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Enhanced Anticancer Potential of Combined Genistein and Dexamethasone Treatment in Melanoma

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Abstract

Background: Advanced malignant melanoma continues to be a highly invasive type of cancer with an unfavorable prognosis and limited therapeutic outcomes. Methods: The current study investigated the cytotoxic potential and morphological effects of genistein (GEN) and dexamethasone (DEX), administered individually and in combination, on murine melanoma cells B164A5, using normal epidermal cells JB6 Cl 41-5a as controls. Results: Treatment with GEN induced a dose-dependent decrease in the viability of melanoma cells, reaching 60.52% at 50 μM, in accordance with its known capacity to both inhibit proliferation and induce apoptosis by modulating NF-κB and Akt signaling pathways. DEX demonstrated moderate cytotoxic activity (71.34% viability at 50 μM), mirroring its recognized adjuvant role in cancer therapy. Combined treatment with both GEN (25 μM) and DEX (50 μM) resulted in the highest cytotoxicity (48.97% viability), suggesting a synergistic effect likely mediated by augmented apoptotic signaling and oxidative stress. The MTT assay and morphological analyses confirmed apoptotic characteristics, including cell contraction and detachment, while normal cells remained over 90% viable. Conclusions: These results show that GEN, especially when combined with DEX, has selective cytotoxicity against melanoma cells and may serve as a potentially promising adjuvant candidate for future pharmacological strategies targeting malignant melanoma.

Keywords: *genistein; dexamethasone; combinatorial treatment; cytotoxicity; apoptosis; melanoma*

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1. Introduction

Cancer is one of the most devastating threats to public health across the world, defined by the uncontrolled proliferation of abnormal cells and their capacity to spread into surrounding tissues or metastasize to distant organs [1]. According to the World Health Organization, both the incidence and mortality rates of cancer keep increasing, emphasizing the urgent necessity for new therapeutic approaches that improve efficacy and minimize toxicity [2]. Traditional cancer therapies, surgery, chemotherapy, and radiation therapy, continue to remain the principal treatment options [3]. Unfortunately, these approaches are frequently limited by severe toxicity, lack of selectivity against malignant cells, the emergence of drug resistance, and significantly decreased quality of life for patients [4]. Considering its limitations, an increasing number of recent studies have been focused on exploring alternative or complementary therapies that can improve conventional treatments and provide safer and more effective outcomes [4]. Natural compounds, particularly phytochemicals, have emerged as potential sources of bioactive molecules showing anticancer activity [5]. These plant-derived compounds are able to inhibit cell proliferation, induce apoptosis, induce angiogenesis, and modulate the immune response by interacting with multiple molecular targets [5–7]. This multitargeted behavior, which is attributed to their various chemical structures, may also allow for synergistic effects when combined with other conventional therapies [6]. Some of the most extensively studied phytochemicals are terpenoids, flavonoids, saponins, and lignans [7]. Genistein, an isoflavone found in soy, has demonstrated potent anticancer properties in experimental models, including

apoptosis induction and metastasis inhibition [8]. Although dexamethasone is a synthetic glucocorticoid rather than a phytocompound, it is often used in combination with natural compounds due to its anti-inflammatory and immunosuppressive effects, which can enhance therapeutic efficacy and relieve cancer-related symptoms [9]. The current study aims to evaluate the therapeutic potential of selected phytocompounds, particularly genistein, in cancer therapy by using in vitro models. The investigation focuses on assessing cytotoxic effects on tumor cells and analyzing related morphological changes. Ultimately, phytocompound-based therapy might be a useful approach in the field of oncology, promising fewer side effects by reducing adverse effects and improving patient tolerance. The results of this work might help us to better comprehend a deeper understanding of the molecular mechanisms underlying the anticancer activity of these compounds and support the foundation for future studies.

2. Materials and Methods

2.1. Materials

2.1.1. Reagents

The reagents used to perform the experiments are presented in **Table 1**.

Table 1. Table of reagents used in in vitro assessments.

Reagent	Providers
Genistein	Sigma-Aldrich (Merck KGaA, Darmstadt, Germany)
Dexamethasone	Sigma-Aldrich (Merck KGaA, Darmstadt, Germany)
DMSO	PAN-Biotech (Aidenbach, Germany)
EMEM—Eagle's Minimum Essential Medium	PAN-Biotech (Aidenbach, Germany)
DMEM—Dulbecco's modified Eagle's Medium	PAN-Biotech (Aidenbach, Germany)
FBS—fetal bovine serum	PAN-Biotech (Aidenbach, Germany)
PBS	Sigma-Aldrich (Merck KGaA, Darmstadt, Germany)
Penicillin/Streptomycin	Sigma-Aldrich (Merck KGaA, Darmstadt, Germany)
Trypsin-EDTA	PAN-Biotech (Aidenbach, Germany)
MTT—cell viability kit	Roche Holding AG (Basel, Switzerland)

2.1.2. Cell Lines Involved in Experiments

Two different cell lines were involved in the study: melanoma B16 4A5 (CVCL_4612; CLS, Cell Lines Service, Eppelheim, Germany) and JB6 Cl 41-5a neonatal BALB/c epidermal cells (CRL-2010TM; ATCC, Manassas, VA, USA). **Table 2** shows the general characteristics of the cell lines.

Table 2. General characteristics of the B16 4A5 and JB6 Cl 41-5a cell lines.

Cell Line Type	Species	Pathology	Category
B16 4A5	Mus musculus (mouse)	Mouse melanoma	Cancer cell line
JB6 Cl 41- 5a	Mus musculus (mouse)	Healthy, skin, epidermis	Normal cell line

2.2. Methods

2.2.1. Cultivation of Cell Lines B164A5 and JB6 Cl 41-5a

The B16 4A5 cell line was cultured in DMEM (Dulbecco's modified Eagle's medium) supplemented with 1% antibiotic mixture (Penicillin–Streptomycin) and 10% FBS. The JB6 Cl 41- 5a cell line was cultured in EMEM supplemented with 1% antibiotic mixture (Penicillin–Streptomycin) and 5% FBS. The cell lines were kept under standard conditions in an incubator at 37 °C and 5% CO_2.

2.2.2. Obtaining Test Samples

To obtain the stock solutions, GEN (genistein) and DEX (dexamethasone) were dissolved in DMSO (dimethyl sulfoxide). The test solutions were prepared in the culture medium specific to each cell line in the experiments, namely DMEM and EMEM, by diluting the stock solutions. During the experiments, the DMSO concentration did not exceed 0.5%.

2.2.3. Evaluation of the Cytotoxicity of Samples Using the MTT Technique (Determination of Cell Viability)

The cytotoxicity of the samples was assessed by investigating cell viability using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide) technique. The assessment consisted of verifying the individual effect of the GEN samples (5, 10, 25, 50 μM) and DEX (5, 10, 25, 50 μM) on cell viability, as well as the association (10, 25, 50 μM) and DEX (5, 10, 25, 50 μM) on cell viability, as well as that of the association between GEN 10, 25 μM and DEX 5, 10, 25, 50 μM. For these experiments, the cells were cultured in 96-well plates and allowed to attach to the plate. Upon reaching the desired confluence, the cells were treated with GEN, DEX, and the combinatorial treatment between them for a period of 24 h. After the treatment time, 10 μL of kit 1 was added to each well, and the plate was incubate for another 3 h. The next step was to add 100 μL of kit 2-solubilization buffer solution, and the plate was kept at room temperature, in a place protected from light for 30 min. The absorbance was read at two wavelengths (570 and 630 nm) using the Cytation 5 multimode Reader (BioTek Instruments, Winooski, VT, USA).

2.2.4. Cellular Morphology Assesment

Cell morphology was analyzed after culturing B164A5 cells in 96-well plates and treating them, when the desired confluence was reached, with GEN (5, 10, 25, 50 μM) and DEX (5, 10, 25, 50 μM) and the combination of GEN 10, 25 μM with DEX 5, 10, 25, 50 μM for 24 h. Morphological analysis was performed by capturing representative images on Lionheart FX by BioTek Instruments (Winooski, VT, USA) (20× magnification), and the images were processed in Gen5TM Microplate Data Collection and Analysis Software version 3.14. The working protocol for all stages of the work is shown in **Figure 1**.

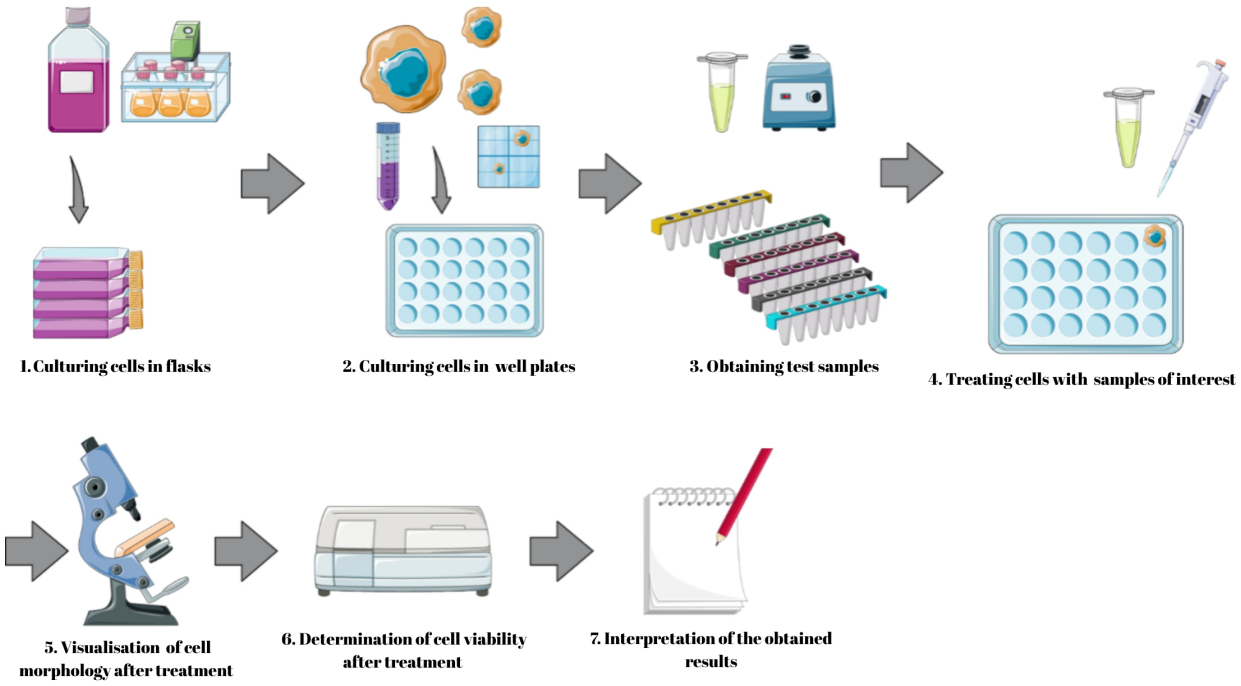

Figure 1. Stages of the working protocol.

3. Results

Melanoma constitutes a malignant neoplasm originated from melanocyte cells, targeting mainly the skin. It is also characterized as the most aggressive form of skin cancer, distinguished by a significantly increased capacity for local invasion and metastasis, even in the early stages of neoplastic development, and it can form de novo or on existing pigmented injuries [10–12].

3.1. Cell Viability

3.1.1. Cell Viability Results—Treatment with Individual Compounds: Genistein and Dexamethasone

Initially, the impact of individual compounds was evaluated over a 24 h period in B164A5 melanoma cells. According to the results illustrated in **Figure 2**, treatment with GEN decreased cell viability in a dose-dependent way, with percentages indicating 86.90% for treatment with 5μM GEN, 73.61% for 10 μM GEN, 69.06% for 25 μM treatment, and 60.52% for the highest GEN concentration treatment, 50 μM. Treatment of B164A5 cells with DEX showed the same dose-dependent trend, reaching 86.71% for treatment with 5 μM DEX, 79.37% for 10μM DEX, 73.61% for DEX 25 μM, and 71.34% for DEX 50 μM. The results of GEN and DEX treatments were compared to the control (untreated cells).

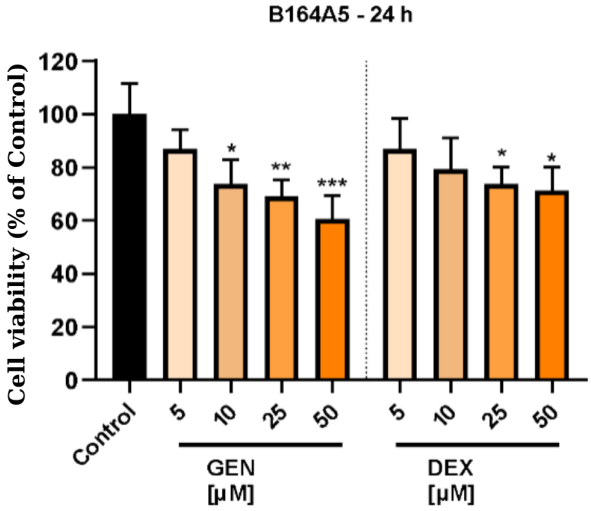

Figure 2. Representative graph showing the effect of GEN (5, 10, 25, 50 μM) and DEX (5, 10, 25, 50 μM) on the viability of malignant melanoma B164A5 cells after 24 h of stimulation. Data are normalized to control and presented as mean values ± standard deviation. For statistical analysis, the one-way ANOVA test was applied, followed by the Dunett test for multiple comparisons (* $p < 0.5$; ** $p < 0.01$; *** $p < 0.001$). GEN = genistein; DEX = dexamethasone.

For in vitro safety assessment, individual GEN and DEX samples were investigated in the healthy JB6 Cl 41-5a cell line for the same period of time, namely 24 h. The results presented in **Figure 3** demonstrate that GEN (5, 10, 25, 50 μM) and DEX (5, 10, 25, 50 μM) did not induce signs of cytotoxicity on normal cells, and there were no statistically significant changes. Furthermore, treatment with GEN 5–25 μM and DEX 5 μM also caused slight cell stimulation. Treatment with GEN at the highest concentration of 50 μM reduced cell viability to 96.32%, while DEX 50 μM reduced it to 86.55%.

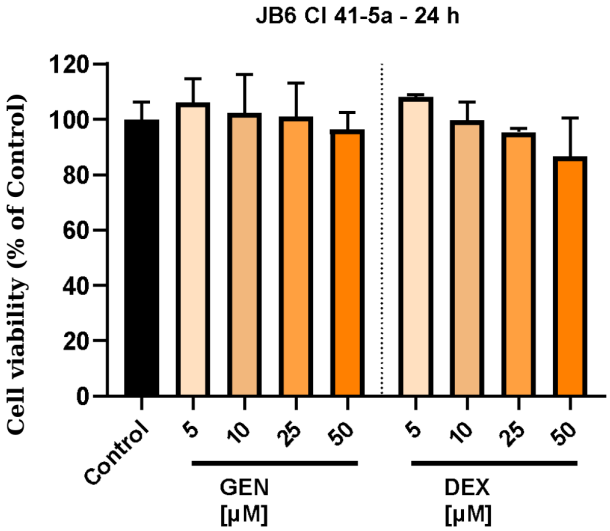

Figure 3. Representative graph showing the effect of GEN (5, 10, 25, 50 μM) and DEX (5, 10, 25, 50 μM) on the viability of JB6 Cl 41-5a epidermal cells after 24 h of stimulation. The data are normalized to control and presented as mean values ± standard deviation. For statistical analysis, the one-way ANOVA test was applied, followed by the Dunnett test for multiple comparisons. GEN = genistein; DEX = dexamethasone.

3.1.2. Cell Viability Results: Combinatorial Treatment between Genistein and Dexamethasone

The next step was to examine the combinatorial treatment of GEN (10 and 25 μM) and DEX (5, 10, 25, 50 μM) on B164A5 cancer cells. According to **Figure 4**, the results indicate a dose-dependent decrease in cell viability. Thus, when GEN 10 μM and DEX (5–50 μM) were combined, the percentages decreased from 62.84% to 54.73% (at the highest concentration—GEN 10 μM + DEX 50 μM), and when GEN 25 μM and DEX (5–50 μM) were used, the cell viability percentages decreased in a dose-dependent manner from 59.31% (GEN 25 μM + DEX 5 μM) to 48.97% (GEN 25 μM + DEX 50 μM).

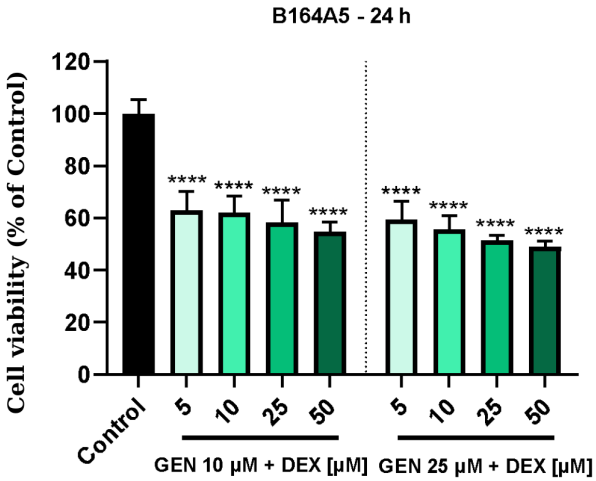

Figure 4. Representative graph showing the effect of combinatorial treatment with GEN (10, 25 μM) and DEX (5, 10, 25, 50 μM) on the viability of malignant melanoma B164A5 cells after 24 h of stimulation. Data are normalized to control and presented as mean values ± standard deviation. For statistical analysis, the one-way ANOVA test was applied, followed by the Dunnett test for multiple comparisons (**** $p \leq 0.0001$). GEN = genistein; DEX = dexamethasone.

Similarly, the combinatorial treatment approach between GEN and QUE was also investigated in the healthy epidermal cell line JB6 Cl 41-5a. As illustrated in **Figure 5**, the combinatorial treatment slightly decreased cell viability, but it did not show any significant signs of cytotoxicity, with all percentages above 90%. At the highest concentrations tested, GEN 10 μM + DEX 50 μM and GEN 25 μM + DEX 50 μM, the cell viability percentages were 94.00% and 92.41%, respectively.

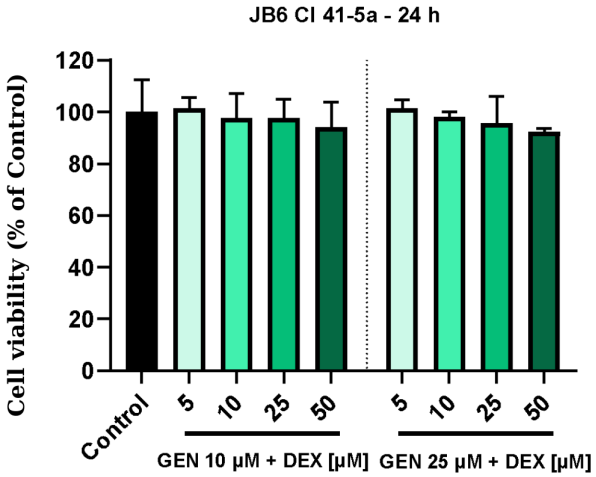

Figure 5. Representative graph showing the effect of combinatorial treatment with GEN (10, 25 μM) and DEX (5, 10, 25, 50 μM) on the viability of JB6 Cl 41-5a malignant melanoma cells after 24 h of stimulation. Data are normalized to control and presented as mean values ± standard deviation. For statistical analysis, the one-way ANOVA test was applied, followed by the Dunnett test for multiple comparisons. GEN = genistein; DEX = dexamethasone.

3.2. Cell Morphology Analysis

According to **Figure 6**, 24 h treatment of B164A5 cancer cells with GEN and DEX produced a dose-dependent decrease in cell confluence, results that are consistent with those obtained from the MTT assay for cell viability. The combinatorial treatment of GEN + DEX maintained the same trend of decreased confluence, dependent on the concentration tested. However, in the case of GEN 10 μM + DEX 25 μM, GEN 10 μM + DEX 50 μM and GEN 25 μM + DEX 10 μM, and GEN 25 μM + DEX 25 μM and GEN 25 μM + DEX 50 μM, the most frequent cellular dysmorphologies (marked with red arrows) were characterized by cell rounding, cell detachment from the plate, cell debris, and cell elongation (observed at the highest concentrations, namely treatment with GEN 10 μM + DEX 50 μM and GEN 25 μM + DEX 50 μM).

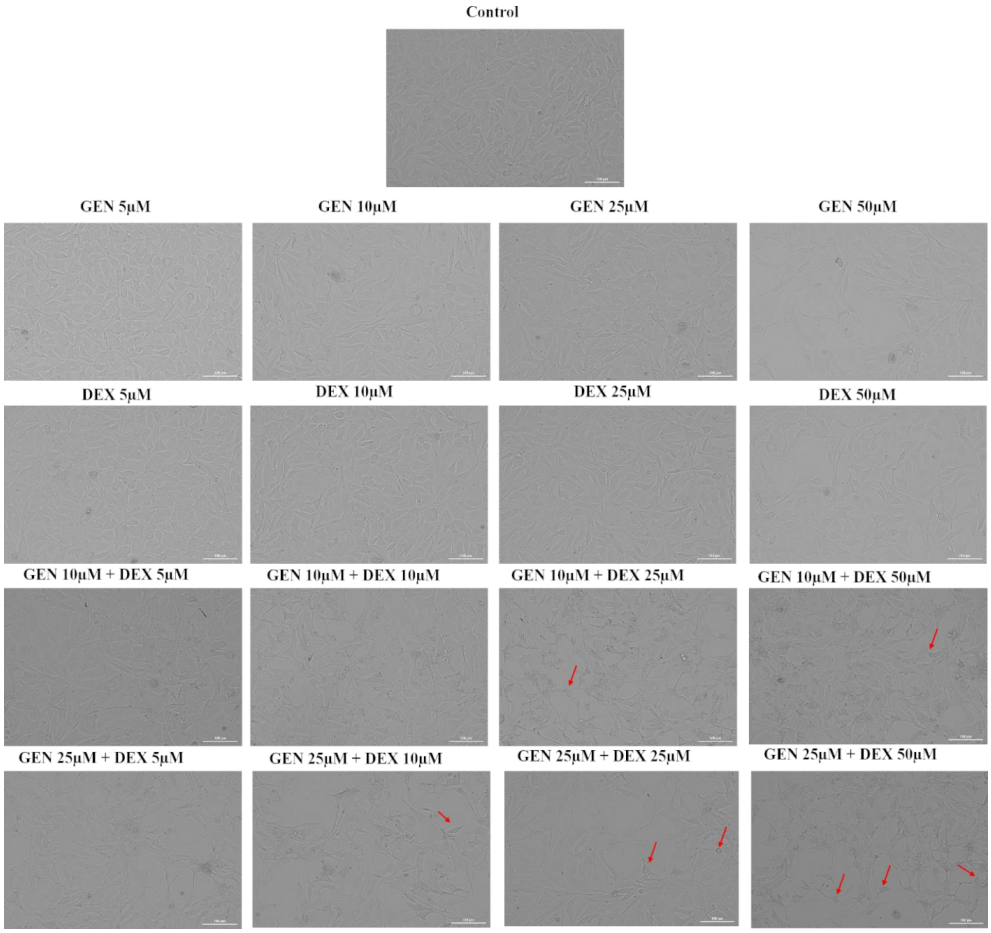

Figure 6. Morphology of B164A5 cells after 24 h treatment with GEN (5, 10, 25, 50 μM), DEX (5, 10, 25, 50 μM), and combined treatment with GEN (10, 25 μM) and DEX (5, 10, 25, 50 μM). The red arrows indicate changes in cell morphology. The scale bar indicates 100 μm.

4. Discussion

Advanced melanoma is a life-threatening type of cancer with a limited life expectancy. The recent introduction of new targeted systemic therapies has provided specialists with the means to prolong survival or even achieve a cure [13]. Cancer is a genetic disease caused by changes in the genes that monitor how the cells of the human body function, particularly when it comes to how cells divide and grow [14]. Cancer is a genetic pathology caused by changes in the genes that monitor how the cells of the human body function, especially when it comes to growth and multiplication [14]. Its etiology involves the interaction of several factors, including genetic factors, environmental factors, and factors related to the patient's lifestyle [14, 15]. Thus, managing cancer remains one of the greatest challenges facing contemporary human society [13]. Cell death is an important process that has been increasingly researched in recent decades. There are two types of cell death: apoptosis and necrosis. Apoptosis (programmed cell death) involves a sequence of closely monitored phenomena and is marked by cell contraction, membrane hemorrhage, and the disappearance of positional organelles, but also DNA condensation and fragmentation. It is based on an active process, which is genetically controlled, through which the cell dies in an orderly manner, without causing inflammatory processes [16]. Apoptosis is mediated, in particular, by the

caspase protein family, which can be differentiated into endogenous apoptosis and exogenous apoptosis [17, 18]. Cells that are distinguished according to their apoptotic form will exhibit membrane contraction, chromatin agglutination, the appearance of apoptotic bodies, and cytoskeletal breakdown [18]. As has been demonstrated, apoptosis is a fundamental biological mechanism of the cell that plays a significant role in the elimination of excess, irreversibly damaged, or potentially harmful cells [18]. Necrosis is a passive process in which the cell loses its membrane integrity, causing the contents to spill into the extracellular space, leading to inflammation [10, 16, 19]. It has no genetically mediated components, but the inflammation that is present damages neighboring tissues and is associated with pathological conditions where trauma or infection processes can be observed [15]. This is a process of uncontrolled cell death caused by external factors that destroy cell integrity, without requiring new protein synthesis and not being regulated by homeostatic processes, and is pathological in nature [17, 19]. The aim of this study was to investigate the phytochemical genistein (GEN) and dexamethasone (DEX) as potential anticancer agents, both individually and by evaluating the combination of the two compounds. The main subject of the evaluations was a melanoma cancer cell line, B164A5, as well as a healthy cell line, represented by JB6 Cl 41-5a, to observe the selectivity of the treatment. The evaluation of cytotoxic effects and cellular morphological changes allowed for an integrated analysis of the action of these compounds in relation to cell viability and selectivity towards normal epidermal JB6 Cl 41-5a cells. Regarding GEN therapy, the results obtained support the existing literature on the anticancer activity of isoflavones, especially GEN, recognized for its ability to inhibit cell proliferation, induce apoptosis, and modulate signaling pathways involved in cancer progression [8, 10–12]. In this study, treatment with GEN reduced the viability of B164A5 cells in a dose-dependent manner, which suggests a directly proportional relationship between the concentration administered and the impact on cell survival. The maximum concentration tested (50 μM) produced a significant decrease in viability, reaching a level of 60.52%, which indicates a potential cytotoxic effect. The literature suggests that anticancer activity may be mediated by interference with essential cellular mechanisms, such as inhibition of kinases involved in the cell cycle (e.g., tyrosine kinases), regulation of proapoptotic gene expression, and suppression of pro-oncogenic transcription factors (e.g., NF-κB or Akt) [8, 20–23]. Similarly, DEX demonstrated a dose-dependent effect on tumor cells, although the magnitude of the decrease in cell viability was slightly lower compared to GEN. This is consistent with the fact that DEX, although part of the pharmacological class of synthetic glucocorticoids, is frequently used in oncological treatments, in adjuvant therapy to control inflammation and adverse reactions, as it does not have a typical profile of a primary cytotoxic agent [20]. However, at high concentrations, DEX can cause changes in the expression of genes involved in apoptosis and may contribute to the sensitization of tumor cells to other therapeutic agents [20]. In the present study, therapy with DEX 50 μM reduced viability to 71.34%, indicating a moderate antitumor effect, but one that is biologically significant [24]. The combination of GEN 25 μM with DEX 50 μM generated the most pronounced cytotoxic effect, with a reduction in viability of up to 48.97%. Compared to individual therapies, this combination appears to intensify cell death mechanisms, probably through the convergence effects on the action of apoptotic signaling pathways, oxidative stress, as well as through cumulative interference with cell division. The additive or synergistic effect of combinatorial therapy could also be explained by the fact that GEN has the ability to modulate the expression of glucocorticoid receptors or to modify the permeability of cell membranes, facilitating the penetration and efficacy of DEX in the intracellular environment. GEN (5–25 μM) has also been tested on other skin melanoma cell lines, such as SK-MEL-28, demonstrating a dose-dependent anticancer effect (viability decreasing to 91.11% at the highest concentration administered) [25]. Also, in the same study and in the same manner, GEN demonstrated selectivity in healthy HaCaT cells. When GEN and doxorubicin were combined, SK-MEL-28 cells were sensitized, showing superior cytotoxicity compared to individual treatments with GEN and doxorubicin [25]. These findings were supported by significantly lower viability when the two compounds were combined, resulting in frequent nuclear dysmorphologies and increased signs of apoptosis [25]. A key aspect of any anticancer treatment is its selectivity towards tumor cells, while maintaining the viability of healthy cells [19]. In this regard, the results obtained from tests on the JB6 Cl 41-5a cell line highlight a favorable profile for both compounds, especially for GEN [19]. At concentrations of up to 25 μM, GEN caused a slight stimulation of normal epidermal cell proliferation, which could be correlated with its antioxidant activity and its role in regulating cellular homeostasis [19]. Only at the maximum concentration of 50 μM was a minor reduction in viability (up to 96.32%) observed, which cannot be considered a significant sign of toxicity [19]. Similarly, DEX did not produce cytotoxic effects in the healthy cell line. Furthermore, the combinatorial GEN + DEX treatment in this cell line maintained a safety profile, with viability above 90% in all conditions tested. These data reinforce the hypothesis that both substances have selective therapeutic potential against cancer cells, which is essential for the development of effective strategic methods with minimal risk of systemic adverse effects. Morphological analysis of B164A5 cells provides additional visual information that supports the results of the MTT test [23]. The MTT test was used to evaluate cell viability following treatment with the compounds studied, generating quantitative data on the cytotoxic effect, while morphological analysis allowed for the observation of structural cell changes associated with cell death, thus providing an integrated interpretation of the biological results [22]. Treatment with GEN and DEX, espe-

cially in combination, led to the appearance of marked dysmorphologies, including cell rounding and detachment, the formation of cellular debris, and changes in the overall architecture of the monoculture. These manifestations suggest loss of cell membrane integrity, cytoplasmic contraction, and possibly the onset of the apoptotic process or necrosis. In particular, the combinations GEN 25 μM + DEX 50 μM and GEN 10 μM + DEX 50 μM showed severe morphological changes, which supports the conclusions regarding the cytotoxic efficacy of the combination treatment. The relevance of these results was in providing a solid experimental basis for continuing preclinical research, including in vivo models. The study demonstrates that GEN can be considered a viable candidate for adjuvant therapy of melanoma, either alone or in combination with established pharmacological agents such as DEX [19]. The combination of these two substances not only maximizes the therapeutic effect by reducing tumor cell viability but also maintains a favorable safety profile for healthy tissues. Given the barriers encountered in the treatment of malignant melanoma as an aggressive form that is often refractory to conventional therapies, the exploration of such therapeutic combinations becomes particularly relevant. Consequently, the present study demonstrates the efficacy of GEN and DEX in reducing the viability of B164A5 melanoma cells, with high effects in combinatorial treatment and a selective cytotoxicity profile [23]. These data support the combinatorial potential of natural compounds with existing pharmacological agents, generating promising prospects for the development of more effective, personalized anticancer therapies with reduced toxicity.

5. Conclusions

The data obtained in this study reveal the potential efficacy of GEN and DEX in inhibiting the proliferation of malignant melanoma B164A5 cells, both individually and, especially, in combination. GEN administration demonstrated a strong, dose-dependent cytotoxic effect associated with its known properties as a proapoptotic agent and modulator of cellular signaling pathways. DEX, although traditionally used as an adjuvant in cancer treatment, showed a moderate antitumor effect, demonstrating a high therapeutic value when administered in combination with GEN. The combined GEN+DEX therapy showed a significant decrease in the viability of tumor cells, without substantially affecting normal JB6 Cl 41-5a epidermal cells, which supports the idea of a selective action profile with synergistic potential. These observations are also supported by the severe morphological changes identified in malignant cells, indicating the triggering of programmed cell death mechanisms. Given these results, the vision of using GEN in adjuvant treatment regimens in combination with glucocorticoids such as DEX to increase the efficacy of antineoplastic therapy in malignant melanoma is emerging.

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Author contributions

Conceptualization: A.T.P. and A.S.; methodology, I.M.; formal analysis: A.S.; investigation: A.T.P. and A.S.; resources: I.M.; writing: A.T.P.; visualization: A.S.; supervision: I.M. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

Data supporting these findings are available within the article or upon request.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Additional information

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