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CYTOTOXIC AND ANTIMICROBIAL EFFECTS OF SELECTED EGYPTIAN ASTERACEAE SPECIES AS WELL AS GC-MS METABOLITE PROFILING OF *SENECIO CRUENTUS* LIPOPHILIC FRACTION

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The ethanol extracts of three ornamental Asteraceae species; Senecio cruentus DC., Dimorphotheca ecklonis DC. and Arctotis aurantiaca L. were studied for their cytotoxicity against Panc1 and antimicrobial activities against selected microbial strains. Lipophilic fraction of S. cruentus showed the most active cytotoxic extract (IC_{50} = 7.63±0.46 µg/ml) and was subjected to metabolite profiling by using GC-MS. Seventeen compounds of different categories were identified. The detection of phytol as well as unsaturated fatty acids/esters; cis-vaccenic acid (C18:1), glycidyl oleate (C21:1), 9,12-Octadecadienoic acid (Z,Z)- methyl ester (C19:2), 9,12,15-(Z,Z,Z)- Octadecatrienoic acid, 2,3-dihydroxypropyl ester, (C21:3) and Z,Z-3,15-Octadecadien-1-ol acetate (C20:2) are suggesting its cytotoxicity. The S. cruentus lipophilic fraction exhibited potent cytotoxic activity against A549 (lung) cancer cells (IC_{50} = 1.919±0.1 µg/ml) through inhibition of cell growth at G1/S stage. All the species displayed moderate antimicrobial activities against certain types of selected strains. The LD_{50} of S. cruentus ethanol extract was determined as 1.5 g/kg.

Keyword: *Asteraceae, Senecio cruentus, Panc1 cells, A549 cells, GC-MS*

INTRODUCTION

The family Asteraceae (Compositae) includes the largest worldwide annual or perennial flowering plants of over 1620 genera and 23600 species.[1] Many species of the sunflower family (Asteraceae) such as *Cichorium intybus* (chicory), *Carthamus tinctorius* (safflower), *Bidens pilosa* (Spanish needles), *Achillea aleppica* and others are popular, cultivated and global used in folk medicine for centuries.[2] The extracts of several Asteraceae species showed common biological activities; antioxidants, anti-inflammatory, antimicrobial and hepatoprotectives due to their flavonoids, terpenoids and volatile oils.[2-5]

Many of Asteraceae plants extracts demonstrated potent cytotoxicity against several cancer cells. In Brazil, the extracts of 11 Asteraceae species exhibited strong cytotoxic activity against U373 (human glioblastoma), NCI-H460 (non-small-cell lung cancer) and HT29 (colon cancer) cells.[6] The ethanol extracts of 10 Mexican Asteraceae plants displayed potent cytotoxicity against HCT-116 (colon cancer cells).[7] The dichloromethane extract of *Anthemis mirheydari* presented significant cytotoxicity against MOLT-4 (leukemia).[8] The Hungarian Asteraceae species; *Centaurea jacea, Cirsium vulgare, Lactuca*

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viminea, *Onopordum acanthium* and *Centaurea spinulosa* together with other 19 species extracts showed significant inhibitory growth activity against MCF7 (breast epithelial adenocarcinoma), A431 (skin epidermoid carcinoma) and HeLa (cervix epithelial adenocarcinoma) cells.[9]

The previous reported phytochemical studies on Asteraceae plants extracts, revealed various cytotoxic chemical compounds of different classes. Eupatoriopicrin, a sesquiterpene lactone isolated from *Eupatorium cannabinum* showed in vivo antitumor activity against lung tumor.[10] Thiarubrine A, a polyacetylene metabolite of *Aspilia* sp. exposed potent cytotoxicity.[11] Montamine, an indole alkaloid isolated from *Centaurea montana*, exhibited strong cytotoxic activity against colon cancer cells.[12] A halimane diterpene (ent-8S,12S-epoxy-7R,16-dihydroxyhalima-5(10),13-dien-15,16-olide) compound of *Alomia myriadenia* exhibited strong cytotoxicity against lung cancer cells (LU 1).[13] Chrysosplenol D and Cirsiliol are flavonoids isolated from *Achillea fragrantissima* and showed potent cytotoxic activity against cervical (HeLa), breast (MCF-7), lung (A549) and prostate (PC3) cancer cells.[14]

In the current study, three ornamental Asteraceae species; *Dimorphotheca ecklonis* DC, *Arctotis aurantiaca* L. and *Senecio cruentus* DC were selected to study their cytotoxicity (Panc1 cancer cells) and antimicrobial activities. Few chemical and biological studies on the selected plants have been previously reported.[15-17] GC-MS metabolite characterization of the most potent cytotoxic fraction against Panc1 was performed to identify its' chemical components. The cytotoxicity of the same fraction against lung (A549), hepatic (HepG2), colon (Caco2) and breast (MCF7) cancer cells was also determined. Cell cycle assay on A549 cells was performed to confirm the cytotoxicity.

MATERIALS AND METHODS

Plant materials

The aerial parts of *D. ecklonis*, *A. aurantiaca* and *S. cruentus* were collected in March 2018, from the Plant Garden of Horticulture and Aromatics, faculty of Agriculture, Minia University, Egypt. A formal permission before collection of the plants was obtained from the director of the Plant Garden, faculty of Agriculture, Minia University. The selected species were taxonomically identified by Dr. Mahmoud Abdelhady Hassan, professor of horticulture and aromatics plants. Voucher specimens of them were placed in the herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Assiut University, Egypt with voucher numbers; 2221983 (*S. cruentus*), 2221984 (*D. ecklonis*) and 2221985 (*A. aurantiaca*).

Extraction and fractionations of plant materials

The aerial parts of selected Asteraceae plants were air dried in shadow at 25ºC and crushed to produce dried plant powders. A hundred grams of each plant were decocted in ethanol (300 ml × 3) for 3 hrs at 50ºC. The ethanol extracts were concentrated at reduced pressure until dryness to produce 13, 15, and 17 g dried extracts of *D. ecklonis*, *A. aurantiaca* and *S. cruentus* respectively, and then stored at 5 ºC until the biological and chemical assays. Five grams of ethanol extract of *S. cruentus* were dissolved in a 50 ml 10% methanol and suspended in 250 ml separating funnel. The aqueous extract was subjected to liquid-liquid extraction using hexane, dichloromethane and ethyl acetate (50 ml × 3 of each solvent). Then, the extracts were dried at reduced pressure to produce 67.5 mg hexane fraction (Lipophilic fraction), 12.5 mg dichloromethane fraction, 26.5 mg ethyl acetate fraction and 3.7 g aqueous fraction.

GC-MS analysis of the lipophilic fraction of *S. cruentus*

The hexane fraction (1 µl of 0.05 mg/ml) was injected into GC-TSQ mass spectrometer (Thermo scientific, Austin, TX, USA). The chromatographic separation of components was carried out on TG-5MS column (30 m × 0.25 mm × 0.25 µm) in 35 min run time. The mobile carrier gas used for separation was helium in a flow rate of 1 ml/min. During the run time, the column temperature was increased by 5 ºC/min from 50 to 250 ºC, after 2 min it also increased by 30 ºC/min until reached 300 ºC and remained for 2 min. The mass parameters for the identification of compounds were EI (Electron Impact) mode of ionization at 70 eV, full scan mass range m/z 50-750 and 200 ºC temperature of the ionization source. The identification of compounds was confirmed based on a comparison of their MS and MS/MS with those of Wiley Regi stry8e and mainlib databases as well as reported data.

Antimicrobial assay

The standard bacterial and fungal strains of the current study (Table 2) were supplied from Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. The antimicrobial activities of ethanol extracts of *D. ecklonis*, *A. aurantiaca* and *S. cruentus* were performed by using agar well diffusion method.[18] Briefly, one hundred µl of each standard strain were cultured in fresh agar medium (10 ml). After the microbial culture reached 10^8 cells/ml for bacteria and 10^5 cells/ml for fungi, a hundred µl of each strain was spread on agar plates. Then, a 100 µl of each ethanol extract (10 mg/ml DMSO) of the selected species was added in triplicates to 6 mm diameter hole in the tested agar cultured plates. Gentamycin antibiotic and ketoconazole antifungal compounds (1 mg/ml) were used as positive. The treated and positive control plates were incubated for 24 h for bacteria and 48 for filamentous fungi. The inhibition of the strain growth in mm (Zone of inhibition) is the indication of the antimicrobial activity. Negative control DMSO solvent was used in the experiments and displayed no zone of inhibition.

Cytotoxic assay

The cancer cells were purchased from the American Type Culture Collection (ATCC), Manassas, Virginia, United States. DMEM (Invitrogen/Life Technologies, Rockville, MD, USA) was used as a culture medium for cancer cells. Other chemical reagents such as Hyclone FBS (Fetal bovine serum), insulin, EDTA, MTT reagent, trypsin and streptomycin were purchased from Invitrogen or Sigma (USA). MTT method of cytotoxic assay used in the current study was the same as one previously described.[19] Briefly, the cancer cells were cultured in 96- well plates containing DMEM medium with 10 % FBS, and incubated for 24hrs at 37 °C. The different concentrations of tested extracts and fractions solubilized in DMSO as well as staurosporine (anticancer positive control) and DMSO (negative control) were added to the cultured cancer cells (triplicates of each concentration). The tested cultured plates were incubated for 48 hrs at 37 °C. MTT reagent (10%) was added to the tested cultured plates' wells and incubated for 2 hrs. The viability of cancer cells was determined by measuring the amount of formazan (Produced from the reaction of MTT reagent with the living cancer cell enzymes) using spectrophotometer plate reader at the wavelength 570 nm. Then, the % of cytotoxicity and the IC_{50} (Concentration that inhibit 50% of cancer cells) of the tested extracts were calculated.

Flow cytometry analysis of the cell cycles

All kits and reagents used in this assay were purchased from Abcam (Abcam technology, Boston, Ma, USA). The detection of the DNA cell contents and cell

cycle status were performed according to the previous reported method.[20] Briefly, A549 lung cancer cells (ATCC, Manassas, Virginia, USA) were cultivated in a single cell suspension (DMEM medium), then fixed in 66% ethanol and stored at +4 °C for 2 hrs. The suspended cells were rehydrated by PBS (5 mL of 10X PBS in 45 mL water) and stained with propidium iodide- RNase enzyme reagent (9.45 mLPBS + 500 µL 20X Propidium Iodide + 50 µL 200X RNase). After 30 min, the intensity of propidium iodide fluorescence was measured using flow cytometer [Excitation maximum = 493 nm; Emission maximum = 636 nm] to determine the amount of cellular DNA and cell cycle status.

Acute toxicity in vivo study of *Senecio cruentus* ethanol extract

Rats used in this experiment were cared in the animal house of Assiut University under controlled hygienic conditions. They were supplied feed and water ad libitum and adapted for 7 days before experiments initiated. The influences of oral doses (250, 500, 750, 1000, 1500 and 2000 mg/kg) of ethanol extract of *S. cruentus* on 24 Wistar albino rats weighting 180 to 250 g (aged 6 weeks) were observed. Animal behavior and mortality were observed for 21 days. This experiment had been approved by the Institutional Animal Care and Use Committee of the Faculty of Pharmacy, Assiut University (Approved No. S29-22) and animal care followed the guidelines of the National Research Council.

RESULTS AND DISCUSSION

GC-MS metabolite profiling of *Senecio cruentus* DC lipophilic fraction

GC-MS metabolite characterization of the lipophilic fraction of *Senecio cruentus* DC is presented in Table 1, Figs. 1 & S1. Seventeen compounds of different categories such as unsaturated fatty acids/esters (31%), saturated fatty acids/esters (27.6 %), hydrocarbons (20.6%), terpenoids (8.83%) and fatty alcohols/ketone (8.35%) were detected (Fig. 2). The unsaturated fatty acids/esters were identified as; cis-vaccenic acid (9.15%), glycidyl oleate (7.73%), 9,12-Octadecadienoic acid (Z,Z)- methyl ester (6.96%), 9,12,15-(Z,Z,Z)- Octadecatrienoic acid, 2,3-dihydroxypropyl ester, (6.24%) and Z,Z-3,15-Octadecadien-1-ol acetate (1.12%). Five saturated fatty acids/esters were also detected and recognized as; hexadecenoic acid, methyl ester (15.26%), hexadecenoic acid (7.42%), methyl stearate (2.05%), myristic acid methyl ester (1.27%) and eicosanoic acid methyl ester (1.11%). Phytol, acyclic hydrogenated diterpene (C20:1) alcohol (5.73%) and globulol, a tricyclic sesquiterpene (C15) aliphatic alcohol (3.10%) were detected as terpenoid compounds of the hexane extract of *S. cruentus*. Additionally, long chain hydrocarbons; nonacosane (16.76%) and dotriacontane (3.84%), 6,10,14-trimethyl-2-Pentadecanone (6.10%) (fatty ketone) as well as 13-heptadecyn-1-ol (1.18%) and 1-heptatriacotanol (1.07) (fatty alcohols) were identified from the lipophilic fraction. The identification of detected compounds was based on their mass, molecular formula and mass fragmentation patterns (Fig. S2) as well as a comparison with those of WileyRegistry8e and mainlib databases and previous reported data.[21-24]

Table 1: GC-MS characterization of Senecio cruentus DC lipophilic fraction.

Peak no.	Retention time (Rt)	Molecular formula	Molecular weight	Area (%)	Identified compound
1	14.4	$C_{15}H_{26}O$	222	3.10	Globulol
2	17.07	$C_{15}H_{30}O_2$	242	1.27	Myristic acid methyl ester
3	18.98	$C_{17}H_{32}O$	252	1.18	13-heptadecyn-1-ol
4	19.13	$C_{18}H_{36}O$	268	6.10	2-Pentadecanone, 6,10,14-trimethyl-
5	20.5	$C_{17}H_{34}O_2$	270	15.26	Hexadecanoic acid, methyl ester
6	21.5	$C_{16}H_{32}O_2$	256	7.42	Hexadecanoic acid
7	23.1	$C_{19}H_{34}O_2$	294	6.96	9,12-octadecadienoic acid (Z,Z)-, methyl ester
8	23.2	$C_{21}H_{36}O_4$	352	6.24	9,12,15-octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z)-
9	23.41	$C_{20}H_{40}O$	296	5.73	Phytol
10	23.62	$C_{19}H_{38}O_2$	298	2.05	Methyl stearate
11	24.13	$C_{18}H_{34}O_2$	282	9.15	cis-vaccenic acid
12	24.95	$C_{37}H_{76}O$	536	1.07	1-heptatriacotanol
13	26.49	$C_{21}H_{42}O_2$	326	1.11	Eicosanoic acid, methyl ester
14	28.16	$C_{20}H_{36}O_2$	308	1.12	Z,Z-3,15-octadecadien-1-ol acetate
15	31.18	$C_{32}H_{66}$	450	3.84	Dotriacontane
16	33.37	$C_{29}H_{60}$	408	16.76	Nonacosane
17	33.95	$C_{21}H_{38}O_3$	338	7.73	Glycidyl oleate

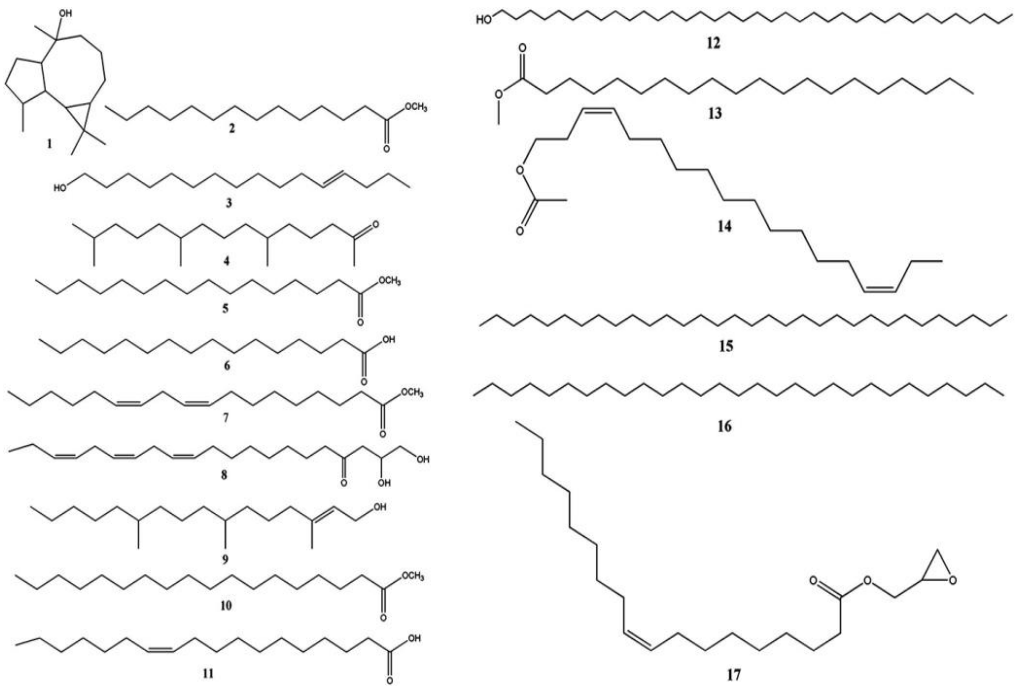

Fig. 1: Structures of compounds detected in *Senecio cruentus* DC lipophilic fraction by GC-MS**.**

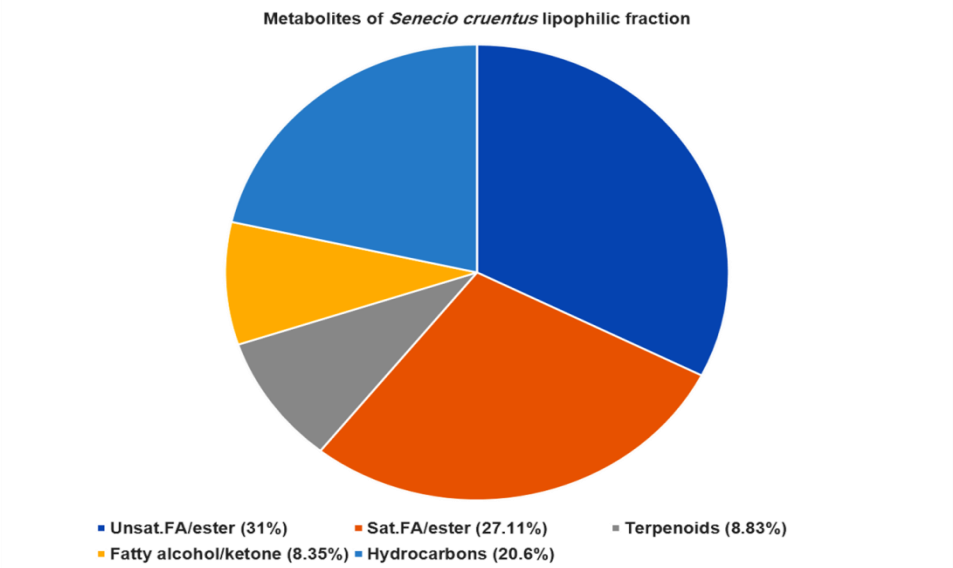

Fig. 2: Summarized result of the metabolite profiling of *Senecio cruentus* DC lipophilic fraction by GC-MS.

Antimicrobial activity of selected Asteraceae species

The ethanol extracts of *D. ecklonis*, *A. aurantiaca* and *S. cruentus* (0.1 mg/well of each extract) were tested for their antibacterial and antifungal activities against selected standard strains (Table 2) by using agar well diffusion method.[18] The results of the antimicrobial activities of the extracts (A mean zone of inhibition mm) are shown in Table 2. According to the previous antimicrobial studies on the plant ethanol extracts against the same microbial strains, both extracts of *Dimorphotheca ecklonis* DC. and *Arctotis aurantiaca* L. displayed moderate to strong wide spectrum antibacterial activities against *Staphylococcus aureus* ATCC 25923 (MSSA), *Escherichia coli* ATCC 25922 and *Klebsiella pneumonia* ATCC 13883, in addition to their antifungal activity against *Candida albicans RCMB* 005003 (1) ATCC 10231.[18] Also, the ethanol extract of *Senecio cruentus* DC. displayed selective moderate to strong antibacterial activity against *Staphylococcus aureus* ATCC 25923 (MSSA).[18]

Table 2: The antimicrobial activities of selected Asteraceae species; *D. ecklonis* (DD), *A. aurantiaca* (AA) and *S. cruentus* (CC).

Sample code / **Tested microorganisms**	**AA**	**CC**	**DE**	**Control**
FUNGI				Ketoconazole
Candida albicans RCMB 005003 (1) ATCC 10231	11	Nil	10	21
Aspergillus fumigatus (RCMB 002008)	Nil	Nil	Nil	19
Gram Positive Bacteria:				Gentamycin
Staphylococcus aureus ATCC 25923 (MSSA)	14	13	11	24
Methicillin-Resistant Staphylococcus aureus (MRSA)	Nil	Nil	Nil	18
Gram Negatvie Bacteria:				Gentamycin
Escherichia coli ATCC 25922	10	Nil	12	30
Klebsiella pneumonia ATCC 13883	8	Nil	9	26

Cytotoxic activity of selected Asteraceae species

The ethanol extracts of *D. ecklonis*, *A. aurantiaca* and *S. cruentus* were screened for their cytotoxic activities against Panc1 (pancreatic cancer cells). All of them showed strong cytotoxic activity of $IC_{50} \leq 20$ µg/ml (Figure 3.A & Table S1) according to the National Cancer Institute (USA).[25] The extract of *S. cruentus* exhibited the most potent cytotoxicity of IC_{50} 9.38±0.3 µg/ml. The cytotoxic activity of *S. cruentus* lipophilic fraction (Ch), dichloromethane fraction (Cd), ethyl acetate fraction (Ce) and aqueous fraction (Ca) are shown in Figure 3.B & Table S2, the lipophilic fraction (Ch) of *S. cruentus* displayed potent cytotoxic activity of IC_{50} = 7.63±0.46 µg/ml, while the other fractions showed weak cytotoxic activity ($IC_{50} \geq 29$ µg/ml). Also, the lipophilic fraction (Ch) exhibited strong cytotoxic activity (Figure 3.C, Table S3) against A549 (lung) cancer cells (IC_{50} = 1.919 ± 0.1 µg/ml), moderate to weak cytotoxicity ($IC_{50} > 10 \leq 36$ µg/ml) against HepG2, Caco2 and MCF7 cancer cells. Among the identified compounds by GC-MS, six unsaturated fatty acids/esters as well as an olefinic long chain (C20:1) diterpene alcohol (Phytol) were detected in the lipophilic fraction of *S. cruentus* (Table 1). The cytotoxicity of phytol against the breast adenocarcinoma MCF-7 and the prostate adenocarcinoma PC-3 cells, as well as the cytotoxicity of unsaturated fatty acids against human breast cancer cells by gamma-linolenate (GLA) were reported in the previous studies.[26,27] The reported data revealed that the cytotoxicity of the unsaturated fatty acids was increased with the decrease in the number of carbon atoms and increase in the number of double bonds.[27] Thus, we suggest the cytotoxic activity of the lipophilic fraction of *S. cruentus* is due to the synergistic cytotoxic effects of detected phytol (C20:1) and unsaturated fatty acids/esters.

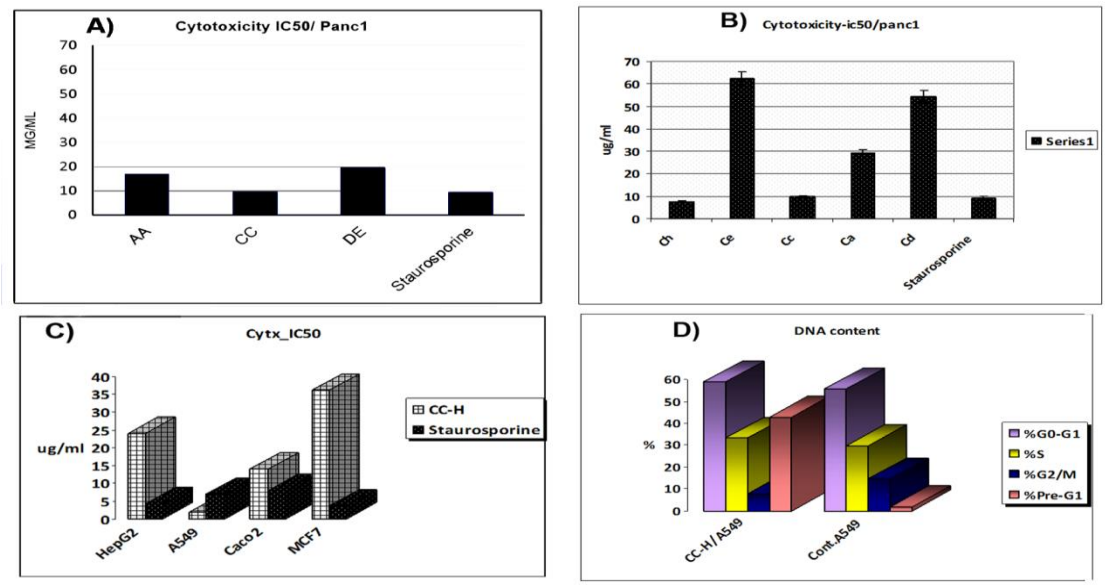

Fig. 3: A) Cytotoxic activity of ethanol extracts of *D. ecklonis* (DE), *A. auranciaca* (AA) and *S. cruentus* (CC) against Panc1.

B) Cytotoxic activity of *Senecio cruentus* hexane (lipophilic) fraction (Ch), dichloromethane fraction (Cd), ethyl acetate fraction (Ce) and aqueous fraction (Ca).

C) Cytotoxic activity of *Senecio cruentus* hexane (lipophilic) fraction (CC-H) against hepatic (HepG2), lung (A549), colon (Caco2) and breast (MCF7) cancer cells.

D) Inhibition of lung (A549) cancer cells growth activity of *Senecio cruentus* hexane (lipophilic) fraction.

Lung cancer cell growth inhibition activity of *Senecio cruentus* hexane extract

The lipophilic fraction of *S. cruentus* (LF) displayed inhibition of growth cancer lung cells especially at G1/S stage of cell cycle (Figure. 3.D, Fig.S4 & Table S4). This result confirms the selective in vitro anticancer activity of *S. cruentus* lipophilic fraction against Panc1 and lung cancers.

Acute toxicity in vivo study of *Senecio cruentus* ethanol extract and GC-MS detection of toxic alkaloids.

The LD_{50} (lethal dose 50) of *S. cruentus* ethanol extract was determined as 1.5 g/kg. The detected LD_{50} is equivalent to 15 g/kg of the dried plant materials. This acute toxicity experiment reveals low to moderate toxicity of the ethanol extract of *S. cruentus* in comparison with the reported plant extracts .[11&28] However, extreme medical cautions should be taken for the use of the plants of genus *Senecio* due to their contents of toxic pyrrolizidine alkaloids that produce liver cirrhosis and necrosis.[11] GC-MS analysis of the dichloromethane fraction of *S. cruentus* led to the detection of 3 hepatotoxic pyrrolizidine alkaloids; senecionine, seneciphylline and 12-hydroxysenecionan-11,16-dione (Fig.S3). Thus, medical precautions should be taken for the use of both dichloromethane and alcohol extracts of *S. cruentus*, while its' hexane extract that contains saturated and unsaturated hydrocarbons/acids/esters is safe to use.

Conclusion

Lipophilic fraction of *S. cruentus* exhibited the most potent cytotoxic extract (IC_{50} 7.63 ± 0.46 µg/ml) against Panc1 cancer cells. It also displayed strong activity against A549 (lung) cancer cells (IC_{50} = 1.919 ± 0.1 µg/ml) through the damage of cancer cell DNA and cell growth arrest at G1/S phase. GC-MS metabolite profiling of the lipophilic fraction led to the identification of 17 components. The detection of phytol and 6 other unsaturated fatty acids/esters are suggesting the cytotoxicity of the lipophilic fraction. All the ethanol extracts of the selected Asteraceae species showed moderate to strong antimicrobial activities against certain types of the selected strains. This study recommends further in vivo and clinical anticancer studies on the hexane extract of *S. cruentus* against pancreatic and lung cancers, in addition to further bio-guided phytochemical studies on *S. cruentus, D. ecklonis* and *A. aurantiaca* ethanol extracts to isolate natural antimicrobial compounds.

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Competing interests

The authors declare no conflict of interest.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author "A.M.Z" on reasonable request.

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نشرة العلوم الصيدلية
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التاثيرات السامة للخلايا السرطانية والمضادة للميكروبات لنباتات مصرية مختارة من العائلة النجمية وكذلك معرفة التركيب الكيميائي لمستخلص هكسان السينيسيو كرونتيس بواسطة GC-MS

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اجريت تجارب سمية خلايا سرطان البنكرياس و مضادات الميكروبات علي خلاصات الايثانول لثلاث نباتات زينة تابعة للعائلة النجمية وهي سينيسيو كرونتيس و ديمورفوتيكا اكلونيس و اريكتوتيس اورينشكا. اوضحت الدراسات ان مستخلص الهكسان لنبات السينيسيو كرونتيس هو الاعلي نشاطا لسمية الخلايا ضد خلايا سرطان البنكرياس (ا. س. ٥٠ = ٧,٧٣ ± ٠,٤٦ مجم/ مللي). تم التعرف علي سبع عشرة مركب مختلفا كيميائيا لمستخلص الهكسان بواسطة جهاز GC-MS . التعرف علي مركب الفيتول و مركبات الاحماض الدهنية الغير مشبعة في مستخلص الهكسان من المحتمل ان تكون المسؤلة عن فاعلية المستخلص ضد خلايا سرطان البنكرياس. تم دراسة تاثيرات مستخلص الهكسان لنبات السينيسيو علي خلايا سرطانية اخري وقد اوضحت الدراسة فاعلية المستخلص ضد خلايا سرطان الرئة (ا. س. ٥٠ = ١,٩١٩ ± ٠,١ مجم/ مللي) من خلال وقف نمو خلايا السرطان في مرحلة G1/S لدورة الخلايا. اوضحت خلاصات الايثانول للنباتات الثلاثة نشاطا متوسط كمضادات للميكروبات المختاره. اوضحت دراسة سمية مستخلص الايثانول علي الفئران ل.د.٥٠= ١,٥ جم/كجم.