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Cytotoxic Activity of Root, Stem, and Flower Essential Oils from *Ferula tenuisecta* Korovin

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Highlights

- The hydrodistillation method was used to obtain essential oil from *Ferula tenuisecta* Korovin.
- The chemical composition of essential oils were identified by Gas Chromatograpy-Mass Spectrometry.
- All samples showed low potency and weak cytotoxicity activity.

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Abstract

This study aims to investigate the phytochemical composition and cytotoxic activities of essential oils derived from *Ferula tenuisecta* Korovin, given its traditional medicinal uses and potential as a source of bioactive compounds. The hydrodistillation method was used to extract essential oils from the root, stem, and flower of *F. tenuisecta*. The yields were calculated as 1.7 mL of essential oil in the roots, 0.03 mL in the flowers and 0.01 mL in the stems. The chemical composition was analyzed by GC-MS, identifying 41 compounds in flower oil accounting for 92.8% of the total essential oil, 40 in stem oil accounting for 83.6% of the total essential oil, and 35 in root oil accounting for 98.5% of the total essential oil. In flower essential oil, camphor (14.8%) and α-pinene (11.5%) were the predominant compounds. Oxygenated sesquiterpenes (32.8%), oxygenated monoterpenes (30.4%), and monoterpenes (19.6%) were the dominant chemical groups. In stem essential oil, osthole (13.9%) and 4-oxo-β-ionol (12.4%) were the main compounds. Oxygenated sesquiterpenes (38.9%), coumarin (13.9%), and aromatics (11.0%) were the dominant chemical groups. In root essential oil, fenchone (25.3%), α-pinene (18.5%), and fenchol (12.0%) were the predominant compounds. Cytotoxic activity was determined by MTT assay. This is the first comprehensive study analyzing the chemical composition and cytotoxic properties of essential oils derived from three parts of *F. tenuisecta*.

1. INTRODUCTION

Medicinal plants have gained importance in healthcare worldwide due to their significant bioactivities against various diseases often due to their anticancer, antiinflammatory and antioxidant ingredients [1-3]. Essential oils are among the most important metabolites obtained from plants, and they are highly beneficial for human health. Various studies showed their antimicrobial, antioxidant and sedative properties [4-6]. Apiaceae family is one of the most widespread plant families on earth and is known for having rich essential oil content. *Ferula* is the third most prevalent genus in Apiaceae family, with approximately 200 species, and is highly reputable due to its many biological activities, including anti-infective, antioxidant, and antispasmodic activities [7]. The genus is widely distributed throughout Asia and the Mediterranean regions. Commonly, *Ferula* species grow in high-elevation areas and dry environments. *Ferula* species have been highly important in various local traditional medicinal systems for centuries due to their efficiency and low side effect profile. *Ferula* species are rich in coumarins, sulfur-containing ingredients, flavonoids and carbohydrates. Moreover, they are rich in essential oils, and they have been thoroughly

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characterized for their phytochemicals, such as α-pinene, β-pinene, myrcene, limonene, β-caryophyllene, germacrene B, germacrene D, δ-cadinene, caryophyllene oxide, α-cadinol, guiaol, spathulenol, sec-butyl (*Z*)-propenyl disulfide and *sec*-butyl (*E*)-propenyl disulfide [8]. *Ferula tenuisecta* is not the official species of *Ferula* genus however is a source of raw materials for industrial production of ferulene, tefestrol, and panopherol preparations. Previously, the drug tefestrol was developed, which is a natural mixture of esters of sesquiterpene alcohols, the main components of which are ferutinin and tenuferidine, obtained from the root of *Ferula tenuisecta* and used as a medicinal product. In addition to ferutin and tenuferidine, *Ferula tenuisecta* roots also contain esters such as ferutin, teferin, and fertidine, which are comparable in estrogenic activity [9].

Investigations on the cytotoxic properties of plants and preparations from plant parts are increasing due to the need for novel anticancer agents. There are numerous studies in the literature in search of novel agents from nature that are screening for cytotoxic properties that might be candidates for further studies. Similarly, essential oils are being prevalently investigated for this purpose. In particular, the search for concurrent utilizations of essential oils with cancer chemotherapeutics might be considered a hot topic in research. Various studies have demonstrated that essential oils might be important candidates for anticancer therapies [10]. Therefore, screening the cytotoxic properties of essential oils might lead to further studies that might be beneficial for cancer treatment. There are no study on the chemical composition and anticancer activities of the root, stem, and flower essential oils of *F. tenuisecta*. This is the first study on the chemical composition and cytotoxic activity of the flower, stem, and root essential oils of *F. tenuisecta*. The chemical composition of the root, stem, and flower essential oils were identified by Gas Chromatograpy-Mass Spectrometry. In addition, the cytotoxic effects were investigated on four different human cell lines. This study aimed to provide information about the traditional medicinal use and bioactive components of *Ferula tenuisecta*.

2. MATERIALS AND METHODS

2.1. Plant Material

The points of study of the *F. tenuisecta* species are given in Table 1; 1- population is located in the Turkestan region, Tolebi district, “Sairam-Ugam State National Natural Park”; and Kapzhailau gorge (height 1795 m above sea level); 2- population was found in the Turkestan region, Tolebi district, “Sairam-Ugam State National Natural Park”, and Sairamsu gorge (height 1500 m above sea level); 3- population was found in the Turkestan region, Tulkubas district, “Sairam-Ugam State National Natural Park”; and Kokbulak forest Turnpike (height 1070 m above sea level) was described. The expedition work was carried out with the participation of PhD student Bekebayeva Madina and her domestic scientific supervisor Nazarbekova S.T.

2.2. Distillation

The dried root, stem, and flower parts of *F. tenuisecta* were chopped into small pieces. The dried plant materials were hydrodistilled with 1 L of H2O for 3 h using a Clevenger apparatus to obtain the essential oils. The apparatus was connected to a condenser, and the temperature was set to 6°C. One hundred grams were weighed for all the samples, and the yields were calculated as 1.7 mL of essential oil in the roots, 0.03 mL in the flowers and 0.01 mL in the stems. All the essential oils were kept in amber vials at –20°C until analysis [11].

Table 1. *Geographical location of the studied populations of F. tenuisecta*

Cenopopulation	Location	Coordinates-by length	Coordinates-in altitude	Height above sea level, m.
Cenopopulation 1 (27.04.2021)	Turkestan region, Tolebi district, "Sairam-Ugam SNNP", Kapzhailau gorge	E070°23.564'	N42°09.405'	1795 m.
Cenopopulation 2 (29.05.2021)	Turkestan region, Tolebi district, "Sairam-Ugam SNNP", Sairamsu gorge	E065°12.422'	N34°05.302'	1500 m.
Cenopopulation 3 (20.07.2021)	Turkestan region, Tulkubas district, "Sairam-Ugam SNNP", Kokbulak forest Turnpike	E070°19'22'	N 42°22'55'	1070 m.

2.3. Phytochemical Determination with GC–MS

Phytochemical compositions of the three essential oil samples were analysed by using Gas Chromatography-Mass Spectrometry technique. A non-polar HP-5MS column (5% phenyl, 95% methyl polysiloxane; 30m×0.25 mm, 0.25 m film thickness) was preferred for the separation. The oven temperature programme was set as follows: starting with 60ºC and holding in that temperature for 1 minute. Then the temperature linearly increased to 246ºC with 3 degree increment every minute. Afterwards, the temperature remained stable for another 30 minutes. He was determined as the transporter gas due to its inert nature, flow rate was set as 0.9 mL every minute and kept stable. Identification of the peaks were done with two different methods. Every peak was investigated through well-known mass spectra libraries (NIST14 and Wiley7) and also relative indices were calculated in comparison with *n*-alkane series (8C to 40 C) and compared with previous literature [4].

2.4. Evaluation of Cytotoxic Activity

The cell lines used to determine the anticancer effect were A549 (human lung adenocarcinoma) (CCL-185), MCF-7 (human breast carcinoma) (HTB-22), U87 (human glioblastoma) (HTB-14), and L929 (mouse fibroblast cell) (CCL-1), all obtained from ATCC (American Type Culture Collection, Rockville, MD, USA). The cells were cultured in DMEM supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin and incubated at 37°C with 5% CO_2. The flower, stem, and root essential oils were dissolved in ethanol at 5 mg/100 µl, with the final concentration of ethanol less than 1%. For the MTT assay, cells were seeded in 96-well plates at a density of 5×10^4 cells per well and exposed to various concentrations of the essential oils (10-250 µg/ml) for 48 hours. At the end of the exposure period, 10 µl of MTT solution (5 mg/ml in PBS) was added to each well and incubated in the dark for 4 hours. After dissolving the formazan crystals with DMSO, absorbance was measured at 570 nm using a microplate reader (Thermo Scientific Multiskan GO), and cell viability was calculated [12]. The cytotoxicity activity assays were done in triplicate.

2.5. Statistical Analysis

The data was analysed using GraphPad Prism 9.5.1. and given as means ± standard errors (SEMs). Differences between means with p values less than 0.001 were considered statistically significant, as determined by one-way ANOVA followed by Dunnett's multiple comparison test. The IC_{50} values, representing the concentrations at which cell viability was reduced by half, were also calculated using GraphPad Prism 9.5.1.

3. RESULTS AND DISCUSSION

3.1. Phytochemical Characterization of the Essential Oils

The chemical composition was analyzed by GC-MS, identifying 41 compounds in flower oil accounting for 92.8% of the total essential oil, 40 in stem oil accounting for 83.6% of the total essential oil, and 35 in root oil accounting for 98.5% of the total essential oil. In flower essential oil, camphor (14.8%) and α-pinene (11.5%) were the predominant compounds. Oxygenated sesquiterpenes (32.8%), oxygenated monoterpenes (30.4%), and monoterpenes (19.6%) were the dominant chemical groups. In stem essential oil, osthole (13.9%) and 4-oxo-β-ionol (12.4%) were the main compounds. Oxygenated sesquiterpenes (38.9%), coumarin (13.9%), and aromatics (11.0%) were the dominant chemical groups. In root essential oil, fenchone (25.3%), α-pinene (18.5%), and fenchol (12.0%) were the predominant compounds. Oxygenated monoterpenes (41.3%), monoterpenes (34.5%), and sesquiterpenes (10.1%) were the dominant chemical groups (Figures 1-3, Table 2).

Various studies in the literature have investigated the compounds of essential oils from different parts of several species in the *Ferula* genus, the phytochemical profiles of which are diverse. More than 150 components have been detected in *Ferula* essential oils, and some of them have been shown to be responsible for various bioactivities [8]. In a study, the compositions of the essential oils of the aerial parts of six *Ferula* species collected from Uzbekistan (*F. caratavica, F. kuchistanica, F. pseudoreoselinum, F. samarcandica, F. tenuisecta*, and *F. varia*) were studied, and the results showed that α-pinene (42.0%), camphene (8.3%), and α-cadinol (8.1%) were present in high amounts in the essential oils of *F. tenuisecta* in the previous study. In contrast, neither compound was detected in *F. varia*, which might be considered an example of severe diversity between species in the *Ferula* genus. Monoterpene hydrocarbons (62.0%) and oxygenated sesquiterpenes (18.5%) were determined to be the dominant groups of *F. tenuisecta* essential oils [13]. Similarly, it was shown in a report that strong variation in chemical profile and yield might be observed between dried and fresh materials of the same sample [14]. Parallel to current results, α-pinene was determined to be the main compound in previous studies. Karakaya et al. reported that 75.9% of α-pinene was the major ingredient in *F. orientalis* [15]. Variation in chemical profiles might be explained by several factors, such as harvesting time, age, product density and geography [16]. Youssef et al. did not detect the other main compounds in the aerial parts of *F. tenuisecta* that were found in the present study, such as camphor, osthole, fenchone, fenchol, and 4-oxo-β-ionol [13]. Additionally, some dominant groups in the present study, such as aromatics and coumarin similarly were not detected in the previous study. This phenomenon might be explained by possible chemovarieties of the plant, which should be investigated in further studies.

Table 2. *The essential oil composition of the roots, stems, and flowers of Ferula tenuisecta*

RRI[1]	RRI Lit.[2]	Compounds	Flower (%)	Stem (%)	Root (%)
934	939	α-Pinene	11.5	3.1	18.5
948	953	Camphane	1.5	0.2	1.3
977	980	β -Pinene	1.2	0.2	1.4
992	991	β-Myrcene	1.4	1.0	2.7
998	996	Mesitylene	0.4	-	-
1006	1005	α -Phellandrene	-	0.3	0.9
1011	1011	delta-3-Carene	-	-	0.3
1027	1026	*p*-Cymene	3.8	6.0	3.2
1031	1031	Limonene	3.4	3.9	9.4
1032	1032	Eucalyptol	4.9	-	-
1038	1050	*trans*-beta-Ocimene	0.6	-	-
1059	1062	γ-Terpinene	-	0.4	-
1090	1096	Fenchone	1.8	2.6	25.3
1120	1123	Fenchol	1.6	2.7	12.0
1149	1143	Camphor	14.8	-	0.7
1142	1137	*trans*-Pinocarveol	-	0.3	-

1149	1145	*trans*-Verbenol	-	0.7	0.9
1165	1164	Pinocarvone	0.4	-	-
1168	1164	*cis*-Chyrsanthenol	0.5	-	-
1171	1169	Borneol	1.1	0.1	1.3
1182	1177	Terpinen-4-ol	0.3	-	-
1194	1183	*p*-Cymen-8-ol	0.5	0.5	0.5
1222	1220	*endo*-Fenchyl acetate	0.4	0.4	0.7
1235	1230	*exo*-Fenchyl acetate	-	-	0.4
1238	1235	Thymol-methyl-ether	-	0.6	0.7
1244	1242	Cuminal	-	0.3	-
1247	1244	Methyl carvacrol	-	1.0	1.5
1248	1243	Carvone	0.4	-	-
1264	1261	*trans*-Chrysanthenyl acetate	2.5	1.3	-
1278	1273	Phellandral	-	0.5	-
1285	1282	*p*-Ethylguaiacol	-	-	2.0
1288	1285	Bornyl acetate	1.2	0.3	-
1303	1290	Thymol	-	0.4	-
1317	1298	Carvacrol	-	0.4	-
1352	1340	δ-Elemene	-	0.3	-
1358	1354	*cis*-Chrysanthenyl propionate	0.5	-	-
1361	1358	Duraldehyde	1.5	1.8	-
1374	1356	Eugenol	-	-	0.3
1387	1384	β-Bourbonene	0.3	-	-
1422	1418	Caryophyllene	0.6	0.3	2.1
1429	1422	β-Maaliene	-	-	1.4
1437	1431	β-Gurjunene	-	-	0.7
1441	1441	Aromadendrene	-	-	0.4
1445	1445	β-Barbatene	-	-	0.6
1456	1454	Humulene	-	-	0.6
1460	1458	(*E*)-β-Farnesene	-	-	0.4
1489	1488	Chrysanthenyl-2-methyl butanoate	0.6	-	-
1490	1485	β-Selinene	-	-	0.7
1498	1441	*trans*-α-Bergamotene	-	-	1.2
1498	1497	Epishyobunone	3.5	6.5	-
1512	1509	β-Bisabolene	-	-	0.4
1518	1513	γ-Cadinene	-	-	0.4
1521	1518	Shyobunone	5.3	7.3	-
1528	1524	δ-Cadinene	0.4	0.4	1.2
1534	1534	Isoshyobunone	1.5	1.1	-
1587	1576	Spathulenol	5.9	1.9	-
1587	1581	Caryophyllene oxide	-	-	0.5
1608	1627	4-Oxo-β-ionol	6.3	12.4	-
1613	1631	3-Oxo-α-ionol	4.3	4.4	-
1629	1632	Acorenone 1	1.1	3.0	-
1637	1645	Dehydroxy-isocalamendiol	-	0.5	-
1644	1624	Isospathulenol	1.0	-	-
1659	1649	β-Eudesmol	0.5	-	-
1661	1640	τ-muurolol	-	-	1.2
1662	1653	α-Cadinol	0.8	1.0	-
1692	1688	α-Bisabolol	0.6	-	-
1700	1669	*trans*-calamenen-10-ol	0.5	0.8	2.7
1851	1846	Hexahydrofarnesyl acetone	0.9	-	-
2149	2143	Osthole	2.5	13.9	-
2305	2300	Tricosane	-	0.4	-

2506	2500	Pentacosane	-	0.4	-
		Monoterpene	19.6	9.1	34.5
		Aromatics	6.2	11.0	8.2
		Oxygenated Monoterpenes	30.4	8.9	41.3
		Hydrocarbons	-	0.8	-
		Sesquiterpenes	1.3	1.0	10.1
		Oxygenated Sesquiterpenes	32.8	38.9	4.4
		Coumarin	2.5	13.9	-
		Total identified compounds	**92.8**	**83.6**	**98.5**

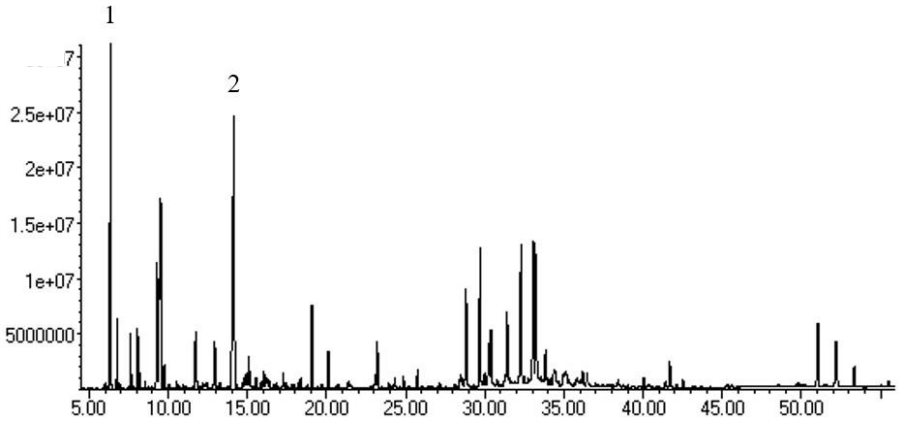


Figure 1. *Chromatogram of flower essential oil (**1:** alpha-pinene; **2:** camphor)*

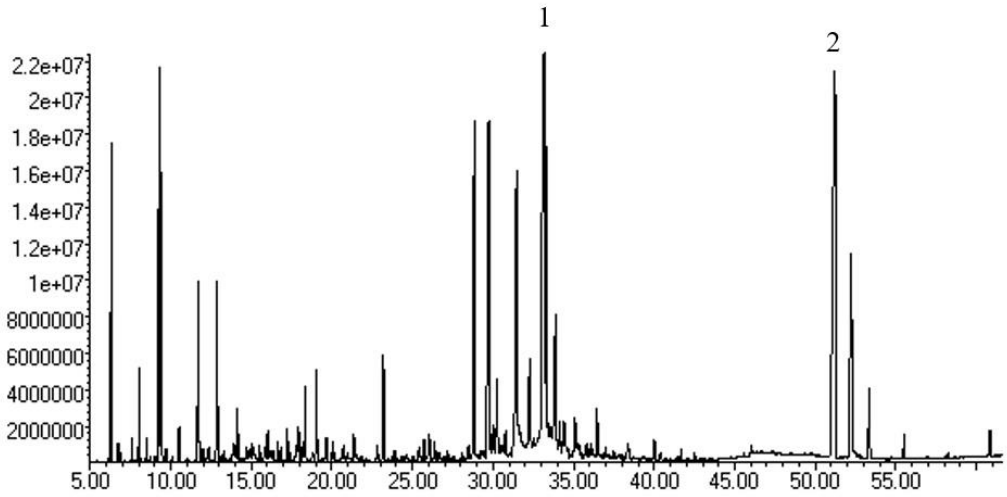


Figure 2. *Chromatogram of stem essential oil (**1:** 4-oxo-β-ionol; **2:** Osthole)*

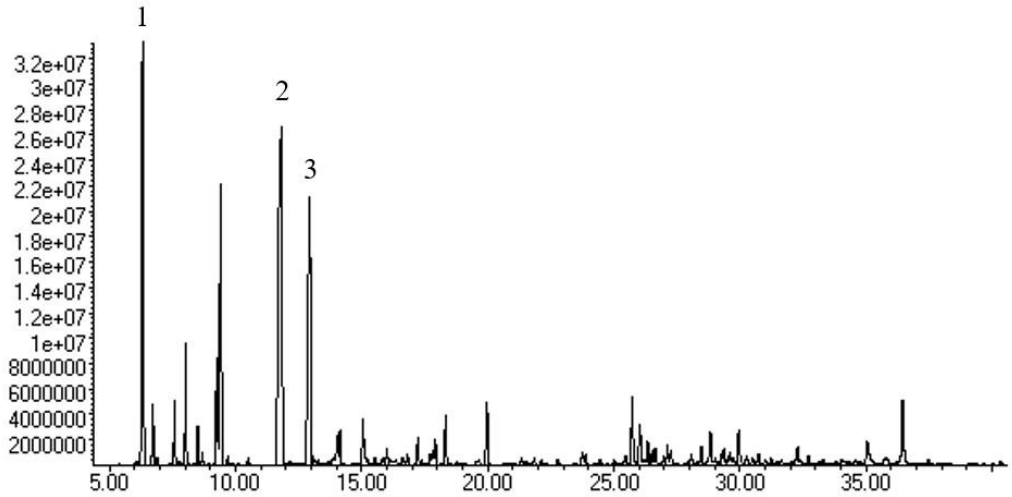


Figure 3. *Chromatogram of root essential oil (**1:** alpha-pinene; **2:** Fenchone; **3:** Fenchol)*

3.2. Cytotoxic Properties of *F. tenuisecta* Essential Oils

The common bioactivities of essential oils include antioxidant, antimicrobial, and antispasmodic activities. And previously, studies have shown that essential oils have a potential anticancer properties [6]. Different parts of *F. tenuisecta* are rich in essential oils with diverse phytoconstituents, which might contribute to its possible cytotoxic bioactivities. For this reason, three essential oils obtained from three different parts of *F. tenuisecta* were investigated for their anticancer activity on three different human cancer cell lines and an animal cell line. Three essential oils showed low potency and weak cytotoxicity activity against the A549 (lung cancer), U87MG (glioblastoma cancer), MCF-7 (breast cancer), and L929 (normal fibroblast cells) cell lines. Unlike in the other essential oils, in the L929 normal cell line, the addition of root essential oil was found to be ineffective. The IC_{50} values of flower essential oil were 140.7, 165.4, 174.3, and 176.1 µg/mL for MCF-7, A549, U87MG, and L929 cell lines respectively. The IC_{50} values of stem essential oil were 151.7, 168.5, 177.6, and 180 µg/mL for MCF-7, A549, U87MG, and L929 cell lines respectively. The IC_{50} values of root essential oil were 200.4, 234.7, and 385.1 µg/mL for MCF-7, U87MG, and A549 cell lines respectively (Table 3, Figure 4). The essential oils from the flowers showed the greatest cytotoxicity, with the lowest IC_{50} values when compared with other essential oils. The difference in the bioactivities may be explained by the variation in phytoconstituents. Unlike stems and roots, flower essential oils are rich in camphor. In a previous study, essential oil from the leaves of *Artemisia judaica* was found to be a strong inhibitor of the MCF-7 cell line, and camphor was determined to be the major ingredient [17]. In another study, camphor was detected as one of the major phytoconstituents of the essential oil from *Curcuma zedoaroides*, and it was found to have cytotoxic effects on several cancer cell lines, including A549 and MCF-7 [18].

Table 3. *Anticancer activity of three essential oils (IC_{50}, µg/mL)*

Essential oils	Cell lines			
	A549	**U87MG**	**MCF-7**	**L929**
Root	385.1	234.7	200.4	-
Stem	168.5	177.6	151.7	180
Flower	165.4	174.3	140.7	176.1

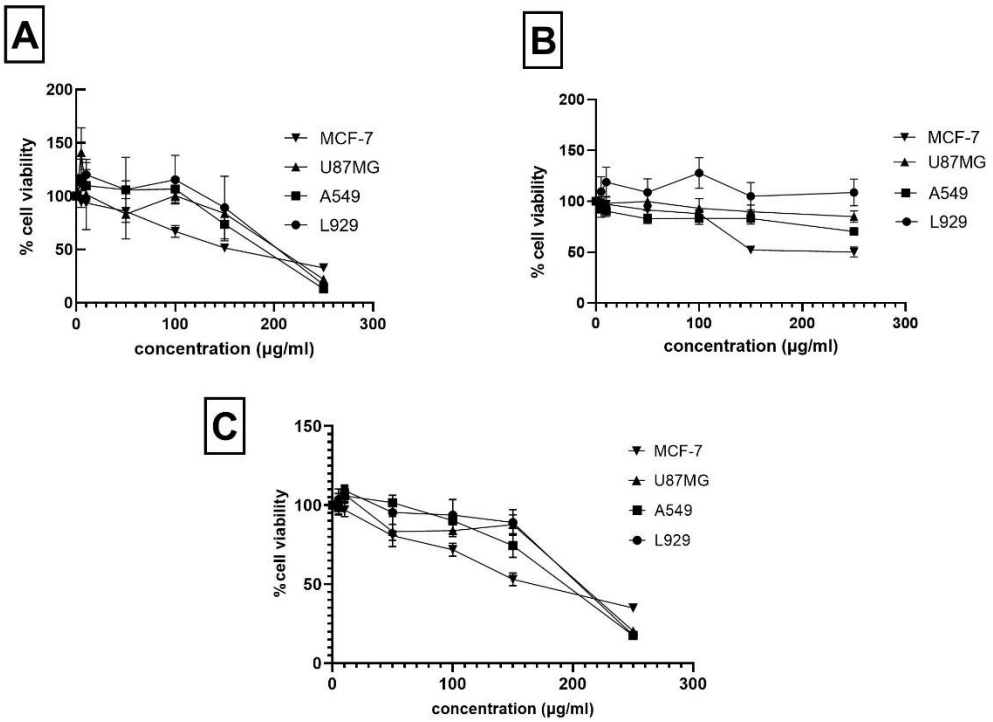


Figure 4. *Analysis of cell viability of Ferula essential oils on A549, MCF-7, U87, and L929 cells using MTT assay. (A) Flower essential oil, (B) Root essential oil, and (C) Stem essential oil*

Although this is the first study investigating the cytotoxicity of *F. tenuisecta*, there are various studies in the literature on this topic. In a study, Elghwaji et al. [19] reported that the essential oils of the flower and leaves of *F. tingitana* were evaluated against HeLa, HepG2, and MCF-7 tumor cell lines. Both essential oils showed significant cytotoxic activity against selected human cell lines, with IC_{50} values between 4.3 and 10.9 µg/mL. The flower essential oils included 3-carene (13.9%), alpha-thujene (13.5%), elemol (8.9%), α-myrcene (8.1%), and sabinene (7.5%), while the essential oils from the leaves included delta-cadinol (13.8%), gamma-eudesmol (9.7%), 7-alpha-Eudesma-3,5-diene (9.0%), elemol (8.3%), and germacrene D-4-ol (7.7%) as the main compounds [19]. In another study, Ben Salem et al. investigated the root essential oil of *F. lutea* and determined that δ-3-carene (72.6%) was the main compound. The cytotoxic activity of the essential oil was studied against the HT-29 and HCT-116 colon cancer cell lines, and the IC_{50} values were calculated to be 26.39 and 81.0 µg/mL against HT-29 and HCT-116, respectively [20]. In the present study, a minor amount of δ-3-carene was found only in the root essential oil. Although there were significant differences between the cytotoxic effects of essential oils from the same genus, this result was likely rooted in the diversity of their phytochemical profiles.

4. CONCLUSION

This study aimed to reveal the detailed phytochemical profile of essential oils obtained from the flowers, roots and stems of *F. tenuisecta.* GC–MS analysis was conducted on three essential oils, and the results revealed that phytochemical profiles of the essential oils are highly variable and might lead to differentiation of possible bioactivities. For the determination of cytotoxicity of the essential oils, four different cell lines were used (A549, U87MG, MCF-7, and L929) and the results showed that essential oils obtained from *F. tenuisecta* had low potency and weak cytotoxicity activity. However, statistically significant differences between essential oils were observed in cytotoxicity test in agreement with the variation in phytoconstituents. This report is the first in the literature that reveals and compares phytochemical profile of three different part of *F. tenuisecta.* Likewise, there is a lack of investigations which investigates cytotoxic properties of the aforementioned essential oils in the literature. When considering the limitations of the study, further studies are needed with multiple routes of clarification with higher amount of plant materials.

CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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