



ORIGINAL ARTICLE

The Anticancer Potential of *Sideritis akmanii* Extract in Melanoma Cells via Oxidative Stress and Cytokine Regulation

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Abstract

Melanoma is one of the most aggressive forms of skin cancer, characterized by its high metastatic potential and resistance to treatment. This study aimed to evaluate the potential anticancer effects of the ethanol-water extract of the endemic plant *Sideritis akmanii* (*S. akmanii*) on the G361 human melanoma cell line. Cell viability was determined using the [2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium salt (WST-1) assay, and oxidative stress parameters such as Total Oxidant Status (TOS), Total Antioxidant Status (TAS), and Oxidative Stress Index (OSI) were calculated. Additionally, Tumor Necrosis Factor Alpha (TNF- α), Transforming Growth Factor Beta (TGF- β), Interleukin 1 Beta (IL-1 β), and Beta Defensin 2 (DEF- β 2) cytokine levels were analyzed using the ELISA method. A dose-dependent decrease in cell viability was observed as a result of the extract application, and it was determined that oxidative balance shifted toward the pro-oxidant direction with an increase in total oxidant levels. Furthermore, examination of the cytokine profile revealed that decreased levels of TNF- α and TGF- β indicated suppressed inflammation, increased levels of IL-1 β indicated activation of the immune response, and decreased levels of DEF- β 2 indicated a change in the tumor microenvironment that supports anticancer potential. These findings suggest that *S. akmanii* extract may have antiproliferative, oxidative stress-inducing, and immunomodulatory effects on melanoma cells. There is a need for more comprehensive studies to understand the mechanisms through which these effects occur.

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Introduction

Melanoma, known as a significant public health issue, ranks 17th among all types of cancer in terms of incidence [1]. Although it accounts for only about 4% of all cancers, it is one of the most dangerous types of cancer because it accounts for about 80% of cancer-related deaths [2]. The melanoma occurs when melanocytes multiply abnormally and fail to respond to regulatory signals from fibroblasts and keratinocytes. The signalling pathways regulating melanocyte proliferation become abnormally activated, and these cells divide to form melanoma [3]. There are various methods available for treating melanoma. Among these techniques, chemo and immunotherapy are known to have damaging effects [4]. Thus, the development of new therapeutic approaches has become imperative.

Pharmaceutical and aromatic plants are used in the treatment of skin diseases and inflammation [5]. Many studies on various cancer cells have reported cytotoxic, antiproliferative, apoptotic, anxiolytic, antimicrobial, and anti-inflammatory properties of *Sideritis* species [6,7]. It has been reported that there are 46 species of the genus *Sideritis* in Türkiye, approximately 79% of which are endemic [8]. Aqueous and ethanol extracts of *S. akmanii*, an endemic species in Türkiye, exhibit protective effects on oxidative stress parameters such as Malondialdehyde (MDA), Glutathione (GSH), Superoxide Dismutase (SOD), and Catalase (CAT) [9]. *S. akmanii* acetone extract was also found to exhibit anticarcinogenic effects in MCF-7 cells subjected to ER stress induced by thapsigargin, through its genotoxic, cytotoxic, and Endoplasmic Reticulum (ER) stress effects [10].

Cytokines are a large group of molecules. The production of these molecules is a feature of immune, stromal, and cancer cells. The cytokines enable communication with the microenvironment of cancer cells. This group of molecules includes chemokines, tumor necrosis factor, interferon, interleukins, and growth factors [11]. It is known that TNF- α , one of these molecular groups, increases migration and invasion in melanoma cells, while TGF- β signaling is associated with metastasis and immune evasion via SMAD pathways [12-14]. IL-1 β is reported to promote angiogenesis, macrophage activation, and invasion in the tumor microenvironment [15]. It has been reported that Antimicrobial peptides, such as DEF β 2, can suppress tumor development by modulating the interaction between the immune system and tumors [16]. Thus, examining parameters such as oxidative stress, cytokine levels, and cell viability together may be beneficial in terms of both anticancer and immunomodulatory potential.

The current study's objective is to thoroughly assess the possible impacts of *S. akmanii* ethanol-water extract on the G361 human melanoma cell line. Cell viability, oxidative stress status, and changes in cytokine levels were evaluated in the study. Thus, the aim is to elucidate both the direct antiproliferative effects of *S. akmanii* on melanoma cells and its immunomodulatory potential via inflammation and oxidative stress pathways.

Materials and Methods

Plant material

S. akmanii plant was collected from Afyonkarahisar, Türkiye, by Aytac, Ekici, and Donmez on 15 July 2023 (38°29'02"N 30°21'40"E) and verified by Dr Olcay Ceylan from Muğla Sıtkı Kocman University. These samples were stored in the university's herbarium. After drying the plant's above-ground parts in the shade, they were ground into powder using a grinder, and the plant material was used to obtain the ethanol–water extract. Ultrasound-based extraction was conducted by treating 20 g of plant samples in 400 mL of a 1:1 ethanol–water mixture at 35°C in an ultrasonic bath [17]. Plant extract was kept at 4°C.



Cell line and culture conditions

S. akmanii plant ethanol-water extract was tested on the G361 cell line to determine its effects. G361 cells were obtained from the Chemistry Department of Afyon Kocatepe University. G361 cells were cultured in appropriate culture medium and incubated for 24 hours at 37°C.

Cytotoxicity analysis

The WST-1 assay was used to determine the cytotoxicity of *S. akmanii* plant extract on the G361 cell line. A cell suspension prepared to a concentration of 5×10^3 cells per 200 μ L medium was seeded into culture plates, and plant extract concentrations (0.98-500 μ g/mL) were added. The plates were then incubated at 37 °C for 24 hours. 10 μ L of WST-1 mixture was added, and incubated in the incubator. The measurement of the absorption was conducted at a wavelength of 450 nanometers (Multiscan Sky, Thermo Fisher Scientific). The percentage % viability was calculated by dividing the absorbance values of *S. akmanii* ethanol–water–treated cells by the absorbance value of the control group and multiplying by 100. According to the doses determined as a result of WST-1 analysis, the experimental groups and the applications are presented in Table 1.

Table 1. Experimental groups and applications.

Groups	Applications
Control (Cnt)	An untreated group (Medium)
<i>S. akmanii</i> IC ₅₀ group	Group treated with <i>S. akmanii</i> at IC ₅₀ dose
<i>S. akmanii</i> ½ x IC ₅₀ group	Group treated with <i>S. akmanii</i> at ½ x IC ₅₀ dose.
<i>S. akmanii</i> 2 x IC ₅₀ group	Group treated with <i>S. akmanii</i> at 2 x IC ₅₀ dose.

Determination of TAS, TOS, and OSI in cell lysate

Total protein levels in cell lysates obtained from treatments applied to G361 cells for analysis were determined commercial kit. TAS and TOS levels were measured using a commercial kit (Elabscience, USA) based on the spectrophotometric method. Standard solutions were prepared at 8 different concentrations (0-0.4-0.8-1.4-1.6-1.8-2 mmol/Trolox) in the kit protocol, and TAS levels were determined according to the calibration curve. TAS levels were expressed as mmol Trolox Equivalent/g-protein by dividing the total protein levels of the samples. According to the kit protocol and calibration curve, TOS levels were determined using the absorbance values obtained. The following formula was used to calculate OSI:

$$\text{Oxidative Stress Index (OSI)} = \left[\left(\frac{\text{TOS}}{\text{TAS}} \right) \times 100 \right] \quad (1)$$

Analyses of cytokine production in G361 cells

The measurement of cytokine levels was conducted at 450 nanometers in G361 cells to determine whether the ethanol-water extract of the *S. akmanii* plant had any effect on the inflammatory process. TNF- α , TGF- β , IL-1 β , and DEF- β 2 levels were determined by creating calibration curves according to the kit protocol. Results obtained from each sample were divided by the total protein levels in each sample, and cytokine levels were given in pg/mg-protein.

Results

The cytotoxic effect of *S. akmanii* on G361 cells

Different doses ranging from 0,98-500 µg/mL were used to determine the cytotoxicity of *S. akmanii* extract in G361 cells. Accordingly, after treatment with 0,98 µg/mL, 1,95 µg/mL, 3,90 µg/mL, 7,81 µg/mL, 15,62 µg/mL, 31,25 µg/mL, 62,50 µg/mL, 125 µg/mL, 250 µg/mL, and 500 µg/mL *S. akmanii* extract, % cell viability 87,27%, 84,11%, 80,19%, 77,16%, 74,21%, 71,45%, 66,22%, 60,35%, 49,59%, and 25,63% respectively. It was determined that doses in the range of 62,5-500 µg/mL may have high cytotoxicity. WST-1 analysis data show that the plant extract decreased cell viability (Figure 1).

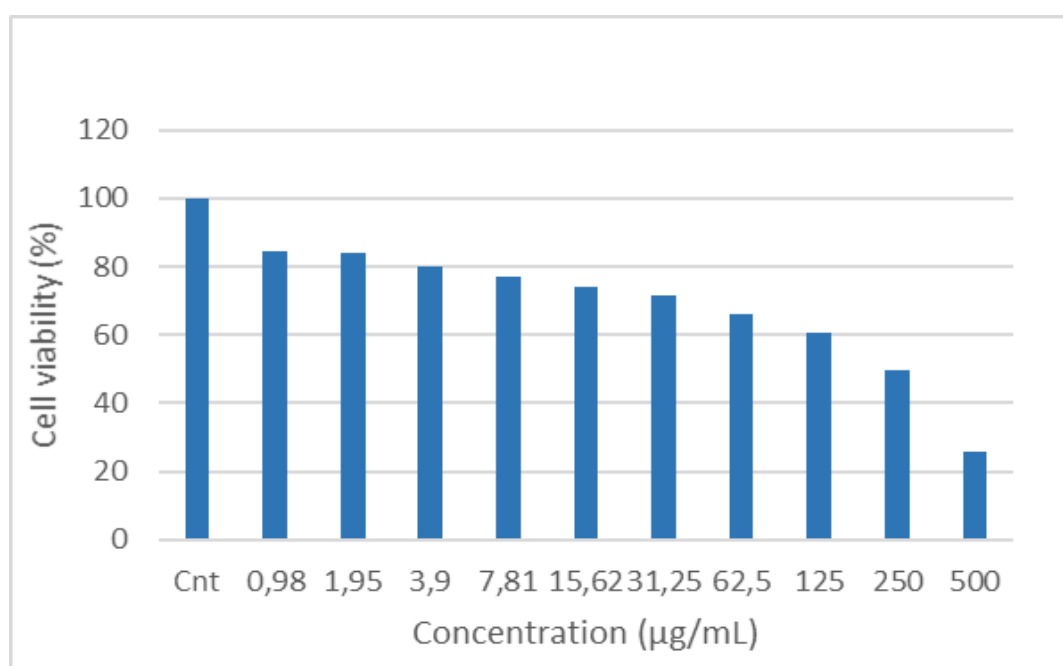


Figure 1. Cytotoxicity level of *Sideritis akmanii* extract in different concentrations in G361 cells.

The effect of *S. akmanii* on oxidative stress in G361 cells

The oxidative stress parameters are demonstrated in Figure 2. The highest TAS value was detected in the $\frac{1}{2} \times IC_{50}$ group as $1,75 \pm 0,01$. The highest TOS value was detected in the $\frac{1}{2} \times IC_{50}$ group as $14,45 \pm 0,24$. The highest OSI value was observed in the $\frac{1}{2} \times IC_{50}$ group.

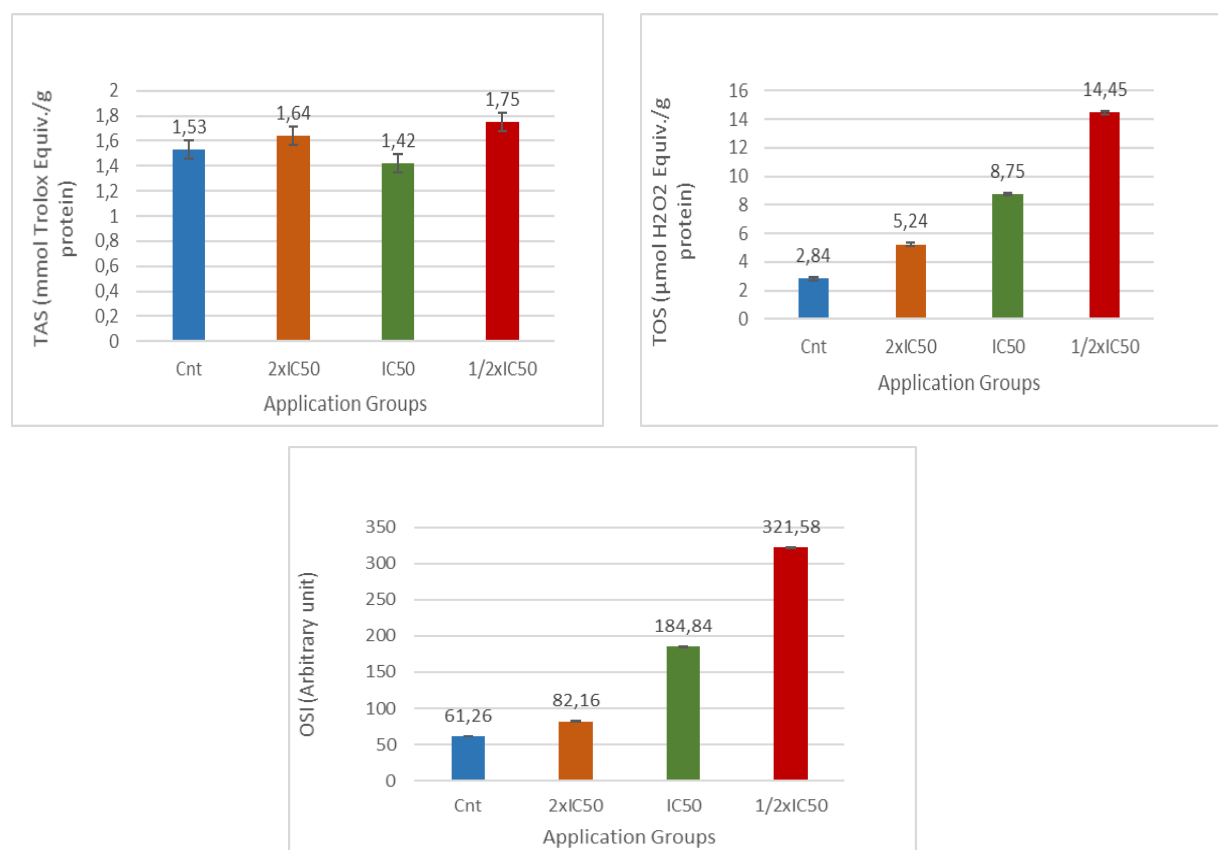


Figure 2. The effect of *Sideritis akmanii* on oxidative stress in G361 cells.

The effect of *S. akmanii* on inflammation in G361 cells

Cytokine levels were determined in G361 cells, and all treatment groups cytokine levels compared to the control group (Figure 3). TNF- α showed the highest level in the control group ($316,10 \pm 9,38$). The lowest TGF- β cytokine value was determined as $2,04 \pm 0,12$ in the $\frac{1}{2} \times IC_{50}$ group. IL-1 β showed the highest in the $\frac{1}{2} \times IC_{50}$ group, and DEF- $\beta 2$ cytokine level was compared to the control group, with the lowest values determined in the $\frac{1}{2} \times IC_{50}$ group.

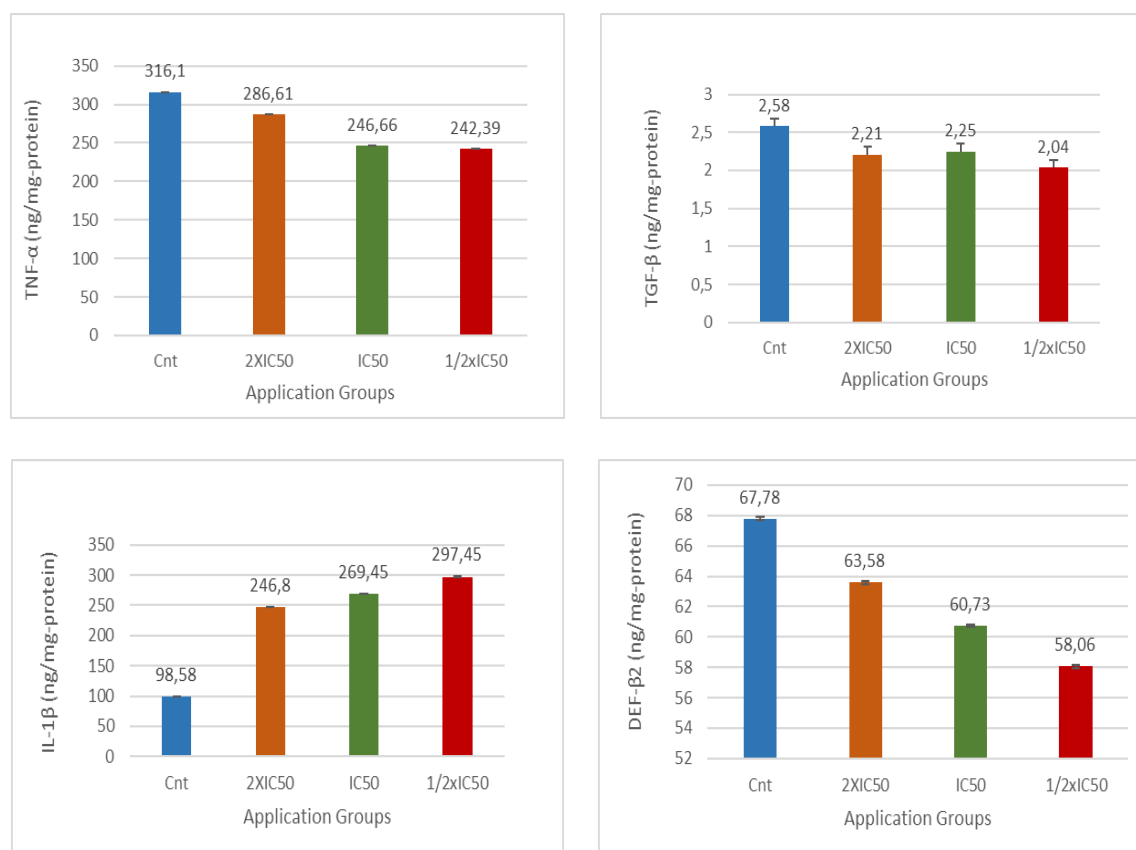


Figure 3. The effect of *Sideritis akmanii* on inflammation in G361 cells.

Discussion

Plants commonly used in traditional medicine are increasingly being evaluated as potential adjuvants in cancer treatment. Species belonging to the *Sideritis* genus, known in folk medicine as “mountain tea” or “meadow tea,” are used particularly for respiratory ailments, cold treatment, and digestive system disorders [8,18,19]. *S. akmanii* ethanol-water extract was assessed for its potential anticancer effects on the G361 human melanoma cell line in this study. Cell viability, oxidative stress parameters (TAS, TOS, OSI), and certain cytokines were examined.

Results showed that *S. akmanii* ethanol-water extract reduced cell viability in the G361 cells. Similarly, various species of *Sideritis* were reported to exhibit antiproliferative and cytotoxic effects on different types of cancer cells. For example, it is stated that the ethanol and acetate extracts of *S. leptoclada* exhibit significant cytotoxic activity in HT-144 cells [20]. *S. euboica* [21] and *S. libanotica* subsp. *linearis* [22] also exhibits cytotoxic activity in A549 cells. *S. trojona* [23] and *S. raeseri* [24] exhibit cytotoxic activity in PC3 prostate cancer cells. *S. scardica* extracts are among the most studied species and are known to exhibit strong cytotoxicity in the B16 and HL-60 cell lines [25]. The antiproliferative effect seen in this study is in line with other research. It has been suggested that the high phenolic and flavonoid compounds contained in *Sideritis* species, along with diterpenoids such as siderol, may contribute to the suppression of proliferation in cancer cells [26,27].

The decrease in cell viability of *S. akmanii* in G361 cells may be related to increased oxidative stress. Oxidative stress plays an important role in all stages of melanoma [28]. Oxidative stress is important. It plays a role in all stages of melanoma, and the excessive production of reactive oxygen species plays a role in both apoptosis and cancer pathogenesis [29]. It has been demonstrated that the ethanol extract of *S. leptoclada* inhibits proliferation and induces apoptosis in the HT-144 cell line. The decrease in

cell viability in this study may similarly be thought to parallel the increase in reactive oxygen species (ROS) [20]. When antioxidant capacity was examined, TAS, TOS, and OSI levels increased. This indicates that the plant's cells experience a shift in oxidative balance. *Sideritis* species are generally reported to have high antioxidant capacity [30].

Analysis of cytokine levels reveals a notable decrease in TNF- α levels. TNF- α plays an important role in processes such as programmed cell death, inflammatory responses, and immunity [31]. It has been reported that this cytokine increases the invasive and migratory properties of human melanoma cells [12]. It is also known that the methanol extract of *S. bilgeriana* reduces cytokine levels in mice [32]. High TNF- α levels are associated with chronic inflammation and tumor progression [33]. In this study, the reduction of TNF- α levels by *S. akmanii* suggests an anti-inflammatory response and a possible tumor-suppressing effect. As a multifunctional cytokine, the role of TGF- β in melanoma is twofold; it affects both tumour cells and cells in the area around the tumour. Activating the TGF- β receptor may stimulate metastatic growth in the liver by altering the tumour microenvironment and immune cell infiltration [14]. The decrease in TGF- β levels in the study suggests that the extract may mildly inhibit this cytokine, which mediates proliferative and immunosuppressive effects in intercellular signaling. However, increased IL-1 β levels indicate a different mechanism. It has been reported that verbascoside, a compound found in *Sideritis* species, reduces high levels of inflammation-related mediators in a mouse model of intracerebral hemorrhage [34]. The increase in IL-1 β observed in this study may contribute to triggering cell death processes. DEF- β 2 is a peptide belonging to the innate immune system that is believed to regulate anti-tumour immunity. This peptide is recommended for use in developing immune therapies for the treatment of melanoma [16]. This study suggests that a decrease in DEF- β 2 levels is also significant and that this decrease may be associated with a potential anticancer response in the tumor microenvironment of *S. akmanii*.

Sideritis species' anticancer mechanisms in the literature have mostly been attributed to apoptosis induction, ROS production, and anti-inflammatory effects. It has been shown that extracts of *S. öztürkii* induce programmed cell death [35]. Additionally, phytochemical analyses conducted on *Sideritis* species have highlighted that flavonoids and phenolic acids possess apoptosis-inducing properties [8]. The investigation into the potential anticancer effects of *S. akmanii* ethanol water extract in G361 cells is the first of its kind. Results are consistent with the literature; further studies are needed to investigate pathways related to inflammation and apoptosis in greater detail.

Conclusion

In conclusion, this study demonstrates that *S. akmanii* possesses anticancer potential in G361 human melanoma cells. The plant extract reduced cell viability, shifted the oxidative balance toward the pro-oxidant side, suppressed inflammation by decreasing TNF- α and TGF- β levels, triggered the immune response by increasing IL-1 β levels, and provided a possible anti-tumor contribution to the tumor microenvironment by decreasing DEF- β 2 levels. *S. akmanii* may be a promising phytotherapeutic candidate for melanoma treatment. However, further studies investigating mitochondrial apoptotic pathways, caspase activations, and ROS levels in greater detail are needed to better understand the mechanisms involved.

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Conflict of interest

No conflict of interest.

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