ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article DOI: 10.62425/rtpharma.1466682

Antitumoral Effect of Syringic Acid on DU-145 Prostate Cancer Cells Antitumoral Effect of Syringic Acid

Yeşim YENİ[1]
Sıdıka GENÇ[2]
[1]Department of Medical Pharmacology, Faculty of Medicine, Malatya Turgut Özal University, Malatya, Türkiye
[2]Department of Medical Pharmacology, Faculty of Medicine, Bilecik Seyh Edebali University, Bilecik, Türkiye

ABSTRACT

Objective: Prostate cancer (PC) is one of the most prevalent reasons for cancer-killing in men worldwide, and new drugs to treat PC are currently being developed. Syringic acid (SA) is a polyphenolic compound that exhibits anti-inflammatory and metabolic regulatory effects and antitumor activities in various tumors. This study purposed to research the antiproliferative and antitumor activities of SA on DU-145 cells.

Methods: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) as used to assign the antiproliferative effect of SA and Superoxide dismutase (SOD)- Malondialdehyde (MDA) analyses were used to determine its antioxidant-oxidant effects.

Results: SA significantly suppressed DU-145 cell proliferation in vitro. Additionally, while it reduced SOD levels, it caused a significant increase in MDA levels.

Conclusion: Our findings revealed the antitumor potential for PC by targeting the curative effect of SA.

Keywords: DU-145, Malondialdehyde, Prostate cancer, Superoxide dismutase, Syringic acid

Received 18.03.2024
Accepted 22.04.2024
Publication Date 03.05.2024

Corresponding author:
Yeşim Yeni
E-mail: yesim.yeni@ozal.edu.tr
Cite this article: Yeni, Y., & Genç, S. (2024). Antitumoral Effect of Syringic Acid on DU-145 Prostate Cancer Cells Antitumoral Effect of Syringic Acid. *Recent Trends in Pharmacology, 2*(1), 1-5.

Introduction

According to World Health Organization GLOBOCAN data, prostate cancer (PC) is the most prevalent type of cancer in men worldwide. It is the 2nd most prevalent cause of death after lung cancer (Siegel et al., 2022). In studies conducted in Türkiye, it is the 3rd most prevalent type of cancer in men and the 4th in cancer-based kills (Sung et al., 2021). PC is more strongly associated with age than other known types of cancer (Jemal et al., 2021). Prostate adenocarcinoma is a heterogeneous group of diseases, and while it has a silent course in some patients, it can have an aggressive course in others (Harlan et al., 2001). Today, androgen-deprived therapies and docetaxel, abiraterone acetate, and enzalutamide-related chemotherapy are standard therapies for forward PC patients (Cornford et al., 2021; Cattrini et al., 2019). However, traditional chemotherapy can with easy reason important side effects in the hematopoietic tract, repeat drug withdrawal reactions, and severe drug resistance, placing a heavy load on patients. For this reason, it is important to research new and effective drugs for PC metastasis and proliferation (Petrylak et al., 2004).

Natural products have been demonstrated to be the most inevitable resource of anticancer drugs like paclitaxel and vincristine, which have succeeded greatly in the clinical therapy of diverse cancers (Kingston, 2009). Natural products generally have lower toxicity and higher efficacy than traditional chemotherapy drugs. In the process of researching drugs for the treatment of PC, various active materials obtained from natural resources have been demonstrated to have anticancer potential (Fontana et al., 2020). SA has shown that it can modulate signaling molecules, transcriptional factors, proteins, and growth factors, especially in diverse cancer cells (Srinivasulu et al., 2018; Rob et al., 2020). SA has diverse physiological functions like anti-oxidant, anti-diabetic, anti-inflammatory, hepatoprotective, anti-cancer, and anti-mitogenic properties (Srinivasulu et al., 2018). Furthermore, research on SA's cytotoxic effect in colorectal, breast, and lung cancer cell lines has produced promising results (Gheena & Ezhilarasan, 2019). Numerous extracts and several plants that contain SA have established anti-inflammatory activities (Ham et al., 2016; Tanaka et al., 2017). Scientific literature suggests that SA may be therapeutic on A549 lung cancer cells (Karthick et al., 2014). Considering the desire to improve recent anti-cancer agents, herb-related bioactive phytochemicals present loud efficiency and low toxicity properties that can ultimately be used in the clinical therapy of PC patients. For this reason, in this work, we researched whether SA exerts any effect on PC cells.

Methods

Cell Culture

The DU-145 cell line was incubated with a medium containing 15% Fetal Calf Serum, Eagle's Minimum Essential Medium, and the antibiotic penicillin-streptomycin (Sigma, USA) at 37°C, 5% CO2, 95% humidity and 25-75 cm2 cell culture flasks. After sufficient consolidation, the 75 cm2 bottle was washed with phosphate-buffered saline (Sigma, USA). Then, the cells were separated from the vial by adding Tyripsin-EDTA (Sigma, USA) and after centrifugation, the cells were transferred to 96-well plates. The cell culture dose of SA was determined with reference to previous studies (Gheena & Ezhilarasan, 2019). When the cells covered approximately 85% of the well surface, SA was applied to the wells at concentrates of 5-10-20- 40, and 80 µg/mL. After 24 hours, cell viability was measured.

Cell Viability

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) (Sigma, USA) test was used to appraise cell viability. 10 µL of MTT resolution was supplemented to all wells and after the incubation period, the formazan crystals were dissolved in 100 µl of dimethyl sulfoxide (Sigma, USA). Finally, the absorbance value was determined at 570 nm in the spectrophotometer (BioTek, USA) (Yeni et al., 2023).

Biochemical Analysis

Cell medium was gathered 1 day after toxicity administration and assayed according to the manufacturer's instructions.

Malondialdehyde (MDA) levels MDA ELISA kit (E-BC-K025-S; Elabscience, USA) was used in the evaluation and the method was performed as in the instructions. Optical density was measured spectrophotometrically at 450 nm wavelengths. MDA activity was stated as nmol/mg Protein.

Superoxide Dismutase (SOD) levels SOD ELISA kit (E-EL-H1113; Elabscience, USA) was used in the evaluation and the method was performed as in the instructions. Optical density was measured spectrophotometrically at 450 nm wavelengths. SOD activity was stated as pg/mL.

Statistical Analysis

Data were analyzed with the GraphPad 8.02 program.

ELISA results were analyzed using the One-way analysis of variance analysis of the variance test. For post-hoc analysis, the Dunnett test was performed.

Results

Cell Viability

The MTT test indicated the cytotoxicity results for all groups 24 hours after application. Figure 1 shows the cytotoxicity of SA at various doses (5-80 µg/mL) against PC cells. Cell viability was considered as 100 in the control group. In the SA group, this rate was shown to be lower than in the control group. No significant results were obtained in SA 5, 10, and 20 µg/ml groups. However, viability was significantly affected at high concentrations. Cell viability significantly was reduced in SA 40 and 80 µg/ml group (p<0.01). A nearly 20% and 40% reduction in this viability verifies the cytotoxic effect of in SA 40 and 80 µg/ml group, respectively.

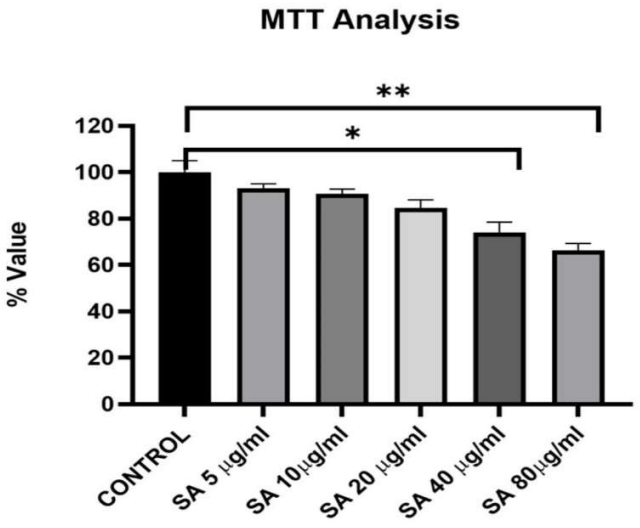

Figure 1. 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) results of the application group. Data are stated as the means ± SD. *p<0.05, **p<0.01 values are very significant for the control group.

SOD-MDA

For samples treated with 40 and 80 µg/ml SA, ROS levels dramatically rose (p<0.01) (Figure 2), whereas oxidative stress in antioxidant enzymes (SOD) decreased, showing the production of ROS (Figure 2). The identification is caused by two methoxy groups linked to the aromatic ring of an SA molecule at positions 3 and 5. SOD level was determined as 44.72 pg/ml in the control group. Upon treatment with the SA group, cell viability began to decrease. Thus, the resulting redox parameters began to affect cell viability. In the SA 40 and 80 µg/ml groups, along with the decrease in cell viability, there was also a severe decrease in sod activities. This value was determined in the SA 80 µg/ml group as 15.97 pg/ml (p<0.01).

Oxidative damage in the cell was determined by MDA. Interestingly, when ROS levels in cells were evaluated after exposure to SA, ROS production was found to increase in a concentration-dependent manner like chemotherapeutics. (Figure 2). However, the ROS level was significantly higher in the 80ug/ml group (25.80 nmol/mg protein) (p < 0.01).

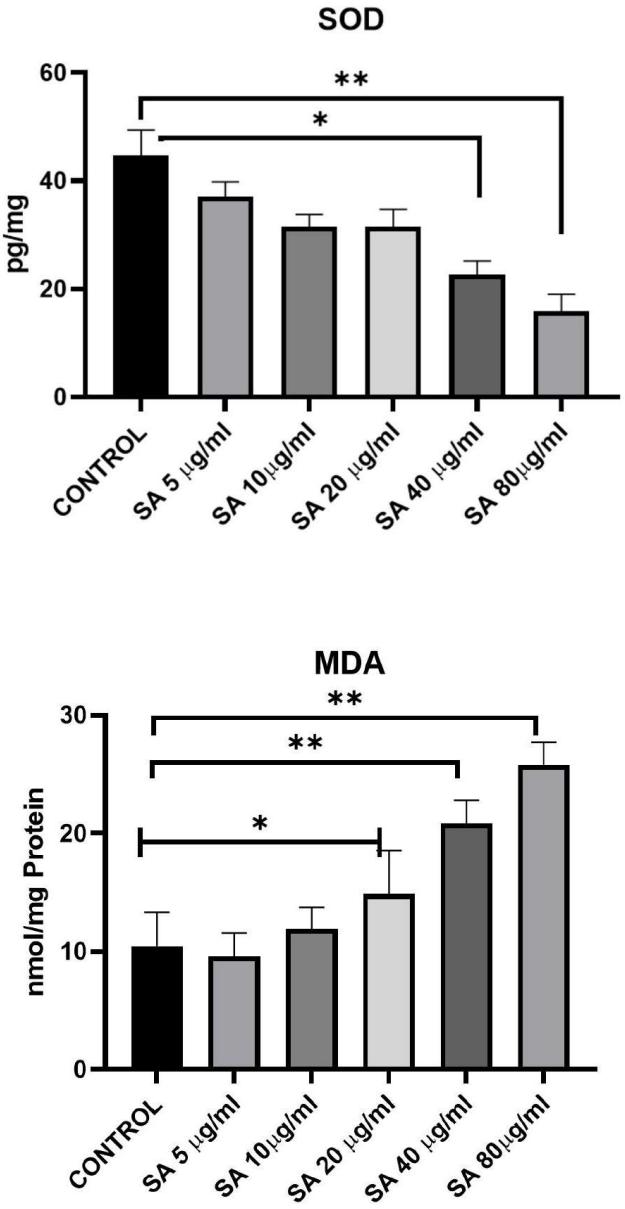

Figure 2. Superoxide dismutase (SOD) and

Malondialdehyde (MDA) results of application group. The values have been displayed as mean ± SD. *p<0.05, **p<0.01 values are very significant for the control group.

Discussion

Cancer is an illness with cell loop irregularity (Park & Lee, 2003). Numerous works have shown that natural products and their simultaneous therapy and chemotherapy are effective in malignant tumors. Active materials extracted from natural products can modulate the cancer microenvironment and various cell signaling cascades, so they play an important role in fighting cancer (Fontana et al., 2020; Dutta et al., 2019; Salehi et al., 2019). SA can stimulate apoptosis in diverse cancer cells (Srinivasulu et al., 2018). It has recently been reported that SA exhibits cytotoxicity features against oral squamous cell carcinoma SCC131 (Velu et al., 2020). In this study, SA depressed the growth of PC cells in a concentrated-dependent manner and demonstrated that the count of dead cells increased in SA-therapy cells. In the present study, the status of antioxidant enzymes in PC cells showed reactive oxygen species accumulation in SA-treated cells. Here we report that SA causes a significant inhibitory effect on PC cell metastasis and growth.

One study showed that treatment with SA led to an increase in the count of ROS-produced SW-480 cell populations compared to controls. More significantly, evaluation of the antioxidant ingredient of the cells demonstrated that SA caused a decrease in the level of antioxidant enzymes like CAT, GST, GPx, GR, and SOD, in tumor cells. For this reason, antioxidant consumption, which has recently been associated with cell killing, is another mechanism for the antitumor effects of SA in colorectal tumor cells (Mihanfar et al., 2021). Besides in vitro works, the antitumor effects of SA have been verified in animal models including diverse types of cancer. In a work conducted on rats, the chemo-protective effects of SA were investigated. A preadministration concentrate of 50 mg/kg was able to decrease the abnormal expression of cytokeratin and positively modulate cell surface glycoconjugates. The findings were also verified in histological investigation; because those pretreated had standard histological results compared with those exposed to the carcinogen alone. Some of these effects were found to be partly mediated by the antioxidant role of SA (Periyannan & Veerasamy, 2018). The incorporation of SA into gastric cancer cells has been shown to inhibit the advancement of inflammatory mediators mainly through regulation of the AKT/mTOR signaling path (Pei et al., 2021). For this reason, SA may be a candidate agent for use in PC treatment with its anti-inflammatory effect.

Conclusion

Studies show the antioxidant, anti-inflammatory, anti-lipid peroxidative, and anticancer effects of SA on PC. This investigation supports the evidence showing the curative effect of SA on PC. Therefore, SA is waiting to serve as a new anticancer drug in the therapy of PC.

Ethics Committee Approval: Since the cell line was studied in vitro, an ethics committee decision is not required.
Informed Consent: Since it is an in vitro study, participant consent is not required.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept – YY; Design - YY; Supervision – YY, SG; Resources – YY; Materials – YY, SG; Data Collection and/or Processing – YY, SG; Analysis and/or Interpretation – YY, SG; Literature Search – YY, SG; Writing Manuscript – YY, SG; Critical Review – YY, SG; Other – YY
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

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