**BIOMEDICAL SCIENCES**

**Seseli petraeum** M. Bieb. (Apiaceae) Significantly Inhibited Cellular Growth of A549 Lung Cancer Cells through G0/G1 Cell Cycle Arrest

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**Abstract:** Seseli L. is an important genus of the Apiaceae family, with a large number of aromatic species. It is used in traditional medicine extensively, but there is quite limited information on their phytochemicals and biological activities. *Seseli petraeum* M. Bieb. grows in Northern Anatolia, and there are no phytochemical studies on this species. In the present study, we aimed to investigate the effect of the extracts of *S. petraeum* on A549 lung cancer cell proliferation. For this purpose, the antiproliferative effect was determined via MTT assay, and the extracts obtained from the root of *S. petraeum* showed a significant inhibitory effect on cell proliferation. The hexane extract of the root exhibited potent inhibition on A549 cancer cell growth at the 24th hour with IC\(_{50}\) value of 3.432 mg/mL. The results also showed that the hexane extract had displayed cytotoxic effect through an arrest at the G0/G1 phase of the cell cycle and induced apoptosis as well as DNA damage of A549 cells. Consequently, this study demonstrated the antiproliferative potential of the extracts from *S. petraeum*, especially hexane extract from the roots. Further studies are required to identify the mechanisms underlying these effects.

**Key words:** A549, Antiproliferative, Apiaceae, Apoptosis, Extract, Seseli petraeum.

**INTRODUCTION**

Aromatic and medicinal plants have attracted attention as a significant source of natural products all over the world (Canter et al. 2005, Singh & Singh 2011, Newman & Cragg 2016). Apiaceae is known as a wealthy family of flowering plants with their aromatic and medicinal properties. It is a cosmopolitan family, and most of the species grow in Asia comprising of 455 genera and over 3700 species throughout the world, mostly in temperate regions (Crowden et al. 1969, Heywood 1979, Davis et al. 1988, Baytop 1999, Pimenov & Leonov 2004, Heywood et al. 2007, Sayed-Ahmad et al. 2017). The Seseli L., as old Greek name (Hamlyn 1969), is one of the most prominent genera of Apiaceae with 125 to 140 taxa (Hedge & Lamond 1972, Davis et al. 1988) and 80 of which are distributed in Asia besides Europe, Africa, North America and Australia (Pimenov & Leonov 1993, 2004, Akalin Uruşak & Kızılaslan 2013, Aytaç & Duman 2013) as narrow endemics (Lyskov et al. 2018). On the other hand, Seseli is well represented in Flora of Turkey, by 12 taxa (Hedge & Lamond 1972, Davis et al. 1988, Duman 2000, Ozhatay et al. 2009), and new species continue to be discovered (Güner et al. 2011, Güner & Duman 2013, Çetin et al. 2015). Since ancient times Seseli is used by Hippocrates and Dioscorides in folk medicine originated from the words “Seseli, seselis, or sesili” (Dioscorides 2002, Stojkovic et al. 2009). Seseli species have been widely used in European traditional medicine, exhibiting antibacterial, antifungal,
insect repellent, emmenagogue, anti-flatulence, anti-inflammatory, antinociceptive, anti-tumor, anti-rheumatic activities, and protective effect on human lymphocytes DNA (Ilic et al. 2015). Moreover, the roots of S. mairei Wolff are known as “Zhu Ye Fang Feng” in Chinese folklore and used as a herbal remedy for human inflammation, swelling, rheumatism, pain, and common cold (Hu et al. 1990). In addition, S. libanotis is used as a cheese preservative and to provide aroma (Ozturk et al. 2000, Öztürk & Erşişi 2006), and the leaves of S. libanotis (Kelemkeşir or kelemenkeşir in Turkish) are consumed as a vegetable especially in the eastern part of Turkey (Baytop 1994). The fruits of S. tortuosum are used as an emmenagogue and in digestive diseases (Baytop 1999). Based on traditional uses, many studies concerning biological activities have been performed on Seseli species; and found that cytotoxic (Hu et al. 1990, Vucković et al. 2007, 2010, Gonçalves et al. 2012), antimicrobial (Singh et al. 2002, Ozturk & Erşişi 2006, Stojkovic et al. 2009, Matejic et al. 2012, Gonçalves et al. 2012), antioxidant (Stojkovic et al. 2009, Matejic et al. 2012, Stankov-Jovanovic et al. 2015) and anti-inflammatory (Kupeli et al. 2006, Khan et al. 2015, Tosun et al. 2016, Chun et al. 2016) properties.

The high demand and curiosity for natural products, especially for the development of new drugs for the treatment of cancer and other threatening diseases, has led us to examine the cytotoxic activity of plant extracts. The literature search revealed that only a few publications on S. petraeum are present (Tosun et al. 2006, Kupeli et al. 2006). S. petraeum M. Bieb. is a perennial plant with a specific fibrous collar, called “Taş çasarı, stone seseli, taş seseli” in Anatolia, grows on rocky slopes in a limited area (Hedge & Lamond 1972). The aim of the present study is to investigate the antiproliferative effects of the extracts from S. petraeum obtained by different polarities on A549 cells as lung cancer is one of the leading causes of death in the world. As a part of our ongoing investigations on Turkish Seseli species, we undertook the present screening study on S. petraeum to evaluate its cytotoxicity potency and apoptosis-inducing effects on A549 cells to determine its probable anticancer properties.

MATERIALS AND METHODS

Plant material

The plant (about 1.5 kg) was collected from the Northern Site of Anatolia (Turkey) called Trabzon-Gümüşhane (Maçka) district (almost 40°28’N and 39°27’E) on 15.07.2017 at an altitude 800 m from the roadside cliffs, in the flowering period. The samples were identified by Prof. Dr. Hayri Duman (Gazi University, Faculty of Science, Department of Biology) and Prof. Dr. Alev Önder (Ankara University, Faculty of Pharmacy, Department of Pharmacognosy). The voucher specimen was kept in AEF (Herbarium of Ankara University Faculty of Pharmacy) under the registration number of AEF 26994.

Extraction

The aerial parts (AE) and roots (R) of the Seseli petraeum (SP) were dried in the shade and powdered by using a laboratory-scale mill. The parts of the SP (each 30 g) were extracted by n-hexane, ethyl acetate (AcOEt), and methanol (MeOH) using the Soxhlet apparatus (x100 mL) for 3 hours, subsequently. Solvents were evaporated to dryness under reduced pressure at 40°C to obtain crude extracts (Table I). Then, six types of extracts in different polarities were obtained, as follows in Table I.

Cell culture and treatments

A549 human lung cancer cells were purchased from the American Type Cell Culture Collection.
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Table I. The amounts of extracts from the different polarity of solvents.

| Plant Samples (30 g) | n-Hexane Extract (g) | Yield % | AcOEt Extract (g) | Yield % | MeOH Extract (g) | Yield % |
|----------------------|----------------------|---------|-------------------|---------|------------------|---------|
| Root                 | [1] 2.69 SPRH        | 8.96    | [2] 1.42 SPRE     | 4.73    | [3] 4.71 SPRM    | 15.7    |
| Aerial part          | [4] 2.50 SPAEH       | 9.33    | [5] 0.91 SPAEE    | 3.03    | [6] 5.45 SPAEM   | 18.16   |

[1]-SPRH: Seseli petraeum root hexane extract; [2]-SPRE: Seseli petraeum root ethyl acetate extract; [3]-SPRM: Seseli petraeum root methanol extract; [4]-SPAEH: Seseli petraeum aerial part hexane extract; [5]-SPAEE: Seseli petraeum aerial part ethyl acetate extract; [6]-SPAEM: Seseli petraeum aerial part methanol extract.

(ATCC, Germany). The cells were cultured in DMEM supplemented with 10% fetal bovine serum (Lonza, Germany) in 5% CO₂ incubator at 37°C. The cells were treated with 0.5, 1, 2.5, 5, and 10 mg/mL concentrations of the extracts from Seseli petraeum and incubated for 24 h under the same culture conditions. The stock solutions of extracts were dissolved in DMSO (Dimethyl sulfoxide), and the final concentration of this solvent was kept constant at 0.01%. The non-treated cells were used as control.

Cell growth assay

Different methods are used to screen anticancer agents. One of the techniques is known as MTT [3-(4,5-dimethylthiazol-2-yl)-2,4-diphenyltetrazolium bromide] assay, which is a reliable and primary method for preliminary evaluation of anticancer agents (Mosmann 1983, Alley et al. 1988). The effect of the extracts on cellular growth of A549 cells was determined by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole] assay. 180 μL of cell suspension from 5x10⁵ cells/mL were plated in a 96-well microplate. The cells were treated with 0.5, 1, 2.5, 5, and 10 mg/mL of the extracts for 24 h. Following incubation, the cells were treated with MTT solution (5 mg/mL) and incubated for 2 h. The absorbance of dissolved formazan crystals was recorded at 540 nm by spectrophotometer (Thermo, Germany). Results are expressed as the mean±S.D. of three independent experiments. The differences are * p<0.01 and **p<0.0001 compared to control. The IC₅₀ value (The half-maximal inhibitory concentration) was calculated through linear regression analysis of cell proliferation results and given in Table II.

Cell cycle analysis

Muse Cell Cycle Assay Kit (Millipore, Germany) has been used to determine the effect of the extract on cell cycle arrest. A549 cells were plated on 12-well plates at a density of 2x10⁴ cells/well and

Table II. IC₅₀ values of extracts determined by MTT assay.

| Extracts | IC₅₀ values (mg/mL) |
|----------|---------------------|
| [1]-SPRH | 3.432               |
| [2]-SPRE | 5.660               |
| [3]-SPRM | 5.661               |
| [4]-SPAEH| 15.567              |
| [5]-SPAEE| 10.604              |
| [6]-SPAEM| 8.318               |
treated with hexane extract of the root (SPRH) at 3.432 mg/mL, which is previously determined as \( \text{IC}_{50} \) value of extract by MTT assay. Following incubation for 24 h, the cells were harvested and then fixed with 70% ethanol at 4°C for 4 h. Cell pellets were then collected by centrifugation at 400 \( \times \) g for 10 min and incubated with assay solution for 30 min. The Muse Cell Analyzer (Millipore, Germany) has been used to detect three phases of the cell cycle, including G0/G1, S, and G2/M.

**Annexin V binding assay**

A549 cells were plated into six-well plates at a density of \( 1 \times 10^6 \) cells per well and incubated for 24 hr. The cells were then treated with 3.432 mg/mL SPRH. Following incubation, the cells were harvested, and the Annexin V assay kit (Millipore) was performed according to the manufacturer’s instructions. Briefly, 100 \( \mu l \) of Annexin V reagent added to 100 \( \mu l \) of cell suspension and incubated for 20 min at room temperature. Then, the apoptotic cell population was detected by Muse Cell Analyzer (Millipore). This assay utilizes Annexin V to detect PS on the external membrane of apoptotic cells. It is excluded from live, healthy cells, as well as early apoptotic cells. Four populations of cells can be distinguished in this assay: non-apoptotic cells: Annexin V (-) and 7-AAD (-); early apoptotic cells: Annexin V (+) and 7-AAD (-); late-stage apoptotic and dead cells: Annexin V (+) and 7-AAD (+); mostly nuclear debris: Annexin V (-) and 7-AAD (+).

**Fluorescence imaging**

The A549 cells were stained to visualize the effects of SPRH on apoptosis, using Annexin V-FITC and PI dye (BD, Germany). The cells were placed into an 8-well chamber slide (Millipore, Germany) at a density of \( 5 \times 10^6 \) cells per well and incubated for 24 h. Then, the cells were treated with 3.432 mg/ml of SPRH and incubated for 24 h again. Following incubation of cells with the extract, cells were incubated with 20 \( \mu l \) of Annexin V-FITC and/or PI dye for 20 min at room temperature in the dark. Images were obtained using an inverted fluorescence microscope (Olympus, Germany).

**Statistical analysis**

Statistical analyses were performed using GraphPad Prism 6.0 version (GraphPad Software Inc.). Data obtained from the cell culture experiments were expressed as mean ± SD, and a one-way ANOVA test was applied for multiple comparisons.

**RESULTS**

In the present study, the plant extracts were obtained by gradually increasing the polarity of solvents (hexane, ethyl acetate, and methanol) in a Soxhlet apparatus. The amounts and yields of extracts are given in Table I.

The cells have proceeded with different concentrations of *Seseli petraeum* extracts between 0.5 to 10 mg/mL for 24 hr, and their cytotoxic effect on A549 human lung cancer cells was evaluated by MTT test (Figure 1). Although our results showed that almost all parts (aerial parts and roots) of the SP had significant effects on the inhibition of cell proliferation, the hexane extract from the root [1]-SPRH was the most potent inhibitor of cell growth with an \( \text{IC}_{50} \) value of 3.432 mg/mL (Table II). The viable cell amount in [1]-SPRH treated group significantly decreased to 75.20±5.22% and 12.64±0.24% at 1 mg/mL and 2.5 mg/mL concentrations, respectively.

The further analyses were performed using extract [1]-SPRH at \( \text{IC}_{50} \) concentration. The cell population percent significantly increased to 11.70±1.50% in [1]-SPRH treated group, whereas it was 1.80±0.06% in the nontreated control group.
The results of cell cycle analysis showed that the extract [1] has significantly induced a cell cycle arrest at the G0/G1 phase (Figure 2).

The effects of extract [1]-SPRH on apoptosis of A549 cells were evaluated by measuring the binding amount of annexin V to phosphatidylserine, which is exposed to cell surface an early marker of apoptosis (Figure 3). In extract [1]-SPRH treated group, the live cell population % significantly decreased to 70.66±1.58 % (p<0.05), while the population % of late apoptosis increased to 21.01±3.37 % (p<0.05). Through fluorescence imaging, it has also been determined that extract [1]-SPRH has induced DNA degradation strongly when compared to control (Figure 4).

Our results showed that, although all extracts prepared from aerial and roots of SP had notable effects on inhibition of cell proliferation, the hexane extract of the roots of this plant [1]-SPRH had a more potent effect compared to the other extracts obtained by the different polarity of the solvents.

DISCUSSION

Cancer is one of the leading causes of death and still maintain to be a significant health problem worldwide. The new anticancer agents from natural sources have yet been discovered in the scientific and commercial field (Parkin et al. 2005, Jemal et al. 2010) but still an urgent need for the development of new anticancer agents. Thousands of plants have been found to have significant anticancer effects (Mukherjee et al. 2001, Balunas & Kinghorn 2005, Cragg & Newman 2005, Srivastava et al. 2005). Since a long time, many studies have indicated that

Figure 1. The effect of the extracts Seseli petraeum on cell growth of A549 human lung cancer cells. The 180 μl of A549 cell suspension from 5x10^4 cells/ml were plated in a 96-well microplate. A549 cells were exposed to different concentrations of extracts (0.5-10 mg/mL) for 24 h. Following incubation, the cells were treated with MTT [3-(4,5-dimethylthiazol-2-yl)-2,4-diphenyltetrazolium bromide] solution (5 mg/mL) and incubated for 2 hours. The absorbance of dissolved formazan crystals was recorded at 540 nm by spectrophotometer (Thermo, Germany). Results are expressed as a percentage of viable cell amount. The non-treated cells were used as control. Each value represents the mean±standard deviation from three independent experiments performed in triplicate. (*p < 0.01, **p < 0.0001, compared to control). (The numbers define the extracts as; [1]-SPRH; [2]-SPRE; [3]-SPRM; [4]-SPAEH; [5]-SPAEE; [6]-SPAEM).
Figure 2. The results of cell cycle analysis. The A549 cells were plated on 12-well plates at a density of 2x10^5 cells/well and treated with 3.432 mg/mL of hexane extract from the root [1] for 24 hr and cell cycle assay was performed according to the instructions as described in the methods section. Later, the cell population percent at different phases of the cell cycle, including G0/G1, S, and G2/M, were detected by Muse Cell Analyzer (Millipore, Germany). The results were given for three independent experiments. The differences are ** from control (p<0.0001).

Figure 3. The results of the Annexin V binding assay. The cells were plated in a 12-well plate at a density of 2x10^5 cells/ml and treated with 3.432 mg/mL of hexane extract from the root [1] for 24 hr, and the apoptosis was detected by the Muse cell analyzer (Millipore). Nontreated cells were used as control. The apoptotic cells were determined by the Annexin V positivity based on phosphatidylserine exposure, and dead cells were determined by the nuclear dye 7-AAD (7-aminoactinomycin D) positivity. Four different cell population were enabled to examine by cytofluorometric separation on a Muse cell analyzer: non-apoptotic live (lower left (LL): 7-AAD negative, apoptosis negative), non-apoptotic dead (upper left (UL): 7-AAD positive, apoptosis negative), apoptotic live (lower right (LR): 7-AAD negative, apoptosis-positive), and apoptotic dead (upper right (UR):7-AAD positive, apoptosis-positive) cells. The results were given for three independent experiments, and the differences are * from control (p<0.01).
the mechanism of action of many anticancer drugs is based on apoptosis induction, and thus opening a new strategy in search of anti-cancer drugs (Cohen et al. 1997, Hanahan & Weinberg 2000, Sun et al. 2004, Wong 2011, Ramasamy et al. 2012).

Despite the high potential of Seseli species to be a valuable source of bioactive molecules, not enough studies have been done on chemical and biological activity. The literature revealed that Seseli species have mainly included coumarins (Barrero et al. 1990, Cecherelli et al. 1990, Glowniak et al. 1991, Tosun et al. 2005), cinnamic acid derivatives (Banerjee et al. 1987), sesquiterpene lactones, phenylpropanoids (Barrero et al. 1994) and essential oil (Bader et al. 2003, Habibi et al. 2003, Kaya et al. 2003). However, Vuckovic et al. (2010) have proved that a prenylated flavanonol named seselinonol from S. annuum L. roots exhibited a beneficial effect by decreasing DNA damage of human lymphocytes using cytochalasin-B blocked micronucleus (CBMN) assay (Vuckovic et al. 2010). Moreover, a tetrahydrofuranoid lignan named seselinone and eudesmin from the aerial parts of S. annuum L. showed cytotoxic activity against C6 rat glioma cell cultures in a different study performed by the same research group (Vuckovic et al. 2007). When the cytotoxic activity of the essential oils of Seseli tortuosum and S. montanum subsp. peixotoanum compared; it was observed that S. tortuosum essential oil has cytotoxic properties to human cells for the assessment of keratinocytes viability when used in concentrations higher than 0.64 µL/mL by MTT assay (Gonçalves et al. 2012). The ethanolic extract of the roots of S. mairei Wolf. have exhibited notable cytotoxic effects against KB, P-388, L-1210 tumor cell lines (ED50 < 20 µg/mL). Later, it was understood that this effect was caused by seselidiol, a polyacetylene derivative in the active fraction (Hu et al. 1990).

In our study, we observed a significant effect on hexane extract of the roots of S. petraeum due to the nonpolar compounds (nonpolar coumarins) mostly pass through the hexane, and the result may depend on it.
Moreover, some of the pyranocoumarin derivatives called as 3',4'-dihydroxy-3',4'-dihydroseselin are also exhibited cytotoxic effects against P-388 lymphocytic leukemia cells (Egan et al. 1990) besides the many other coumarin derivatives which are displayed anticancer potential (Kaur et al. 2015, Venugopala et al. 2013). In a previous study, the pyranocoumarin-type coumarins have been isolated from the hexane extract of Seseli gummiferum ssp. corymbosum (Tosun et al. 2005, 2007, Tosun 2006). Moreover, one of the pyranocoumarin called corymbocoumarin isolated hexane extract of this plant has been found active for lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages, and consider that it could be a useful therapeutic approach for inflammation-associated diseases (Chun et al., 2016). The hexane extracts of not only Seseli species but also other species had been found active against some of the cancer cell lines. For example, the hexane extract of the peels of Citrus hystrix (Rutaceae) fruits exhibited preferential cytotoxicity against PANC-1 (human pancreatic cancer cells) using a nutrient-deprived medium. This bioactive extract has furanocoumarins, and simple coumarins, which were tested for their preferential cytotoxicity against three different human pancreatic cancer cell lines (PANC-1, MIA PaCa-2, and PSN-1), and bergamottin was found the most active furanocoumarin (Sun et al. 2018). The bioassay-guided fractionation of the n-hexane extract of Citrus reticulata Blanco stem bark led to several coumarins and evaluated using MTT assay against three human cancer cell lines (human lung adenocarcinoma cell line A549, human breast adenocarcinoma cell line MCF7, and human Caucasian prostate adenocarcinoma cell line PC3). A significant activity of the n-hexane (IC₅₀ = 45.6 μg/mL) and the dichloromethane extracts (IC₅₀ = 54.7 μg/mL) have been found against the breast cancer cell line MCF7 (Tahsin et al. 2017).

The present study has demonstrated that the extracts of Seseli petraeum have a potent antiproliferative effect against A549 lung cancer cells through induction of cell cycle arrest at G0/G1 phase and within the lowest IC₅₀ value, the hexane extract from the root coded as [1]-SPRH has significantly induced apoptosis of A549 cells as well as DNA damage. Further analyses will be helpful to identify the mechanisms underlying these effects. Furthermore, this effect could be attributed to coumarins passing towards the non-polar solvent (like hexane), which is usually present in the aglycone structure.

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A.S.C. Supplied the plant material from nature, extraction; F.B.A. Performed cell culture experiments, interpreted the results, and wrote the paper; A.O. Created the idea and organized the assays, prepared the manuscript, interpreted the results.

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