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The Effect of Resveratrol and Static Magnetic Field Interactions on the Oxidation–Reduction Parameters of Melanoma Malignant Cells

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Abstract: Background: Scientific research has confirmed the biological activity of resveratrol, which includes its antioxidant, anti-inflammatory, cardioprotective and anticancer properties. There is no known interaction between a static magnetic field and resveratrol that can modulate resveratrol's effect on cells. Thus, the main aim of our research was to assess the effect of the co-exposure to resveratrol and a static magnetic field on the oxidation–reduction homeostasis of C32 and Colo829 melanoma cells. **Methods**: The studies consisted of determining the activity of the antioxidant enzymes that constitute the body's first line of defense—SOD, GPx and CAT—and determining the lipid peroxidation product—MDA—and the value of the total antioxidant status of melanoma cells. **Results and conclusions**: Resveratrol was shown to exhibit anticancer properties, possibly through the ferroptosis of melanoma cells. A static magnetic field was also found to abolish the anticancer properties of resveratrol and to have a protective effect against melanoma cells by restoring the redox balance in the cells.

Keywords: resveratrol; static magnetic fields; C32 cells; Colo829 cells; anticancer properties

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1. Introduction

An imbalance between the production of free radicals and the body's antioxidant defenses is called oxidative stress. Free radicals can also arise as a result of the action of external factors (UV radiation, ionizing radiation) and during the defense reactions of the human immune system. The production of free radicals also occurs during the normal physiological processes in cell compartments. An important element in the fight against oxidative stress is compounds that have antioxidant properties, among which polyphenols play an important role. Bioactive substances of plant origin have gained popularity in connection to their wide pro-health and pharmacological properties in the last few years [1].

In recent years, some of the most popular sources of antioxidants among consumers are fruits, vegetables and their preserves. Resveratrol, which belongs to the stilbenes, has a wide biological activity. This antioxidant is mainly found in fruits and their preserves, especially in grapes and in high concentrations in red wine. The phenomenon of the French paradox increased the interest in resveratrol. This relationship has broadened the scope of action on the human body in both the cure and prevention of many diseases [2,3].

A rich source of resveratrol is knotweed (Polygonum cuspidatum) and, more specifically, its root, which is mainly grown in China and Japan. Black grape varieties are the best natural source of resveratrol and red grapes contain more resveratrol than green grapes. There is 50–100 mg/g of this polyphenol in fresh grape skins and the highest content of resveratrol is found in red grapes of the Pinot noir variety [4,5]. Berries are also a good source of resveratrol (mulberries, cranberries, bilberries, blueberries, black currants, strawberries, raspberries) and it has also been found in jackfruit, apples, nuts, peanuts and in

some herbs. Moreover, this compound has also been found in cocoa, chocolate and tomato peels [6,7]. In the human body, resveratrol occurs in the small intestine. It is transformed in the liver with the participation of cytochrome P450 and its half-life decay is small and ranges from 8 to 14 min. The final metabolites in resveratrol are conjugated forms with sulfuric or glucuronic acid, which are present in the blood for up to nine hours, after which they are excreted via urine [8].

In their studies, many researchers have confirmed the positive role of resveratrol in preventing cardiovascular diseases by inhibiting lipid peroxidation, reducing the uptake of oxidized LDL cholesterol by macrophages and increasing muscle relaxation smooth vessels and inhibiting platelet aggregation [9]. The anti-inflammatory action of resveratrol is mainly due to its inhibition of the synthesis and secretion of inflammatory mediators, including lymphotoxin, a factor that stimulates granulocyte and macrophages (GM-CSF); interleukin 8 (IL-8); and histamine. In addition, resveratrol can reduce the synthesis and release of interleukins 1 (IL-1) and 6 (IL-6), a chemotactic protein for tumor necrosis factor α (TNFα). This inhibition of the inflammatory reaction by resveratrol is also related to its ability to block the translocation of the NF-κB transcription factor into the nucleus [10]. Moreover, the anti-cancer properties of resveratrol are the result of the participation of resveratrol in the removal of free radicals and their chemical [11].

Static magnetic fields are widespread in our homes and in the environment. Many researchers are looking for an answer to the question of what the effects of the body's exposure to a magnetic field may be. Daily exposure to a magnetic field can negatively affect our cells and tissues and cause diseases. Despite the medical use of static magnetic fields (SMFs) for many years, scientific research does not give a clear answer as to whether a static magnetic field has an antioxidant effect or can cause a disturbance of the oxidation–reduction balance of cells [12,13].

Due to the search for alternative methods of therapy for hard-to-cure cancers, a combination of physical factors (SMFs) and bioactive substances is increasingly being used; therefore, the main purpose of our study was to determine the co-exposure effect of melanoma cells to a static magnetic field and resveratrol on the oxidation–reduction parameters of cells. To date, there have been no studies on the interaction of an SMF and resveratrol. Thus, it is not known whether a magnetic field could enhance the anticancer properties of resveratrol or have a protective effect on melanoma cells.

2. Materials and Methods

2.1. Chemicals

Sigma Aldrich (St Louis, MO, USA): penicillin, amphotericin B, DMSO (dimethyl sulfoxide), resveratrol, protease inhibitor, phosphatase inhibitor, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide), ABTS 2,2′-azynobis(3-etylobenzotiazolino-6-sulfonian), potassium peroxydisulfate.

Lonza (Basel, Switzerland): DMEM (Dulbecco's modified Eagle medium), fetal bovine serum, trypsin EDTA solution, PBS (buffered saline solution).

Invitrogen (Carlsbad, CA, USA): 0.4% trypan blue.

2.2. Cell Culture Conditions

Amelanotic melanoma cells (C32 cell line) and melanoma malignant cells (Colo829 cell line) were purchased from ATCC (CRL-1585, CRL-1974; Manassas, VA, USA). The C32 and Colo829 cultures were grown in a DMEM medium. The medium was supplemented with 10% fetal bovine serum, penicillin (10,000 U/mL) and amphotericin B (0.25 mg/mL) and the cells were placed in an incubator at 37 °C in a 5% CO_2. After staining cells with 0.4% trypan blue, the number of cells and their viability were assessed using a Countess TM Automated Cell Counter (Invitrogen, Waltham, MA, USA). Melanoma cells from passages three to five with at least a 95% viability were used for this study.

2.3. Resveratrol Cytotoxicity

The MTT 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide method was used to determine the cytotoxicity of resveratrol on the melanoma cells at concentrations ranging from 50 μM to 1000 μM. The appropriate amount of resveratrol was weighed and dissolved in DMSO and dilutions of the stock solution were made in the cell culture medium. Two independent experiments were performed over a 24 h incubation period to evaluate the resveratrol toxicity.

In the MTT test, the ability of the cells to convert MTT is indicative of the mitochondrial activity and consequently cell viability. The C32 and Colo829 cells were cultured in 96-well culture plates at a density of 5000 cells/well. After 24 h of resveratrol treatment, the medium was drained and MTT (1 mg/mL) was added; then, it was incubated for three hours (at 37 °C), after which 100 μL DMSO was added to each well and the absorbance was read at 540 nm on a Wallac 1420 VICTOR microplate reader.

2.4. Exposure of the Melanoma Cells to Resveratrol and an SMF

The melanoma cells (C32 and Colo829) were treated with resveratrol (500 μM) and then placed in a test chamber with permanent magnets that generated an SMF (0.7 T). The 500 μM concentration of resveratrol was selected for the study based on the MTT results because it was cytotoxic to both the C32 and Colo829 cells but was not toxic to the normal cells.

Magnetic chambers that were composed of permanent magnets and a ferromagnetic yoke were used (patent P-396639). A ferromagnetic yoke is the bottom and cover of the chamber and there is a window in the front wall of the chamber that is matched to the dimensions of the cell culture flask [14]. A homogeneous distribution of the magnetic induction over the surface of the flask is conditioned by the structure of the test chamber. The static magnetic field is generated by neodymium magnets and the magnetic field intensity is proportional to the magnetic field strength. The chambers are constructed with the following materials: N42SH magnets, Br = 1.28–1.34 T, HcB $\geq$ 955 kA/m, HcJ $\geq$ 1512 kA/m, (BH)max = 310–342 kJ/m^3, S235JR steel and a diamagnetic material. The maximum operating temperature of the chambers is 150 °C. A chamber with a field induction of 0.7 T, which was checked with a gauss meter before each experiment, was used for the tests. The control chamber was made of steel instead of permanent magnets and the field induction in this chamber was 0 T. The cultures were maintained at 37 °C in a 5% CO_2 incubator for 24 h in the test chambers. Next, the cells were washed with PBS and the cell numbers were determined by cell counting in a Countess TM Automated Cell Counter (Invitrogen, Waltham, MA, USA) after staining them with 0.4% trypan blue.

2.5. Preparing the Cell Lysates

In the final stage of the experiment, the C32 and Colo829 cells were lysed. First, the cells were detached from the culture flask using a trypsin/EDTA solution and then they were neutralized with DMEM and centrifuged for 10 min at 2000 RPM, and the resulting cell pellets were used to prepare the lysates. Protease inhibitor (1.4 mg) was weighed out for every 1 mL of PBS and 10 μL of phosphatase inhibitor was also added to the solution. The lysates were prepared by dissolving the cell pellets in a lysis buffer using the rule of a 100 μL buffer for every 106 cells. The cell lysates were placed in liquid nitrogen for 30 min and then stored at −80 °C until the biochemical assays were performed.

2.6. Biochemical Determinations

The frozen cell lysates were thawed and then centrifuged, and the obtained supernatant was used for the biochemical analysis. The results of the biochemical assays were converted into 10^6 cells.

2.6.1. Assay of the Activity of the Antioxidant Enzymes

The activity of the antioxidant enzymes—superoxide dismutase, catalase and glutathione peroxidase—was determined according to the manufacturer's protocol, and the tests were purchased from Cayman Chemicals, Ann Arbor. MI, USA. A reaction of xanthine with a tetrazolium salt was used to form formazan to determine SOD activity, which was measured spectrophotometrically at 440–460 nm. The spectrophotometric method was also used to determine the GPx activity. To determine the GPx activity, a reduction reaction of cumene hydroperoxide to oxidized glutathione was used, which was then reduced, and was accompanied by a decrease in absorbance at 340 nm. The catalase activity was measured by reacting CAT with methanol, the product of which is formaldehyde, which was then measured spectrophotometrically using purpald as the chromogen.

2.6.2. Total Antioxidant Status (ABTS) Assay

The total antioxidant potential was determined based on the ABTS radical method, which consists of the reaction of potassium persulfate and ABTS. The absorbance reduction was measured at 734 nm and then the potential was read from the standard curve for the Trolox rotatable [15].

2.6.3. Lipid Peroxidation Assay

The concentration of MDA, which is a marker of the lipid peroxidation process, was determined using a Bioxytech MDA-586 assay test kit (OxisResearch, Foster City, CA, USA). The absorbance of the product of the reaction of N-methyl-2-phenylindole (NPMI) with MDA at 45 °C was measured at 586 nm.

2.6.4. Statistical Analyses

All data are expressed as the mean ± the standard deviation of separate experiments. An ANOVA and Tukey's post hoc test were used to evaluate the results of the experiments. The statistical calculations were performed using STATISTICA 12.0 and the statistical significance was defined at $p < 0.05$.

3. Results

Resveratrol cytotoxicity against C32 and Colo829 malignant melanoma cells was assessed in this study, ranging from 50 µM to 1000 µM (Figures 1 and 2). The concentration of 500 µM was selected for the experiment due to a statistically significant decrease in the viability of both of the melanoma cells and thus the cytotoxic effect.

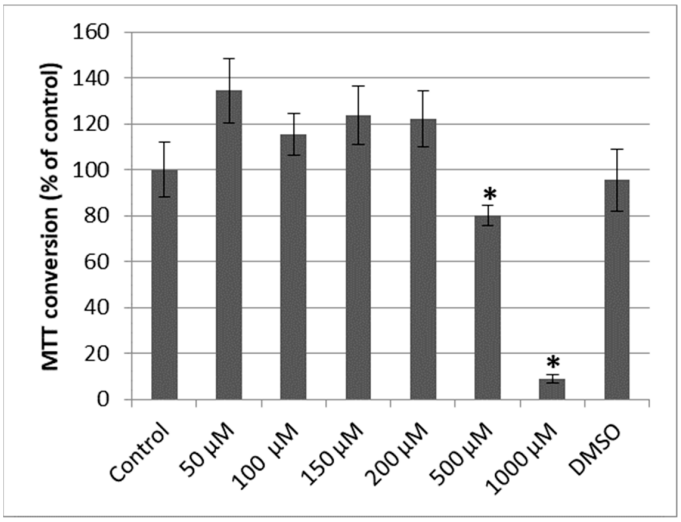

Figure 1. Cell viability in amelanotic malignant cultures (C32) that had been exposed to resveratrol (between 50 and 1000 µM for 24 h). Each bar represents the mean ± SD of two independent experiments. Statistical significance, * $p < 0.05$ vs. control (F = 24.31).

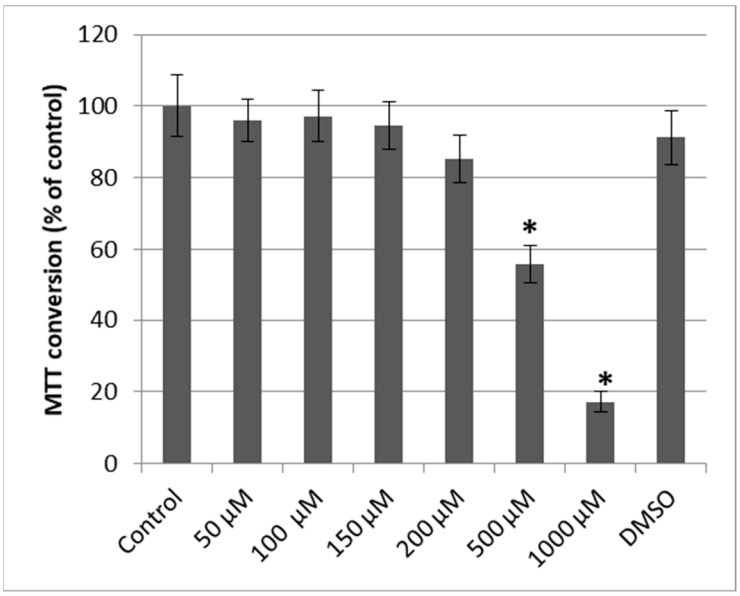

Figure 2. Cell viability in melanoma malignant cultures (Colo829) that had been exposed to resveratrol (between 50 and 1000 µM for 24 h). Each bar represents the mean ± SD of two independent experiments. Statistical significance, * $p < 0.05$ vs. control (F = 32.03).

The results of the activity of the antioxidant enzymes that constitute the first line of defense of a cell (SOD, GPx and CAT) that were obtained in this study indicate that, in both the C32 and Colo829 melanoma cells that had been exposed to resveratrol, there was a statistically significant reduction in the activity of these enzymes relative to the control cells (Figures 3–5). The addition of resveratrol to the melanoma cells caused a significant decrease in the SOD activity by 35% (C32) and 63% (Colo829). Moreover, the activity of GPx and CAT under the influence of resveratrol was also statistically significantly decreased by 34% (C32) and 61% (Colo829) for GPx and by 40% (C32) and 24% (Colo829) for CAT, respectively.

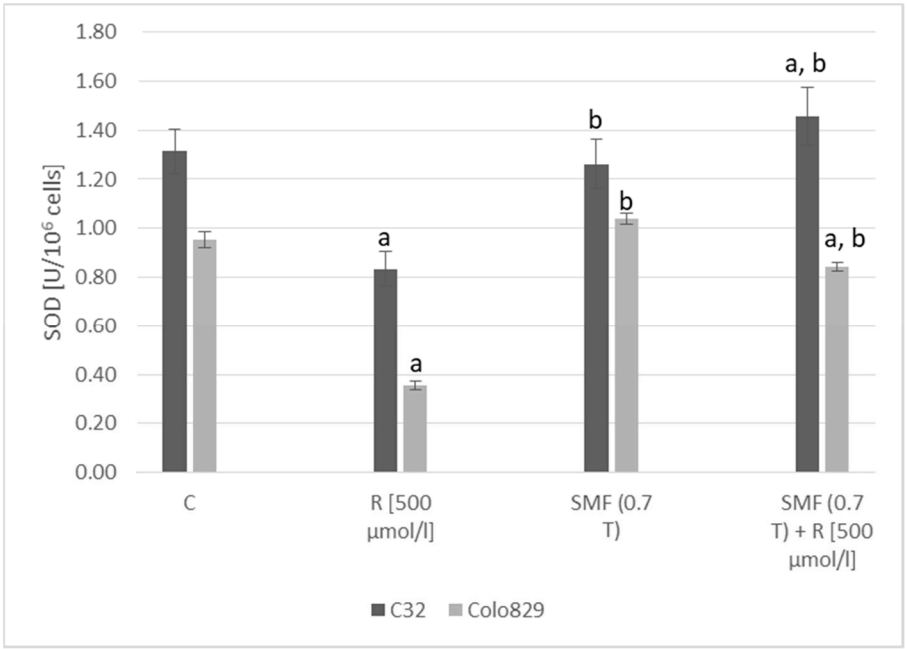

Figure 3. Effect of resveratrol and an SMF on the SOD activity in the melanoma cell cultures (C32, Colo829). The results are presented as the mean ± SD; [a] $p < 0.05$ vs. C (control); [b] $p < 0.05$ vs. (R) resveratrol (F = 54.43).

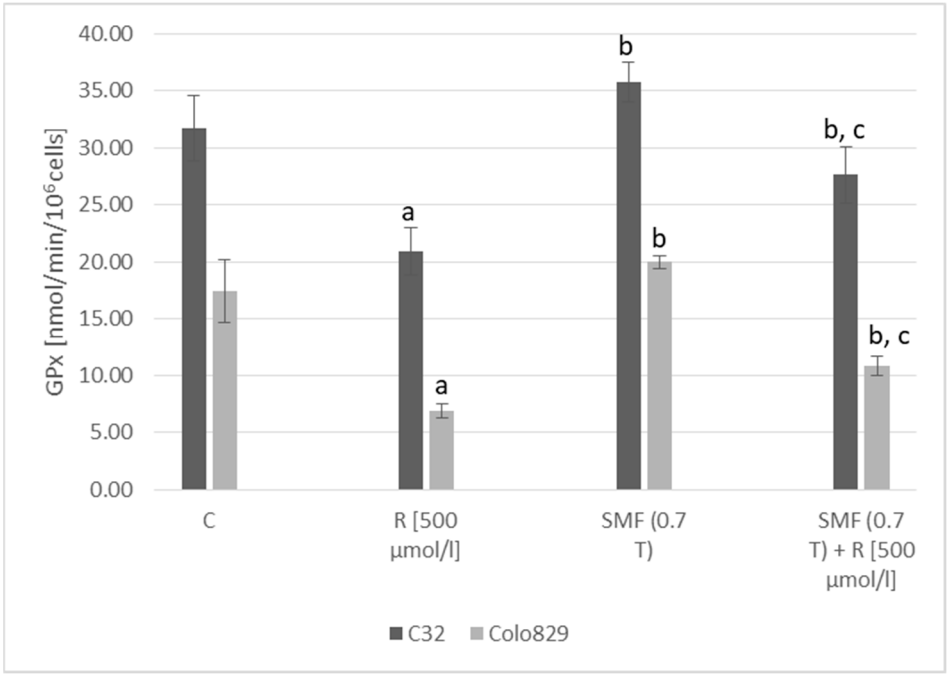

Figure 4. Effect of resveratrol and an SMF on the GPx activity in the melanoma cell cultures (C32, Colo829). The results are presented as the mean ± SD; [a] $p < 0.05$ vs. C (control); [b] $p < 0.05$ vs. (R) resveratrol; [c] $p < 0.05$ vs. SMF (F = 48.63).

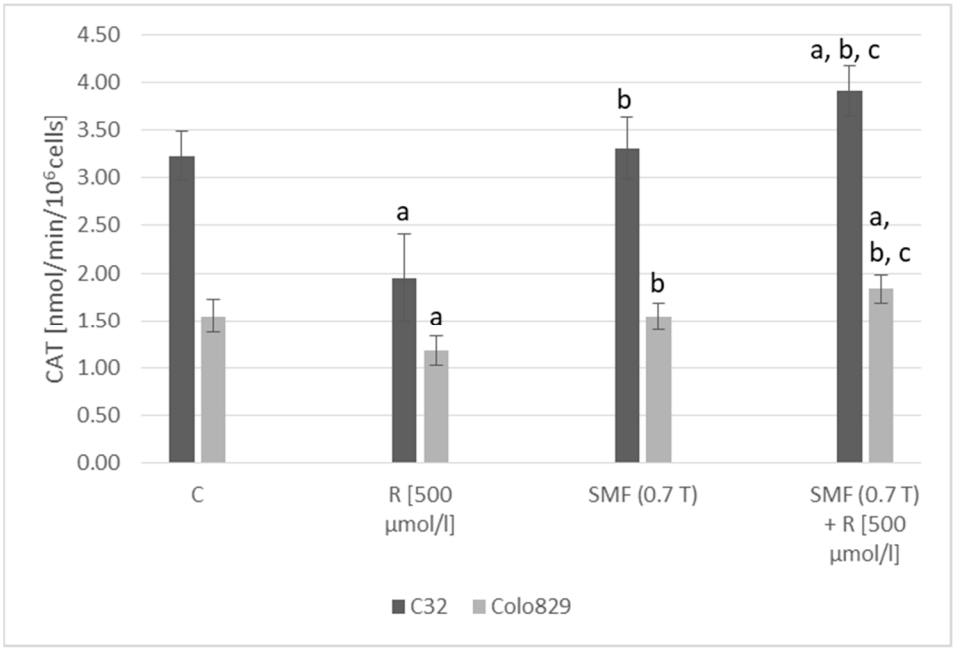

Figure 5. Effect of resveratrol and an SMF on the CAT activity in the melanoma cell cultures (C32, Colo829). The results are presented as the mean ± SD; [a] $p < 0.05$ vs. C (control); [b] $p < 0.05$ vs. (R) resveratrol; [c] $p < 0.05$ vs. SMF (F = 88.6).

In the melanoma cells of both of the studied cell lines that had been exposed to resveratrol (500 µM), there was a statistically significant increase (Table 1) in the concentration of MDA relative to the control cultures. The addition of resveratrol to the culture caused a significant increase in the concentration of the lipid peroxidation marker by 40% for the C32 line and by 22% for the Colo829 line.

Table 1. Effect of resveratrol and an SMF on the MDA concentration and total antioxidant status in the melanoma cell cultures (C32, Colo829). The results are presented as the mean ± SD; [a] $p < 0.05$ vs. C (control); [b] $p < 0.05$ vs. (R) resveratrol; [c] $p < 0.05$ vs. SMF.

	MDA [nmol/10^6 Cells]		ABTS [nmol/10^6 Cells]	
C	31.65 ± 1.52	24.65 ± 1.03	411.6 ± 28.1	380.3 ± 11.9
R [500 µmol/L]	44.4 ± 2.7 [a]	30.02 ± 1.08 [a]	565.3 ± 33.2 [a]	506.7 ± 33.1 [a]
SMF (0.7 T)	29.01 ± 0.9 [b]	25.26 ± 1.7 [b]	420.2 ± 21.4 [b]	379.9 ± 27.5 [b]
SMF (0.7 T) + R [500 µmol/L]	33.69 ± 1.83 [b,c]	27.51 ± 1.3 [a,b]	455.9 ± 25.6 [b]	370.4 ± 24.2 [b]
	C32	**Colo829**	**C32**	**Colo829**

In the cultures of melanoma cells that had been exposed only to a static magnetic field induction of 0.7 T, there was no statistically significant changes in the activity of first line of defense enzymes (Figures 3–5), the MDA concentration and the ABTS status (Table 1) compared to the control cultures that had not been exposed to an SMF. In the cultures of melanoma cells that had been treated with resveratrol and exposed to an SMF and a normalization in the activity of antioxidant enzymes SOD, GPx and CAT, there were values that were similar to those in the control cultures. The activity of the determined antioxidant enzymes in the cultures that had been exposed to an SMF and resveratrol differed by 11% (C32) and 12% (Colo829) for SOD, 13% (C32) and 38% (Colo829) for GPx and 21% (C32) and 19% (Colo829) for CAT from the control cultures, respectively.

Additionally, the concentration of MDA and the antioxidant potential normalized to values that were close to those measured in the control cultures. The difference in the MDA concentration between the tested and control cultures was 6% for the C32 cell cultures and 12% for the Colo829 cell cultures.

4. Discussion

For several years, interest in the subject of healthy food and its impact on the human body has significantly increased in society. People are increasingly aware of the products that they consume and the fact that many diseases are diet-related, which has been confirmed by scientific studies. Consumers are choosing functional products that contain pro-health ingredients, and one of these is certainly fruit preserves that contain resveratrol. Resveratrol is also used in dietary supplements as well as in cosmetology. The reason for this may be the belief that substances of natural origin have a milder and more comprehensive effect on the body. However, it should be remembered that high concentrations of antioxidants may have a pro-oxidative effect, which could lead to a disturbance in the oxidation–reduction homeostasis of cells. Oxidative stress in neoplastic cells can lead to their damage and thus polyphenols may exhibit anti-cancer activity [16,17].

Resveratrol cytotoxicity against C32 and Colo829 malignant melanoma cells was assessed in this study, ranging from 50 µM to 1000 µM. The concentration of 500 µM was selected for the experiment due to the statistically significant decrease in the viability of both melanoma cells and thus its cytotoxic effect. A study by Amorntaveechai et al. [18] found that, at a concentration of 400 µM, resveratrol was cytotoxic to head and neck cancer cells (HN-30). In addition, in the studies of Venkatadri et al. [19], it was found that, at a concentration of 200 µM, resveratrol was cytotoxic to breast cancer cells. Moreover, a study by Sujin et al. [20] confirmed that resveratrol (100 µM) also causes a decrease in the proliferation of gastric cancer cells. The resveratrol-mediated chemotherapeutic mechanism is apoptosis, which is associated with the activation of p53, a tumor suppressor, and induces the activation of the death receptor Fas/CD85/APO-1 in diverse cancer cells [21]. Resveratrol has also been demonstrated to activate the expression of p21 and p27, which promotes cell cycle arrest in melanoma cells [22].

Many scientific reports have suggested that if the amount of reactive oxygen species in a cell is low, the defense mechanisms are activated and the activity of antioxidant enzymes increases, whereas high ROS levels lead to the impairment of the enzymatic defense mechanisms, which results in a decrease in the activity of the antioxidant enzymes [23,24]. The addition of resveratrol to the culture of melanoma cells disturbed the oxidation–reduction balance of cells and the oxidative stress increased. The anti-cancer properties of resveratrol are probably due to its pro-oxidative effect on cells. Research has confirmed that polyphenols including resveratrol exhibit antioxidant and pro-oxidative properties that depend on the doses that are used. The cytotoxic effect of resveratrol may induce the formation of large amounts of ROS, which may lead to the failure of a cell's defense mechanisms and its death. In addition, resveratrol can induce oxidative stress in the endoplasmic reticulum and reticulum stress can then lead to cell apoptosis. In the study by Heo et al. [25], resveratrol inhibited the viability of melanoma (A375SM) cells by increasing the expression of p21 and p27, which inhibited the expression of cyclin B and promoted cell cycle death. In addition, resveratrol increased the production of cellular ROS and simultaneously induced the ER stress pathway in the melanoma cells. Moreover, in this study, resveratrol induced the mitochondrial apoptotic pathway in the melanoma cells through the ROS-p38-p53 pathway by upregulating the p-p38 MAPK protein and also via the p53 and ER stress pathway by upregulating the p-eIF2α and CHOP protein expression. Enhanced ROS-p38-p53 and ER stress pathways promoted apoptosis by downregulating Bcl-2 and upregulating Bax. In the studies of Lei et al. [26], it was found that resveratrol caused a significant decrease in the proliferation rate of melanoma cells (HT-144 line). It was observed that the decrease was dependent on the dose of resveratrol that had been used. Another MEK $\frac{1}{2}$ factor, which is a member of the MAPK signaling pathway, is responsible for ERK $\frac{1}{2}$ inhibition. In turn, Nivelle et al. [27] investigated whether the anticancer effect of resveratrol is related to the change in the cell cycle of melanoma. Their studies showed a strong accumulation in the S phase and a very strong decrease in the G1 phase, and immunoblotting analyses showed that resveratrol caused an increase in the expression of cyclin A.

In a study by Kil et al. [28], it was confirmed that, at a concentration of 80 µM, resveratrol had a cytotoxic effect on the cells of murine macrophages (RAW264.7) by producing large amounts of free radicals. Moreover, in the studies by Zhang et al. [29], it was found that resveratrol and its synthetic derivatives can act against cancer by initiating the lipid peroxidation process in colon cancer cells, thus leading to the phenomenon of ferroptosis. Ferroptosis is a non-autophagous programmed cell death that results from the accumulation of lipid peroxidation products and is dependent on iron ions and free radicals. Many researchers believe that the induction of ferroptosis in cancer cells may be the one of the most effective methods of fighting cancer [30,31]. The free radical process of lipid peroxidation occurs during the course of physiological metabolism. However, when the concentration of free radicals that can initiate it increases, this process is stimulated. Increased lipid peroxidation damages the cell and subcellular membranes, thereby disrupting the transport of ions and metabolites. In our study, the concentration of malondialdehyde (MDA), one of the markers that are used to assess the advancement of the lipid peroxidation process, was also determined. The accumulation of MDA probably leads to ferroptosis and contributes to the oxidation–reduction damage in melanoma cells. Wang et al. [32] also reported that the use of immunotherapy caused an increased lipid peroxidation, MDA accumulation and ferroptosis, which led to the death of ovarian and melanoma cancer cells.

The main purpose of our study was to investigate the effect of the co-exposure of C32 and Colo829 cells to a static magnetic field and resveratrol on the oxidation–reduction parameters of cells. To date, there have been no studies on the interaction of an SMF and resveratrol; therefore, it is not known whether a magnetic field will enhance the anticancer properties of resveratrol or will have a protective effect on melanoma cells. In a study by Zhang et al. [33], it was found that the induction of a 1 T SMF increased the anticancer efficacy of an mTOR inhibitor in nasopharyngeal cancer cells. Moreover, in their studies,

Sabo et al. [34] confirmed that an SMF with an induction of up to 1 T may have an anticancer effect on leukemic cells (HL-60). On the other hand, in our previous research, we found that a static magnetic field (0.7 T) eliminated the anticancer effects of baicalin and baicalein in melanoma cells [35].

The differences in the obtained test results among different researchers may result from the fact that a static magnetic field can be generated by special discs, permanent magnets or a magnetic coil. In this study, a static magnetic field was generated using special chambers into which the flasks with the cultures of melanoma cells were placed. The decrease in the anticancer activity of resveratrol by an SMF and its protective effect on the C32 and Colo829 cells may possibly be due to the fact that an SMF may influence the conformation of the resveratrol molecule, which consequently modifies its properties. Research by Kotani et al. [36] showed that a strong 1 T static magnetic field can change the structure of molecules and thus modify their properties However, Panczyk et al. [37] suggested that it is quite unlikely that a static magnetic field can lead to any changes in the structure of small molecules because the Lorentz forces do not affect the ions or larger molecules in solutions. There are simply no physical reasons for the generation of Lorentz forces on the atoms within a molecule, or at least the forces that are strong enough. Diamagnetic force appears in the field gradient but it is very weak. In turn, in the studies of Lv et al. [38], it was found that an SMF can counteract the oxidative stress that is caused by iron ions in rat liver cells. SMF exposure acts as a redox system balancer to decrease lipid peroxidation and increase antioxidant capacity in the liver. The mitochondrial electron transport chain is a major source of cellular ROS. SMF exposure plays a role in regulating the mitochondrial respiratory chain complexes to improve the mitochondrial function of the liver in mice via activation of Nrf2 /HO-1 antioxidant pathway. In this study, resveratrol caused oxidative stress in melanoma cells; thus, perhaps a static magnetic field acts as an equivalent of the redox system, which leads to an increase in the antioxidant capacity of melanoma cells, i.e., the abolition of the pro-oxidant effect of resveratrol.

5. Conclusions

In conclusion, we have shown that resveratrol can exhibit anticancer properties against C32 and Colo829 melanoma cells by disrupting redox homeostasis and the accumulation of lipid peroxidation products in cells. A static magnetic field was found to protect against melanoma cells and decrease the anticancer effects of resveratrol.

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