relationship was observed along the tested dose range. It was seen that cotoneaster extract manifested moderate

antimutagenicity at concentrations of 10000, 5000, 1000, and 100 mg (40%, 38%, 36%, and 27%, respectively) against SA, while 10 mg dose of extract was found to be weak antimutagenic with a ratio of 20% in the absence of S9 mix in TA100 strain. Except for 100 and 10 mg, all tested doses exhibited strong antimutagenic activity against 2-AA in the presence of metabolic activation system. The highest inhibition ratio (59%) was observed in 10000 mg/plate dose of the extract, followed by 1000 mg (58%) and 5000 mg (55%). Meanwhile, the extracts at concentrations of 100 and 10 mg were found to be weak antimutagenic capacities with S9 in TA 100 strain. Accordingly, it appeared that cotoneaster water extract had significant antimutagenic capacity in the presence of metabolic activation enzymes (S9) for TA98 at concentrations of 10000, 5000,1000, and 100 mg/plate against 2-AF, for TA100 strain at concentrations of 10000, 5000,1000 mg/plate against 2-AA [102].

Crocus sativus

Extract of saffron (Crocus sativis) inhibited colony formation and cellular DNA and RNA synthesis by HeLa cells *in vitro* [103-105].

The anti-proliferative effect of *Crocus sativus* extract and its major constituent, crocin, was studied on three colorectal cancer cell lines (HCT-116, SW-480, and HT-29). The cell growth inhibition effect was compared to that of non-small cell lung cancer (NSCLC) cells. In addition, *Crocus sativus* effect on non-cancer cells was also evaluated. Significant concentration-related inhibitory effects of the extract on all three colorectal cancer cell lines were observed ($p<0.01$). The proliferation was reduced most significantly in HCT-116 cells (to 45.5%) at 1 mg/ml and (to 6.8%) at 3 mg/ml. Crocin at 1 mM, significantly reduced HCT-116, SW-480, and HT-29 cell proliferation to 2.8%, 52%, and 16.8%, respectively ($p<0.01$). Since 3 mg/ml *Crocus sativus* extract contained approximately 0.6 mM crocin, the observed effects suggest that crocin was the major responsible constituent in the extract. Significant anti-proliferative effects were also observed in non-small cell lung cancer cells. However, *Crocus sativus* extract did not significantly affect the growth of non-cancer young adult mouse colon cells [106].

The potential of the ethanolic extract of saffron to induce antiproliferative and cytotoxic effects was tested in cultured carcinomic human alveolar basal epithelial cells in comparison with non-malignant (L929) cells. Both cells were cultured in Dulbecco's modified Eagle's medium and treated with the ethanolic extract of saffron at various concentrations for two consecutive days. The results showed that the ethanolic extract of saffron decreased cell viability in malignant cells in a concentration and time-dependent manner. The IC_{50} values against the lung cancer cell line were determined as 1500 and 565 µg/ml after 24 and 48 h, respectively. However, the extract at different concentrations could not significantly decrease the cell viability in L929 cells. Morphology of MCF7 cells treated with the ethanolic extract confirmed the MTT results [107].

In order to examine saffron's anti-proliferative and pro-apoptotic effects in colorectal cancer cells, two p53 isogenic HCT116 cell lines (HCT wildtype and HCT p53-/-) were treated with different doses of the drug and analyzed cell proliferation and apoptosis in a time-dependent manner. Saffron extract induced a p53-dependent pattern of cell cycle distribution with a full G2/M stop in HCT116 p53 wildtype cells. However, it induced a remarkable delay in S/G2 phase transit with entry into mitosis in HCT116 p53 -/- cells. The apoptotic Pre-G1 cell fraction as well as Annexin V staining and caspase 3 cleavage showed a more pronounced apoptosis induction in HCT116 p53 wildtype cells. Obviously, the significantly higher DNA-damage, reflected by ɣH2AX protein levels in cells lacking p53, was coped by up-regulation of autophagy. The saffron-induced LC3-II protein level was a remarkable indication of the accumulation of autophagosomes, a response to the cellular stress condition of drug treatment [108].

The cytotoxic and apoptotic effects of the ethanolic extract of saffron were evaluated on carcinomic human alveolar basal epithelial cells (A549), a commonly used cell culture system for *in vitro* studies on lung cancer. The cells were cultured in Dulbecco's modified Eagle's medium with 10% fetal bovine serum and treated with different concentrations of the ethanolic extract of saffron for two consecutive days. Cell viability was quantitated by the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide assay. Apoptotic cells were determined using annexin V-fluorescein isothiocyanate by flow cytometry. Saffron decreased the cell viability in the malignant cells as a concentration- and time-dependent manner. The IC_{50} values against the A549 cell lines were determined as 1,200 and 650 µg/ml after 24 and 48 h, respectively [109].

The cytotoxic effect of saffron extract was evaluated on HepG2 and HeLa cell lines. Malignant and non-malignant cells (L929) were cultured in DMEM medium and incubated with different concentrations of ethanolic saffron extract. Cell viability was quantitated by MTT assay. Apoptotic cells were determined using PI staining of DNA fragmentation by flow cytometry (sub-G1 peak). ROS was measured using DCF-DA by flow cytometry analysis. Saffron decreased cell viability in malignant cells in a concentration and time-dependent manner. The IC_{50} values against HeLa and HepG2 were determined as 800 and 950 microg/ml after 48 h, respectively. Saffron induced a sub-G1 peak in flow cytometry histogram of treated cells compared to control, which indicated that apoptotic cell death

was involved in saffron toxicity. This toxicity was also independent of ROS production [110].

The cytotoxic effect of aqueous extract of saffron was evaluated in human transitional cell carcinoma (TCC) and mouse non-neoplastic fibroblast cell lines. After 24 hours, morphological observations showed growth inhibitory effects at saffron extract concentrations higher than 200 microg/ml for mouse non-neoplastic fibroblast (L929) cells and at concentrations of 50 to 200 microg/ml for the TCC cells. These changes became more prominent after 48 hours. However, significant growth inhibitory effects of the extract were shown at concentrations of 400 and 800 microg/ml. Higher concentrations of saffron correlated inversely with cell population of both cell lines. Significant reduction of the survived cells was seen at concentrations of 400 and 2000 microg/ml for TCC and L929 cell lines, respectively. After 120 hours, decrease in the percentage of survived cells at higher concentrations of saffron extract was seen in both cell lines. At a concentration of 800 microg/ml, the survived L929 cells plummeted to less than 60% after 120 hours, while no TCC cells survived at this time. No L929 cells survived at 2000 microg/ml [111].

In order to compare the sensitivity of malignant and non-malignant cells to saffron, the effect of the extract was studied on macromolecular synthesis in three human cell lines: A549 cells (derived from a lung tumor), WI-38 cells (normal lung fibroblasts) and VA-13 cells (WI-38 cells transformed *in vitro* by SV40 tumor virus). It appeared that the malignant cells were more sensitive than the normal cells to the inhibitory effects of saffron on both DNA and RNA synthesis. There was no effect on protein synthesis in any of the cells [103].

The anticancer activity of saffron extract (dimethyl-crocetin) against a wide spectrum of murine tumors and human leukemia cell lines was studied. Dose-dependent cytotoxic effect to carcinoma, sarcoma and leukemia cells *in vitro* were noted. Saffron delayed ascites tumor growth and increased the life span of the treated mice compared to untreated controls by 45-120%. In addition, it delayed the onset of papilloma growth, decreased incidence of squamous cell carcinoma and soft tissue sarcoma in treated mice. It appeared that saffron (dimethyl-crocetin) disrupted DNA-protein interactions e.g. topoisomerases II, important for cellular DNA synthesis [104, 112].

The mutagenic, antimutagenic and cytotoxic effects of saffron and its main components were studied on the growth of different human malignant cells *in vitro*. Colony formation assay was used to determinate the cytotoxic activity of saffron extract and its components on human tumor cells *in vitro*. Mutagenicity and antimutagenicity assays were performed by the Ames method. Saffron was non-mutagenic, non-antimutagenic and non-comutagenic. Saffron extract itself and some of its ingredients displayed a dose-dependent inhibitory activity against different types of human malignant cells *in vitro*. HeLa cells were more susceptible to saffron than other tested cells [113].

The antiproliferative effects of saffron extract (SE) and its major constituent crocin was investigated on 5 different malignant and 2 nonmalignant prostate cancer cell lines. All cells were incubated with different concentrations of SE or crocin for 48 h. Cell cycle and apoptosis were also evaluated. In a time- and concentration-dependent manner, both SE and crocin reduced cell proliferation in all malignant cell lines with IC_{50} values ranging between 0.4 and 4 mg/ml for SE and 0.26 and 0.95 mM/ml for crocin. Nonmalignant cells were not affected. Flow cytometry profiles revealed that most cells were arrested at G0/G1 phase with a significant presence of apoptotic cells. Western blot analysis revealed that the expression of Bcl-2 was strikingly downregulated, whereas Bax was upregulated. Analysis of caspase activity indicated a caspase-dependent pathway with involvement of caspase-9 activation, suggesting an intrinsic pathway [114].

The beneficial effect of saffron (*Crocus sativus*) aqueous extract (SAE) on the 1-Methyl -3-nitro -1- nitrosoguanidine (MNNG)-induced gastric cancer was investigated in rats. MNNG was used to induce gastric cancer and then, different concentrations of SAE were administered to rats. After sacrificing, the stomach tissue was investigated by both pathologist and flow cytometry, and several biochemical parameters was determined in the plasma (or serum) and stomach of rats. Pathologic data indicated that the induction of cancer at different stages from hyperplasia to adenoma in rats, was inhibited by SAE administration; 20% of cancerous rats treated with higher doses of SAE was completely became normal at the end of experiment and there was no rat with adenoma in the SAE treated groups. In addition, the results of the flow cytometry/ propidium iodide staining showed that the apoptosis/proliferation ratio was increased in the SAE treated cancerous rats. Moreover, the significantly increased serum LDH and decreased plasma antioxidant activity due to cancer induction fell backwards after treatment of rats with SAE. But changes in the other parameters (Ca^{2+}), tyrosine kinase activity and carcino-embryonic antigen) were not significant [115].

The potential of saffron to induce cytotoxic and apoptotic effects in lung cancer cells (A549) and the caspase-dependent pathways activation of saffron-induced apoptosis against the A549 cells were investigated. A549 cells were incubated with different concentrations of saffron extract; then cell morphological changes, cell viability, and apoptosis

were determined. The proliferation of the A549 cells were decreased after treatment with saffron in a dose- and time-dependent manner. The percentage of apoptotic cells were increased with saffron concentrations. Saffron induced morphological changes, decreased percentage of viable cells, and induced apoptosis. Saffron induced apoptosis in the A549 cells and activate caspase pathways. The levels of caspases involved in saffron-induced apoptosis in the A549 cells indicating caspase-dependent pathway were induced by saffron. The anticancer activity of the aqueous extract of saffron could be attributed partly to its inhibition of the cell proliferation and induction of apoptosis in cancer cells through caspase-dependent pathways activation [116].

Antitumor activity of saffron (*Crocus sativus*) extract was studied against intraperitoneally transplanted sarcoma-180 (S-180), Ehrlich ascites carcinoma (EAC) and Dalton's lymphoma ascites (DLA) tumours in mice. Oral administration of 200 mg/kg bw of the extract increased the life span of S-180, EAC, DLA tumour bearing mice to 111.0%, 83.5% and 112.5%, respectively. The same extract was found to be cytotoxic to P38B, S-180, EAC and DLA tumour cells *in vitro*. Thymidine uptake studies indicated that the effect was mediated via inhibition of DNA synthesis [117].

Saffron treatments were given both before and after the induction of skin carcinogenesis. Standard histological examination of mice skin demonstrated that saffron ingestion inhibited the formation of skin papillomas and reduced their size also. The inhibition of skin carcinoma of early saffron treatment was attributed to the induction of cellular defense systems in mice [118].

To investigate the mechanism of saffron-induced cytotoxicity, the role of caspases and Bax protein in saffron induced apoptosis in MCF-7 cells, a commonly used cell culture system for *in vitro* studies on breast cancer, was investigated . Cells were incubated with different concentrations of saffron extract. Cell viability was quantitated by MTT assay. Apoptotic cells were determined using PI staining of DNA fragmentation by flow cytometry (sub-G1 peak). Role of caspase were studied using the pancaspase inhibitor. Bax protein expression was analysed by western blotting. Saffron extract (200-2000 g/ml) decreased cell viability in MCF-7 cells as a concentration- and time dependent manner with an IC_{50} of 400 ± 18.5 microg/ml after 48 h. Analysis of DNA fragmentation by flow cytometry showed apoptotic cell death in MCF-7 cell treated with saffron extract. Saffron-induced apoptosis could be inhibited by pan-caspase inhibitors, indicating caspase-dependent pathway was induced by saffron in MCF-7 cells. Bax protein expression was also increased in saffron-treated cells [119].

MTT assay was performed to detect the inhibitory action of crocin on the proliferation of ovarian cancer HO-8910 cells. Flow cytometry was used to test the cell cycle distribution and apoptosis rate of ovarian cancer HO-8910 cells. Western blot analysis was utilized to measure the levels of apoptotic proteins such as p53, Fas/APO-1, and Caspase-3. MTT analysis revealed that crocin significantly inhibited the growth of HO-8910 cells. Additionally, flow cytometry illustrated that crocin raised the proportion of HO-8910 cells in the G0/G1 phase and increased their apoptosis rate. Furthermore, Western blot analysis revealed that crocin up-regulated the expression of p53, Fas/APO-1, and Caspase-3. Accordingly, crocin significantly inhibited the growth of HO-8910 cells and arrest them in the G0/G1 phase. Crocin also promoted ovarian cancer HO-8910 cell apoptosis, most likely by increasing p53 and Fas/APO-1 expression, and activating the apoptotic pathway regulated by Caspase-3 [120].

Cuminum cyminum

At a concentration of 0.1 microl/ml, oil of *Cuminum cyminum* destructed Hela cells by 79% [121]. Cancer chemopreventive potentials of different doses of a cumin seed-mixed diet were evaluated against benzo(α)pyrene [B(α)P]-induced forestomach tumorigenesis and 3-methylcholanthrene (MCA)-induced uterine cervix tumorigenesis. Results showed a significant inhibition of stomach tumor burden by cumin. Tumor burden was 7.33 ± 2.10 in the B(α)P-treated control group, whereas it reduced to 3.10 ± 0.57 ($p<0.001$) by a 2.5% dose and 3.11 ± 0.60 ($p<0.001$) by a 5% dose of cumin seeds. Cervical carcinoma incidence, compared with the MCA-treated control group (66.67%), reduced to 27.27% ($p<0.05$) by a diet of 5% cumin seeds and to 12.50% ($p<0.05$) by a diet of 7.5% cumin seeds. The effect of 2.5 and 5% cumin seed-mixed diets was also examined on carcinogen/xenobiotic metabolizing phase I and phase II enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase (LDH), and lipid peroxidation in the liver of Swiss albino mice. Levels of cytochrome P-450 (cyt P-450) and cytochrome b5 (cyt b5) were significantly augmented ($p<0.05$) by the 2.5% dose of cumin seed diet. The levels of cyt P-450 reductase and cyt b5 reductase were increased (from $p<0.05$ to $p<0.01$) by both doses of cumin. Among the phase II enzymes, glutathione S-transferase specific activity increased ($p<0.005$) by the 5% dose, whereas that of DT-diaphorase increased significantly ($p<0.05$) by both doses used (2.5 and 5%). In the antioxidant system, significant elevation of the specific activities of superoxide dismutase ($p<0.01$) and catalase ($p<0.05$) was observed with the 5% dose of cumin. The activities of glutathione peroxidase and glutathione reductase remained unaltered by both doses of cumin. The level of reduced glutathione measured as nonprotein sulfhydryl content was elevated (from $p<0.05$ to

p<0.01) by both doses of cumin. Lipid peroxidation measured as formation of MDA production showed significant inhibition (p<0.05 to p<0.01) by both doses of cumin. LDH activity remained unaltered by both doses of cumin. The results were strongly suggested the cancer chemopreventive potentials of cumin seed and could be attributed to its ability to modulate carcinogen metabolism [122-123].

Cumin seeds also augmented the levels of carcinogen/xenobiotic metabolizing phase I enzymes, cytochrome P-450 (cyt P-450) and cytochrome b5 (cyt b5), the levels of cyt P-450 reductase and cyt b5 reductase, and the phase II enzymes, such as glutathione-*S*-transferase and DT-diaphorase. These results, in addition to antioxidant effects, strongly suggest the cancer chemopreventive potential of cumin seed, which attributed to its ability to modulate carcinogen metabolism. Cumin seeds also decreased significantly the incidence of both B[*a*]P-induced neoplasia and 3'MeDAB induced hepatomas in Wistar rats [124-125].

Cupressus sempervirens

Antiproliferative activity of *Cupressus sempervirens* ssp. pyramidalis essential oils was tested on amelanotic melanoma C32 cells and on renal cell adenocarcinoma cells, using the sulphorhodamine B assay. *Cupressus sempervirens* ssp. pyramidalis leaf oil exerted the highest cytotoxic activity with an IC_{50} value of 104.90 microg/ml against C32 [126-127].

The ethanolic fruit extract of *Cupressus sempervirens* (CS), inhibited proliferation of human BPH-stromal cells and the activity was localized to its chloroform-soluble, diterpene-rich fraction. Eight major diterpenes isolated from this fraction exhibited moderate to potent activity and the most active diterpene (labda-8(17),12,14-trien-19-oic acid) exhibited an IC_{50} of 37.5 µM (antiproliferative activity against human BPH-stromal cells). It significantly inhibited activation (phosphorylation) of Stat-3 in BPH-stromal cells and prevented transactivation of androgen sensitive KLK3/PSA and TMPRSS2 genes in LNCaP cells. Labda-8(17),12,14-trien-19-oic acid-rich CS fraction prevented prostatic hyperplasia in rat model and caused TUNEL labeling of stromal cells with lower expressions of IGF-I, TGF-ß and PCNA, and bcl-2/bax ratio. Human BPH tissues exhibited precise lowering of stromal component after incubation in labda-8(17),12,14-trien-19-oic acid, ex vivo [128]. Taxodione isolated from *Cupressus sempervirens* cones (fruits) showed potent cytotoxic activity [129].

The antihepatotoxic and antimutagenic activities of hydroethanolic extract of *Cupressus sempervirens* was studied in experimental rat model of paracetamol-induced liver toxicity in rats, comparing with silymarin as reference agent. The results revealed that the pre-treatment with either hydroethanolic extract (250 mg/kg/day, po) or silymarin (50 mg/kg/day, po) for 4 weeks has good safety profile in normal rats and exhibited a marked hepatoprotection against single toxic dose of paracetamol (4 g/.kg bw, po) as proved from marked decline in the DNA fragmentations and inhibition in the percentage of chromosomal aberrations in bone marrow cells [130].

Cuscuta planiflora

The minimum inhibitory concentration and cytotoxic activities of the methanolic extract were carried out using broth dilution assay and brine shrimp lethality bioassay. The methanol extract showed lethality against brine shrimp nauplii (LC_{50} was 36.31 µg/ml and LC_{90} was 83.18 µg/ml) [131].

The cytotoxic effects of chloroform and hydroalcoholic extracts of the plant was evaluated on human breast carcinoma cell line (MDA-MB-468), human colorectal adenocarcinoma cell line (HT29) and human uterine cervical carcinoma (Hela). Using maceration method, different extracts of aerial parts of the plant were prepared. Extraction was performed using chloroform and ethanol/water (70/30). The results showed that the hydroalcoholic extracts of *C.* epithymum only significant decreased the viability of MDA-MB-468 cells (IC_{50} = 340 µg/ml)[(15)]. The *in vitro* antioxidant potential of methanolic extract was evaluated by DPPH, hydroxyl and superoxide radical scavenging assays. The radical scavenging activity was found to be concentration dependent and increased with increasing concentrations and produced maximum scavenging activity at a dose of 360µg [132].

Cydonia oblonga

Moreover the cytotoxic effects of lipophilic quince wax extract (QWE) and an aqueous fermented one (QAFE) against human HepG2, A549, and HeLa cell lines were evaluated. The two preparations exerted a different effect on the proliferation of the three tested cell lines. Noteworthy, QAFE was almost always more active than QWE but, sometimes, its effects seemed to be strongly dependent on exposure time [134-135].

The antiproliferative properties of quince (*Cydonia oblonga* Miller) leaf and fruit (pulp, peel, and seed) was investigated against human kidney and colon cancer cells. Quince leaf and fruit extracts exhibited distinctive antiproliferative activities. The extracts from quince leaf showed concentration-dependent growth inhibitory activity toward human colon cancer cells (IC_{50} = 239.7 ±43.2 microg/ml), while no effect was observed in renal adenocarcinoma cells. The seed extracts exhibited no effect on colon cancer cell growth, whereas a strong antiproliferative efficiency against renal cancer cells was observed for the highest concentration assayed (500 microg/ml) [136].

Cynodon dactylon

Anticancer activity of *Cynodon dactylon extract* was evaluated in Swiss albino mice after inoculated with Ehrlich ascites carcinoma (EAC) cells. The extract were administered orally as three doses, 100, 200 and 400 mg/kg bw for ten consecutive days. Anticancer activity of the *Cynodon dactylon* extracts was evaluated by mice life span, which increased based on mean survival time (MST) [137].

The anticancer activity of methanolic extracts of leaves of *Cynodon dactylon* was studied in ascitic lymphoma (ELA) in Swiss albino mice. The tumor was induced in mice by intraperitoneal injection of EAC (1 × 10^6cells/mouse). The result revealed that methanolic extract of *Cynodon dactylon* possessed significant antitumor and hepatoprotective effect [138].

The antiproliferative, apoptotic and antioxidant potentials of *Cynodon dactylon* were investigated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, nitric oxide radical scavenging activity (NO^-) and MTT assay on four cancer cell lines (COLO 320 DM, MCH-7, AGS, A549) and a normal cell line (VERO). *In vivo* chemopreventive property of the plant extract was studied in DMH-induced colon carcinogenesis. The methanolic extract of *Cynodon dactylon* was found to be antiproliferative and antioxidative at lower concentrations and induced apoptotic cell death in COLO 320 DM cells. Treatment with methanolic extract of *Cynodon dactylon* also increased the levels of antioxidant enzymes and reduced the number of dysplastic crypts in DMH-induced colon of albino rats [139].

Cyperus rotuntdus

Brine shrimp bioassay was used to investigate the toxic action of *Cyperus routunds* ethanolic extract in comparison to etoposide standard. *Cyperus routunds* ethanolic extract showed non toxic significant effects at 10, 100, 1000 µg/ml concentrations [140].

Different concentrations of oil of *Cyperus rotuntdus* were prepared using DMSO (100, 50 and 25 µg/ml) and screened *in vitro* using Ehrlich ascites carcinoma cells (EAC) 25 x 10^6 tumor cells per ml suspended in phosphate buffer saline. 0.1 ml of the prepared oils were added to the suspension and kept at 37°C for two hours. Trypan blue dye exclusion test was carried out to calculate the percentage of non viable cells. Oils were also tested for cytotoxic activity against the human tumor cell lines (brain tumor cell line) and Hela (cervix carcinoma cell line) at concentration between 1-10 µg/ml using SRB assay. Ehrlich ascites carcinoma cells *in vitro* showed that the oil exerted significant antitumour activity. *Cyperus rotuntdus* essential oils showed 100% inhibition of tumour cells at all concentrations tested (25, 50 and 100 µg/ml). But when the oils tested against the human tumour cell lines (U 251 and Hela) they showed negative results [141].

The mutagenic and antimutagenic effects of aqueous, total oligomers flavonoıds (TOF), ethyl acetate and methanol extracts from aerial parts of *Cyperus rotundus* were assayed by *Salmonella typhimurium* assay system. The different extracts showed no mutagenicity when tested with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1538, either with or without the S9 mix. On the other hand, the results showed that all extracts possessed antimutagenic activity against aflatoxin B1 (AFB1) in TA100 and TA98 assay system, and against sodium azide in TA100 and TA1535 assay system. TOF, ethyl acetate and methanol extracts exhibited the highest inhibition level of the Ames response induced by the indirect mutagen AFB1. Furthermore, ethyl acetate and methanol extracts exhibited the highest level of protection toward the direct mutagen, sodium azide, induced response. In addition to antimutagenic activity, these extracts showed an important free radical scavenging activity toward the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical with IC_{50} value of 15, 14 and 20 g/ml, respectively [142].

The n-hexane fraction of an ethanol extract of *Cyperus rotundus* rhizomes was found to inhibit cell growth in ovarian cancer (A2780, SKOV3 and OVCAR3) and endometrial cancer (Hec1A and Ishikawa) cells. Among the thirteen sesquiterpenes isolated from the n-hexane fraction, some patchoulane-type compounds, but not eudesmane-type compounds, showed moderate cytotoxic activity in human ovarian cancer cells. In particular, the patchoulane sesquiterpene 6-acetoxy cyperene had the most potent cytotoxicity. Propidium iodide/Annexin V staining and terminal deoxynucleotidyl transferase dUTP (deoxynucleotide triphosphate) nick end labeling assay were performed to study cell cycle progression and apoptosis. 6-acetoxy cyperene induced apoptosis, as shown by the accumulation of sub-G1 and apoptotic cells. Furthermore, treatment with 6-acetoxy cyperene stimulated the activation of caspase-3, caspase-8 and caspase-9 and poly (ADP-ribose) polymerase in a dose-dependent manner. Pretreatment with caspase inhibitors neutralized the pro-apoptotic activity of 6-acetoxy cyperene [143].

To investigated the mode of anticancer effect of *Cyperus rotundus*, the pro-apoptotic effects of *Cyperus rotundus* rhizomes was studied in a human breast carcinoma MDA-MB-231 cell model. Treatment of MDA-MB-231 cells with an ethanol extract (EECR) and a methanol extract of *Cyperus rotundus* rhizomes (MECR), but not a water extract of *Cyperus rotundus* rhizomes, resulted in potent antiproliferative activity. The activity of the EECR was higher than that of the MECR and was associated with the induction of apoptosis. The induction of apoptosis by the EECR was

associated with upregulation of death receptor 4 (DR4), DR5 and pro-apoptotic Bax, as well as down-regulation of anti-apoptotic survivin and Bcl-2. EECR treatment also down-regulated Bid expression and activated caspase-8 and -9, the respective initiator caspases of the extrinsic and intrinsic apoptotic pathways. The increase in mitochondrial membrane depolarization was correlated with activation of effector caspase-3 and cleavage of poly (ADP-ribose) polymerase, a vital substrate of activated caspase-3. Blockage of caspase activation by pretreatment with a pan-caspase inhibitor consistently inhibited apoptosis and abrogated growth inhibition in EECR-treated MDA-MB-231 cells. Although reactive oxygen species (ROS) increased following treatment with the EECR, inhibiting ROS with a ROS scavenger did not attenuate EECR-induced apoptosis. Furthermore, inhibitors of phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activatedprotein kinase (MAPK) signaling pathways failed to reverse EECR-induced apoptosis and growth inhibition. These results revealed that the pro-apoptotic activity of the EECR may be regulated by a caspase-dependent cascade through activation of both intrinsic and extrinsic signaling pathways that was not associated with ROS generation or the PI3K/Akt and MAPK pathways [144].

Conclusion:

This review was designed as a second part of a previously published review to cover the medicinal plants with anticancer activities.

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