

Anti-Colorectal Cancer Effects of Medicinal Plants: *Euphorbia helioscopia*, *Ferula elaeochytris*, and *Sideritis albiflora*

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Abstract: Phytochemicals, extracts, and mixtures obtained from plants have been offered as an option for cancer treatment and prevention for modern drug discovery in recent years. For this purpose, in this study, anti-colorectal cancer effects of the hexane, acetone, methanol, and water extracts obtained by sequential extraction from *Euphorbia helioscopia* L., *Ferula elaeochytris* Korovin, and *Sideritis albiflora* Hub.-Mor. on DLD-1 cell line were investigated *in vitro* by using Alamar blue assay. Dose-dependent inhibition was detected in the viability of DLD-1 cell line. In all three plants species, *E. helioscopia* (IC₅₀: 140.83±0.31 µg/mL), *F. elaeochytris* (IC₅₀: 67.93±0.12 µg/mL), and *S. albiflora* (IC₅₀: 85.12±0.10 µg/mL) methanol extracts showed higher anti-colorectal effects on DLD-1 cell line compared to other extracts tested for the same species. In addition, the IC₅₀ value of doxorubicin used as a standard was found as 6.10±0.55 µg/mL. With the results obtained, as the first report highlighting *in vitro* anti-colorectal cancer effects of the studied plant species on DLD-1 cell line, promising marks were obtained from the analysis of the extracts as anti-cancer sources for plant-derived drug applications.

Keywords: Plant species, extracts, cytotoxic activity, DLD-1 cell line, Alamar blue assay.

Tıbbi Bitkilerin Anti-Kolorektal Kanseri Etkileri: *Euphorbia helioscopia*, *Ferula elaeochytris* ve *Sideritis albiflora*

Öz: Bitkilerden elde edilen fitokimyasallar, ekstraktlar ve karışımlar, son yıllarda modern ilaç keşfi için kanser tedavisinde ve önlenmesinde bir seçenek olarak sunulmuştur. Bu amaçla, bu çalışmada sıralı ekstraksiyon kullanılarak *Euphorbia helioscopia* L., *Ferula elaeochytris* Korovin ve *Sideritis albiflora* Hub.-Mor. bitkilerinden elde edilen hekzan, aseton ve metanol ekstraktlarının DLD-1 hücre hattı üzerindeki anti-kolorektal kanser etkileri Alamar mavisi testi kullanılarak *in vitro* olarak incelendi. DLD-1 hücre hattının canlılığında doza bağlı inhibisyon tespit edildi. Üç bitki türünün hepsinde, *E. helioscopia* (IC₅₀: 140.83±0.31 µg/mL), *F. elaeochytris* (IC₅₀: 67.93±0.12 µg/mL) ve *S. albiflora* (IC₅₀: 85.12±0.10 µg/mL) metanol ekstraktları aynı türler için test edilen diğer ekstraktlara kıyasla DLD-1 hücre hattı üzerine daha yüksek anti-kolorektal kanser etkisi gösterdi. İlave olarak kullanılan doksorubisinin IC₅₀ değeri 6.10±0.55 µg/mL olarak belirlendi. İncelenen bitki türlerinin DLD-1 hücre hattı üzerindeki *in vitro* anti-kolorektal kanser etkilerini vurgulayan bu ilk çalışma ile bitki kaynaklı ilaç uygulamaları için anti-kanser kaynakları olarak ekstraktların analizinden umut verici sonuçlar ortaya çıkarıldı.

Anahtar kelimeler: Bitki türleri, ekstre, sitotoksik aktivite, DLD-1 hücre hattı, Alamar mavisi testi.

1. Introduction

Throughout history, people have preferred and used plants in nature for the treatment of many diseases (Aras et al., 2021). Although developing technology and newly produced treatment techniques have brought new drugs, the dangerous side effects of these drugs have reached levels that cannot be ignored and the interest in scientific studies on plants and their bioactive properties has deepened (Yuan et al., 2016). It has been reported that the population benefiting from plants containing phytochemical compounds with bioactive properties in the treatment/prevention of many health problems constitutes 80% of the whole world population and this rate is even higher in developing countries (Ozkan et al., 2016). The concept of treatment named 'Complementary Medicine' has gained more importance from the past to the present, and in some countries, government incentives are

also given for research on the discovery of endemic plant species and their medical properties (Tekeli et al., 2019; Vickers & Zollman, 1999). The World Health Organization (WHO), in a report prepared based on scientific studies on medical plants by researchers from 91 countries, reported that there are approximately 20,000 species of plants used in the treatment of diseases (Patra et al., 2018). So far, it is known that around 10,000 phytochemical compounds have been identified in the plant kingdom, including tannins, flavones, triterpenoids, phenolics, steroids, saponins, polysaccharides, and alkaloids and still a large percentage has not been identified (Barbosa et al., 2013). In recent studies, natural phytochemicals with antioxidant, antimicrobial, antifungal, antidiabetic, anti-inflammatory, anticancer, and antihypertensive properties have been suggested as valuable for human health (Demir & Akpınar, 2020). The use of plants for medicinal purposes has increased with the discovery that chemical compounds

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used in drug production show similarities with plant active substances. In the past, the use of plant origin drugs was more common; this rate has gradually decreased as a result of the development of chemical applications. However, in recent years, with the research and development of new therapeutic uses of plants, the demand for natural herbal products has increased (Ekor, 2013). Due to the rich chemical structures of plants, it has been one of the research areas of pharmacology to use it for the development of new and highly effective drug formulations. In developed and developing countries, 25% of prescription medicines consist of active ingredients obtained from plants (Demir & Akpınar, 2020).

Cancer is defined as an abnormality in the structure of the cell as a result of genetic or epigenetic changes. This negative change occurs in cancer cells uncontrolled and rapidly. In addition, cancer cells have the ability to escape from physiological suppressors and spread (metastasize) with the mutations they undergo. These rapid and active growth processes of tumor cells cause cancer (with 277 different types) to be the second major disease-causing death worldwide (Hassanpour & Dehghani, 2017). It has been stated that colorectal cancer is in the third place after lung and breast cancer deaths in females, and lung and prostate cancers in cancer deaths in males. Approximately one million people get colorectal cancer every year and around five hundred thousand people die from this

disease (Bar-Shalom et al., 2019). At the same time advanced age, adenomas, genetic factors, family history, obesity, lifestyle, unbalanced eating habits, radiation, and some chronic diseases such as chronic inflammatory and diabetes mellitus are effective in the etiology of the disease (Aiello et al., 2019).

Nowadays, the low selectivity of drugs used in routine cancer therapies and the side effects they cause in multiple drug use increase the importance of drug researches on this subject. In this direction, the plant kingdom is seen as the most valuable source of new generation treatment agents in terms of drug discovery. In this study, anti-colorectal cancer effects of *Euphorbia helioscopia* L., *Ferula elaeochoytris* Korovin, and *Sideritis albiflora* Hub.-Mor. extracts on the DLD-1 cell line were investigated.

2. Material and Methods

2.1. Plant materials

The herbarium numbers, collection areas, and information about the other characteristics of the studied plant species were given in Table 1. The voucher specimens have been deposited at the herbarium of Natural Products Laboratory of Muğla Sıtkı Koçman University, Muğla, Turkey.

Table 1. Herbarium numbers, collection areas, and information about other characteristics of the studied plant species

	Species		
	<i>Euphorbia helioscopia</i> L.	<i>Ferula elaeochoytris</i> Korovin	<i>Sideritis albiflora</i> Hub.-Mor.
Herbarium number	MUMED1235	MUMED1051	EGE42372
Common name	Spurge-(Sütleğen)	Rod-(Çakşır)	Mountain tea-(Dağ çayı)
Genus	<i>Euphorbia</i>	<i>Ferula</i>	<i>Sideritis</i>
Family	Euphorbiaceae	Apiaceae	Lamiaceae
Collection area	Artvin-Turkey	Bayburt-Turkey	Muğla-Turkey
Bioactive properties of species	Antioxidant, anti-proliferative, anti-inflammatory, anti-bacterial, anti-fungal, anthelmintic, wound healing, anticholinesterase, and anti-urease activities (Deveci et al., 2018a; Yang et al., 2021)	Antioxidant, anti-diabetic, anti-tyrosinase, anticholinesterase, and cytotoxic activities (Baykan et al., 2020; Deveci et al., 2018b; Deveci et al., 2020)	Antioxidant, anti-ulcer, anti-diabetic, anti-tyrosinase, and anticholinesterase activities (Askun et al., 2009; Deveci et al., 2019; Deveci et al., 2020)

2.2. Extraction

Powdered *E. helioscopia*, *F. elaeochoytris*, and *S. albiflora* samples were separately extracted with *n*-hexane, acetone, and methanol (24 h and 4 times at room temperature) to produce the extracts, respectively. After filtration, the remaining solvents were removed by evaporation at 40°C under vacuum to give the extracts. The remaining plant parts were extracted with water at 80°C for one day and lyophilized to obtain the water extracts. All extracts were stored at +4°C until analysis.

2.3. Cell viability

RPMI-1640 growth medium (ATCC, Virginia, USA) and incubation conditions of 10% fetal bovine serum (FBS), 1% penicillin/streptomycin, 2 mM L-glutamine (Sigma, St. Louis, Missouri, USA) in 5% CO₂ at 37°C and 90-95% humidity were used for cultivation of DLD-1 (colorectal cancer) cell line.

2.4. Cell viability assay

1x10⁴ cells with growth medium were placed into 96-well

plate and left to incubate in 5% CO₂ at 37°C for 24 h until attachment occurred to the bottom. After addition of different concentrations of the plant extracts in the range of 1 µg/mL and 1000 µg/mL to the each well, viability and proliferation of the cells were determined in refer to Alamar Blue assay as defined previously (Karakurt & Adali, 2016; Deveci et al., 2021). The results were measured at 570 nm and 610 nm by using a 96-well microplate reader (MultiskanGo, Thermo Scientific Co., MA, USA). Doxorubicin was used as a standard. IC₅₀ values of the plant extracts were estimated as µg/mL through the sigmoidal curve plotted between the inhibition rate (%) and the concentration (µg/mL). Anti-colorectal cancer effect results were measured and calculated by using GraphPad Prism (GraphPad Software v5.0, USA).

2.5. Statistical analysis

All data on anti-colorectal cancer effect tests were the average of three parallel sample measurements. Data were recorded as mean ± S.E.M. Significant differences between means were determined by *t*-test, *p* values <0.05 were regarded as significant.

3. Results

Anti-colorectal cancer effects of the hexane, acetone, methanol, and water extracts of *E. helioscopia* and *F. elaeochoytris*, the hexane and methanol extracts of *S. albiflora* on DLD-1 cell line were screened by Alamar blue assay. The results in Table 2 showed the IC₅₀ values of the extracts. The cell viability (%) values of *E. helioscopia* extracts were presented in Fig. 1a, *F. elaeochoytris* extracts

in Fig. 1b, *S. albiflora* extracts in Fig. 1c. Heat Map analysis of the dose-dependent inhibition of the extracts on DLD-1 cell line were given in Fig. 2. Dose-dependent inhibition was detected in the viability of DLD-1 cell line. In all plant species, *F. elaeochoytris* (IC₅₀: 67.93±0.12 µg/mL), *S. albiflora* (IC₅₀: 85.12±0.10 µg/mL), and *E. helioscopia* (IC₅₀: 140.83±0.31 µg/mL) methanol extracts showed higher anti-colorectal cancer effects on DLD-1 cell line compared to other extracts tested for the same species.

Table 2. IC₅₀ values (µg/mL) of the extracts

Plant species	Extracts	Code	DLD-1 cell line
<i>E. helioscopia</i>	Hexane	EHH	142.01±0.06
	Acetone	EHA	245.38±0.92
	Methanol	EHM	140.83±0.31
	Water	EHW	> 250
<i>F. elaeochoytris</i>	Hexane	FHH	> 250
	Acetone	FHA	102.95±0.41
	Methanol	FHM	67.93±0.12
	Water	FHW	187.44±0.24
<i>S. albiflora</i>	Hexane	SAH	> 250
	Acetone	SAA	NT ^c
	Methanol	SAM	85.12±0.10
	Water	SAW	NT ^c
Standard	Doxorubicin ^b		6.10±0.55

^a IC₅₀ values represent the means ± SEM of three parallel measurements ($p < 0.05$). ^b Positive control. ^c Not tested.

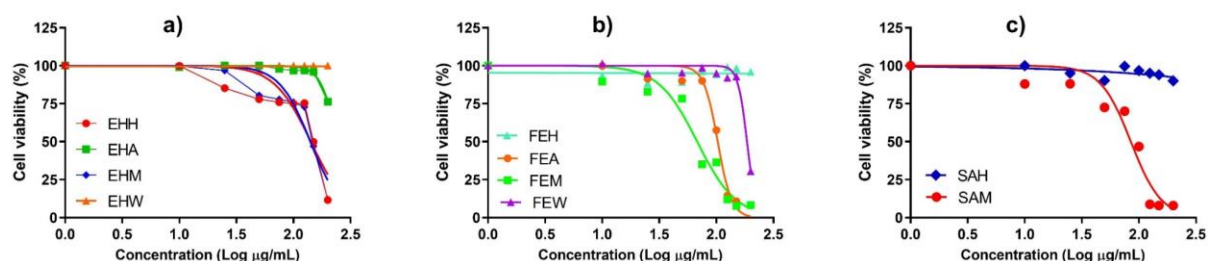


Figure 1. Cell viability (%) values of a) *E. helioscopia* extracts b) *F. elaeochoytris* extracts c) *S. albiflora* extracts. Coded as: hexane (EHH), acetone (EHA), methanol (EHM), water (EHW) extracts of *E. helioscopia*; hexane (FEH), acetone (FEA), methanol (FEM), water (FEW) extracts of *F. elaeochoytris*; hexane (SAH), methanol (SAM) extracts of *S. albiflora*

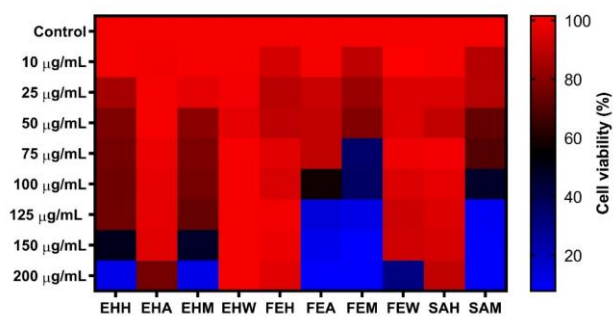


Figure 2. Heat Map analysis of the dose-dependent inhibition of the extracts on DLD-1 cell line. Cell viability decreased from red to blue color. Coded as: hexane (EHH), acetone (EHA), methanol (EHM), water (EHW) extracts of *E. helioscopia*; hexane (FEH), acetone (FEA), methanol (FEM), water (FEW) extracts of *F. elaeochoytris*; hexane (SAH), methanol (SAM) extracts of *S. albiflora*.

4. Discussion

In recent years, phytochemicals in plants have been presented as an option for the treatment and prevention of cancer in terms of complementary medicine as they have fewer side effects. (Chromanska et al., 2017). It is known that natural products of plant origin are better tolerated and these properties attract the attention of modern drug discovery. Estimated statistics revealed that only 10% of

the plant population was studied for pharmacological applications (Singh et al., 2016a; Wu et al., 2017). Approximately 60% of anti-cancer drugs are of natural origins such as microorganisms, vertebrates, plants, and invertebrates. Many studies have confirmed that most chemotherapeutic drugs target proliferative cells unspecifically and are cytotoxic. This situation later leads to the poor prognosis of cancer patients. Therefore, it is aimed to research and develop new anti-cancer agents that selectively affect cancer cells (Singh et al., 2016a; Singh et al., 2016b). The development of plant ingredients forms the beginning of traditional medicine and today plants still remain an important source of pharmaceutical agents. Particularly, the basis of cancer chemotherapy has been established especially by natural products for the last few years. Although combinatorial chemistry affords a wide diversity of new and synthetic drugs, natural products can offer effective compounds for the development of new agents with improved biological properties (Lahlou, 2013). This success in drug discovery is due to the high chemical diversity of natural resources; however, the chemical variability occurring in the plant population complicates the characterization processes of a large number of metabolites. The conventional methods used to discover the most active molecules have different disadvantages, consisting of a complex structure and long periods of time

such as separation, isolation, and identification studies from a crude extract. The screening of plant-derived mixtures is becoming an effective way to quickly select metabolites with biological properties (Kocuyigit et al., 2016).

Herein, *F. elaeochytris* methanol extract showed the highest anti-colorectal cancer effect on DLD-1 cell line. Also, all methanol extracts revealed the highest anti-colorectal cancer effect on DLD-1 cell line when compared to other extracts. In our previous study, catechin hydrate (105.5±2.3 µg/g) was reported as a major phenolic compound in *F. elaeochytris* methanol extract (Deveci et al., 2018b). It is elucidated that catechin derivatives act by suppressing the levels of phospho-AKT and nuclear β-catenin in colorectal cancer models and induction of apoptosis in different animal models (Yang et al., 2014). *S. albiflora* methanol extract was found as the second anti-colorectal cancer active extract and we identified caffeic acid (8.915±0.005 µg/g) as the major phenolic compound in our previous research (Deveci et al., 2019). Chiang et al. (2014) documented that caffeic acid derivatives suppress the PI3K/Akt and integrin-mediated signaling pathways and the proliferation of colorectal cancer cells through induction of cell cycle arrest in the G0/G1 phase. It has also been proven in previous studies that methanol is a more selective solvent for the extraction of bioactive compounds. The higher effects of the methanol extracts may be due to the synergistic effects of other secondary compounds in addition to the reported phenolic compounds (Altemimi et al., 2017; Truong et al., 2019).

There is a limited number of studies in the literature on anti-colorectal cancer effects of plant species belonging to *Euphorbia*, *Ferula*, and *Sideritis* genus. This is the first report highlighting anti-colorectal cancer effects of *E. helioscopia*, *F. elaeochytris*, and *S. albiflora* extracts on the DLD-1 cell line. Previously, the infusion of *Sideritis syriaca* was reported to inhibit HT-29 cell growth with value of ~ 60% at 1.00 µg/µL concentration after 48 h by Kogiannou et al. (2013). The IC₅₀ value of siderol, a well-known major constituent of the genus *Sideritis*, was calculated as 26.4±3.7 µM in DLD-1 cell line (Tomou et al., 2020). The hexane extract of *Ferula hermonis* root (IC₅₀: 25 µg/mL) was found to have moderate sensitivity on the LoVo cell line (Abutaha et al., 2019). In a different study, cytotoxic activities of the methanol 80% extracts and the hexane, chloroform, and methanol fractions of *Ferula szowitsiana*, and *Ferula hirtella* were tested on the HT-29 line. The IC₅₀ values were in the methanol 80% extracts and hexane, chloroform and methanol fractions were found as 36, 33, 102, > 300 µg/mL for *Ferula szowitsiana*; 89, 26, 110, > 300 µg/mL for *Ferula hirtella* (Hamzelooghdam et al., 2013). Growth inhibition rates of *Euphorbia helioscopia* petroleum ether, chloroform, ethyl acetate, and *n*-butanol extracts on SW-480 cell line were reported as ~ 80, 65, 45, 80% at 150 µg/mL concentration and ~ 75, 60, 40, 75% at 200 µg/mL concentration (Wang et al., 2012). Cytotoxicity of euphodendrophanes A, B, C, D, E, F, and tigliane euphodendriane A isolated from *Euphorbia dendroides* on DLD-1 line was reported with IC₅₀ values of 59.3, 22.1, 42.7, 37.9, 75.3, and 27.4 µM, respectively (Aljancic et al., 2011). Superior cytotoxic effect was observed in the methanol extract of *Euphorbia hierosolymitana* on HCT-116 cell line with IC₅₀ value of 4.22 µg/mL (El-Hallouty et al., 2020). Mesas et al. (2021) reported the cytotoxic effect of *Euphorbia*

lathyris ethanol extract (IC₅₀: 72.9±1.27 µg/mL) against HCT-115 cell line. In a study on *Euphorbia macrorrhiza*, inhibition ratios of Caco-2 cell line were recorded in the essential oil, hexane, chloroform, and ethyl acetate fractions as 96.32, 72.52, 8.52, 2.32% for root parts and 96.12, 83.57, 68.22, 4.61% for aerial parts at 250 µg/mL concentration. In addition, *n*-butanol and residual methanol fractions of both parts of *Euphorbia macrorrhiza* were found as inactive (Lin et al., 2012). There are similarities and differences between our results and the literature. These differences may be due to effects such as discrepancy of plant species, cell line, extraction solvent, and methods.

In conclusion, this study is the first to examine anti-colorectal cancer effects of *E. helioscopia*, *F. elaeochytris*, and *S. albiflora* against DLD-1 cell line. The results support that the studied plant species will be an important step in the discovery of effective natural agents in the treatment of colorectal cancer and will illuminate further studies.

Ethics committee approval: Ethics committee approval is not required for this study.

Conflict of interest: The authors declares that there is no conflict of interest.

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