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Original Article

UPLC-HR-ESI-MS ANALYSIS AND ANTIPROLIFERATIVE AND ANTI-DIABESITY SCREENING OF FLOWERS, ROOTS, AND AERIAL PARTS OF *SOLANUM ELAEAGNIFOLIUM CAV.*

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ABSTRACT

Objective*: Solanum elaeagnifolium* Cav. is an invasive summer-growing wild perennial herb but is traditionally used to treat some health conditions, including toothache and constipation. This study aimed to identify the chemical composition of various parts of this herb (flowers, roots, and aerial parts) and explore its biological properties.

Methods: Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS) was used for the first time for the root to analyze the hydro-alcoholic extract besides flowers and aerial parts of *S. elaeagnifolium.* Sulforhodamine B (SRB) assay was used to assess the antiproliferative effects of the same extracts on the colorectal cancer cell lines (CACO2, SW620, HT29, and HCT116). The aqueous extracts of the plant's three parts were evaluated *in vitro* for their anti-diabesity properties.

Results: For the first time, other compounds in three plant parts were identified using UPLC-MS: hyperoside and apigenin (flavonoids), in flowers and roots, naringin (flavonoid) in the roots, and apigenin (flavonoid) in aerial parts, diosgenin (steroids sapogenin) solamargine, and solasodine (alkaloids) in the three parts. In addition to the previously identified compounds; chlorogenic acid and kaempferol were in the aerial part, and flowers; and luteolin (flavonoids) were in the aerial parts. Pharmacologically, the aqueous extracts of flowers and roots proved anti-diabesity activity, and no anti-proliferative effect was detected for their hydro-alcoholic extracts. Neither anti-obesity nor anti-proliferative activities were detected in the aerial part extracts.

Conclusion: Further *in vivo* and *in vitro* investigations are required for the different parts of *S. elaeagnifolium* to explore more biological activities and evaluate the plant's toxicity.

Keywords: Aerial parts, Colorectal cancer, Flowers, Obesity, Roots, *Solanum elaeagnifolium* Cav., UPLC-MS

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INTRODUCTION

According to the World Health Organization (WHO) [1], obesity is becoming more prevalent worldwide, and without interventions by 2030 half of the world's population might be obese [2]. Weight loss is necessary to improve the quality of life and prevent chronic diseases such as diabetes, dyslipidemia, hypertension, polycystic ovary syndrome, degenerative diseases, and cancers [3]. Most practices for weight management include diet, exercise, medications (lorcaserin, acarbose, orlistat, or liraglutide), and natural supplements [4-8]. Due to the lack of rapid results from diet and exercise and the fear of side effects from medications, people tend to trust natural methods for weight reduction [9]. Several *in vitro, in vivo,* and clinical trials have demonstrated that anti-oxidants found in natural products can manage oxidative stress in obesity and its related diseases [9-11]. Therapeutically, one of the substantial approaches in the management of obesity is the inhibition of the absorption and digestion of carbohydrates and fats from different foods and nutrients. The two commonly used drugs with these activities are orlistat and acarbose [4, 9]. These synthetic drugs inhibit human pancreatic lipase (PL) and alpha-amylase enzymes respectively [9, 12]. Still, the anti-obesity of the plants is correlated to the occurrence of specialized metabolites i.e. flavonoids, phenolic acids, or alkaloids [4, 11, 13].

Studies identified high body mass index and obesity as risk factors for breast, esophageal, kidney, gallbladder, uterine, pancreatic, liver, and colorectal cancers and interrelated both factors to the incidence and mortality. The high body mass index is one of the causes of about one–third of cancer deaths [3, 14]. In addition, one of the obesity consequences is insulin resistance, which contributes to colorectal progress [15]. Universally, chemotherapy is the main treatment of colorectal (colon cancer), which is one of the most prevalent cancers [14]. In 2012, it was described as the second (9.2%) and the third (10%) most common cancer in women and men respectively, in 180 countries worldwide. Further, in Jordan, it is the second most incidence of cancer [16].

Jordan is well-known for its diverse flora then numerous plants have been studied for their anti-proliferative and anti-diabesity properties [17, 18]. Herbal medicine is still a common traditional practice, principally in the rural regions of Jordan [8, 19-21]. Due to the resistance to conventional chemotherapy and the side effects, they have limited use. However, several plants have been screened and approved in an attempt to find an alternative treatment to treat or/and at least prevent various cancers, including colon cancer. [17-19]. Some plants in Jordan, including *Arum hygrophilum, Echium judium*, and *Salvia triloba* [18-21] have been screened for their anticancer activities and many others still need to be tested.

Among the genera of the family Solanaceae, the genus *Solanum*, with about 1700 species, is the most widely spread genus. This genus is represented in Jordan with eight wild-growing species, namely *S. esculentum* L., *S. nigrum* L., *S. luteum* Miller. *S. cornutum* Lam., *S. sinaicum* Boiss. *S. incanum* L., *S. dulcamara* L., and *S. elaeagnifolium* Cav [22]. The latter species is a problematic perennial herb with pale to dark green leaves and purple or white flowers. It has deep roots and yellow to green spherical berries that threaten the native biodiversity and agriculture worldwide. Moreover, without efficient integrated management, *S. elaeagnifolium* might continue to cause environmental and economic damage as it can regenerate asexually, spreading quickly within different regions [23].

Nevertheless, *S. elaeagnifolium* is used traditionally to treat different ailments in diverse countries. In India, the roots of the plant are chewed to treat snakebites and to remove tooth pain, and in Mexico, the plant is utilized to treat constipation and sneezing [23, 24]. Moreover, gastrointestinal disorders, sore throats (as an antiseptic), toothaches, and cancer are other traditional uses of the plant [24]. Also, several other studies reported diverse biological properties of *S. elaeagnifolium*; for example, anti-oxidant, anti-inflammatory, anti-microbial, analgesic, and hepatoprotective activities. Anti-proliferative properties were tested against numerous cell lines, including colon cancer (LIM-1863), melanoma, liver cancer (HPG2), breast cancer (MCF7), and cervical carcinoma (HeLa) [25, 26].

Phyto-chemically, alkaloids and flavonoids were detected [24]. Diabesity (a metabolic disorder linked to obesity) has been treated with active phytochemicals in medicinal herbs [4]. Therefore, the current study aimed to explore the secondary metabolites of different plant parts (flowers, roots, and aerial parts) using the UPLC-MS method and to screen their anti-proliferative properties. The Pancreatic Triacylglycerol Lipase (PL) inhibitory potentials and alpha-amylase of *S. elaeagnifolium* extracts were further screened. The reported incidence of morphological and genetic variations in this weed worldwide supports the biological and chemical screening of *S. elaeagnifolium* growing wild in Jordan [27-29].

MATERIALS AND METHODS

Instruments, chemicals, and biochemical

High-Resolution Mass Spectrometric (HR-MS) records were done using a Thermo QExactive Plus mass spectrometer with a heated electrospray ionization source operational on both negative and positive ionization modes (Thermo Fisher Scientific, Germany). All chemicals and reagents were obtained from Sigma (Dorset, UK), the Glucose GOD-PAP kit from BioLabo Reagents (France), Sonicator (Bandelin Sonorex, Bandelin Electronics, Germany), rotary evaporator from Laborota 4000-efficient (Heidolph, Germany), RPMI 1640, from PAA Laboratories GmbH (Austria) and UV-VIS spectrophotometer from Spectro Scan 80D (UK).

Plant collection

The plant was collected from Deir Alla, North of Jordan Valley, in July 2022. The plant material was identified by Prof. Fatma Afifi (Department of Pharmaceutical Science, Faculty of Pharmacy, The University of Jordan, Jordan). Flowers and roots were separated from the stems and leaves; the latter two organs are referred to as aerial parts, prepared for extraction. A voucher specimen has been kept in the Department of Basic Medical Sciences, Faculty of Medicine, Al-Balqa Applied University (KMJ-SOLA-SE2k).

Preparation of *S. elaeagnifolium* extracts of (flowers, roots, and aerial parts)

S. elaeagnifolium aqueous extracts of flowers, roots, and aerial parts were prepared using every ten grams of plant material and refluxed with 100 ml distilled water for 15 min. The extracts were kept overnight, filtered twice using filter paper, and completed to 100 ml to obtain the final 10% (w/v) extracts. For PL experiments, lyophilized water extracts were used. The collected solid residue was kept in dry conditions till analysis. For the preparation of the hydro-alcoholic extracts, every ten grams of the fresh and coarsely chopped (flowers, roots, or aerial parts) were refluxed for 30 min with 70% ethanol and kept overnight and processed as the water extracts. For the cytotoxicity experiments stock was prepared from the extracts after complete drying of each 100 mg extract and dissolving in 10 ml DMSO [18].

Chemical profiling of *S. elaeagnifolium* Hydro-alcoholic extracts (flowers, roots, and aerial parts) using Ultra-performance-liquid-chromatography high-resolution mass spectrometric (UPLC-HR-ESI-MS)

UPLC-HR-ESI-MS analysis was used for the chemical profiling of *S. elaeagnifolium* hydro-alcoholic extracts following the method published earlier [17, 30] To collect data, the QExactive Plus was adjusted from 150 to 2000 m/z at 70 000 resolution.

In vitro anti-proliferative evaluation of *S. elaeagnifolium* extracts

The three hydro-alcoholic extracts of *S. elaeagnifolium* were screened for their anti-proliferative activities using an *in vitro* Sulforhodamine B (SRB) colorimetric assay [18]. The obesity-related colorectal cells (HCT116, HT29, SW480, SW620, and CACO2) are gifts from Prof. Bustanji, (School of Pharmacy Department of Biopharmaceutics and Clinical Pharmacy, The University of Jordan). Human periodontal fibroblasts (PDL) were used to validate the cytotoxicity selectivity. Cisplatin was used as a positive control (0.1-200 µg/ml concentrations range; [Sigma-Aldrich, purity: ≥ 99%]. The experiments were in quadruplicate and the anti-proliferative activities were represented as the IC_{50} mean±SD (n = 4).

Pancreatic lipase inhibition assay of the aqueous extracts (flowers, roots, and aerial parts) of *S. elaeagnifolium*

The enzymatic inhibition property of PL was evaluated *in vitro* for the aqueous extracts of *S. elaeagnifolium* (flowers, roots, or aerial parts), using Orlistat as a reference drug, according to [18]. Orlistat and the three extracts were measured in comparison to control readings to determine the concentration required for PL_{50}% inhibition (IC_{50}) [17].

In vitro enzymatic starch digestion assay

In vitro, starch digestion efficacy of *S. elaeagnifolium* aqueous extracts was studied in seven concentrations (1, 5, 10, 12.5, 25, 50, and 100 mg/ml using acarbose as the reference drug [Sigma-Aldrich, purity: ≥95%]. The control was free of *S. elaeagnifolium* extracts and acarbose (distilled water only) [17].

Statistical analysis

Statistical analysis was performed with GraphPad Prism 8.4.2 (GraphPad Software, Inc., San Diego, CA, USA). The cell viability was calculated for the three to four independent experiments as:

$$\frac{\text{Mean[A (T) – A (B)]}}{\text{Mean [A (C) – A (B)]}} \times 100\%$$

A: Absorbance B: Blank C: Control T: Test.

The results are shown as mean± (SD). Then a one-way analysis of variance (ANOVA) was used and followed by Tukey's multiple-comparison posttest whenever applicable, with $\alpha = 0.05$. Values were described as significantly different if $P<0.05$.

RESULT

The current study aimed to screen the phytochemical components in flowers, roots, and aerial parts of *S. elaeagnifolium* using different reference compounds in UPLC-HRESIMS analysis. Resulting in the identification of different compounds for the first time in the ethanolic extracts of the three plant parts: hyperoside, apigenin, and naringin (flavonoids) in roots, hyperside (a flavonoid) in flowers, apigenin (a flavonoid) in the aerial parts, solamargine and solasodine (alkaloids), and diosgenin (steroidal sapogenin) in the three parts. In addition to previously identified compounds; chlorogenic acid and kaempferol were identified in both the aerial parts and flowers and luteolin (flavonoids), the aerial parts as shown in table 1.

Table 1: The summary of the identified secondary metabolites in the roots, flowers, and aerial parts of *S. elaegnifolium using* UPLC-MS

Secondary metabolites	Roots	Flowers	Aerial parts
Flavonoids	Hyperside	Hyperside	Apigenin
	Apigenin	Kaempferol	Kaempferol
	Naringin	-	Luteolin
Steroidal sapogenin	Diosgenin	Diosgenin	Diosgenin
Alkaloids	Solamargine	Solamargine	Solamargine
	Solasodin	Solasodine	Solasodine
Phenolic acid	-	Chlorogenic acid	Chlorogenic acid

UPLC-HR-ESI-MS analysis of the hydro-alcoholic extracts of (Flowers, roots, and aerial parts) of *S. elaeagnifolium*

UPLC-HR-ESI-MS analysis using different standards compounds revealed the identification of four compounds for the first time in *S. elaeagnifolium* roots; naringin (flavonoid), diosgenin (a steroidal sapogenin), solamargine, solasodine (alkaloids). In the flowers extract, six compounds were identified, four of them for the first time in this species; diosgenin, solamargine, solasodine, and

hyperoside in addition to chlorogenic acid and kaempferol. This is the first report to screen secondary metabolites in *S. elaeagnifolium* aerial parts using UPLC-HRESI-MS; chlorogenic acid, kaempferol, luteolin, apigenin, solamargine, solasodine, and diosgenin, all the identified secondary metabolites are shown in (table 1). The (+)-HR-ESI-MS and (+)-ESI-SIC of the recognized secondary metabolites in the hydro-alcoholic extracts compared to the used standards are shown in fig. 1-6 for roots, flowers, and aerial parts.

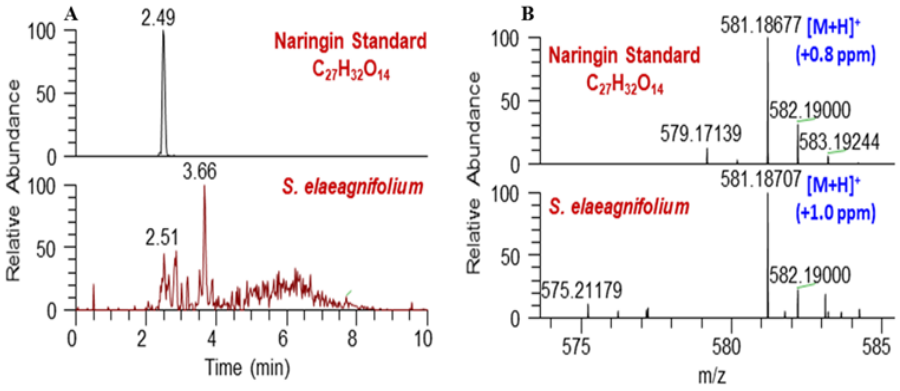

Fig. 1: (A) (+)-ESI SIC of Naringin standard and *S. elaeagnifolium* roots extract. (B) (+)-ESI HRMS of Naringin standard and in *S. elaeagnifolium* roots extract

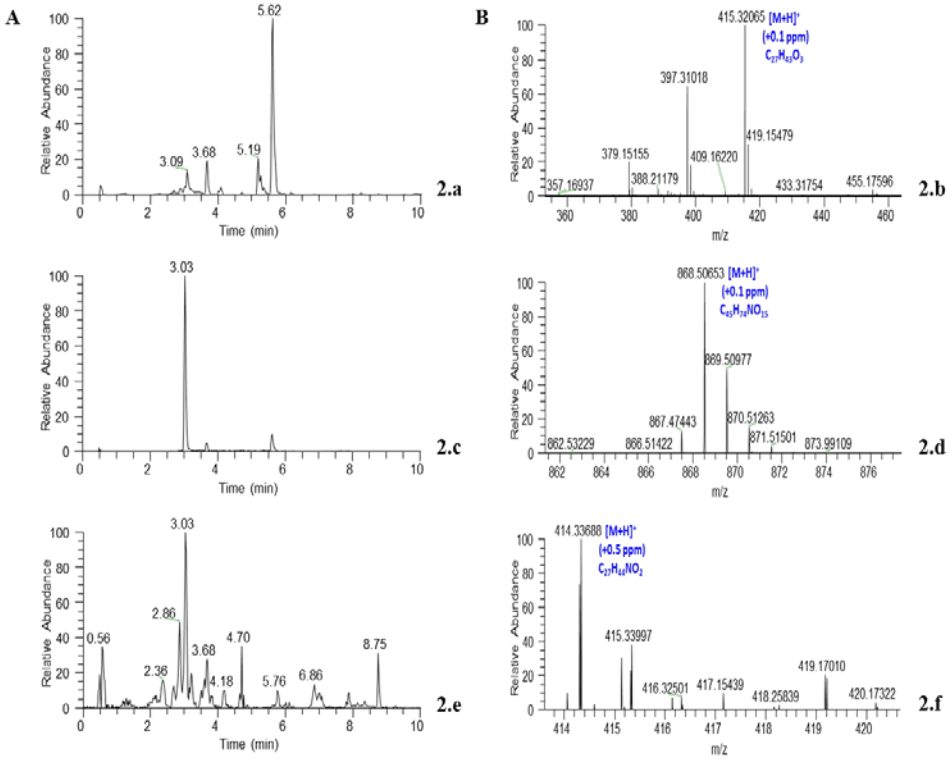

Fig. 2: MS detection of alkaloids in *S. elaeagnifolium* roots extract (A) (+)-ESI SIC of *S. elaeagnifolium* roots extract (m/z: 415; diosgenin), (m/z: 414; solasodine), (m/z: 869; solamargine), fig. 2. a, 2. C, and 2. e respectively. (B) (+)-ESI HRMS of diosgenin, solamargine and solasodine. Fig. 2. b, 2. d, and 2. f respectively

Pancreatic lipase inhibition assay of the aqueous extracts of *S. elaeagnifolium*

(Flowers, roots, and aerial parts) and enzymatic starch digestion

In the present study, the PL-modulatory profiles of the aqueous extracts of *S. elaeagnifolium* are listed in table 2. Orlistat's PL-IC_{50} of 114.0±4.0 ng/ml (0.2±0.0 µM) is comparable to the described PL-IC_{50} values earlier [17]. A clear concentration-dependent PL inhibitory activity was attained for the three extracts (similar to orlistat performance). PL-IC_{50} values attained for a minimum of four independent investigations are also shown in table 2. With the reference drug acarbose, glucose liberation from starch was inhibited highly substantially with an IC_{50} value of 0.2±0.02 µg/ml. Additionally, aqueous roots and flower extracts had highly substantial dose-related reductions in aldohexose release from culinary polymeric cornstarch with IC_{50} (mg/ml) values enlisted in table 2. Both roots and flower extracts proved potent in modulating pancreatic digestive enzymes' bioactivities; aerial parts extract was conversely inactive.

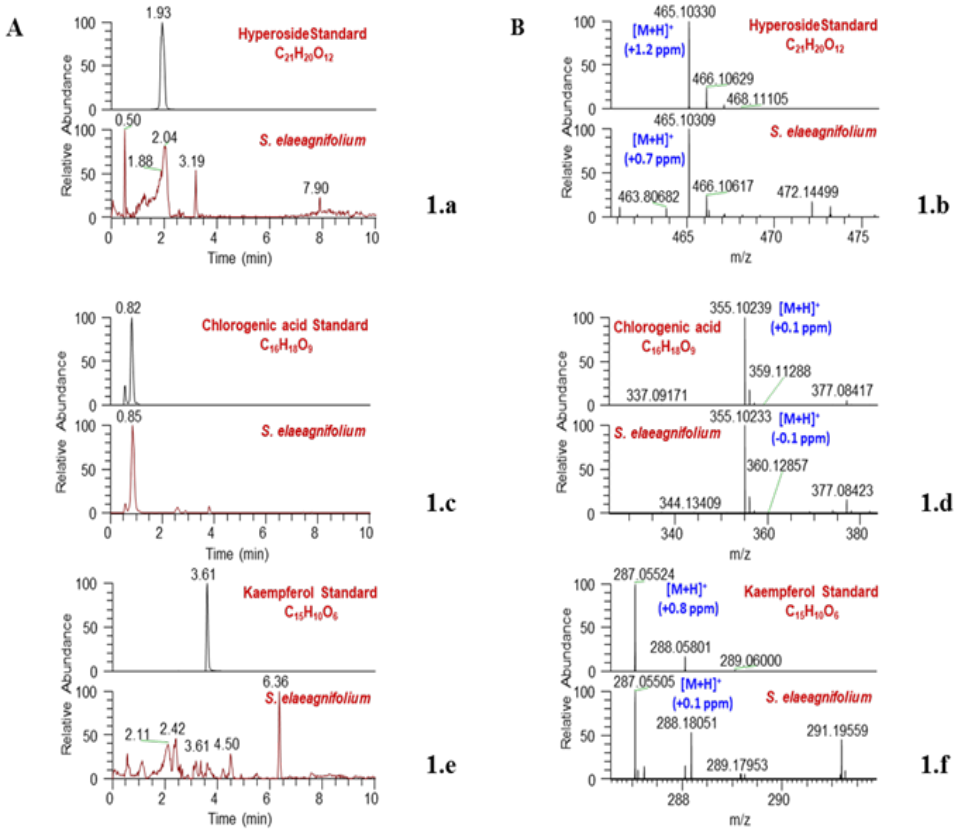

Fig. 3: (A) (+)-ESI SIC of different flavonoids standards and *S. elaeagnifolium* flowers extract, fig. 1. a, 1. c and 1. e. (B) (+)-ESI HRMS of the flavonoids and in *S. elaeagnifolium* roots extract; fig. 3. b, 3. d, and 3. F

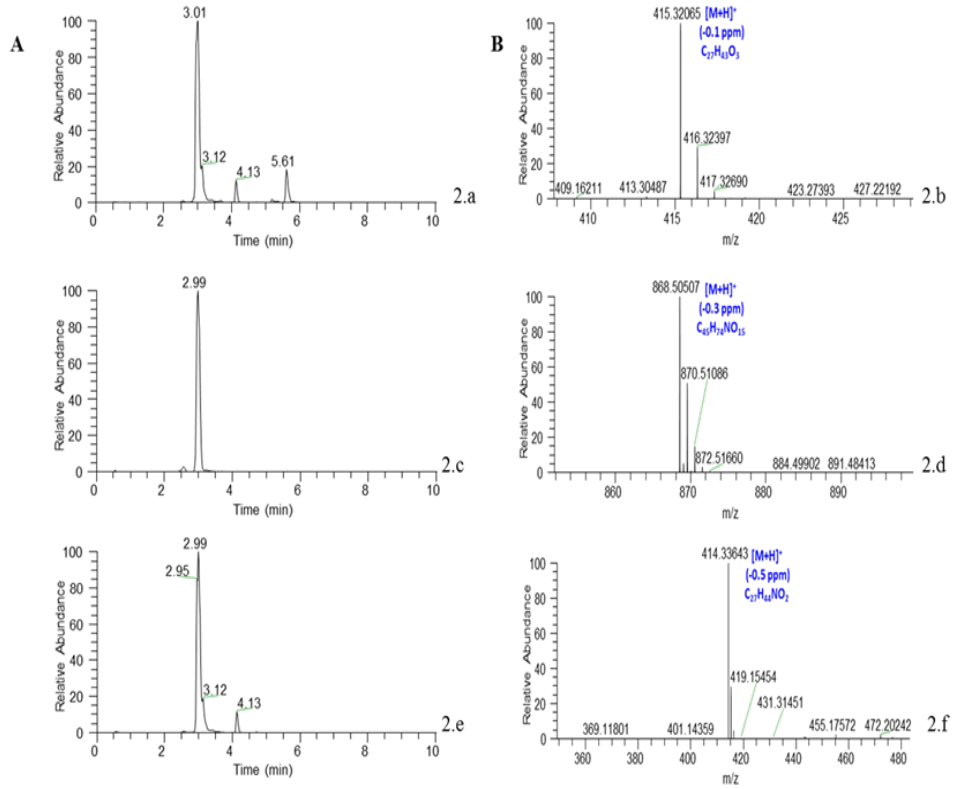

Fig. 4: MS detection of alkaloids in *S. elaeagnifolium* flowers extract (A) (+)-ESI SIC of *S. elaeagnifolium* flowers extract (m/z: 415; diosgenin), (m/z: 414; solasodine), (m/z: 869; solamargine), fig. 4. a, 4. C, and 4. e, respectively. (B) (+)-ESI HRMS of diosgenin, solamargine and solasodine. Fig. 4. b, 4. d, and 4. f respectively

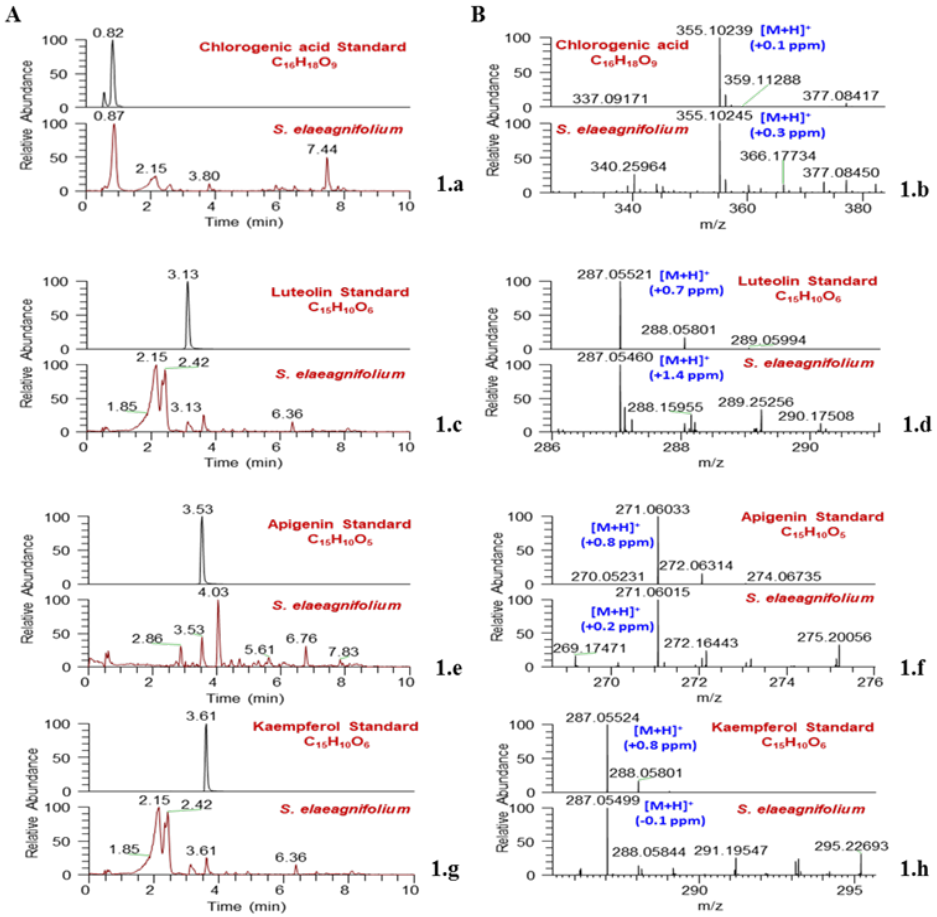

Fig. 5: (A) (+)-ESI SIC of flavonoids standards and *S. elaeagnifolium* aerial parts extract. Fig. 5. a, 5. c, 5. e, and 5. g. (B) (+)-ESI HRMS of the flavonoids in aerial parts extract; fig. 5. b, 5. d, 5. f, and 5. H

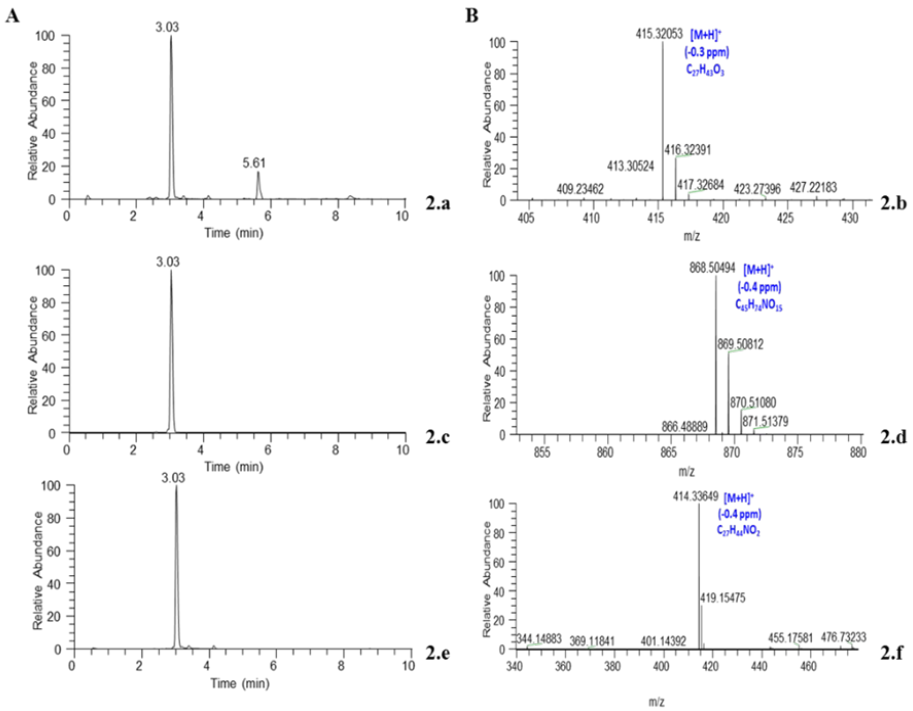

Fig. 6: MS detection of alkaloids in *S. elaeagnifolium* aerial parts extract (A) (+)-ESI SIC of *S. elaeagnifolium* flowers extract (m/z: 415; diosgenin), (m/z: 414; solasodine) (m/z: 869; solamargine), fig. 6. a, 6. C, and 6. e, respectively. (B) (+)-ESI HRMS of diosgenin, solamargine and solasodine. Fig. 6. b, 6. d, and 6. f respectively

Table 2: Enzymatic starch digestion and *in vitro* PL IC_{50} values for *S. elaeagnifolium* aqueous extracts of (Flowers, roots, and aerial parts), orlistat, and acarbose

S. Elaeagnifolium aqueous extract	Pancreatic triacylglycerol lipase IC_{50} (µg/ml)*	Enzymatic starch digestion IC_{50} (mg/ml)*	Sugar (mm) interferences AT 100 mg/ml
Flowers	34.9±3.44	2.7±0.41	2.47
Roots	38.25±2.47	3.01±0.45	2.25
Aerial parts	Non-inhibitory	Non-inhibitory	-
Reference	Orlistat	Acarbose	-
Drugs	0.114±0.01 µg/ml	0.2±0.02 µg/ml	-

*Results are represented as mean±SD (n = 3 independent triplicates)

Anti-proliferative property of the hydro-alcoholic extracts of distinct parts of *S. elaeagnifolium* against obesity-related colorectal cancer cell lines

Medicinal herb crude extract has prophylactic or therapeutic effects if its anti-proliferative IC_{50} value is less than 30 µg/ml (according to the National Cancer Institute (NCI)) [17]. The current study tested the antiproliferative activities of the reference drug cisplatin and the *S. elaeagnifolium* extracts against selected colorectal carcinoma cell lines and fibroblasts. All the hydro-alcoholic extracts lack anti-proliferative activities in any of the colorectal carcinomas panel incubations as shown in table 3.

Table 3: *In vitro* anti-proliferative property of ethanolic extracts of *S. elaeagnifolium* (flowers, root, and aerial parts) on the cell lines of colorectal cancer (IC_{50} values (µg/ml)

S. elaeagnifolium hydro-alcoholic extract	Cytotoxicity (% Control) IC_{50} (µg/ml)*					
	HT29	HCT116	SW620	CACO2	SW480	Fibroblasts
Flowers	3790.8±522.6	158.6±15.5	140.9±7.0	66.3±5.5	NI	3783.2±533.3
Roots	NI	NI	NI	NI	NI	NI
Aerial parts	NI	121.5±18.2	NI	132.8±19.9	696.1±104.4	103±15.5
Cisplatin	2.4±0.13	0.04±0.006	2.2±0.1	3.52±0.4	2.06±0.32	2.4±0.13

*The results are represented as mean values±Standard deviation) (n = 4 separate determinations). IC_{50} values were calculated as (The concentration at which 50% inhibition of cell proliferation occurs compared to an untreated basal 72 h incubation) and were considered in the 0.1-200 µg/ml range.

DISCUSSION

Globally and more spread in developing countries, herbs and plants are used in the treatment of numerous minor and major ailments. This common practice is supported by their easy accessibility and also considering their affordable costs [19]. Varied species of the genus *Solanum* are used traditionally for various diseases, and many of them were supported experimentally, including cancer, hyperlipidemia, and diabetes [24]; their therapeutic benefits are typically related to their secondary metabolites, such as alkaloids, flavonoids, and phenolic acids [4, 5]. Moreover, the extraction of the same plant part using different solvents results in variable secondary metabolites affecting the extracts' pharmacological activities [31]. Also, various parts of *S. elaeagnifolium* exhibited diverse pharmacological properties, and it is worth continuing in search of additional biological activities of the different extracts of this species, considering its surplus availability and its morphological and genetic variations [27-29].

In the current study, the extract of the aerial parts of *S. elaeagnifolium* did not exhibit anti-diabesity activity. Similar observations were made earlier with the berries [17]. However, the aqueous extracts of the flowers and roots exhibited potent anti-diabesity effects, as other species of the genus *Solanum* with reported anti-diabetic and antihyperlipidemia activities. The fruit extract of *S. anguivi*, the leaf extract of *S. pubescens*, and the root extract of *S. xanthocarpum* showed anti-diabetic properties [13] Unlike the berries of *S. elaeagnifolium,* in the present study, none of the tested hydro alcoholic extracts exhibited anti-proliferative activities, despite the secondary metabolite profiles of all the plant parts are almost similar [17]. In a study screening the cytotoxic activities of the Negev desert plants, the aqueous extract of the aerial parts of *S. elaeagnifolium* exhibited more than 97% activity against melanoma cell lines [32]. Flavone glycosides extracted from *S. elaeagnifolium,* growing in Egypt, exhibited cytotoxicity against breast (MCF7) and liver (HPG2) cancer cell lines [33]. Methanol extract from the leaves and seeds of *S. elaeagnifolium,* with identified glycoalkaloids, were reported to have insecticidal properties and considered in Egypt as a natural pesticide against nematodes and weeds [34].

Phytochemically, this is the first report of the identification of flavonoids and alkaloids in the flowers, roots, and aerial parts of *S. elaeagnifolium* using UPLC-MS. Earlier different phenolic acids (salicylic-, cinnamic-, sinapic-, ferulic-, chlorogenic-and gallic acids), and flavonoids (quercetin, rutin, and kaempferol) were reported in the various parts of *S. elaeagnifolium*. These compounds have antioxidant properties and contribute to the various biological effects of this species (anticancer, anti-inflammatory, anti-diabetic, and anti-microbial) [31]. Besides, the identified flavonoid naringin has evidenced (*in vitro, in silco, and in vivo*) anti-diabetic effects [35, 36]. As reported earlier, the alkaloid solasodine, isolated from the fruits of *S. sisymbriifolium* is an effective anti-cancer agent for the treatment of various cancers such as pancreatic cancer [37]. In the current study, solasodine and solamargine were detected in the hydroalcoholic extracts of roots, flowers, and aerial parts. Both alkaloids were also detected in the ripe and unripe fruits of *S. elaeagnifolium* grown in Jordan [17].

CONCLUSION

Different organs of *S. elaeagnifolium* screened chromatographically revealed the occurrence of secondary metabolites with diverse biological effects. The aqueous extracts of the roots and flowers exhibited anti-obesity activity, while the extracts of the aerial parts did not show this activity. The tested extracts lacked anti-proliferative effects against the selected cell lines. Further studies are recommended using other cancer cell lines. Also, to establish the usefulness of *S. elaeagnifolium* as a curative medicinal herb in managing diabesity, additional *in vitro* and *in vivo* experiments are recommended. Further *in vivo* and *in vitro* investigations are required for the different parts of *S. elaeagnifolium* to explore more biological activities and evaluate the plant's toxicity.

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Nil

AUTHOR CONTRIBUTION

All the work have been carried out by me.

CONFLICT OF INTERESTS

Declared none

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