Research Article

Anticancer screening of medicinal plants growing in the Northern region of Saudi Arabia

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Abstract

Background: Desert condition in which plants grow and survive and altering biochemical properties of plants are known to increase the secondary metabolite induction in a variety of medicinal plants. Cancer is a terrible disease and fighting it is of abundant significance to public health. **Aims and Objective:** To search for new compounds with cytotoxic activity isolated from natural source. In this article, we studied the anticancer properties of three plants (*Farsetia aegyptia, Lactuca serriola,* and *Santolina chamaecyparissus)* growing under desert condition of the Northern Region of Saudi Arabia. **Materials and Methods:** Hydromethanol extracts of the plants were investigated *in vitro* against four different cell lines. Anticancer activities were assayed with standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric procedure against A549, HCT116, Hep G2, and MCF7 cell lines. **Result** : From the analysis, it was found that *Lactuca* and *Santolina* sp. showed 71% and 66% cytotoxic activity against Hep G2 and inhibited cell line at 100 μg/mL tested dose; *F. aegyptia* showed 74% cytotoxic activity against A549 and inhibited cell line at 100 μg/mL. But, the three plants did not show much anticancer activity against HCT116 cancer cell line. Methanol extracts were subjected to gas chromatography-mass spectrophotometry (GC-MS) in order to evaluate the chemical constituents of these plants. **Conclusion:** It can be concluded that, in *F. aegyptia, L. serriola,* and *S. chamaecyparissus,* which grow undrer dry desert condition of Northern Borders Region, the stress condition makes the plant accumulate active compounds that possess anticancer properties against nonsmall cell lung adenocarcinoma and human hepatocellular liver carcinoma.

KEY WORDS: Anticancer; *Farsetia aegyptia*; *Lactuca serriola*; *S antolina chamaecyparissus*

Introduction

Plants have long been used as remedies, and botanical literature has described the use of plant extracts. Cancer is a terrible disease and battling it is of abundant significance to public health. There is a requirement to quest for new compounds with cytotoxic activity. This is because cytotoxicity has made the treatment of cancer with the available anticancer drugs unsatisfactory. Phytochemical examination has made swift advancement, and herbal products are becoming popular as sources of possible anticancer compounds.[1]

The 5-year survival rate for lung cancer (16.3%) is lesser than several other foremost cancer spots, such as the colon (65.2%), breast (90.0%), and prostate (99.9%). The 5-year survival rate for lung cancer is detected in 52.6% cases when the disease is still localized (within the lungs). However, only 15% of lung cancer cases are detected at an initial phase. For distant tumors (i.e., those that have spread to other organs), the 5-year survival rate is only 3.5%. A great number of people with lung cancer die within 1 year after being diagnosed.[2]

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Lactuca serriola is a roadside weed plant with two or three inches lobed or pinnatifid leaves that clasp the stem. The plant is between two and four feet in height. The plant starts out with a single stem, but as it flowers it sends out additional stems off the main stem. The flowers are dandelion-like, yellow, and after blooming has seeds that float when the wind blows, similar to dandelion. In the west, it is found below 7,500 feet and more common from 4,000 to 6,000 feet. It is also found in waste places, walls, and occasionally on more or less stable dunes; it is a biennial plant that grows to 1.5 m. It flowers from July to September, and its seeds get ripe from August to September.[3] The plant is used for multiple purposes in traditional medicines, such as sedative, hypnotic, expectorant, cough suppressant, purgative, demulcent, diuretic, antiseptic, vasorelaxant, and antispasmodic and hence used to manage bronchitis, asthma, pertussis, gastrointestinal, and other various ailments.[4]) The alkaloid and lactucin isolated from the seeds exhibited antipyretic activity, and a triterpenoid saponin isolated from the stem had antibacterial activity.[5,6] The pharmacological investigations of the plant revealed its analgesic, anti-inflammatory,[7] and antioxidant activities as a result of the high total phenolic contents, which have efficient free radical scavenging potential like quercetin.[8,9]

Buolos mentions that the plant, *Santolina chamaecyparissus* is used in North Africa as a remedy against intestinal worms and as a spasmolyticum, among other uses.[10]

The pharmacological activity of several extracts together with the lyophilized infusion of *S. chamaecyparissus* subsp. *squarrosa* was investigated. The lethal dose 50% (LD_{50}) effect on animal metabolism, mechanical and thermic analgesia, and spontaneous, anti-inflammatory and antiulcer activities have been determined. Studies on isolated organs (rat's duodenum and uterus) were also carried out. The hexanic and chloroformic extracts were potent antagonists of the thermic analgesia test; the former extract was also active in the mechanical analgesia test. The chloroform extract and, to a lesser extent, the ethyl acetate extract and lyophilized infusion demonstrated notewthy activity as anti-inflammatory agents. No extract produced an ulcerogenic effect. Hexanic extract showed the highest inhibitory effect against each induced contraction of rat's duodenum, and the ethyl acetate extract of oxytocin induced the contraction of rat's uterus.[11]

Farsetia aegyptia is a medicinal plant that belongs to the family Cruciferae and is used by the Bedouins as an antidiabetic and antispasmodic medicines. It is used to alleviate rheumatic pains and is taken as a cooling medication after pounding.[12]

A new kaempferol trioside, kaempferol-3-O-(2″-α-L-arabinopyranoside)-α-L-rhamnopyranoside-7-*O*-α-L-rhamnopyranoside, along with eight known flavonoid compounds was isolated from the methanolic extract of *F. aegyptia* Turra growing in Egypt.[13]

The ethanol (EtOH) extract of the aerial parts of the Egyptian medicinal plant, *F. aegyptia* (Forssk.) Boiss. was investigated *in vitro* for cytotoxicity against HCT116, Hep G2, and MCF7 cell lines. It resulted in IC_{50} = 4.65, 12.60, and 17.90 μg/mL, respectively. Doxorubicin (+ ve control) showed *in vitro* cytotoxic activity with IC_{50} = 3.64, 4.57, and 2.97 μg/mL, respectively, The phenolic-rich fraction of the EtOH extract was subjected to further fractionation and led to the isolation of new flavonoid (kaempferol 7,8-diglucoside), which had high cytotoxicity against Hela and MCF7 cell lines.[14]

Although there are many studies on these plants (*F. aegyptia, L. serriola,* and *S. chamaecyparissus*), there are no researches on the high value and antitumor activity of these plants, which are distributed in the Northern Region of Saudi Arabia. Thus, the aim of this work is to evaluate the importance of these plants and the accumulation of active compounds, especially terpene and the role of these compounds in anticancer activity against different cell lines. This study was undertaken to explore the anticancer effects of these plants.

Materials and Methods

Plant

The aerial parts of all the plants, *F. aegyptia, S. chamaecyparissus,* and *L. serriola* were collected from Arar-Rafha Road, North Region, Saudi Arabia, during spring season. Arar is a famous region of Northern Border Region of Saudi Arabia. It is a fertile land for natural vegetation and herbs, which grow wildly in locations such as Awaisi and Bednah Valley. The plant samples were identified by Dr. Ahmed Kamal, Professor of Plant Taxonomy, Botany Department, Northern Border University. The plant materials were air-dried in the shade and ground to a fine powder in order to carry out phytochemical and biological investigations.

Preparation of Plant Extracts

The dried (100 g) powder of each plant material was filled separately in the thimble and extracted with 80% methanol using a Soxhlet extractor. Later, it was distilled and evaporated. The plant powder was placed in a cellulose thimble in an extraction chamber and placed on top of a collecting flask beneath a reflux condenser. Five hundred milliliter methanol (80%) was added to the flask for each plant, and the set up was heated under reflux. When a certain level of condensed solvent had been accumulated in the thimble, it was siphoned into the flask beneath. Nearly 10 cycles were repeated for 72 h for all the plant species. After extraction, the solvent was removed by rotary evaporator under reduced pressure at temperature not exceeding 40°C. About 2.5 g, 3.2 g, and 1.5 g plant extracts were obtained from (*F. aegyptia, L. serriola,* and *S. chamaecyparissus*) respectively, which were used for gas chromatography analysis and cytotoxic assay.

Analysis

The extracts and active fractions were analyzed by gas chromatography-mass spectrophotometry (GC-MS), as reported by Adams.[15] GC-MS analyses were carried out on a Shimadzu GC-MS-QP2010 gas chromatography-mass spectrometer equipped with capillary column DB-5-ms Agilent (30 m × 0.25 mm; film thickness, 0.25 μm) under the following conditions. Helium was used as a carrier gas at

a pressure of 81.90 KPa, with a flow of 1.33 mL/min; the temperature in the injector was 250°C. The temperature of the oven progressed from 60°C to 240°C and then 3°C min^{-1}. The ionization mode used was the electronic impact at 70 eV. Later, under the same experimental conditions, each fraction was coinjected with a homologous series of linear hydrocarbons. This was done to accomplish the calculations of the retention index (RI) of each constituent of the samples, using the equation of Van Den Dool and Kratz. The compounds were identified by analysis and comparing the mass spectra with a database of Wiley 7 libraries and comparing RI with those of the literature.[16–19]

Cytotoxic Assay Procedures:

- ***Human tumor cell lines:*** Authentic cultures of HCT116 (human colon carcinoma), A549 (nonsmall cell lung adenocarcinoma), Hep G2 (Human hepatocellular liver carcinoma), and MCF7 (human breast carcinoma) cells were obtained in frozen state under liquid nitrogen (-180°C) from the American Type Culture Collection. The tumor cell lines were maintained by serial subculturing in the National Cancer Institute, Cairo, Egypt.
- ***Culture media:*** HCT116, Hep G2, and MCF7 cells were suspended in RPMI-1640 medium supplemented with 10% fetal calf serum, 1% antibiotic antimycotic mixture (10.000 U/mL K-penicillin, 10.000 μg/mL streptomycin sulfate, and 25 μg/mL amphotericin B) and 1% L-glutamine (all purchased from Lonza, Belgium).
- ***Assay method for cytotoxic activity:*** The cytotoxicity against A549, HCT116, Hep G2, and MCF7 cells was tested in the National Cancer Institute based on the SRB (Sulforhodamine B) assay using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method given by Skehan et al. Adriamycin® (Doxorubicin, 10 mg vials; Pharmacia, Sweden) was used as the reference drug. Briefly, cells were seeded in 96-multiwell plates at densities of 5 × 10 cells/well in a fresh media. They were incubated under normal growth condition for approximately 24 h before treating with the tested sample to allow the cells to attach to the wall of the plate. Then, 200 μL aliquots of serial dilution with DMSO (100%) of alcoholic extract and isolated compound (25, 50, 100 μg/mL) were added. The plates were incubated for 24, 48, and 72 h at 37°C in a humidified incubator containing 5% CO_2. Control cells were treated with vehicle alone. Four wells were prepared for each individual dose. At 24-, 48-, and 72 h-treatment, cells were fixed, washed, and stained with SRB stain (Sigma USA). Color intensity was measured in an ELISA reader spectrophotometer (Tecan Group Ltd., Sunrise Germany).

Statistical Analysis

All values were expressed as the percentage mean of inhibition cells of the four replicates for each treatment. Data were subjected to SPSS software (version 8.0), and $P < 0.05$ was regarded as significant.

Result

Screening of hydromethanolic extracts of *F. aegyptia, L. serriola,* and *S. chamaecyparissus* resulted in good anticancer activities against Hep G2 and A549, but all the extracts were not active against MCF7 and HCT116 cell lines. The inhibitory properties of these extracts are compared with reference drug (doxorubicin). The crude extract of *F. agyeptia* (100 and 50 μg/mL) showed high cytotoxicity activities against A549 (73.73 and 47.60%, respectively) and good cytotoxicity against Hep G2 (47.03% and 26.10%) [Table 1].

L. serriola, flower extract (LC2) showed high cytotoxicity against Hep G2 (71.36% and 47.90%) at 100 and 50 μg/mL concentration and good cytotoxicity against A549 (33.93% and 11.1%). *L. serriola* arial part (LC1) showed normal cytotoxicity against A549 (28.13% and 13%) at 100 and 50 μg/mL concentrations and good cytotoxicity against Hep G2 (61.633% and 12.00%) [Table 1]. *Santolina* extract (100 μg/mL) showed high cytotoxicity against Hep G2 (66.7%) and high cytotoxicity against A549 (62.1% and 34.6%) at 100 and 50 μg/mL, respectively [Table 1].

Anticancer activities of three plants were studied, and all showed high cytotoxic potential. Thus, these extracts are considered as promising. Further work is in progress to evaluate the chemical constituents present in these plants. We can mention here that some compounds were investigated and analyzed by GC-MS, and some others were identified from the methanolic extract of *Lactuca* and *Santolina*. Methanol extract of *F. aegyptia* and other subfractions from LC and SC were analyzed by GC-MS [Table 2]. The dominant components in the total compounds of methanolic extract of *F. aegyptia* were piperidin-2-imino, 2 pyrrolidinone and 3-O-acetyl-6-methoxy-cycloartenol. This method has already been adopted for many species.

Gas chromatography-mass spectroscopy is designed to separate volatile compounds from a complex mixture. In this technique, vaporization temperature specific to each compound is used to separate them from a solution. This is done by passing the sample through a heated column, where it is partitioned between an inert gas under pressure, and a thin layer of nonvolatile liquid is coated on an inert support inside the column.[20]

Discussion

The analysis of plant extracts using GC-MS and other methods revealed the presence of triterpene compounds, urs-12-ene, olean-12-ene-acetoxy, betulin, ursolic acid, germanicol, and lupane acetate [Figure 1]. Other heterocyclic compounds, piperidin-2- imine and pyrrolidinone-1,2-hydroxyethyl were detected. The major compounds in all three plants detected were triterpene. So, we can compare the antitumor activities of *Lactuca* and *Santolina* and triterpene activity. There are many references on the antitumor activity of terpenoid compounds against the different cell lines. The antiproliferative activity of

Table 1: Cytotoxic activity of methanol extracts against cultured different cell

Cell line/plant extract	Concentrations				
	100 µg/mL	50 µg/mL	25 µg/mL	12.5 µg/mL	6.25 µg/mL
Hep G2					
LCf	33.9	11.1	0	0	0
LC	71.3	47.9	11.9	3.7	3.1
SC	66.7	47.1	19.7	8.2	9.1
FA	47.0	26.1	13.4	2.1	2.3
A549					
LCf	61.63	12.03	3	0	0
LC1	28.13	13.76667	0	0	0
SC	62.1	34.46667	10.5	3.1	2.1
FA	73.73	47.6	22.1	5.2	4.9
HCT116					
LC	0	0	0	0	0
LCf	0	0	0	0	0
SC	23.33	0	0	0	0
FA	32.6	0	0	0	0
MCF7					
LCf	-52.66	0	0	0	0
LC	-122.66	-10.66	0	0	0
SC	-29.33	0	0	0	0
FA	-30.10	0	0	0	0

LC: Arial part of *Lactuca serriola*, LCf: flower, SC: *Santolina*, FA: *Farsetia aegyptia.*

Table 2: GCMS of plant extracts and fractions

Lactuca serriola	*Farsetia aegyptia*	*Santolina chamaecyparissus*
Lupan-3-ol-acetate	Coumaran	Vanillin
Urs-12-ene	Vanillin	Farnesol
Sclareol	–	Humuladienone
d-Orandrostane	Quinic acid	Lanosterin
4,4-Dimethylandrost-1-en-3-one	2-Pyrrolidinone	Gamm-sitosterol
1,2-Epoxycholestan-3-one	piperidin-2-imine	Cyclolaudenol
–	Pyrrolidinone, 1,2-hydroxyethyl	Urs-12-en
Chrysene	Chrysene, 1,2,3,4,4a,4b,5,6,10,10a, 10b,11-dodecahydro	3-O-Acetyl-delta-24-cycloartenol
–	3-O-Acetyl-6-methoxy-cycloartenol	9,19-Cyclolanost-24-en-3-oil, acetate, (3beta)
9,19-Cyclolanost-23-ene-3,25-diol, 3-acetate, (3beta,23E)	–	9,19-Cyclolanost-23-ene-3,25-diol, 3-acetate, (3.beta,23E)

ursolic acid has been reported in a wide variety of cancer cell lines.[21] Triterpene compounds, especially oleanen and ursolic acid inhibit the growth of numerous tumor cell lines including colon, breast, liver, prostate, and leukemia. They aslo inhibit the expression and activity of cyclooxygenases. Among the triterpenoids, ursolic acid is the most studied. Ursolic acid has been found to induce apoptosis in tumor cells by activation of caspases and modulation of other pathways involved in cell proliferation and migration. These compounds may therefore play a complementary or synergistic role together with other constituents in chemoprevention.[22]

Oleanolic acid (3β-hydroxy-olea-12-en-28-oic acid) and its isomer, ursolic acid (3β-hydroxy-urs-12-en-28-oic acid) are triterpenoid compounds which exist widely in nature in free acid. Ursolic acid has been reported to be effective at different stages for tumor prevention and inhibition: it inhibits tumor genesis,[23] differentiation,[24] and promotion.[25] While *F. aegyptia* besides triterpene contains other alkaloid and heterocyclic compounds, and it has high cytotoxcity against A549. So, alkaloid compound may be responsible for these activities or two alkaloids and terpene. Many studies have proved this immune modulatory activity and induction apoptosis of alkaloids. Triterpenes extracted

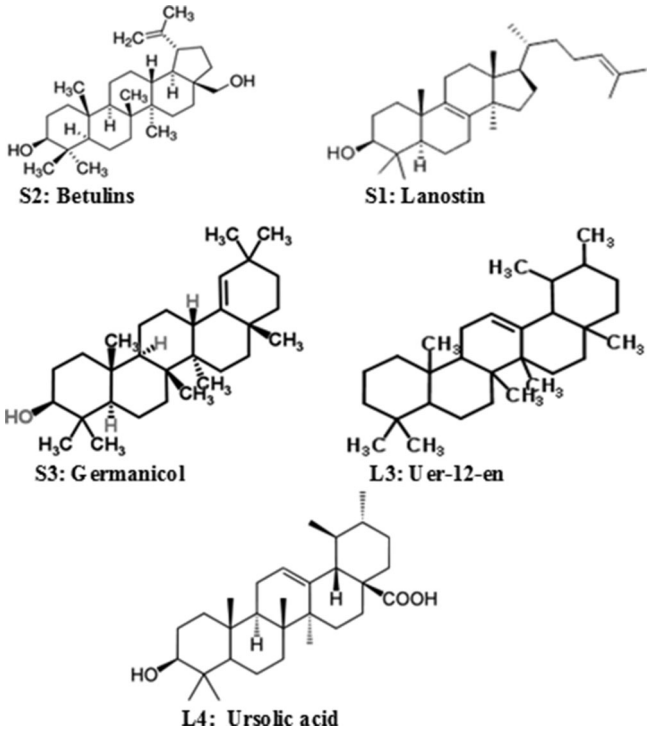

Figure 1: Structure of identified triterpenoid compounds.

from *Alstonia scholaris* leaves were evaluated for the first time in tumor-bearing C57BL/6 mice and in A549 cells. Alkaloids and triterpenes synergistically inhibited tumor growth *in vivo* and proliferated cell *in vitro* by modulating immune stimulation and inducing apoptosis. The underlying mechanism might be associated with the promotion of cytokine production (IL-6 and TNF-α), induction of cell cycle arrest in the S phase, and progression of apoptotic cell death by down-regulation of Bcl-2 expression and increased caspase-8 cleavage.[26]

Our data indicated that the extracts of the three plants might be beneficial for the prevention and treatment of lung and liver cancer. Further studies on bioavailability and activity of the compound are needed.

Conclusion

From the analysis above, it can be concluded that, in *F. aegyptia, L. serriola,* and *Santolina,* which grow undrer dry desert condition of Northern Border Region, the stress condition makes the plant accumulate active compounds which possess anticancer properties against nonsmall cell lung adenocarcinoma and human hepatocellular liver carcinoma. The experimental analysis of these plants would definitely reveal the important chemical constituents terpene compounds responsible for cancer cell death. Polar components (e.g. glucosides) have not received much attention in chemical and biological evaluations in this study. This could be an important field for future phytochemical investigations of these plants.

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