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Research Article/Araştırma Makalesi

Investigation of in *vitro* Cytotoxic Activity of Arbutin on Human Ovarian Cancer Cell Line

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Abstract: Arbutin is one of the chemical compounds commonly found in cosmetics. Arbutin's potential effects on ovarian cancer were investigated in this study using the human serous cystadenoma cancer cell line (SKOV3). Cytotoxicity levels and IC50 values of arbutin were determined using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) method. Depending on the increase in the applied doses, arbutin was found to have toxic activity on cancer cells. As a result of the immunocytochemical analysis performed on the cells applied with the IC50 value, it was found that arbutin at the IC50 dose increased Caspase 3 immunoreactivity in SKOV3 cells compared to the control group. Considering that arbutin increased apoptotic Caspase 3 activation in SKOV3 cells at the IC50 dose, elucidation of the molecular mechanisms behind these effects of arbutin may contribute to the development of a new perspective in treatment.

Keywords: Arbutin, Ovarian cancer, SKOV3, cytotoxicity, caspase-3.

Arbutinin İnsan Yumurtalık Kanseri Hücre Hattında *in vitro* Sitotoksik Aktivitesinin Araştırılması

Öz: Arbutin kozmetik ürünlerde sıklıkla kullanılan aktif bileşiklerden biridir. Bu çalışmada arbutinin yumurtalık kanseri üzerindeki olası etkileri insan seröz kistadenoma kanser hücre hattında (SKOV3) belirlenmiştir. Arbutin sitotoksisite düzeyleri ve IC50 değerleri 3-(4,5-dimetil-2-tiyazolil)-2,5-difenil-2H-tetrazolium bromür (MTT) yöntemi kullanılarak belirlenmiştir. Uygulanan doz artışına bağlı olarak arbutinin hücreler üzerinde toksik aktiviteye sahip olduğu görülmüştür. IC50 değeri uygulanan hücrelerde yapılan immünositokimyasal analiz sonucunda arbutinin IC50 dozunda SKOV3 hücrelerinde kontrol grubuna göre Kaspaz 3 immünreaktivitesini artırdığı bulunmuştur. Arbutinin IC50 dozunda SKOV3 hücrelerinde apoptotik Kaspaz 3 aktivasyonunu artırdığı göz önüne alındığında, arbutinin bu etkilerinin ardındaki moleküler mekanizmaların aydınlatılması, tedavide yeni bir bakış açısı geliştirilmesine katkı sağlayabilir.

Anahtar kelimeler: Arbutin, Ovaryum kanseri, SKOV3, sitotoksisite, kaspaz-3.

1. Introduction

Around the world, ovarian cancer (OC) is still among the most common causes of cancer-related mortality for women. The American Cancer Society estimates that by 2024, some 19.680 newly identified cases of OC will be diagnosed and the disease would be linked to 12.740 fatalities. Geographically, the incidence varies; higher-income countries tend to have greater rates (Siegel et al., 2024). Ovarian cancer is typically detected at a late stage and is frequently mistaken for other illnesses due to its nonspecific symptoms that include abdominal bloating, pelvic pain, early satiety, and frequent urination (Gajjar et al., 2012). In current treatment, cytoreductive surgery is applied following chemotherapy. Although it varies according to the stage, platinum derivatives such as cisplatin and carboplatin used together with taxanes are used as chemotherapy agents (Chen et al., 2013). There is still no fully effective treatment for ovarian cancer as the majority of the late grade cases relapse due to drug resistance (Kim et al., 2017).

Conventional chemotherapy treatments have numerous adverse reactions or toxic side effects such as gastrointestinal discomfort, polyneuropathy, musculoskeletal pain, prolonged fatigue, and cognitive impairment (Berliere et al., 2021). In contrast, phytochemicals that can be isolated from many sources are becoming a popular and promising therapeutic option for clinical applications with their low toxicity, minimal side effects, and easy absorption properties (Naeem et al., 2022).

The hydroquinone glycoside arbutin (1, C12H16O7) was initially identified when it was extracted from the leaves of Arbutus unedo L. (family: Ericaceae). Alpha and beta arbutin are the two isomers of arbutin that differ based on how hydroquinone binds to the anomeric carbon atom in the glucose complex. About more than fifty plant families have been found to contain arbutin since it was first discovered. Since this glycoside can prevent melanin synthesis by blocking tyrosinase, it has long been utilized as a skin-whitening (depigmentation) ingredient in a variety of commercially available topical cosmetic products. Arbutin, which has been used for skin whitening for years, has been shown to have various therapeutically important biological potentials such as antioxidant, antimicrobial, anti-inflammatory (Xu et al., 2022; Shen et al., 2017), and anticancer (Nahar et al., 2022). According to studies, this substance is cytotoxic to a variety of human cancer cell lines, including those from the bladder, brain, breast, cervix, and skin (Hazman et al., 2021; Li et al., 2011; Su et al., 2020; Surapaneni & Arulselvan, 2021; Yang et al., 2021).

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This study aimed to examine the cytotoxic effects of Arbutin on the SKOV3 ovarian cancer cell line and to assess its potential as a therapeutic agent for ovarian cancer.

2. Materials and Methods

2.1. Cell Culture

The Human ovarian serous adenocarcinoma cell line SKOV3 was used to assess cytotoxic activity. SKOV3 cells were cultivated in RPMI 1640 media enriched with 10% fetal bovine serum (FBS), 2 mM/L glutamine, 100 U/mL penicillin, and streptomycin. The cells were kept at 37°C in an atmosphere of humidity providing 5% CO_2. Cell lines were purchased from ATCC (American Tissue Culture Company), a company that provides validated cell lines, and experiments were performed when the cells reached 70%–80% confluency.

2.2. MTT Assay and Calculation of IC_{50} Arbutin

An enhanced colorimetric MTT test (Mosmann, 1983) was used to assess the cytotoxicity of arbutin (A4256, Sigma Aldrich, USA) based on cell viability. The spectrophotometer (Thermo Multiskan Spectrum, Bremen, Germany) was used to measure optical density (OD) three times at 490 nm. The cells were initially seeded at a density of $1x10^4$ cells/mL in 96-well plates and they were subsequently incubated for 24 hours. A stock solution of arbutin was made at a concentration of 5 mM in phosphate-buffered saline (PBS) (Lim et al., 2009). Following the treatment with arbutin at different doses (1-200 mM), the cells were cultured for a further 48 hours at 37°C. All experiments were performed in six replicates. Following incubation with arbutin, the percentage of viable cells in each culture was calculated to assess cell viability. According to the following formula, the viability (%) was determined:

%Viable cells = 100 x [(absorbance of the treated cells) - (absorbance of blank)] / [(absorbance of control) - (absorbance of blank)].

Using a four-parameter logistic model, the data was fitted to a sigmoidal curve to determine the half-maximal inhibition of growth (IC50) values. The average of three independent observations was used to illustrate the findings. Using Prism 10 software (GraphPad10, San Diego, CA, USA), the IC50 values were calculated and given with a 95% confidence interval. Relative to the untreated controls, the IC50 was computed by subtracting the absorbance values from the blank wells from the treated and control cell wells.

2.3. Immunofluorescence Staining

Immunofluorescence staining was performed to determine the effectiveness of arbutin application on the apoptosis. 10 mm round coverslips were placed in 24-well plates and SKOV3 cells were seeded on them. Arbutin application was performed at an IC50 dose. Following the treatment for 48 hours, cells were fixed with 4% paraformaldehyde and rinsed with PBS. Then, they were kept in a blocking solution for 1 hour. After blocking, they were incubated with anti-caspase 3 primary antibody (PA5-77887, Thermo Scientific; USA) for overnight. After secondary antibody Alexa Fluor Plus 488 (A32790, Thermo Scientific, USA) application, nuclei were stained with 4',6-diamidino-2-phenylindole (DAPI) (P36962, Thermo Scientific, USA). Cells were examined under a fluorescent microscope (Zeiss Axio Observer, Germany).

2.4. Statistical Analysis

Normality tests were performed using the Shapiro-Wilk test. Parametric data were analyzed using One way-ANOVA followed by Tukey post hoc test, while non-parametric data were analyzed using Kruskal-Wallis test followed by post hoc Dunn's test. GraphPad Prism software version 9 was used for all statistical analyses and statistical significance was determined as P-value<0.05.

3. Results

The cytotoxic effects of arbutin were measured against the SKOV3 cell line after 48 h incubation. The arbutin exhibited a statistically significant ($p<0.05$) and concentration-dependent inhibitory effect on the viability of the SKOV3 cell line. Arbutin exhibited inhibition rates of 11.23% at a concentration of 5 mM, 14.5% at 10 mM, 18.7% at 25 mM, 19.8% at 50 mM, 56.4% at 75 mM, 81.6% at 100 mM, and 93.4% at 200 mM on the SKOV3 cell line. Paclitaxel (positive cytotoxic control agent) demonstrated inhibition rates of 20.9% at 1 µM, 42.3% at 2 µM, 56.2% at 4 µM, 69.5% at 6 µM, 75.4% at 8 µM, 91.8% at 10 µM, and 99.3% at 20 µM on the SKOV3 cell line.

The cytotoxic effect of arbutin on SKOV3 cells was dose-dependent. The half-maximal inhibitory concentration (IC_{50}) value was calculated as 68.94 mM using non-linear regression analysis. Each data point in the dose-response curve represents mean±standard deviation (SD) from three independent experiments (n=3). The regression model showed good fit with an R^2 value of 0.97 and the 95% confidence interval for the IC_{50} was calculated (Fig. 1). As a positive control, paclitaxel also showed a dose-dependent cytotoxic effect on SKOV3 cells. The IC_{50} value of paclitaxel was calculated as 2.85 µM using non-linear regression analysis. The data represents mean±SD from three independent experiments (n=3). The regression model showed good fit with an R^2 value of 0.98 and the 95% confidence interval for the IC_{50} was determined. (Fig. 2).

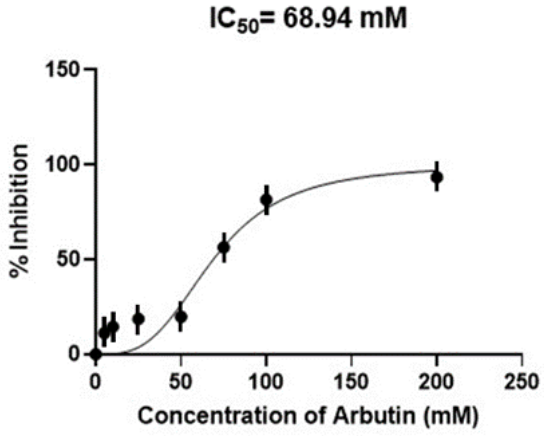

Figure 1. Dose-response curve showing the inhibitory effect of arbutin on SKOV3 cells after 48 h of treatment. The IC_{50} value was determined as 68.94 mM using non-linear regression analysis. Data are presented as mean±SD from three independent experiments (n = 3). The curve fitting showed a good correlation (R^2 = 0.97). Error bars represent the standard deviation.

To investigate the possible mechanism of arbutin-induced apoptosis, we performed immunofluorescence staining to examine the expression of caspase-3 at the cellular level. Quantitative analysis of fluorescence intensity showed that the arbutin-treated group had significantly higher caspase-3 expression than the control group ($p<0.05$, Fig. 3). All data are presented as mean±standard deviation. Statistical significance was accepted at $p<0.05$.

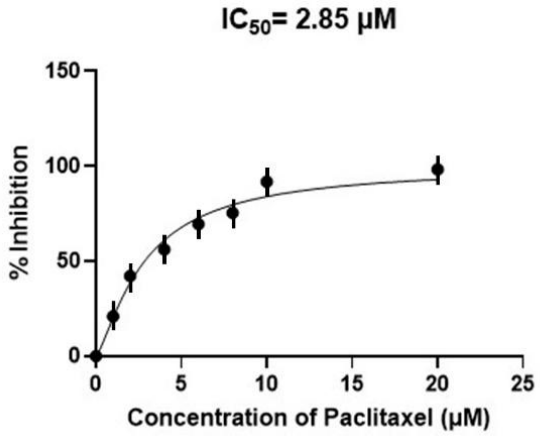

Figure 2. Dose-response curve showing the inhibitory effect of paclitaxel on SKOV3 cells after 48 h of treatment. The IC_{50} value was calculated as 2.85 µM using non-linear regression analysis. Data are presented as mean±SD of three independent experiments (n = 3). The regression model showed a good fit ($R^2 = 0.98$). Error bars indicate the standard deviation.

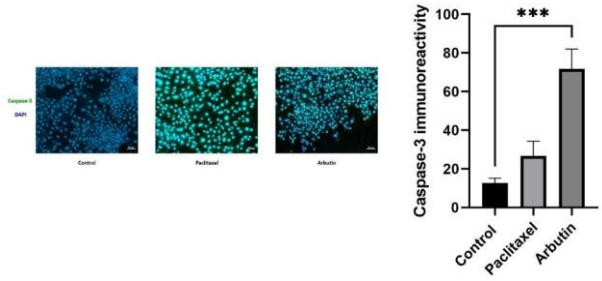

Figure 3. Immunofluorescence microscope images taken after arbutin and paclitaxel application on SKOV3 cells. Nuclei within the cell are shown with DAPI (blue fluorescence) and caspase-3 (green fluorescence), which is a marker of apoptosis. Quantitative analysis of fluorescence intensity revealed that the arbutin-treated group exhibited significantly higher caspase-3 expression compared to the control group ($p<0.05$). Data are presented as mean±SD.

4. Discussion and Conclusion

Ovarian cancer is among the most common female cancers and is one of the leading causes of cancer-related deaths among women. In most cases, survival rates are quite low because the cancer is detected in advanced stages. Unfortunately, despite current standard treatments, finding the most appropriate treatment option for both initial and relapsed cases have not yet been fully realized. In recent years, researchers have been conducting intensive scientific studies to identify compounds that can be beneficial for humans and have anticancer activity from natural sources (Chan et al., 2008). Numerous natural compounds have been found to have cytotoxic effect, particularly in SKOV3 ovarian cancer cells, as well as to alter the cell cycle and induce apoptosis (Hu et al., 2020; Liu et al., 2018; Qiao et al., 2025).

Arbutin is a bioactive hydrophilic polyphenol and it has been utilized in phytotherapy and phytocosmetics as a medicinal plant. Also, it comes from a variety of natural and artificial sources such as different plant species, enzyme reactions, and microorganism metabolic engineering. (Saeedi et al., 2021).

In our study, we observed that arbutin application in ovarian cancer can show toxic activity in the cell in a way that correlates with increasing doses and we calculated the IC50 value. Arbutin has been tested by many researchers on different cancer cells and has been shown to have cytotoxic activity. According to a study by Li et al.(2011) on a human bladder cancer cell line, arbutin inhibits cell proliferation in a way that depends on time and concentration. In a study investigating the possible effects of arbutin on breast cancer by Hazman et al. (2021), it was shown that both forms of arbutin had cytotoxic activity on human breast adenocarcinoma (MCF-7) cells at different concentrations. In addition, Hazman et al.'s study used MTT analysis data to compute lethal doses of α-arbutin, β-arbutin, and cisplatin in HepG2 cells. The lethal dose of β-arbutin in HepG2 cells was determined to be 61.270 mM (Hazman et al., 2022). In addition to the anticancer effects of arbutin, there are scientific studies showing its cytoprotective effects on normal cells (Pečivová et al., 2014; Khadir et al., 2015). In this respect, it is considered a safe treatment agent. The IC50 values and cytotoxic effects of pharmacological agents may vary depending on the cell line used and the application method (Cortés et al., 2001). In the light of these results, it was evaluated as an indication that the IC50 value may vary depending on the cell type and application conditions.

Caspases are catalytic activators that play a role in the initiation of apoptosis in cells. Caspase-3, a member of this family, is activated by both intracellular and extracellular apoptotic signals (Yadav et al., 2021). The goal of our study was to examine at the effects of arbutin on caspase 3 in SKOV3 ovarian cancer cells and as a result, we found that arbutin caused an increase in caspase 3 activity level in the treated cells. In one study, the genes for the apoptotic proteins Bax and Caspase 3 were expressed more in rat C6 glioma cells treated with varying concentrations of arbutin (30 and 40 µM) (Yang et al., 2021). In addition, as a result of gene expression analysis and immunocytochemical analysis performed with RT-PCR device, it was shown that the application of β-arbutin at LD50 dose increased caspase 3 activity in MCF-7 cells (Hazman et al., 2021). In light of our findings, considering that the IC50 dose increased apoptotic caspase 3 activation in SKOV3 cells, determining the mechanism behind these effects of arbutin may contribute to the development of a new perspective in treatment.

In conclusion, it is our opinion that this molecule in particular will provide insight into ovarian cancer research because, to the best of our knowledge, our work is the first to examine the impact of arbutin on ovarian cancer cells in the literature. A naturally occurring phytochemical called arbutin decreased the viability of ovarian cancer cells and activated caspase 3 to cause apoptosis. Consequently, we think that arbutin may be a promising ovarian cancer treatment. Arbutin's effects on different types of cancer cells as well as its impacts at the gene and protein levels

should be investigated for clinical research. Given the results, in vivo experimental animal investigations should be carried out in addition to in vitro studies.

This study has some limitations. Caspase-3 immunocytochemical staining provided supportive evidence for the apoptotic effects of arbutin in SKOV3 cells. However, for more detailed confirmation of caspase-3 activation at gene and protein levels, it would be useful to apply more quantitative techniques such as Western blot or qPCR in future studies. However, the immunocytochemical approach used in our study is widely accepted in the literature to evaluate apoptosis in similar cell culture models and was found to be sufficient to meet the objectives of our study. Future studies using more comprehensive molecular techniques will contribute to support these findings and reveal the apoptotic pathways associated with arbutin in more detail.

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

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

Author Contributions: Conception – S.K.S.; Design – S.K.S.; Supervision – S.K.S.; Fund – S.K.S.; Materials - S.K.S.; Data Collection and Processing – S.K.S., R.K.; Analysis Interpretation – R.K.; Literature Review – S.K.S., R.K.; Writing – S.K.S., R.K.; Critical Review – S.K.S., R.K.

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