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Research Article

Anti-Leukemic Effect of Malachite Green-Mediated Photodynamic Therapy by Inducing ER Stress in HL-60 Cells

Metin Caliskan[1], Gulsen Bayrak[2], Sercin Ozlem Caliskan[3]

[1]Uşak University, Faculty of Medicine, Department of Medical Biology, Uşak, Türkiye
[2]Uşak University, Faculty of Medicine, Department of Histology and Embryology, Uşak, Türkiye
[3]Uşak University, Faculty of Medicine, Department of Biophysics, Uşak, Türkiye

Abstract

Aim: Our objective is to explore the relationship between the anti-leukemic impact of malachite green-mediated photodynamic therapy (PDT) and the induction of endoplasmic reticulum (ER) stress in acute promyelocytic leukemia cells (HL-60).
Material and Method: For one hour the cells were incubated with different concentrations (3.125, 1.56, 0.78, 0.39, 0.195, 0.0975, 0.04875 μM) of malachite green and then were exposed to 0.47 mW/cm^2 irradiance and 0.84 J/cm^2 fluence for 30 minutes. Also, HL-60 cells were exposed to PDT with light only and both in the presence or absence of malachite green. MTT assay was used to determine cell viability, and immunocytochemical staining was used to detect the expression of ER stress markers Protein Kinase R-like ER Kinase (PERK) and Glucose-regulated protein 78 (GRP78).
Results: The cell viability of the treatment group (combination of malachite green and light) was significantly decreased compared to the malachite green, control group, and light control. Moreover, immunocytochemical staining scores showed that PERK and GRP78 were significantly upregulated in the treatment group compared with other groups.
Conclusion: Our results indicate that ER stress may contribute to the cytotoxicity occurring in HL-60 cancer cells after malachite green-mediated PDT. Future studies will be crucial in shedding light on the molecular mechanisms underlying ER stress that may occur after PDT. These findings lay the foundation for further investigations in this area.

Keywords: Acute myeloid leukemia, malachite green, photodynamic therapy, ER stress, Protein Kinase R-like ER Kinase, Glucose-regulated protein 78

INTRODUCTION

Acute Myeloid Leukemia (AML), which causes symptoms associated with bone marrow failure and infiltration of organs, is a highly aggressive malignancy of leukocytes. If left untreated, AML invariably leads to fatality, and potentially life-threatening complications can swiftly emerge even in initially asymptomatic patients (1). Chemotherapy, radiotherapy, and allogeneic stem cell transplantation are the main current treatments for leukemia; However, these therapies can cause serious side effects, such as normal cell cytotoxicity, drug resistance, and increased risk of infection, during or after treatment (2). Therefore, there has been a greater focus on seeking physical alternative approaches such as light and sound.

The basis of photodynamic therapy (PDT) is cell death as a result of a series of photochemical/photophysical reactions that occur when light activates photosensitizers at the appropriate wavelength in the presence of oxygen. The activated photosensitizer in the unstable excited structure transfers the excess energy to the surrounding molecules via two types of mechanisms. The sensitizer One is the direct energy transfer to molecular oxygen, which forms singlet oxygen, and the other is the transfer of energy to an electron or proton, which produces reactive

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Corresponding Author: Sercin Ozlem Caliskan, Uşak University, Faculty of Medicine, Department of Biophysics, Uşak, Türkiye
E-mail: srn.ozlem@gmail.com

oxygen species (ROS) (3). While it is acknowledged that both possibilities contribute to cell death, the specific mechanism that predominantly leads to cell death varies depending on the presence of oxygen, the concentration of substrates, and especially the photosensitizer used (4). Singlet oxygen and/or hydroxyl radicals generated through photosensitizer activation are highly reactive and have a very short lifespan (0.04 microseconds). As a result, they are effective within a very small region (0.02 μm) (5). These parameters suggest that PDT is a localized treatment. PDT has serious advantages over traditional cancer therapies as it can be repeated in multiple doses and is a minimally invasive and localized therapy method. There is no risk of cancer cells developing resistance to PDT (6).

ER is the primary organelle in the cell that performs many cellular functions such as maintenance of cellular homeostasis, intracellular Ca^{2+} storage, protein folding, modification, and assembly (7). PDT causes apoptosis as a result of oxidative stress through the production of large amounts of ROS, and ER stress, which is one of the mechanisms underlying cancer cell death, as a result of the induction of GRP78, a chaperone in the ER and critical modulator of the unfolded protein response (UPR), through the accumulation of unfolded proteins (8-11). Under non-stress conditions, PERK, an ER membrane protein with luminal stress-sensing domains, forms a complex with a significant amount of the ER chaperone immunoglobulin binding protein. This interaction keeps PERK inactive, and when ER stress occurs, it becomes active and phosphorylates factors that will reduce new protein translation (12). In addition, excessive protein accumulation in the ER lumen results in an increased need for proteins essential for protein folding (11,13). The safety and effectiveness of PDT largely depend on photosensitizers, which are considered an important factor with specificity and phototoxicity. Malachite green is a triarylmethane dye with an absorption band at approximately 617 nm (14). Triarylmethane dyes are of interest as antimicrobial and anticancer agents due to their selective localization and structural properties (15). In this study, we examined the effect of malachite green-mediated PDT on ER stress in HL-60 cells.

MATERIAL AND METHOD

Cell Culture

HL-60 cells were cultured in RPMI 1640 (+) L-glutamine medium supplemented with 1% Penicillin-Streptomycin and 10% FBS in 25cm^2 flasks in a humidified and 5% CO_2 incubator at 37°C. In laminar airflow, the culture medium was renewed every 2-3 days.

Photosensitizer

In this study, malachite green, which has a cationic structure, was used as a photosensitizer. Malachite green stock solution was prepared in PBS. Final experimental malachite green concentrations were determined as 3.125, 1.56, 0.78, 0.39, 0.195, 0.0975, and 0.04875 μM. Cells ($1x10^5$) were exposed to malachite green at 37°C for one hour.

Study Design

In this study, 4 different groups were studied using different concentrations of malachite green.

Group 1: Control: No exposure (malachite green or light)

Group 2: Light control: Only exposure to red light for 30 minutes

Group 3: Malachite green: Only exposure to all concentrations of malachite green for one hour

Group 4: Malachite green mediated PDT: One hour of exposure to malachite green followed by 30 minutes of exposure to red light from a distance of 10 cm

Malachite Green Mediated Photodynamic Therapy Using Red Light

After exposure to malachite green for one hour, centrifugation was performed at 250 g for five minutes and the supernatant was discarded to remove any remaining free malachite green and fresh PBS was added over the cell sediment. Centrifugation, discarding the supernatant, and adding fresh PBS were repeated 3 times in all groups. The light source utilized was an LED system (O'melon Omega Led) comprising 283 units across three panels emitting red light at a wavelength of 640 nm, which is optimal for activating malachite green. A power meter (Newport, USA) was used to measure light output; An irradiance of 0.47 mW/cm^2 was quantified and a fluence of 0.84 J/cm^2 in 30 minutes was calculated. Following the applications, fresh medium was added to all groups and incubated at 37°C for 24 hours.

Analysis of Cell Viability of HL-60 Cells by the MTT

3-(4,5-Dimetiltiazol-2 yl)-2,5-Diphenyltetrazolium Bromide (MTT) is a water-soluble tetrazolium salt that, if degraded by the dehydrogenase enzyme in viable cell mitochondria, is converted into a soluble formazan. Cells were assessed by a spectrophotometric method using MTT solution in 96 microplates. After treatment, the MTT reagent was applied equally to all groups, followed by a 24-hour incubation period. The solubilization buffer was added and left to incubate at 37°C overnight. Cell viability percentages were calculated using optical density (OD) measurements taken from each well in the wavelength range of 550 to 600 nm using a microplate spectrophotometer.

ER Stress Analysis

Immunocytochemical Markers

The cells were centrifuged and then the pellet was spread on the slides and then the slides were allowed to dry. The cells were then fixed with cold methanol. After fixation, slides were washed with PBS and were kept in for 10 minutes with 3% hydrogen peroxide to block

endogen peroxidase. Then the slides were washed with PBS and after dropped onto the slides normal goat serum (Invitrogen- 50062Z) for blocking for 8 minutes. After blocking, the slides were incubated overnight at +4°C with primary antibodies: Anti-PERK (1:100, bs2469R; Bioss) and anti-GRP78 BiP/HSPA5 (1:100, PB9640; Boster). Following this incubation period, the slides were treated with anti-rabbit IgG secondary antibody (1/200, Thermo Scientific, 65-6140) for 30 minutes, followed by a thorough PBS wash. Subsequently, Horseradish peroxidase (HRP, 1/200, Thermo Scientific, 43-4323) was introduced and allowed to incubate for an additional 10 minutes at room temperature in the dark. The reaction was developed using chromogen diaminobenzidine (DAB, Abcam, ab64238). After washing the slides with distilled water, they were mounted with entellan. Finally, the slides were examined under a light microscope (Olympos BX50) and images were captured using the attached camera. For immunocytochemical scoring, 100 cells were counted in 4 different areas at X400 magnification and the staining intensities of these cells were scored as strong (++++), medium (+++), weak (++), or absent (+). All slides were evaluated by the same histologist.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to determine our data to assess potential differences between at least two groups (IBM SPSS Statistics 25, USA). ANOVA followed by the Tukey test was used as a post-hoc analysis for further evaluation. Statistical significance was accepted as p-value≤0.05.

RESULTS

Cytotoxic Activity of Malachite Green and Malachite Green Mediated PDT in HL-60 Cells

The results showed that malachite green-mediated PDT exposure caused a significant decrease in the viability of HL-60 cells. Cell viability at all concentrations of the malachite green-mediated PDT group was significantly lower than the same concentrations of the malachite green and other groups (p<0.001). Cell viability percentages of control, light control, and malachite-mediated PDT groups were determined as 95.2±1.70%, 92.4±1.15%, 75.6±3.59%, 74.8±1.65%, 72.9±1.95%, 68.6±0.72%, 60.5±1.94%, 52.1±2.85%, and 36.2±2.15%, respectively. The results demonstrated that malachite green-mediated PDT significantly increased the cytotoxicity in HL-60 cells, and cell survival is positively correlated with malachite green concentration. There was no significant difference in cell viability between the control and light control groups (p=0.797). In the malachite green group, cell viability percentages were determined as 87.4±0.92%, 85.1±2.66%, 85.8±2.04%, 79.4±0.95%, 77.3±2.08%, 71.6±1.52%, and 63.3±1.52% from low to high concentration, respectively. It was observed that the cell viability of malachite green group was higher than the malachite mediated PDT group (Figure 1).

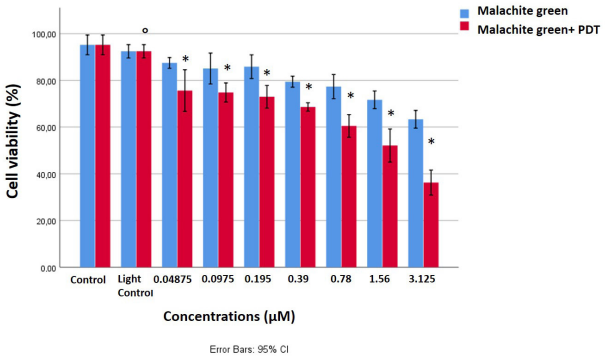

Figure 1. Evaluation of cytotoxicity after treatment with control, light control, MG and MG-mediated PDT. The data represent the means±standard deviations (SDs) of 3 independent experiments. * indicates statistically significance compared to control group (p<0.001); º indicates not statistically significance compared to control group (p>0.05), Error bars 95% confiedence interval

Examination of Immunostaining Markers of ER Stress after Malachite Green, Malachite Green- Mediated PDT

Immunocytochemistry analysis was performed by examining the changes in GRP78 and PERK staining in control, light control, malachite green, and malachite green-mediated PDT groups. In the control group, GRP78 (Figure 2I, 3H) and PERK (Figure 4I, 5H) were found to be weakly stained. There was no significant difference in staining intensity when the control and light control groups were compared (Figure 2H, 4H). In both the malachite green group and the malachite green-mediated PDT group, both GRP78 and PERK staining intensities increase as the malachite green concentration increases (Figure 3A-H and Figure 5A-H) (Figure 2A-H and Figure 4A-H). As shown in Figure 6, both GRP78 and PERK staining showed a significant increase in the malachite green-mediated PDT group compared to the malachite green group, light control group, and control group (p<0.001, Figure 6A-D).

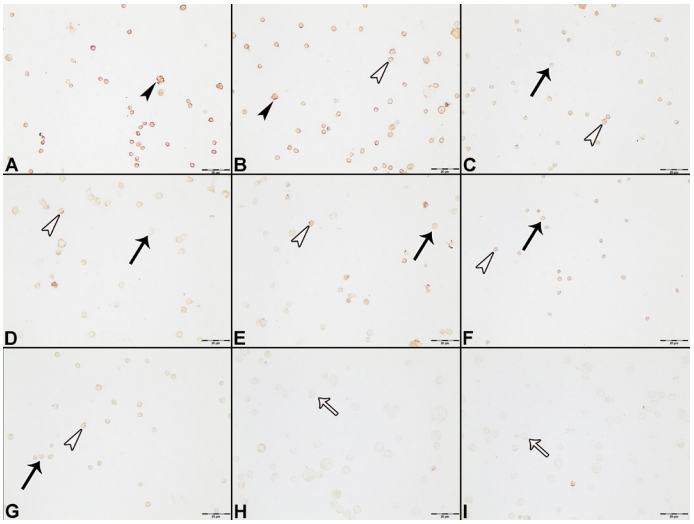

Figure 2. GRP78 immunostaining of Malachite green mediated PDT groups. 3.125µM Malachite green mediated +PDT (**2A**); 1.56µM Malachite green mediated +PDT (**2B**); 0.78µM Malachite green mediated +PDT (**2C**); 0.39µM Malachite green mediated +PDT (**2D**); 0.195µM Malachite green mediated +PDT (**2E**); 0.0975µM Malachite green mediated +PDT (**2F**); 0.04875µM Malachite green mediated +PDT (**2G**), light control (**2H**) and control (**2I**). Strong staining (black arrowhead), medium staining (white arrowhead), weak staining (black arrow), absent staining (white arrow). All photos imagination X400

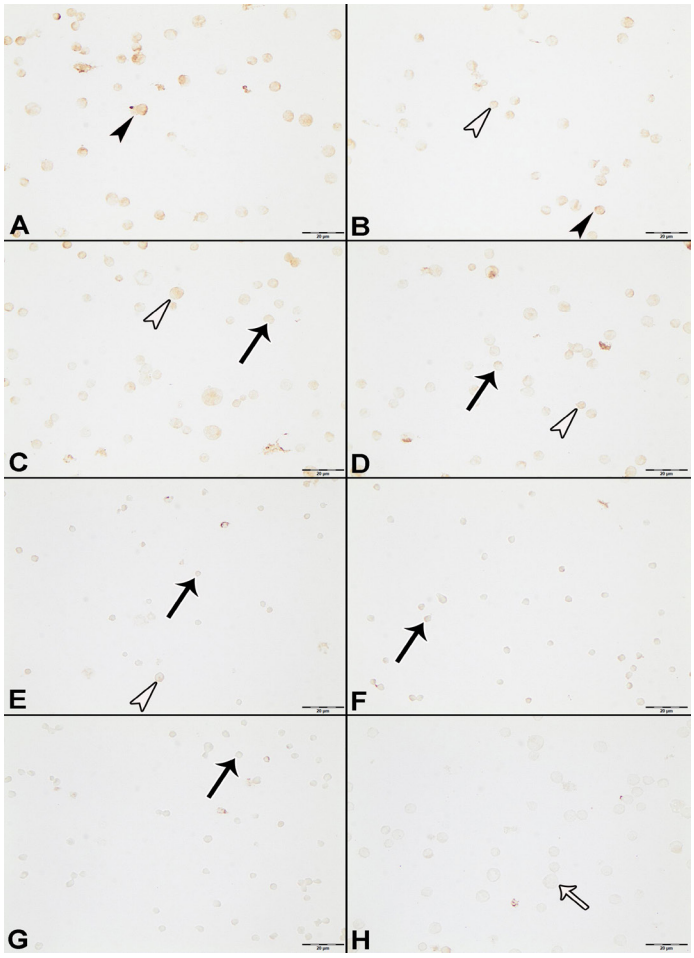

Figure 3. GRP78 immunostaining of malachite green groups. 3.125µM malachite green (**3A**); 1.56µM malachite green (**3B**); 0.78µM malachite green (**3C**); 0.39µM malachite green (**3D**);0.195µM malachite green (**3E**); 0.0975µM malachite green (**3F**); 0.04875µM malachite green (**3G**) and control (**3H**). Strong staining (black arrowhead), medium staining (white arrowhead), weak staining (black arrow), absent staining (white arrow). All photos imagination X400

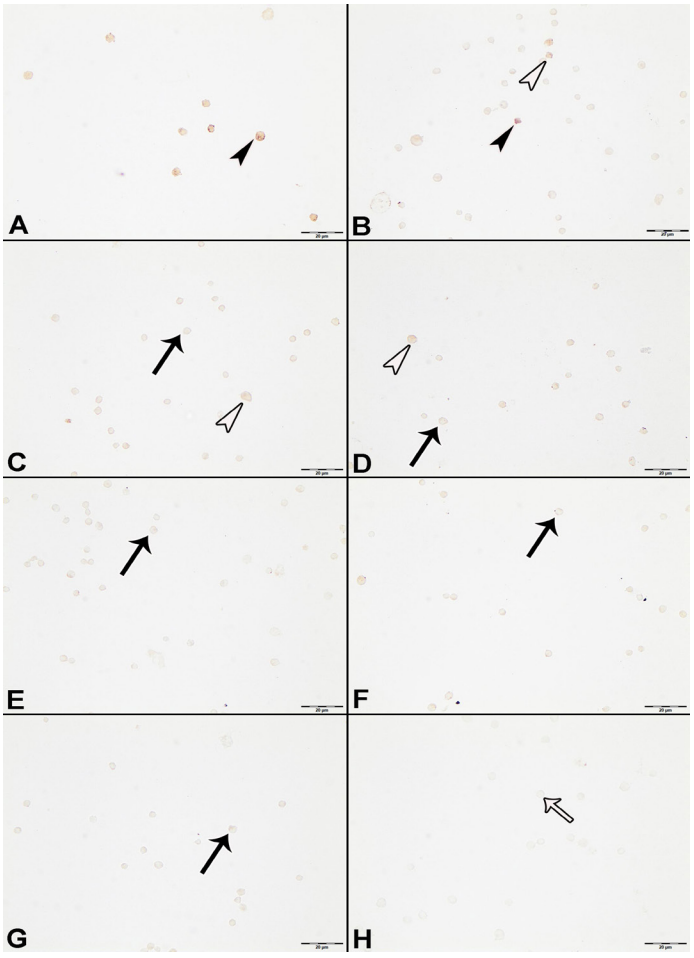

Figure 5. PERK immunostaining of malachite green groups. 3.125µM malachite green (**5A**); 1,56µM malachite green (**5B**); 0.78µM malachite green (**5C**); 0.39µM malachite green (**5D**); 0.195µM malachite green (**5E**); 0.0975µM malachite green (**5F**); 0.04875µM malachite green (**5G**), and control (**5H**). Strong staining (black arrowhead), medium staining (white arrowhead), weak staining (black arrow), absent staining (white arrow). All photos imagination X400

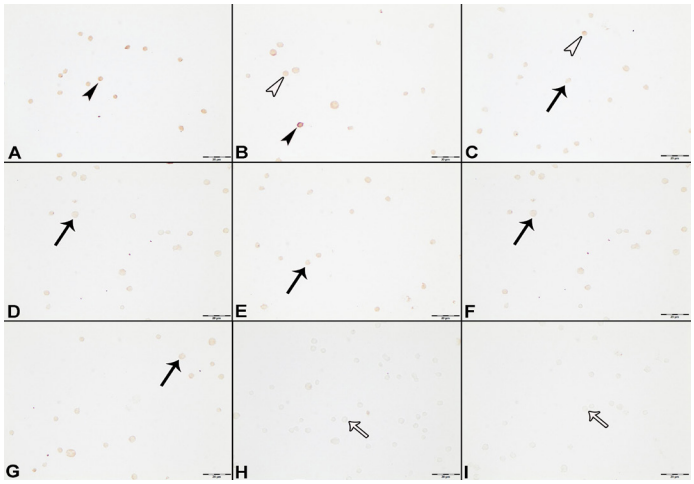

Figure 4. PERK immunostaining of malachite green mediated PDT groups. 3.125µM malachite green mediated PDT (**4A**); 1.56µM malachite green mediated PDT (**4B**); 0.78µM malachite green mediated PDT (**4C**); 0.39µM malachite green mediated PDT (**4D**);0.195µM malachite green mediated PDT (**4E**); 0.0975µM malachite green mediated PDT (**4F**); 0.04875µM malachite green mediated PDT (**4G**), light control (**4H**) and control (**4I**). Strong staining (black arrowhead), medium staining (white arrowhead), weak staining (black arrow), absent staining (white arrow). All photos imagination X400

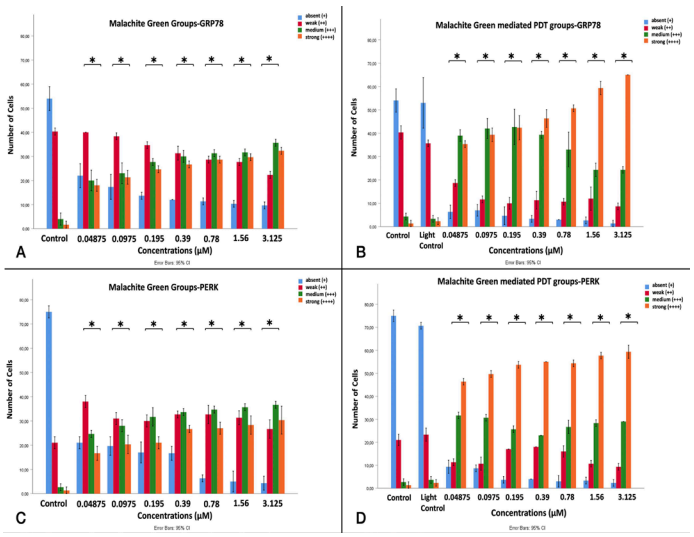

Figure 6. Statistical analysis of GRP78 malachite green groups (**6A**), GRP 78 malachite green mediated PDT groups (**6B**), Statistical analysis of PERK malachite green groups (**6C**), PERK malachite mediated PDT groups (**6D**). *Significance according to the control groups. The data represent the means±standard deviations (SDs) of 3 independent experiments. Error bars 95% confiedence interval

DISCUSSION

The classical treatments for leukemia come with specific drawbacks. Transplantation of allogeneic hematopoietic stem cells may cause significant risks for both the recipient and the donor. Chemotherapy can cause severe and various side effects and may lose its effectiveness as a result of drug resistance. High-dose radiotherapy may not eliminate cancer cells and may cause various side effects during or after treatment (16). PDT stands out as a minimally invasive treatment method for a wide range of malignancies. It is the subject of clinical research both as a treatment and as a complementary therapeutic procedure to other treatments (13). Although previous studies have shown that acute monocytic leukemia and chronic myeloid leukemia cells can be effectively killed using a variety of classical photosensitizers such as zinc phthalocyanine, Nile blue, 5-aminolevulinic acid (5-ALA), hypericin, malachite green, and Photolon® (17-22), the use of PDT It has received relatively less interest in the treatment of leukemia. The results of our study showed that malachite green-mediated PDT caused a significant decrease in the proliferation of HL-60 cells compared to both controls and malachite green.

ER stress induced by therapeutic agents contributes to cancer cell death and often occurs simultaneously with oxidative stress. However, the molecular mechanisms that will explain the relationship between ROS and apoptosis caused by ER stress are not yet known (23). Apart from therapeutic agents, PDT provides cancer cell death by creating harmful levels of ROS in the tumor tissue (13). Buytaert et al. have reported that hypericin, which is localized in the ER membrane and activated by light, produces ROS, which rapidly depletes ER Ca2+ stores, resulting ultimately in apoptotic cell death and mitochondrial dysfunction (24).

PDT-induced ER stress is a cause of cancer cell death (10). When ER stress is excessive, it initiates the ER-associated apoptotic pathway, leading to cellular apoptosis (25,26). ROS promotes the expression of apoptotic proteins by triggering ER stress, thus causing apoptosis, and is one of the most important executors of apoptosis (27). Chirante et al. have shown that following lipophilic copper(II) phthalocyanine (Pc9)-mediated PDT on CT26 colorectal cancer cells, the expression of various ER chaperones such as Hsp90, Hsp110, calnexin, and GRP78/BIP, increased. Additionally, they demonstrated that ER stress provided to apoptotic cell death by activating the mitochondria-dependent apoptotic pathway (28). Firczuk et al. have shown that Photofrin®-mediated PDT induces upregulation of GRP78 protein expression in Du145 prostate cancer cells (11). Zuo et al. reported that pheophorbide a-based PDT on HOS human osteosarcoma cells could induce cell apoptosis and increase GRP78 expression (29). Moserova and Kralova reported in their study on HL-60 acute promyelocytic leukemia and 4T1 mouse mammary carcinoma cells that the activation of the PERK pathway is a crucial trigger point for the ER stress induced by mTPP(EG)4-mediated PDT (30). It has been reported that the PERK plays a role in inducing autophagy or apoptosis in tumor cells during ER stress and after PDT treatment in many studies (31,32).

In our study, we observed upregulation of PERK and GRP78, markers of cell death and ER stress, in HL-60 cells following malachite green-mediated PDT. We conclude that further studies on ER stress may contribute to the success of treatment.

Limitations

This study has several limitations. One limitation is that our study is an in vitro study and it is unclear what the outcome will be in the patient. Another limitation is that not all proteins involved in the UPR response were examined. Finally, the mechanism that causes cell death has not been demonstrated. The strength of our study is that it provides preliminary information for the development of treatment focused on ER stress in malachite-mediated PDT.

CONCLUSION

We observed that malachite green-mediated PDT caused ER stress in HL-60 cells. Therefore, malachite green-mediated PDT may be a treatment option or an adjunct method in the treatment of acute myeloid leukemia through ER stress-induced cytotoxicity. In conclusion, a significant relationship was observed between cell death and ER stress markers. We are planning studies to observe the underlying molecular mechanisms.

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Conflict of Interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *Since the methodological structure of the study is a "cell culture study", it does not require ethics committee approval in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research on Humans".*

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