ORIGINAL PAPER

JMS Journal of Medical Science

Evaluation of the Anticancer Potential of *S. euphratica*, *S. staminea*, and *S. trichoclada* in Colon Cancer: Monotherapy and Combination with Cisplatin

Aydın Sever
Department of Pharmacy Services, Vocational School of Health Services, Bingol University, Bingol, Türkiye
https://orcid.org/0000-0002-6727-1556
Corresponding author: asever@bingol.edu.tr

Mehmet Kadir Erdoğan
Department of Molecular Biology and Genetics, Faculty of Arts and Sciences, Bingol University, Bingol, Türkiye
https://orcid.org/0000-0002-1579-5737

Ramazan Gündoğdu
Department of Pharmacy Services, Vocational School of Health Services, Bingol University, Bingol, Türkiye
https://orcid.org/0000-0001-5230-2121

İbrahim Halil Geçibesler
Department of Occupational Health and Safety, Faculty of Health Science, Bingol University, Bingol, Türkiye
https://orcid.org/0000-0002-4473-2671

Lütfi Behçet
Department of Molecular Biology and Genetics, Faculty of Arts and Sciences, Bingol University, Bingol, Türkiye
https://orcid.org/0000-0001-8334-7816

https://doi.org/10.20883/medical.e1469

Keywords: phytotherapy, salvia, cancer

Received 2025-10-27
Accepted 2025-12-09
Published 2025-12-29

How to Cite: Sever A, Mehmet KE, Ramazan G, İbrahim HG, Lütfi B. Evaluation of the Anticancer Potential of *S. euphratica*, *S. staminea*, and *S. trichoclada* in Colon Cancer: Monotherapy and Combination with Cisplatin. Journal of Medical Science. 2025 December;94(4);e1469. https://doi.org/10.20883/medical.e1469

ABSTRACT

Introduction. The use of herbal products in the treatment of colon cancer appears promising. Numerous *Salvia* species have been identified to exhibit cytotoxic properties. In this study, ethanolic extracts of three *Salvia* species collected from the Bingöl region (*Salvia euphratica, Salvia staminea, and Salvia trichoclada*), which have not been sufficiently investigated for their anticancer potential, were applied to the HT-29 colon cancer cell line both as monotherapies and in combination with cisplatin.

Material and methods. A crystal violet assay was performed to assess cell viability. Changes in cellular functions were evaluated using colony-formation and 3D soft agar assays for colony-forming ability, wound-healing assays for migration, and Western blot analyses for protein expression levels.

Results. The IC_{50} values were determined as 38.16, 40.85, and 43.40 µg/ml, respectively. In synergy assays with cisplatin, the combination indices were 9.54, 9.37, and 9.61, respectively. It was observed that the *Salvia* species alone reduced colony-forming ability in both 2D and 3D cultures, whereas this effect diminished when combined with cisplatin. The wound closure percentage decreased under combination treatment. Furthermore, although mTOR and AKT protein levels were reduced in combination treatments compared with monotherapy, p53 and c-PARP levels were elevated.

Conclusions. Although the examined *Salvia* species exhibited strong cytotoxic effects when used alone, these effects were attenuated when combined with cisplatin. Further investigations are needed to elucidate the underlying mechanisms of this phenomenon.

Introduction

Cancer is a disease in which pathophysiological changes occurring in the cell division process and DNA repair mechanisms are ineffective, causing the death of millions of individuals worldwide every year [1]. Colorectal cancer (CRC) is the third most commonly diagnosed cancer type in both men and women [2]. Of the 19.3 million new cancer cases observed in 2020, approximately 2 million were CRC. In the same year, nearly 900 thousand cancer deaths were attributed to the CRC group [1,3]. According to estimates for 2030, 1.1 million deaths and 2.2 million new cases related to CRC are expected [4]. Another study reports an estimated 3.2 million CRC-related deaths for the year 2040 [1]. Population growth and the proportion of older adults will likely increase CRC incidence [5].

Among the agents used in CRC chemotherapy, Cisplatin (Cis) forms cross-links by binding to DNA. These bonds damage DNA, leading to apoptosis in cells [6]. Although Cis is widely used for therapeutic purposes in many cancer types, it causes many undesirable outcomes and significant side effects, similar to other chemotherapeutic agents [7].

It has been reported that, compared with current colon cancer therapies, plant-based treatments cause fewer side effects and should be considered an alternative [8]. Studies have shown that some plant species support CRC treatment by inhibiting cell proliferation and inducing cell death [9]. The use of natural products together with synthetic drugs in CRC treatment has become a standard therapeutic approach in recent years. The protective and cytotoxic effects of herbal products on cancer cells are essential in this context [10]. It has been reported that the efficacy of chemotherapeutic agents used in CRC treatment is altered when they are combined with various plants [11]. *Salvia* species are used in multiple regions of the world in the prevention and treatment of many diseases [12]. Several studies have shown that *Salvia* species possess anticancer properties across various cell lines [13–15]. Previous phytochemical studies on these species have revealed that they are rich in rosmarinic acid, ferulic/vanillic acids, linalyl acetate, linalool, caryophyllene oxide, spathulenol, β-pinene, and related terpenoids [16–18]. In this study, the ethanol extracts of three different *Salvia* species collected from Bingöl province, which have not been sufficiently investigated in terms of anticancer properties *(Salvia euphratica* (SEE), *Salvia staminea* (SSE), *Salvia trichoclada* (STE)), were examined for their anticancer activity in a colon cancer cell line (HT-29) both as monotherapy and in combination with Cis.

Material and methods

Chemicals and reagents

Phosphate-buffered saline (PBS), Dulbecco's modified Eagle medium (DMEM), penicillin/streptomycin, trypsin-EDTA, and fetal bovine serum (FBS) were obtained from Gibco (Grand Island, NY, USA). Trypan blue, dimethyl sulfoxide (DMSO), methanol, acetic acid, and ethanol were obtained from Sigma Aldrich (St. Louis, MO, USA). Antibodies were obtained from Santa Cruz (Dallas, TX, USA). TEMED, Tris, KCl, NaCl, HCl, NaF, Na_3VO_4, Coomassie blue-G250, NaN_3, luminol, nonfat dry milk, Ponceau S, H_3PO_4, p-coumaric acid, PMSF, DTT, benzamidine, ethanol, glycerin, glycerol, sodium dodecyl sulfate (Sigma-Aldrich, Burlington, MA, USA); Tris HCl, DMSO, Tween-20, bromophenol blue, β-mercaptoethanol, NP-40, EDTA, EGTA, glycerophosphate, H_2O_2, NaOH, glycine (Merck, Darmstadt, Germany); 0.45 µm PVDF membrane (Millipore, Darmstadt, Germany); 25 and 75 cm² cell culture flasks (Sarstedt, Numbrecht, Germany); microcentrifuge tubes, 15 and 50 mL Eppendorf tubes (Isolab, Eschau, Germany); 6- and 96-well microplates (Corning, NY, USA); 5-, 10-, and 25-mL sterile pipettes and plastic pipette tips, 3- and 6-cm Petri dishes (Costar, Washington, DC, USA).

Plant extraction

Salvia species were collected during the flowering period from Bingöl, Türkiye. The identification was carried out by Prof. Dr Lütfi Behçet in accordance with the Flora of Turkey [19]. Specimens of the *Salvia* species were recorded in the Bingöl University Herbarium as *S. euphratica* (BIN 11635), *S. staminea* (BIN 11637), and *S. trichoclada* (BIN 11636). The aerial parts of the plants were ground using a laboratory-type grinder. From

each sample, 100 g were taken and extracted with ethanol in round-bottom flasks according to the method described by Erdoğan et al [20].

Cell culture

The HT-29 colon cancer cells used in the study were obtained from the Cancer Research Laboratory of Bingöl University. RPE-1 cells were used as the healthy cell line. All cell culture procedures were carried out in accordance with GCCP (Good Cell Culture Practice) aseptic standards. The cells were cultured in DMEM medium supplemented with 10% fetal bovine serum (FBS), 64 µg/mL penicillin, and 100 µg/mL streptomycin in a humidified cell culture incubator at 37°C containing 5–6% CO_2. Cells have been routinely screened for mycoplasma and other contaminants.

Cell viability

For the cell viability assay, the protocol described by Parker et al. was optimised and applied [21]. In summary, cells were seeded into 24-well plates at a density of 50,000 cells per well. After confirming cell attachment, 72-hour treatment was applied. Following the treatment, the DMEM medium was removed, and the surface was washed twice with PBS. Then, 1 mL of methanol-acetic acid (3:1) solution was added to each well, and the cells were fixed at room temperature for 5 minutes. The fixation solution was removed, and the wells were treated with 1 mL of 0.5% crystal violet dye. After 15 minutes of incubation at room temperature, the stained wells were carefully washed, and 1 mL of 10% acetic acid solution (prepared by mixing 1 mL of 100% acetic acid with 9 mL of ddH_2O) was added to each well and placed on a shaker for 5 minutes. Subsequently, the acetic acid from the wells was transferred to spectrophotometer cuvettes, and absorbance was measured at 595 nm to analyse cell viability. The data were then evaluated statistically.

Determining Synergy

To assess synergism between sage species and cis treatment in the HT-29 colon cancer cell line, the combination index (CI) was calculated. According to the calculation of the drug-sage extract interaction, CI > 1 indicates antagonism, CI = 1 indicates an additive effect, and CI < 1 indicates synergism [22]. The combination index was calculated using the formula reported in the literature [23]. The formula used in our analysis has now been clearly stated in the Methods section:

$$CI = \frac{(A_{CIS})_{50}}{(B_{SAL})_{50}} + \frac{(A_{SAL})_{50}}{(B_{CIS})_{50}}$$

In this equation:

- $(A_{CIS})_{50}$: cisplatin concentration required to reduce viability to 50% when *Salvia* extract is applied at $IC_{50}/2$,
- $(B_{SAL})_{50}$: IC_{50} of *Salvia* extract in monotherapy,
- $(A_{SAL})_{50}$: *Salvia* concentration needed to reduce viability to 50% when cisplatin is applied at $IC_{50}/2$,
- $(B_{CIS})_{50}$: IC_{50} of cisplatin in monotherapy.

Colony formation

The colony formation assay was performed to assess the effects of various treatments on cell colony-forming ability. For this assay, cells were seeded into 6-well plates at a density of 5 × 10^2 cells per well. The following day, after confirming cell attachment, the cells were treated with *Salvia* extracts and Cis for 72 hours. After treatment, the medium was removed, and the cells were incubated in fresh medium for 15 days (37 °C, 5% CO_2, 95% humidity). After this period, the medium was removed, the cells were washed with PBS, fixed in methanol: acetic acid (3:1) for 5 minutes, and stained with crystal violet for 15 minutes. The wells were then carefully washed, and the colonies were counted under a microscope. A formation of at least fifty cells was considered a colony [24].

Wound healing

The in vitro wound-healing assay was performed as modified from the method described by Zomer et al. [25]. Cells were seeded into 6-well plates, and the next day, a scratch was created using a sterile 100 µL pipette tip. The detached cells were removed by washing twice with PBS. Afterwards, photographs of the wounds were taken. The treatment group was then exposed to the respective plant extracts and chemotherapeutic agents. At 0, 6, 12, and 24 hours, the wound areas were photographed under a microscope and measured using ImageJ software. The percent-

age of wound closure for each group was calculated by normalising images acquired at 0, 6, 12, and 24 hours.

3D Soft Agar

The effect of the applied treatments on the colony-forming ability of the cells was evaluated using the soft agar assay [26]. To each well of the 6-well plates, 1 mL of agar-medium mixture was added, and the plates were incubated in a culture cabinet for 30 minutes to allow the bottom agar layer to solidify. A 0.5% agarose solution containing 6×10^3 cells and the respective treatment agents in cell culture medium (DMEM, 20% FBS) was mixed at a 1:1 ratio (final agarose concentration 0.5%) and incubated in a 36°C water bath for 15 minutes. Then, 1 mL of the agarose-cell-medium mixture (6×10^3 cells) was carefully overlaid on the solidified 0.5% agarose bottom layer. The cells were incubated for 7–21 days in a humidified cell culture incubator at 37°C with 5% CO_2, and every 3–4 days, fresh medium containing treatment agents was added onto the top agar layer. At the end of the experiment, colony formation was examined under a microscope, and the formed colonies were stained with 0.005% crystal violet prepared in methanol for 15 minutes. The experiment was performed with at least two replicates for each group, including the control.

Western blotting

Western blotting was used to assess changes in protein expression in cells treated with the applied treatments [24]. For protein sample analysis, a vertical SDS-PAGE tank system (Bio-Rad Mini-PROTEAN Tetra Cell) was used. Cells seeded in 6-cm wells were washed twice with cold PBS (without Ca^{2+}/Mg^{2+}) to remove them from the plates after 72 hours of treatment. The collected cells were suspended in PBS, centrifuged at 1100 RPM for 5 minutes at room temperature, and the supernatant was partially aspirated. The obtained pellet was resuspended in an adequate amount of lysis buffer (100 µL for 0.5×10^6 cells), and effective homogenization and protein extraction were achieved using a 1 mL pipette. The samples were incubated on ice for approximately 1 hour, then centrifuged at 15,000 RPM for 10 minutes at 4°C. The resulting supernatants were transferred into pre-prepared, labelled microcentrifuge tubes. Total protein concentration was determined using the Bradford method. According to the calculations, equal amounts of protein (30 µg per lane) were loaded into each well of the SDS-PAGE gel and electrophoresed. Protein concentrations were determined manually using the Bradford reagent with Coomassie Brilliant Blue G-250, and equal loading was confirmed with Tubulin as a loading control. To prevent protein degradation, the lysis buffer was supplemented with protease inhibitors and reducing agents, specifically 1 mM DTT, one mM Benzamidine, 0.5 mM PMSF, and 1 mM Leupeptin. The proteins were then transferred onto PVDF (polyvinylidene fluoride) membranes and incubated for 1 hour in blocking buffer (5% milk powder in TBS-T). After blocking, the membranes were incubated overnight at 4°C with the appropriate primary antibody (diluted in 5% milk powder) with rotation. The membranes were washed with TBS-T (3 × 10 minutes) and then incubated for 2 hours at room temperature with the relevant HRP-conjugated secondary antibody (diluted in 5% milk powder). The membranes were rewashed with TBS-T (3 × 10 minutes). Detection was performed using a chemiluminescence-based ECL kit. The signals on the membrane were transferred to film using an X-ray imaging system. Finally, densitometric analysis of the band intensities was performed using ImageJ software (National Institutes of Health, USA).

DNA Agarose Gel Assay

One method for visualising DNA damage and breaks is the DNA agarose gel assay. DNA fragments placed in the gel under an electric field are separated according to their sizes [27]. A. A sufficient amount of agarose and Tris-acetate (TAE) buffer was mixed and gently shaken. It was then heated in a microwave until it began to boil. At intervals, the flask was removed from the microwave and mixed. After complete dissolution, Ethidium Bromide (EtBr) was added, and the solution was shaken to ensure uniform dispersion. The cooled solution was slowly poured into a tray. It was left to polymerise. Once polymerisation was complete, the gel was placed in the tank, and TAE was added until it covered the gel. Samples were mixed with five µL of loading buffer and loaded into the gel. A marker was also loaded into one well. Electrophoresis was performed at 80 V for 20 minutes.

Statistical analysis

All experiments were performed in triplicate unless stated otherwise. Graphical and statistical analyses were conducted using GraphPad Prism (GraphPad Software, USA). The obtained data were analysed using Tukey's multiple comparisons test and One-Way ANOVA. A p-value of < 0.05 was considered statistically significant.

Results and Discussion

Since ancient times, plants have been the focus of attention in healthcare. Herbal products are used in the treatment of numerous diseases within traditional medicine. They are sometimes used in the diet and sometimes as herbal medication [28,29]. Colon cancer is a significant health issue affecting human health, as it is the third most common cause of cancer-related deaths in both men and women [30]. Cisplatin (Cis), a drug commonly used in the chemotherapy of many cancers, including CRC, exerts its effects by inducing oxidative stress and DNA damage in cells [31]. In addition to chemotherapeutic agents, plant-derived products that have long been used in cancer treatment are available. Plants can not only prevent cancer but also enhance the efficacy of other cancer treatments [32]. It is predicted that the discovery of new plants may yield greater benefits in cancer treatment [33].

Cell Viability Findings

Salvia species have been reported to possess anticancer properties across multiple cancer types, including CRC, owing to their bioactive constituents (see **Figure 1**). *Salvia* and its derived compounds have been reported to exhibit anticancer effects in various cancer cell lines [34–37]. High *levels* of phenolic compounds and antioxidant properties characterise the Salvia species used in this study [16–18]. In our study, consistent with the literature, the *Salvia* species tested exhibited cytotoxic effects on the HT-29 cell line, with vigorous cytotoxic activity observed at 40 µg/mL and above. The obtained IC_{50} and $IC_{50}/2$

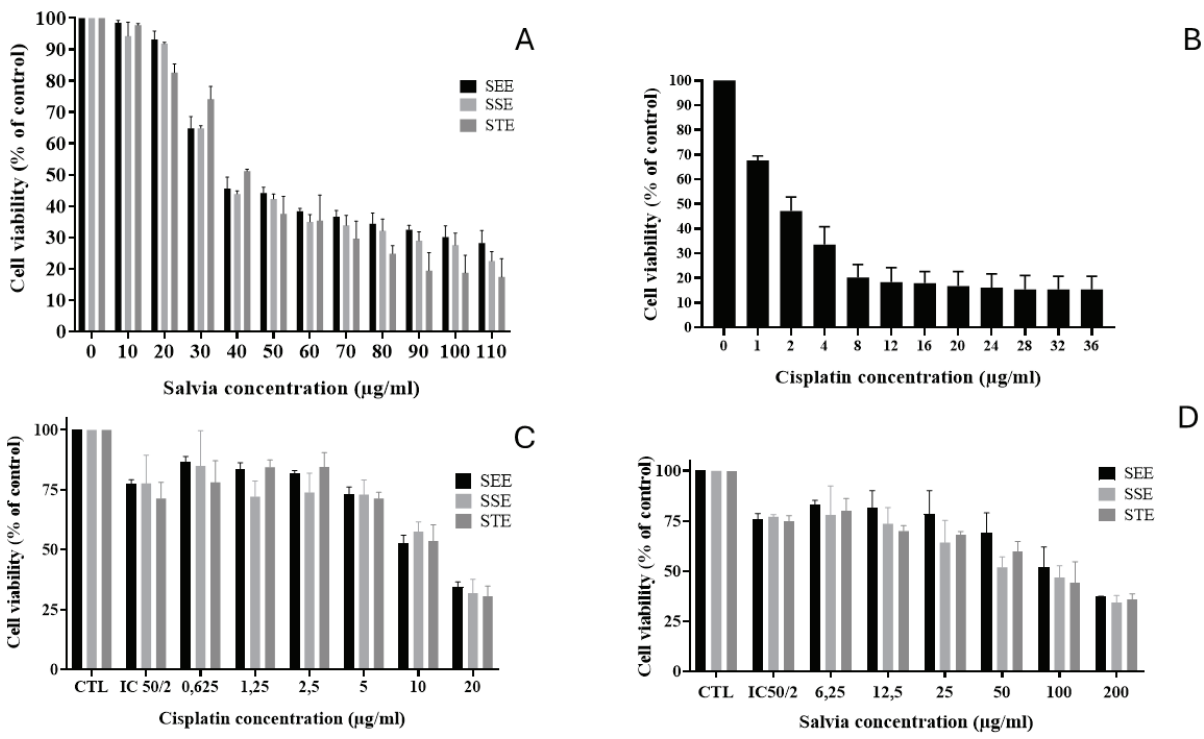

Figure 1. Viability graph. Cell viability of HT-29 cells treated with *Salvia* species for 72 hours at increasing concentrations (A), cell viability of HT-29 cells treated with cisplatin for 72 hours at increasing concentrations (B), viability assay with increasing cisplatin concentrations while keeping the *Salvia* dose constant (C), viability assay with increasing *Salvia* concentrations while keeping the cisplatin dose constant (D). (n=3, SD, ANOVA, p<0.05). Source: Author's own data.

doses are presented in **Table 1**. To assess the selectivity of the cytotoxic effects, the extracts were also tested on the healthy human retinal pigment epithelial (RPE-1) cell line. The IC_{50} values for SEE, SSE, and STE in RPE-1 cells were 89.67, 95.15, and 89.58 µg/ml, respectively. These values are approximately 2-2.5 times higher than those observed in HT-29 cancer cells, indicating a favourable selectivity index towards the colon cancer cells.

Cis is an important chemotherapeutic agent used in the treatment of many types of cancer. However, its use is associated with significant side effects. Using Cis in combination with plants is a critical approach to reducing these side effects [38]. Combining plants with chemotherapeutic agents holds promise for mitigating the adverse effects of chemotherapy. The use of natural compounds to reduce the side effects of current CRC therapies has been reported to have multiple beneficial effects [39]. However, in some cases, natural products can be ineffective in cancer treatment; in certain situations, they may even reduce the efficacy of the drug used [40,41]. Studies indicate that components exhibiting anti-inflammatory properties reduce the activity of cis [42]. It is emphasised that, owing to their high antioxidant capacity, *Salvia* species may reduce the efficacy of chemotherapeutic agents that act through oxidative stress. In a previous study, rosmarinic acid derived from *Salvia* species was found to diminish the effect of Cis [43]. In our study, we observed that the cytotoxic effect decreased when Cis and *Salvia* species were combined. In the synergism experiments, IC_{50} values increased. This phenomenon may be related to the reduction of Cis's oxidative effects, one of its essential mechanisms of action, by *Salvia* species with high antioxidant properties. The IC_{50} values and combination index (CI) results obtained from the synergism experiments are summarised in **Table 2**.

Colony Formation Findings

The colony formation assay is a technique used to assess the antiproliferative effect of treatments applied in cell culture [44]. Various plants have been shown to reduce the colony-forming ability of cancer cells. *Salvia* species and their derived compounds have been shown to inhibit colony formation in many cell lines [34,45–48]. Consistent with the literature, our study showed that Salvia *treatment* reduced the colony-forming ability of the HT-29 cell line. Although plant-derived products often show synergistic effects with many chemotherapeutic agents, antagonistic effects can also occur in some cases [49]. The combined use of Cis and *Salvia* species was observed to reduce colony-forming ability less than monotherapy ($p < 0.05$) (see **Figure 2**).

Table 1. $IC_{50}/2$ and IC_{50} values obtained after the viability assays. Source: Author's own data.

	$IC_{50}/2$	IC_{50}
CİS	1,43 µg/ml	2,92 µg/ml
SEE	18,21 µg/ml	38,16 µg/ml
SSE	19,89 µg/ml	40,85 µg/ml
STE	23,86 µg/ml	43,40 µg/ml

Table 2. IC_{50} values and combination indexes obtained in the synergism experiments. Source: Author's own data.

	IC_{50}	Combination Index (CI)
SEE $IC_{50}/2$+Cis	16,1	9,54
Cis $IC_{50}/2$+SEE	154	
SS $IC_{50}/2$+Cis	17,1	9,37
Cis $IC_{50}/2$+SSE	144	
ST $IC_{50}/2$+Cis	18	9,61
Cis $IC_{50}/2$+STE	150	

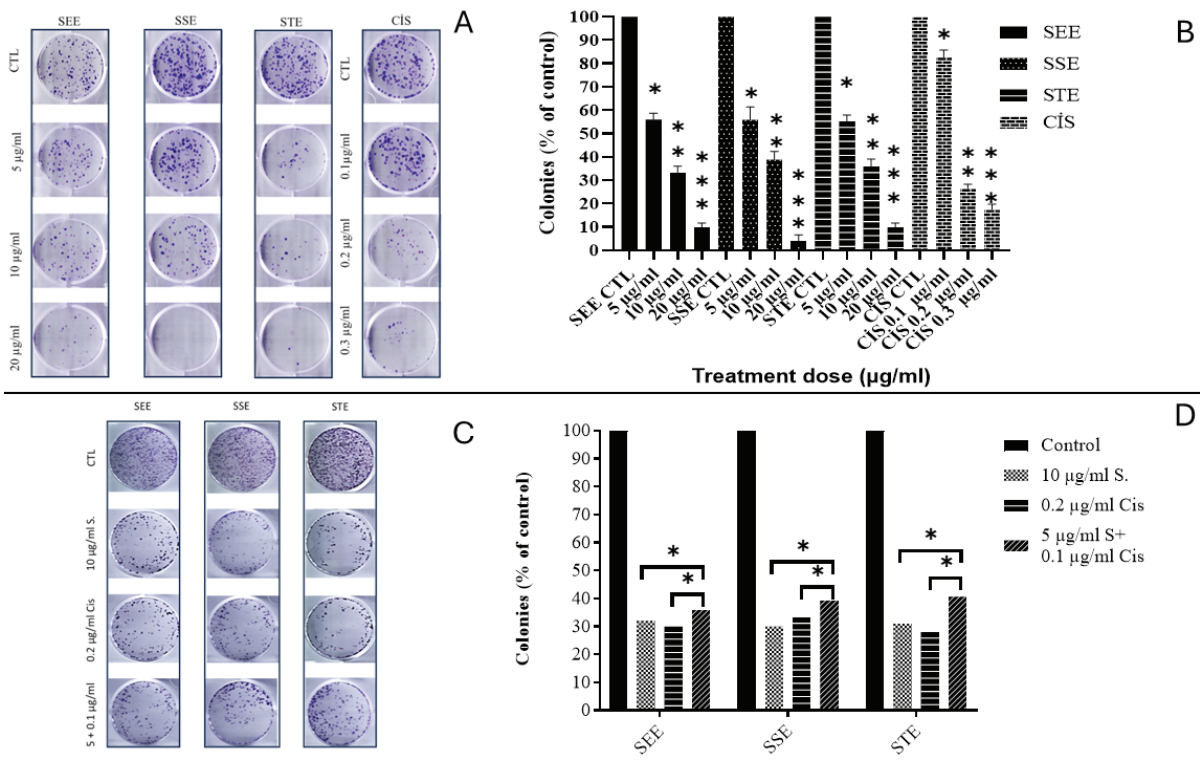

Figure 2. After seeding HT-29 cells into 6-well plates, they were treated with the determined IC_{50} and $IC_{50}/2$ doses of Cis and *Salvia* species. For monotherapy, IC_{50} doses were used, while for combination treatments, $IC_{50}/2$ + $IC_{50}/2$ doses were applied (n = 3, SD, ANOVA, $p < 0.05$). Source: Author's own data. * $p < 0.05$

Soft Agar Findings

Given the difficulty of monitoring tumour development in vivo, the soft agar technique remains an essential method for measuring cancer cell proliferation in a semi-solid environment [50]. Studies have shown that various *Salvia* species reduce the colony-forming ability of cancer cell lines in soft agar [48,51–54]. Consistent with the literature, our study demonstrated that the *Salvia* species used decreased the colony-forming ability of cells in soft agar when used as monotherapy, but that combining it with Cis reduced the effectiveness of Cis (see **Figure 3**).

Wound Healing Findings

The wound-healing assay is a standard in vitro technique used to analyse 2D cell migration. Cells migrate into a gap created mechanically, thermally, or chemically, and the percentage of gap closure is examined under a microscope [55]. Treatments with *Salvia* species have been shown to reduce migration ability in various cell lines [37,56,57]. In our study, treatment with *Salvia* species reduced the migration ability of HT-29 cells. As observed in the viability and colony formation assays, the effectiveness of the combination therapy was reduced (see **Figure 4**).

Normalised percentage graph of wound closure areas captured at 6, 12, and 24 hours (*$p < 0.05$; compared to control, **$p < 0.01$; compared to control, $^{\#}p < 0.05$; compared to the group treated with Cis only, $^{\#\#}p < 0.01$; compared to the group treated with Cis only).

Western blot findings

It is well established that many cancer therapies increase p53 levels. In colon cancer cell lines, 5-FU and various plant extracts have been shown to elevate p53 levels [58]. Similarly, various *Salvia* species have been reported to increase p53 protein levels in cells [59,60]. In our study, p53 levels were significantly higher in all groups treated with *Salvia* species and cisplatin for 72 hours than in the control group (see **Figure 5**). The p-values were $p < 0.001$ for the cisplatin group and $p < 0.05$ for the *Salvia* groups. In combination therapy groups, p53 protein levels were significantly lower compared to the cisplatin group ($p < 0.001$). Given the role of p53 in apoptotic processes and cellular stress, these

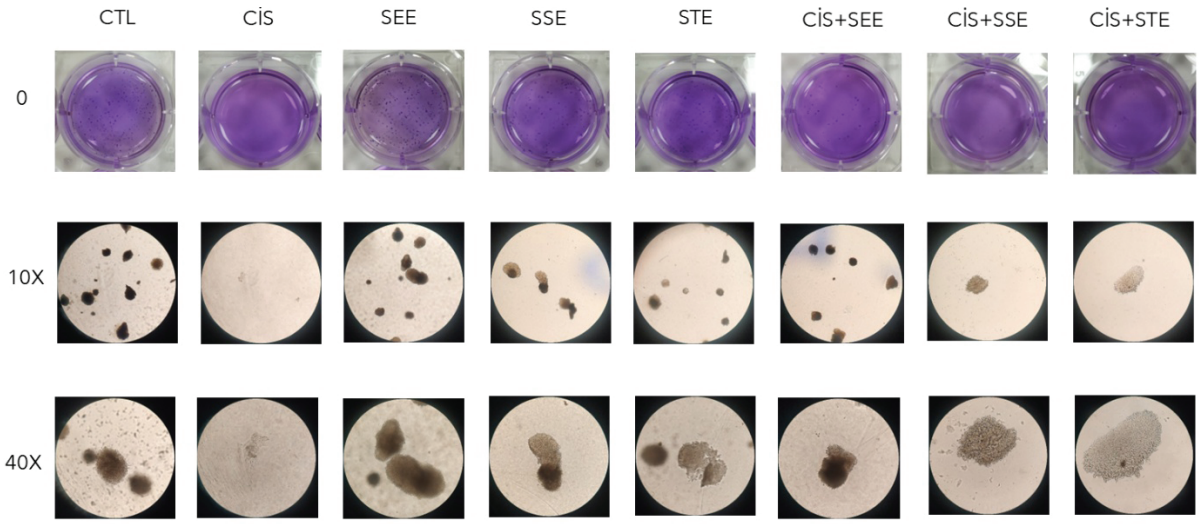

Figure 3. Microscopic images of the Soft Agar assay performed with HT-29 cells. Cells seeded in 6-cm well plates were treated with IC50 doses for monotherapy and IC25 + IC25 doses for combination therapies. During the 21-day experimental period, DMEM supplemented with 20% FBS, without treatment agents, was added to the plates at 5-day intervals. At the end of day 21, the colonies were stained as described in the Materials and Methods section to visualise their formation. Images of the plates were captured using an external camera at 10× and 40× magnification. (n=3). Source: Author's own data.

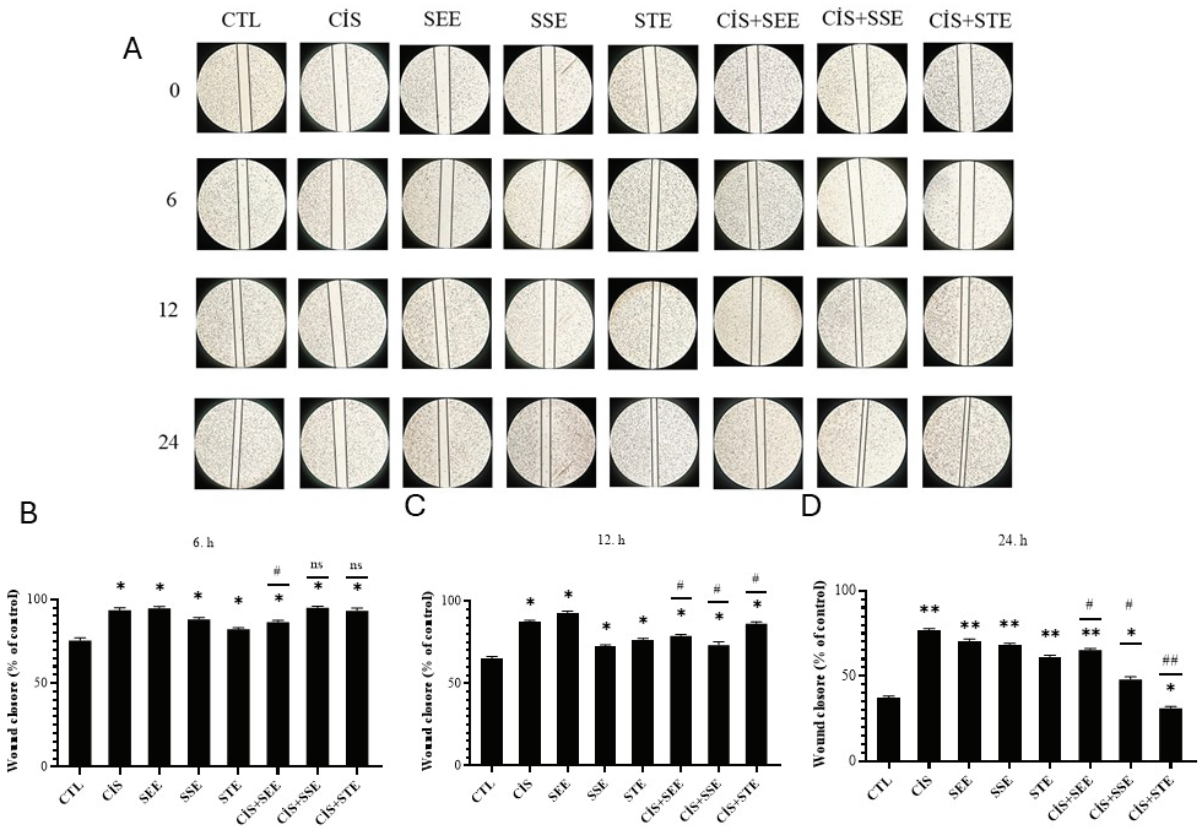

Figure 4. Microscopic images of the wound areas. HT-29 cells were seeded into 6-well plates. After ensuring cell attachment and sufficient confluency, scratches were created using a sterile pipette tip. Treatments were applied using the IC_{50} and IC_{50}/2 doses obtained from the viability assays. Images were captured under a microscope at 0, 6, 12, and 24 hours. (n=3, SD, ANOVA, p<0.05). Source: Author's own data. *p< 0.05, **p< 0.01, $^{\#}$p<0.01, $^{\#\#}$p<0.01

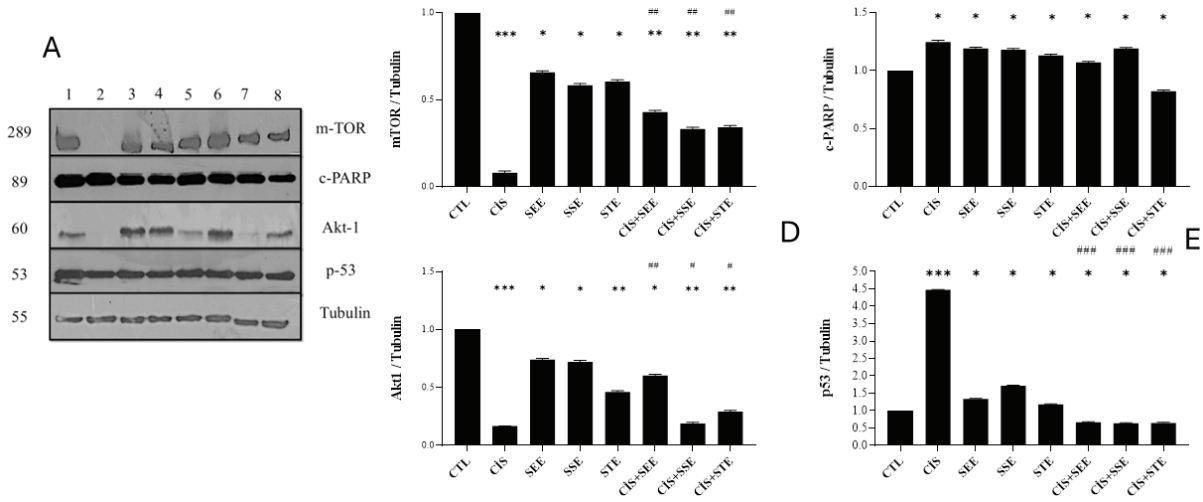

Figure 5. Band images of protein levels in HT-29 cells after treatment (A), quantitative graphs showing the expression levels of mTOR (B), c-PARP (C), Akt1 (D), and p53 (E). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ns: $p > 0.05$, compared to control. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$, compared to cisplatin-treated cells. (n=3, SD, ANOVA, $p<0.05$) Source: Author's own data.

results are consistent with the literature, which shows that *Salvia* species and cisplatin induce stress and apoptosis when used alone in colon cancer cell lines. However, monotherapy appears to induce more stress and apoptosis compared to combination therapy.

c-PARP, a form of PARP-1, is associated with the late stage of apoptotic cell death [61]. As a biomarker in apoptosis, c-PARP levels have been found to increase in parallel with apoptotic processes [62]. Many chemotherapeutic agents and plant-derived products, including *Salvia* species, are known to elevate c-PARP levels [59,63]. Consistent with this information, c-PARP levels increased with monotherapies in our study ($p < 0.05$). In combination therapies, a significant decrease was observed relative to cisplatin treatment, indicating that DNA damage induced by monotherapy is reduced in combination therapy.

Akt, a central molecule in the PI3K-Akt signalling pathway, has been associated with multiple cancer types when abnormally activated. Cancer cell migration is closely linked to Akt, which transmits signals from growth factors and oncogenes to downstream targets [64,65]. Chemotherapeutic agents, *Salvia* species, and their derived compounds have been reported to reduce Akt1 protein levels in cancer cells [66–68]. In our study, monotherapy significantly decreased Akt1 levels, consistent with the literature. However, combination therapy showed a significant increase compared to cisplatin treatment.

mTOR is a protein that regulates cell growth, mRNA translation, ribosome biogenesis, autophagy, and metabolism, and it is hyperactivated in many cancer types [69]. Both chemotherapy and various plants, including *Salvia*, are known to reduce mTOR levels in cancer cells [66,70]. In our study, treatment with cisplatin and *Salvia* significantly decreased mTOR levels. However, combination therapy showed an increase relative to monotherapy, indicating reduced cytotoxicity in the combination.

DNA agarose gel findings

Kemoterapik Chemotherapeutic agents and substances with anticancer properties target cancer cells by inducing DNA damage in rapidly dividing cells, either directly or indirectly [71]. The cellular response to the resulting DNA damage is closely related to both cancer progression and the outcomes observed after chemotherapy. Modulating the DNA damage response system is considered an essential target for enhancing treatment efficacy in cancer therapy [72]. Various *Salvia* species are known to induce DNA damage in cancer cell lines [36,73,74]. In our study, DNA fragmentation was markedly more pronounced in monotherapies with cisplatin and *Salvia* species than

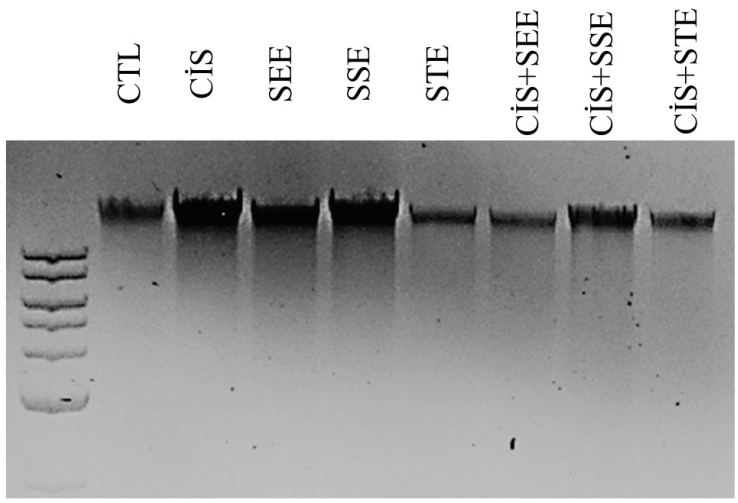

Figure 6. DNA Agarose Gel Image of HT-29 cells treated with Cis, SEE, SSE, STE, Cis+SEE, Cis+SSE, and Cis+STE. HT-29 cells were treated for 72 hours with IC_{50} and $IC_{50}/2$ doses and then subjected to an electric field using a vertical system. (n = 3). Source: Author's own data.

in the control group (see **Figure 6**). However, in combination therapy, fragmentation was less pronounced compared to the cisplatin group. This indicates that monotherapy alone induces greater DNA damage. The reduced DNA damage observed in combination treatments suggests that the plants may decrease the efficacy of cisplatin.

Conclusion

In conclusion, the studied *Salvia* species exhibited cytotoxic effects on HT-29 cell lines. Following treatment with *Salvia* species, colony formation and migration abilities of the cells decreased; levels of proteins associated with apoptosis, autophagy, and DNA damage (p53, c-PARP) increased; and the level of mTOR, which is related to cell proliferation, decreased. In combination treatments, results were less effective than those of monotherapy, indicating that the combination reduced the efficacy of cisplatin. Based on these findings, an antagonistic interaction between the studied *Salvia* species and cisplatin was observed. These results can be further supported by future *in vitro* and *in vivo* studies, which will provide clearer insights into the use of these plants in cancer therapy.

Disclosures

Conflict of interest

The authors declare no conflicts of interest.

Authors' Contributions

Lütfi Behçet collected the plants. İbrahim Halil Geçibesler performed the plant extractions. Mehmet Kadir Erdoğan conducted the cell viability and colony formation assays. Ramazan Gündoğdu performed the wound healing assays. Aydın Sever carried out the soft agar, Western blot, and DNA agarose experiments. Each author wrote the sections corresponding to their respective experimental work. All authors approve the final version of the manuscript.

Data Availability Statement (DAS)

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

Ethical approval was not required for this study as it did not involve human participants or animals.

Funding Statement

This study was supported by Bingöl University, grant number BAP-FEF.2023.005.

References

1. Chhikara BS, Parang K. Global Cancer Statistics 2022: the trends projection analysis. Chem Biol Lett. 2023;10(1):451. Available from: https://pubs.thescienceincein.org/journal/index.php/cbl/article/view/451
2. Thanikachalam K, Khan G. Colorectal cancer and nutrition. Nutrients. 2019;11(1):164. https://doi.org/10.3390/nu11010164
3. Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi DJ, John A, Lim YC, Kibria KMK, Mohiuddin AKM, Ming LG. Colorectal cancer: a review of carcinogenesis, global epidemiology, current challenges, risk factors, preventive and treatment strategies. Cancers (Basel). 2022;14(7):1732. https://doi.org/10.3390/cancers14071732
4. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin. 2023;73(3):233–54. https://doi.org/10.3322/caac.21772.
5. Araghi M, Soerjomataram I, Jenkins M, Brierley J, Morris E, Bray F, Arnold M. Global trends in colorectal cancer mortality: projections to the year 2035. Int J Cancer. 2019;144(12):2992–3000. https://doi.org/10.1002/ijc.32055
6. Ghosh S. Cisplatin: the first metal based anticancer drug. Bioorg Chem. 2019;88:102925. https://doi.org/10.1016/j.bioorg.2019.102925
7. Makovec T. Cisplatin and beyond: molecular mechanisms of action and drug resistance development in cancer chemotherapy. Radiol Oncol. 2019;53(2):148. https://doi.org/10.2478/raon-2019-0018
8. Asadi-Samani M, Kooti W, Aslani E, Shirzad H. A systematic review of ıran's medicinal plants with anticancer effects. J Evidence-Based Complement Altern Med. 2016;21(2):143–53. https://doi.org/10.1177/2156587215600873
9. Xavier CPR, Pereira-Wilson C. Medicinal plants of the genuses Salvia and Hypericum are sources of anticolon cancer compounds: Effects on PI3K/Akt and MAP kinases pathways. PharmaNutrition. 2016;4(2):112–22. https://doi.org/10.1016/j.phanu.2015.11.002
10. Hien NM, Nguyen TYN, Le NTH, Le TNT, Chau NTN, Le TMH, Nguyen BQH. Medicinal plants as a potential resource for the discovery of novel structures towards cancer drug resistance treatment. Heliyon. 2024. https://doi.org/10.1016/j.heliyon.2024.e39229
11. Jung T, Cheon C. Synergistic and additive effects of herbal medicines in combination with chemotherapeutics: a scoping review. Integr Cancer Ther. 2024;23:15347354241259416. https://doi.org/10.1177/15347354241259416
12. Al-Jaber HI. Essential oil composition, total phenolic and total flavonoid content and in-vitro antioxidant properties of hydro-alcoholic and water extracts of salvia deserti growing wild in jordan. Jordan J Chem. 2017;12(1):11–9. wosuid: wos:000410352300002
13. Choudhary MI, Hussain A, Ali Z, Adhikari A, Sattar SA, Ayatollahi SAM, Rahman A, Majid A. Diterpenoids including a novel dimeric conjugate from Salvia leriaefolia. Planta Med. 2012;78(3):269–75. https://doi.org/10.1055/s-0031-1280454
14. Kamatou GPP, Makunga NP, Ramogola WPN, Viljoen AM. South African Salvia species: A review of biological activities and phytochemistry. J Ethnopharmacol. 2008 Oct 28;119(3):664–72. https://doi.org/10.1016/j.jep.2008.06.030
15. Moridi Farimani M, Miran M. Labdane diterpenoids from Salvia reuterana. Phytochemistry. 2014;108:264–9. https://doi.org/10.1016/j.phytochem.2014.08.024
16. Zengin G, Llorent-Martínez EJ, Fernández-de Córdova ML, Bahadori MB, Mocan A, Locatelli M, Aktumsek A. Chemical composition and biological activities of extracts from three Salvia species: S. blepharochlaena, S. euphratica var. leiocalycina, and S. verticillata subsp. amasiaca. Ind Crops Prod. 2018;111:11–21. doi:10.1016/j.indcrop.2017.09.065
17. Çolak NU, Yıldırım S, Bozdeveci A, Yaylı N, Çoşkunçelebi K, Fandaklı S, Yaşar A. Essential oil composition, antimicrobial and antioxidant activities of Salvia staminea. Rec. Nat. Prod. 2018. https://doi.org/10.25135/rnp.08.17.03.013
18. Kilic O. Chemical composition of four Salvia L. species from Turkey: A chemotaxonomic approach. J Essent Oil Bear Plants. 2016;19(1):229–35. https://doi.org/10.1080/0972060X.2014.958560
19. Hedge IC. Salvia l. Flora Turkey East Aegean islands. 1982;7:400–61.
20. Erdogan MK, Toy Y, Gundogdu R, Gecibesler IH, Sever A, Yapar Y, Behçet L, Zengin G. Assessment of cytotoxic, apoptotic, enzyme inhibitory, and antioxidant properties, and phytochemical characterization of ethanolic extract from Cionura erecta. Food Biosci. 2025;65:106082. https://doi.org/10.1016/j.fbio.2025.106082
21. Parker C, Chambers AC, Flanagan DJ, Ho JWY, Collard TJ, Ngo G, et al. BCL-3 loss sensitises colorectal cancer cells to DNA damage by targeting homologous recombination. DNA Repair (Amst). 2022;115:103331. https://doi.org/10.1016/j.dnarep.2022.103331
22. Chou TC. Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. Pharmacol Rev. 2006;58(3):621–81. https://doi.org/10.1124/pr.58.3.10
23. Li J, Wang R, Kong Y, Broman MM, Carlock C, Chen L, Li Z, Farah E, Ratliff TL, Liu X. Targeting Plk1 to enhance efficacy of olaparib in castration-resistant prostate cancer. Mol Cancer Ther. 2017;16(3):469–79. https://doi.org/10.1158/1535-7163.MCT-16-0361
24. Gomez V, Gundogdu R, Gomez M, Hoa L, Panchal N, O'Driscoll M, Hergovich A. Regulation of DNA damage responses and cell cycle progression by hMOB2. Cell Signal. 2015;27(2):326–39. https://doi.org/10.1016/j.cellsig.2014.11.016
25. Zomer HD, Varela GK dos S, Delben PB, Heck D, Jeremias T da S, Trentin AG. In vitro comparative study of human mesenchymal stromal cells from dermis and adipose tissue for application in skin wound healing. J Tissue Eng Regen Med. 2019;13(5):729–41. https://doi.org/10.1002/term.2820
26. Bettoun A, Joffre C, Zago G, Surdez D, Vallerand D, Gundogdu R, Sharif AAD, Gomez M, Cascone I, Meunier B, White MA, Codogno P, Parrini MC, Camonis JH, Hergovich A. Mitochondrial clearance by the STK38 kinase supports oncogenic Ras-induced cell

transformation. Oncotarget. 2016 ;7(28):44142–60. https://doi.org/10.18632/oncotarget.9875
27. Lee PY, Costumbrado J, Hsu CY, Kim YH. Agarose gel electrophoresis for the separation of DNA fragments. JoVE (Journal Vis Exp. 2012;(62):e3923. https://doi.org/10.3791/3923
28. Balewska A, Szczechla M. Plants: past and present in the battle against diabetes. J Med Sci. 2024;93(1):e896–e896. https://doi.org/10.20883/medical.e896
29. Monika K, Anna B, Jana K, Daniel P, Bogusław C. Products of plant origin–benefits and the potential risk for the consumer. J Med Sci. 2017;86(1). https://doi.org/10.20883/jms.2017.143
30. Okolie NP, Olude OM. Isolation of some bioactive compounds in the methanol extract of ficus exasperata leaves and the effect of the extract on ınflammatory markers in 1, 2 dimethylhydrazine ınduced colorectal cancer in rats. J Med Sci. 2025;94(1):e1232–e1232. https://doi.org/10.20883/medical.e1232
31. Tang C, Livingston MJ, Safirstein R, Dong Z. Cisplatin nephrotoxicity: new insights and therapeutic implications. Nat Rev Nephrol 2022 191 [Internet]. 2022 [cited 2023 Jan 3];19(1):53–72. https://doi.org/10.1038/s41581-022-00631-7
32. Ahmed M, Khan MI, Khan MR, Muhammad N, Khan AU, Khan RA. Role of medicinal plants in oxidative stress and cancer. Open Access Sci Reports. 2013;2(2):2–4. doi:10.4172/scientificreports.641
33. David B, Wolfender JL, Dias DA. The pharmaceutical industry and natural products: historical status and new trends. Phytochem Rev. 2015;14(2):299–315. https://doi.org/10.1007/s11101-014-9367-z
34. Bai J, Qin Q, Li S, Cui X, Zhong Y, Yang L, An L, Deng D, Zhao J, Zhang R, Bai S. Salvia miltiorrhiza inhibited lung cancer through aerobic glycolysis suppression. J Ethnopharmacol. 2024;331. https://doi.org/10.1016/j.jep.2024.118281
35. Nasrabadi NS, Vedad A, Asadi K, Poorbagher MRM, Tabrizi NA, Dorooki K, Sabouni RS, Moghadam MB, Shafaei N, Karimi E, Oskoueian E. Nanoliposome-loaded phenolics from Salvia leriifolia Benth and its anticancer effects against induced colorectal cancer in mice. Biotechnol Appl Biochem. 2024;(71):641–50. https://doi.org/10.1002/bab.2564
36. Nicolella HD, Fernandes G, Ozelin SD, Rinaldi-Neto F, Ribeiro AB, Furtado RA, Senedese JM, Esperandim TR, Veneziani RCS, Tavares DC Manool, a diterpene from Salvia officinalis, exerts preventive effects on chromosomal damage and preneoplastic lesions. Mutagenesis. 2021;36(2):177–85. https://doi.org/10.1093/mutage/geab001
37. Keshavarz M, Bidmeshkipour A, Mostafaie A, Mansouri K, Mohammadi-Motlagh H. Anti tumor activity of Salvia officinalis is due to its anti-angiogenic, anti-migratory and anti-proliferative effects. Cell J. 2011;12(4):477–82.
38. Dasari S, Njiki S, Mbemi A, Yedjou CG, Tchounwou PB. Pharmacological effects of cisplatin combination with natural products in cancer chemotherapy. Int J Mol Sci. 2022;23(3):1532. https://doi.org/10.3390/ijms23031532
39. Rejhová A, Opattová A, Čumová A, Slíva D, Vodička P. Natural compounds and combination therapy in colorectal cancer treatment. Eur J Med Chem. 2018;144:582–94. https://doi.org/10.1016/j.ejmech.2017.12.039
40. Ju YH, Doerge DR, Woodling KA, Hartman JA, Kwak J, Helferich WG. Dietary genistein negates the inhibitory effect of letrozole on the growth of aromatase-expressing estrogen-dependent human breast cancer cells (MCF-7Ca) in vivo. Carcinogenesis. 2008;29(11):2162–8. https://doi.org/10.1093/carcin/bgn161
41. Heaney ML, Gardner JR, Karasavvas N, Golde DW, Scheinberg DA, Smith EA, O'Connor OA. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. Cancer Res. 2008;68(19):8031–8. https://doi.org/10.1158/0008-5472.CAN-08-1490
42. Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. J Pharmacol Exp Ther. 2005;314(3):1052–8. https://doi.org/10.1124/jpet.105.087601
43. Vatan, Ö. (2019). Rosmarinik asidin cisplatine karşı antisitotoksik ve antigenotoksik etkisinin a549 ve beas-2b hücre hatlarında araştırılması. Uludağ Üniversitesi Tıp Fakültesi Dergisi, 45(3), 263-270. doi:10.32708/uutfd.613912
44. Guzmán C, Bagga M, Kaur A, Westermarck J, Abankwa D. ColonyArea: an ImageJ plugin to automatically quantify colony formation in clonogenic assays. PLoS One. 2014;9(3):e92444. https://doi.org/10.1371/journal.pone.0092444
45. Dai Y, Sun X, Li B, Ma H, Wu P, Zhang Y, Zhu M, Li HM, Qin M, Wu CZ. The effect of hispidulin, a flavonoid from salvia plebeia, on human nasopharyngeal carcinoma Cne-2z cell proliferation, migration, invasion, and apoptosis. Molecules. 2021;26(6):1604. https://doi.org/10.3390/molecules26061604
46. Chen B, Huang C, Zhang Y, Tang X, Li S, Wang Q, Lin Y. Salvia bowleyana Dunn root is a novel source of salvianolic acid B and displays antitumor effects against gastric cancer cells. Oncol Lett. 2020;20(1):817–27. https://doi.org/10.3892/ol.2020.11611
47. Jiang YL, Xun Y. Molecular mechanism of salvia miltiorrhiza in the treatment of colorectal cancer based on network pharmacology and molecular docking technology. Drug Des Devel Ther. 2024;425–41. https://doi.org/10.2147/DDDT.S443102
48. Zanrè V, Campagnari R, Cerulli A, Masullo M, Cardile A, Piacente S, Menegazzi M. Salviolone from Salvia Miltiorrhiza roots impairs cell cycle progression, colony formation, and metalloproteinase-2 activity in A375 melanoma cells: involvement of P21 (Cip1/Waf1) expression and STAT3 phosphorylation. Int J Mol Sci. 2022;23(3):1121. https://doi.org/10.3390/ijms23031121
49. Golden EB, Lam PY, Kardosh A, Gaffney KJ, Cadenas E, Louie SG, Petasis NA, Chen TC, Schönthal AH. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid–based proteasome inhibitors. Blood, J Am Soc Hematol. 2009;113(23):5927–37. https://doi.org/10.1182/blood-2008-07-171389
50. Horibata S, Vo T V., Subramanian V, Thompson PR, Coonrod SA. Utilization of the soft agar colony forma-

tion assay to identify inhibitors of tumorigenicity in breast cancer cells. J Vis Exp. 2015;2015(99):e52727. https://doi.org/10.3791/52727
51. Abi-Rizk A, Rayess Y El, Iriti M, Tabet E, Mezher R, Beyrouthy M El. Chemical composition, antitumor and antioxidant effects of four lebanese plants extracts on human pulmonary adenocarcinoma. Nat Prod Res. 2021;35(22):4861–4. https://doi.org/10.1080/14786419.2020.1737056
52. Allegri L, Domenis R, Navarra M, Celano M, Russo D, Capriglione F, Damante G, Baldan F. Dihydrotanshinone exerts antitumor effects and improves the effects of cisplatin in anaplastic thyroid cancer cells. Oncol Rep. 2021;46(3):1–16. https://doi.org/10.3892/or.2021.8155
53. Cao Y, Tang H, Wang G, Li P, Song Z, Li W, Sun X, Zhong X, Yu Q, Zhu S, Zhu L. Targeting survivin with Tanshinone IIA inhibits tumor growth and overcomes chemoresistance in colorectal cancer. Cell Death Discov. 2023;9(1):351. https://doi.org/10.1038/s41420-023-01622-8
54. Kashyap A, Umar SM, JR AD, Prasad CP. Dihydrotanshinone-I modulates epithelial mesenchymal transition (EMT) thereby impairing migration and clonogenicity of triple negative breast cancer cells. Asian Pacific J Cancer Prev APJCP. 2021;22(7):2177. https://doi.org/10.31557/APJCP.2021.22.7.2177
55. Jonkman JEN, Cathcart JA, Xu F, Bartolini ME, Amon JE, Stevens KM, Colarusso P. An introduction to the wound healing assay using live-cell microscopy. Cell Adh Migr. 2014;8(5):440–51. https://doi.org/10.4161/cam.36224
56. Atmaca H, Bozkurt E. Apoptotic and anti-angiogenic effects of Salvia triloba extract in prostate cancer cell lines. Tumor Biol. 2016;37(3):3639–46. https://doi.org/10.1007/s13277-015-4208-2
57. Zare H. Effects of salvia officinalis extract on the breast cancer cell line. SciMedicine J. 2019;1(1):25–9. https://doi.org/10.28991/SciMedJ-2019-0101-4
58. Erdoğan MK, Ağca CA, Aşkın H. İnsan kolorektal kanser hücrelerinde Pistacia eurycarpa ekstraktlarıyla kombine 5-florourasilin artırılmış antiproliferatif ve apoptotik etkileri. Biol Divers Conserv. 2019;12(1):27–38. doi:10.5505/biodicon.2019.57441
59. Muscella A, Stefàno E, De Bellis L, Nutricati E, Negro C, Marsigliante S. Antitumor and antimigration effects of Salvia clandestina L. extract on osteosarcoma cells. Ann N Y Acad Sci. 2021;1500(1):34–47. https://doi.org/10.1111/nyas.14601
60. Sinala S, Dewi STR, Pakadang SR, Sabir M, Kamal SE. Anti-cancer potential of Nggorang leaves extract (Salvia occidentalis Sw.) as a protein P53 supressor in T47D cells. Pharmacogn J. 2021;(13):1036–45. doi:10.5530/pj.2021.13.134
61. Sittihan S, Sopha P, Ruchirawat S. Synthesis and anticancer activity of pentafluorobenzenesulfonamide derivatives as caspase-dependent apoptosis-ınducing agents. ChemMedChem. 2022;17(3):e202100637. https://doi.org/10.1002/cmdc.202100637
62. Yosef R, Pilpel N, Papismadov N, Gal H, Ovadya Y, Vadai E, Miller S, Porat Z, Ben-Dor S, Krizhanovsky V. p21 maintains senescent cell viability under persistent DNA damage response by restraining JNK and caspase signaling. EMBO J [Internet]. 2017 [cited 2022 Nov 4];36(15):2280. https://doi.org/10.15252/embj.201695553
63. Xia R, Sheng X, Xu X, Yu C, Lu H. Hesperidin induces apoptosis and GO/G1 arrest in human non-small cell lung cancer A549 cells. Int J Mol Med. 2018 Jan 1;41(1):464–72. https://doi.org/10.3892/ijmm.2017.3250
64. Crowell JA, Steele VE, Fay JR. Targeting the AKT protein kinase for cancer chemoprevention. Mol Cancer Ther. 2007;6(8):2139–48. https://doi.org/10.1158/1535-7163.MCT-07-0120
65. Islam M, Jones S, Ellis I. Role of akt/protein kinase B in cancer metastasis. Biomedicines. 2023;11(11):3001. https://doi.org/10.3390/biomedicines11113001
66. Erdoğan MK, AĞCA CA, Askin H. Enhanced antiproliferative and apoptotic effects of 5-fluorouracil by combined with Pistacia eurycarpa extracts on human colorectal cancer cells. Biol Divers Conserv. 2019;12(1):27–38. https://doi.org/10.5505/biodicon.2019.57441
67. Jin U, Suh S, Chang HW, Son J, Lee SH, Son K, et al. Tanshinone IIA from Salvia miltiorrhiza BUNGE inhibits human aortic smooth muscle cell migration and MMP-9 activity through AKT signaling pathway. J Cell Biochem. 2008;104(1):15–26. https://doi.org/10.1002/jcb.21599
68. Jiang Y, Ji F, Liu Y, He M, Zhang Z, Yang J, Wang N, Zhong C, Jin Q, Ye X, Chen T. Cisplatin-induced autophagy protects breast cancer cells from apoptosis by regulating yes-associated protein. Oncol Rep. 2017;38(6):3668–76. https://doi.org/10.3892/or.2017.6035
69. Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. Cancer Cell. 2007;12(1):9–22. https://doi.org/10.1016/j.ccr.2007.05.008
70. Yu J ru, Liu Y yue, Gao Y yang, Qian L hui, Qiu J lin, Wang PP, Zhan GJ. Diterpenoid tanshinones inhibit gastric cancer angiogenesis through the PI3K/Akt/mTOR signaling pathway. J Ethnopharmacol. 2024;324:117791. https://doi.org/10.1016/j.jep.2024.117791
71. Woods D, Turchi JJ. Chemotherapy induced DNA damage response: convergence of drugs and pathways. Cancer Biol Ther. 2013;14(5):379–89. https://doi.org/10.4161/cbt.23761
72. Goldstein M, Kastan MB. The DNA damage response: Implications for tumor responses to radiation and chemotherapy. Annu Rev Med. 2015;66(1):129–43. https://doi.org/10.1146/annurev-med-081313-121208
73. Mauri G, Arena S, Siena S, Bardelli A, Sartore-Bianchi A. The DNA damage response pathway as a land of therapeutic opportunities for colorectal cancer. Ann Oncol [Internet]. 2020;31(9):1135–47. doi:10.1016/j.annonc.2020.05.027
74. Telang N. Anti-proliferative and pro-apoptotic effects of rosemary and constituent terpenoids in a model for the HER-2-enriched molecular subtype of clinical breast cancer. Oncol Lett. 2018;16(4):5489–97. https://doi.org/10.3892/ol.2018.9238