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Protective effects of quercetin on methylglyoxal-induced neurotoxicity in SH-SY5Y cells

Kuersetinin SH-SY5Y hücrelerinde metilglioksal kaynaklı nörotoksisite üzerindeki koruyucu etkileri

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ABSTRACT

Aim: Methylglyoxal (MG) is a dicarbonyl compound produced during cellular metabolism, and it can be found in cells under normal or pathological conditions. Quercetin, known for its antioxidant, anti-apoptotic, and neuroprotective effects, is investigated in this study to determine whether it reduces methylglyoxal-induced toxicity in neuron-like SH-SY5Y cells.

Materials and Methods: The effective toxic dose of MG was determined by adding different concentrations (0-1000 µM) of MG to the culture medium, and cell viability was evaluated by MTT test after 24 hours of incubation. Then, quercetin (0.1 and 1 µM) was added to the culture medium together with MG, and cell viability, cell morphology, apoptotic cell death, reactive oxygen species (ROS) formation, total antioxidant capacity (TAC), and total oxidant stress (TOS) were assessed.

Results: MG concentration-dependently increased cell death in SH-SY5Y cells, worsened the morphological features of the cells, and caused a rise in apoptotic cell death and ROS formation. Additionally, TOS levels were significantly higher in MG-added cells than in the control ($p<0.005$). However, when quercetin was added together with MG, there was a statistically significant improvement in cell death and all other parameters.

Conclusion: The study demonstrated that MG has a dose-dependent toxic effect on human SH-SY5Y cells, and oxidative damage may be responsible for this toxic effect. Moreover, the results indicated that quercetin may have protective effects against MG-induced cell damage.

Keywords: Methylglyoxal, neutoxicity, oxidative stress, cell death, quercetin.

ÖZ

Amaç: *Bir dikarbonil bileşiği olan metilglioksal (MG), hücresel metabolizmanın bir ürünü olarak normal veya patolojik koşullarda tüm hücrelerde bulunur. Kuersetinin antioksidan, anti-apoptotik ve nöroprotektif etkileri olduğu bilinmektedir. Bu çalışmanın amacı, kuersetinin nöron benzeri SH-SY5Y hücrelerinde metilglioksal kaynaklı toksisiteyi azaltıp azaltmadığını araştırmaktır.*

Gereç ve Yöntem: *MG'nin etkin toksik dozunu belirlemek için kültür ortamına farklı dozlarda (0-1000 µM) MG ilave edildi ve 24 saat inkübasyondan sonra MTT testi ile hücre canlılığı belirlendi. Daha sonra kuersetin (0.1 ve 1 µM), MG ile birlikte kültür ortamına verildi ve hücre canlılığı, hücre morfolojisi, apoptotik hücre ölümü, reaktif oksijen türlerinin oluşumu (ROS), total antioksidan kapasitesi (TAC) ve total oksidan stres (TOS) değerlendirildi.*

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Bulgular: *MG, konsantrasyona bağlı olarak SH-SY5Y hücrelerinde hücre ölümünü artırdı. MG, hücrelerin morfolojik özelliklerinde önemli bozulmalara, apoptotik hücre ölümünün artmasına ve reaktif oksijen türlerinin oluşumuna neden oldu. Ayrıca toplam oksidan stres düzeyleri MG eklenen hücrelerde kontrole göre daha yüksek bulundu (p<0.005). MG ile birlikte kuersetin eklendiğinde hücre ölümü ve diğer tüm parametrelerde istatistiksel olarak anlamlı düzelme olduğu gözlendi.*

Sonuç: *Bu çalışmanın sonuçları, MG'nin insan SH-SY5Y hücreleri üzerinde doza bağımlı toksik etkiye sahip olduğunu ve bu toksik etkiden oksidatif hasarın sorumlu olabileceğini gösterdi. Ayrıca bulgular, kuersetinin MG ile indüklenen hücre hasarına karşı koruyucu etkilere sahip olabileceğini ortaya koydu.*

Anahtar Sözcükler: *Metilglioksal, nörotoksisite, oksidatif stress, hücre ölümü, kuersetin.*

INTRODUCTION

Methylglyoxal (MG), a dicarbonyl compound, is endogenously produced through the fragmentation of the triosephosphates glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP) during glycolysis. MG can also be found in cells as a by-product of lipids, proteins, and other metabolic pathways (1, 2). In addition to the endogenous MG in the body, it has been reported that its cellular accumulation is related to dietary intake and especially high temperature and low humidity cooking (frying, grilling, oven) methods (3). On the other hand, it has been reported that dietary intake of MG is significantly reduced by increasing the intake of fish, low-fat dairy products, vegetables, fruits, and grains, and reducing the consumption of fats, fatty meats, high-fat dairy products, and highly processed products (4).

Methylglyoxal can effortlessly pass through the cell membrane and accumulate inside cells. It reacts quickly with proteins, lipids, and nucleic acids, forming advanced glycation end products (AGEs). These AGEs have been linked to neurodegenerative diseases and diabetes (2, 5). In case of excessive AGE production in cells, it causes cellular damage in several tissues due to its pro-oxidant and inflammatory effects (6, 7).

Oxidative stress is a condition that arises when there is an imbalance between oxidants, such as reactive oxygen species (ROS), and antioxidants in the body. This condition can lead to irreversible damage by disrupting the functions of cells (8). Studies have shown that MG can exacerbate oxidative stress by enhancing the activity and expression of various prooxidant enzymes, such as NADPH oxidase, p38 MAPK, JNK, and PPAR-α (9). In addition, MG can directly increase the production of free radicals and reduce the levels of antioxidants like glutathione (GSH), glutathione peroxidase, and glutathione reductase in different cells, thus inducing oxidative stress.

Cells possess various detoxifying mechanisms such as glyoxalase, aldose reductase, and aldehyde dehydrogenase to counteract the cytotoxic effects of MG. Particularly, the glyoxalase system is an important defense mechanism against MG and other reactive dicarbonyl compounds that protects cells from glycation and oxidative stress (8, 10, 11). The glyoxalase system involves two sequential enzymatic reactions catalyzed by glyoxalase-1 (Glo-1) and glyoxalase-2 (Glo-2), using glutathione as a co-factor, and is crucial for metabolizing MG (12). The rate of glyoxalase activity varies depending on the type, location, and environment of the cell. By functioning effectively, the glyoxalase system helps to reduce the amount of MG in cells and prevents its accumulation (2, 13).

Since most of the MG is produced as a byproduct of glycolysis, the generation of MG increases when glucose uptake is enhanced. In the case of hyperglycemia, the rise in MG formation causes cytotoxicity in pancreatic β cells, resulting in reduced insulin secretion. Consequently, this exacerbates hyperglycemia and complications related to diabetes. (14).

Impaired glucose metabolism, increased lipolysis and proteolysis and fructose metabolism in hyperglycemia may aggravate DNA damage by inducing some oxidative pathways. Overproduction of MG induces the production of AGEs and ROS as well as depletes GSH. MG and AGEs can cause the formation of protein aggregates, as well as trigger neuronal dysfunction and cell death with an increase in ROS production. It has also been shown that MG has neurotoxic effects on hippocampal and cortical neurons and is potentially harmful to cognitive functions, causing cell death (15).

Quercetin (3, 3′,4′, 5,7-pentahydroxyflavone) is a bioactive flavonoid found in many vegetables and fruits. The average daily intake of quercetin is estimated to be 10 mg/day (16). Quercetin is known to have protective effects against cancer and allergies, apart from antibacterial and antiviral effects. In addition to immunomodulation, quercetin has also been shown to have antioxidant, anti-apoptotic (17), anti-proliferative (18) and neuroprotective effects (19). In addition, it has been shown that quercetin can suppress the formation of AGEs mediated by MG and ROS (20). Studies have shown that methylated, sulfated, and glucuronide metabolites are the most prominent quercetin metabolites found in plasma (16).

Although there are various studies showing the cytoprotective effects of quercetin against various drugs and toxic agents, its effect against MG toxicity in neural cell cultures has not been studied yet. Therefore, in the current study we purposed to investigate whether quercetin has protective effect on MG-induced neuronal damage.

MATERIALS and METHODS

Chemicals and reagents

SH-SY5Y human neuroblastoma cell line was purchased from American Type Culture Collection (ATCC), Germany. Quercetin was obtained from Calbiochem. TAc/TOS assay kit was obtained from Rel Assay Diagnostics, Türkiye. DCFDA was obtained from Invitrogen, USA. All other reagents were purchased from Sigma-Aldrich GmbH, Germany.

Cell cultures

After thawing process, cells were seeded in a 25 cm^2 flask and incubated in an incubator at 37^{o}C with 95% humidity and 5% CO_2. High glucose DMEM medium containing 10% fetal bovine serum (FBS), 1% L-glutamine, 1% penicillin-streptomycin and 1% amphotericin was used as growth medium for cultures. Cell proliferation was visualized using an inverted phase contrast microscope (Olympus CKX53, Japan) (21, 22).

Methylglyoxal treatment

To determine the effective toxic dose of MG, cells were seeded into 96-well plates at a density of $4×10^4$ cells per well and incubated with 200 µL of complete medium for 24 hours. Next, the medium was removed and replaced with fresh medium containing various doses of MG (10 µM, 50 µM, 100 µM, 250 µM, 500 µM, and 1000 µM) and incubated for another 24 hours (23). The effective toxic dose of MG was determined using the MTT assay, and subsequently, different doses of quercetin were added to the cultures to assess its neuroprotective effect. All experiments were conducted in triplicate.

Quercetin treatment

Different doses of quercetin (0.1 µM, 1 µM and 10 µM) prepared in fresh medium containing 0.1% DMSO were added to the wells to test whether quercetin had cytotoxic effect. Cells were incubated for 24 hours at 37^{o}C, 5% CO_2 incubator. Cell viability was evaluated using the MTT test (24).

Evaluation of neuroprotective effects of quercetin on MG toxicity

During neuroprotection experiments, SH-SY5Y cells seeded in 96-well plates at $4×10^4$ cells/well were treated with effective dose of MG and different doses of quercetin (0.1 µM, 1 µM and 10 µM). The plate was incubated for 24 hours at 37^{o}C, 5% CO_2 incubator. The morphological changes in the cultures were examined under an inverted phase contrast microscope. Cell viability was then assessed with the MTT assay (21).

Assessment of cell viability

The cell viability was determined using the 3-(4,5-dimethyltriazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The absorbance of the plates was measured using a microplate reader (Multiscan Go, Thermo Fisher Scientific Inc., USA) at a wavelength of 570 nm. The cell viability rate was calculated using the following formula: (21).

Cell viability (%) = (Optical $density_{treatment}$/Optical $density_{control}$) × 100

Nuclear staining

SH-SY5Y cells were seeded in 12-well culture plates and incubated for 24 hours. Then, the medium was removed, and different doses of freshly prepared MG and quercetin were added to the cultures. After 24 hours of incubation, apoptotic cell death was determined using the Hoechst 33258 (bisbenzimide) assay. The changes in the nuclei of cells and DNA fragmentations were examined under a fluorescent microscope (21, 22).

Evaluation of reactive oxygen species (ROS)

The formation of reactive oxygen species in cells was evaluated by 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) oxidation method. The green fluorescence in the cells was evaluated under a fluorescent microscope (Olympus CKX53, Japan). The fluorescence intensity of each photo was quantified by using ImageJ software and expressed as mean fluorescence intensity (23).

Evaluation of total antioxidant capacity (TAC) and total oxidant status (TOS)

Evaluation of TAC and TOS was performed by using colorimetric assay kits (Rel Assay Diagnostics, Türkiye) according to the manufacturer's instructions. The absorbance of each well was recorded on a microplate reader (Multiscan Go, Thermo Fisher Scientific Inc., USA). The results were calculated according to the formula given in the kit. Total antioxidant capacity was expressed as mmol Trolox Eq/L and total oxidant status was expressed as µmol H_2O_2 Eq/L (25).

Statistical analysis

Data were given as mean ± standard error (SEM). One-way analysis of variance (ANOVA) and post-hoc Tukey HSD test were used for statistical evaluation of the data. A value of $p<0.05$ was considered statistically significant.

RESULTS

Dose-dependent effects of methylglyoxal and quercetin on SH-SY5Y cells

To determine the toxic dose, different concentrations of MG (0-1000 µM) and quercetin (0.1-10 µM) were tested on the cells. Our results showed that MG in doses of 10 µM and 50 µM reduced cell viability to 88.81% ± 13.95 and 41.13% ± 5.68 ($p<0.001$), respectively (Figure-1).

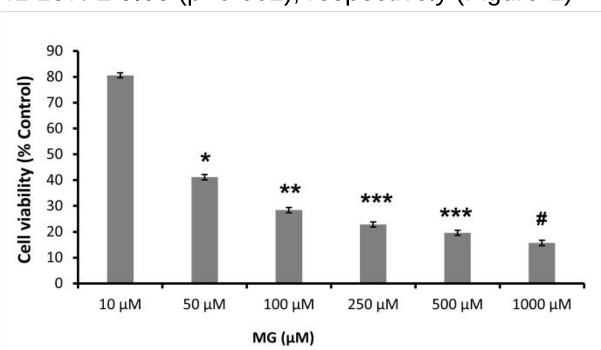

Figure-1. Dose-dependent effect of methylglyoxal on cell viability. The results are expressed as percentages of the control. The data are presented as the mean ± SEM. *p<0.001, **p<0.0001, ***p<0.00005, #p<0.00001 vs. control group.

According to the results obtained by the analysis of the dose-response curve, the dose that reduced cell viability to 50% (IC50) was determined to be 40 µM, and MG was used as 40 µM in the next experiments. As seen in Figure-2, cell viability was measured as 103.23% ± 18.7, 125.05% ± 19.91 and 71.38% ± 13.52, respectively, in cells treated with 0.1 - 10 µM quercetin for 24 hours compared to the control. Quercetin in doses of 0.1 and 1 µM doses of were used in subsequent experiments, since 10 µM dose adversely affected cell viability ($p<0.05$).

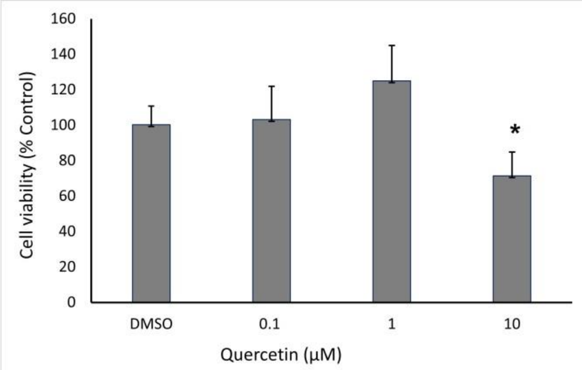

Figure-2. Effects of different doses of quercetin on cell viability. The results are expressed as percentages of the control. The data are presented as the mean ± SEM. (*p<0.05 vs. control).

Quercetin reduced methylglyoxal toxicity

To evaluate the protective effects of quercetin against methylglyoxal toxicity, MG was added as 40 µM alone or together with two different doses of quercetin (0.1 µM and 1 µM). Cell viability was measured as 62.48 ± 2.16% in MG treated cells ($p<0.00001$ vs. control), 93.78% ± 7.36 ($p<0.0001$ compared to MG) cells in which 0.1 µM quercetin was added with MG, and 99.69 ±1.13% in 1 µM quercetin added cells ($p<0.0001$ vs. MG). These results revealed that quercetin significantly reduced MG toxicity in both doses used (Figure-3).

In addition, evaluation of cell morphology revealed that the cells in the control and DMSO groups were normal in terms of density and intercellular connections, while the cell density was lower in the MG added group compared to the other groups. In addition, it was observed that the connections between the cells in this group were significantly impaired and there were shrinkage and deformations in the bodies of the cells. However, when the quercetin added groups were compared with the MG group, these changes were much less. These results supported the protective effects of quercetin against MG toxicity (Figure-4).

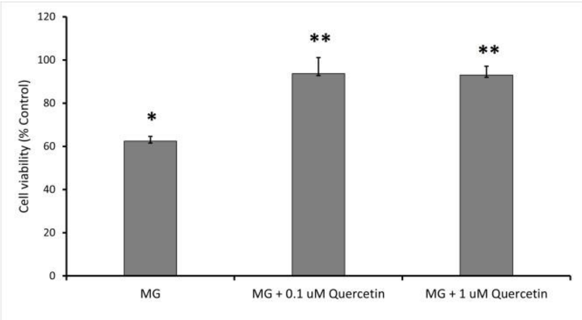

Figure-3. Evaluation of cell viability in cultures treated with methylglyoxal and quercetin (*p<0.00001 vs. control; **p<0.0001 vs. MG). The results are expressed as percentages of the control. The data are presented as the mean ± SEM. Statistical analyses were performed by one-way ANOVA and post-hoc Tukey HSD test.

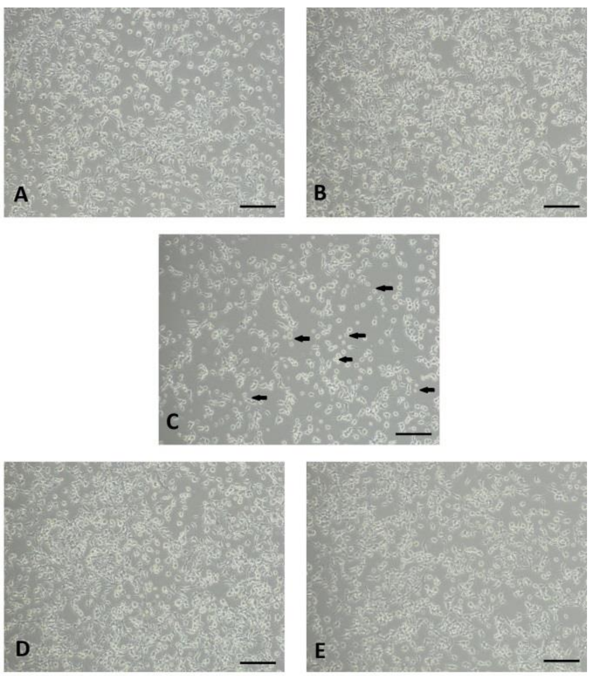

Figure-4. Morphological evaluation of methylglyoxal and quercetin added cells.

A-Control, B- DMSO, C- MG, D- MG + Quercetin (0.1 µM), E- MG + Quercetin (1 µM), Cell density was lesser in the MG group compared to the other groups. Morphologically, connections between the cells in MG group were significantly impaired and cells demonstrated shrinkage and deformations (showed by arrows). Quercetin prevented these alterations and saved cellular integrity against MT toxicity. Bars=100 µM.

Evaluation of apoptotic cell death

Nuclear Hoechst 33258 staining was used to determine whether MG caused apoptotic cell death in SH-SY5Y cells. Accordingly, control and DMSO groups had 2.29 ± 0.31 and 2 ± 0.33 apoptotic cells in each field, respectively, while the number of cells showing apoptotic features in the MG group was 6.14 ± 0.5 (p<0.0001 vs. control). On the other hand, addition of 0.1 and 1 µM quercetin to the medium significantly reduced the number of apoptotic cells (p<0.005 and p<0.001, respectively) upon MG injury by 40-50%. These results revealed that MG caused significant apoptotic cell death in SH-SY5Y cells, whereas the quercetin treatment significantly diminished apoptotic cell damage (Figure-5).

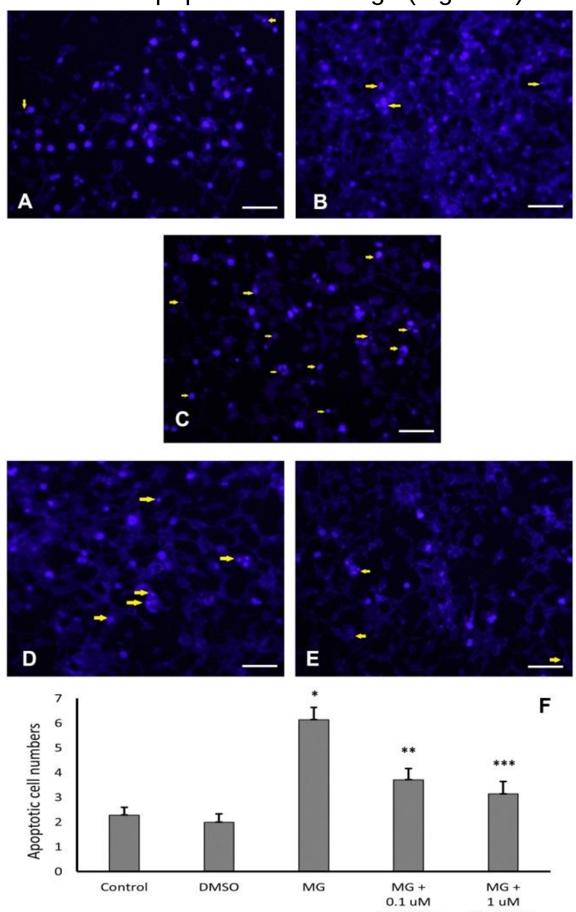

Figure-5. Evaluation of apoptosis in cells treated with methylglyoxal and quercetin.

A-Control, B- DMSO, C- MG, D- MG + Quercetin (0.1 µM), E- MG + Quercetin (1 µM), F- Apoptotic cell numbers. Apoptotic cells were identified as fragmented/condensed nuclei. The arrow shows apoptotic cells. (*p<0.0001 vs. control, **p<0.005 and ***p<0.001 vs. MG). Bars=100 µM.

Quercetin suppressed ROS generation

The generation of ROS in the cultures was evaluated by the DCFDA oxidation method. Accordingly, while there was no significant change in fluorescence intensity in the DMSO group compared to the control, the measured DCF fluorescence intensity in the MG group was 468.66 ± 46.84%, which was significantly higher than the control ($p<0.00001$). However, treatment with quercetin effectively reduced MG-induced ROS generation, as evidenced by the lower DCF fluorescence intensity in quercetin treated groups compared to the MG group ($p<0.0001$ and $p<0.00001$, respectively), (Figure-6). These results indicated that quercetin was effective in counteracting MG-induced ROS generation in SH-SY5Y cells.

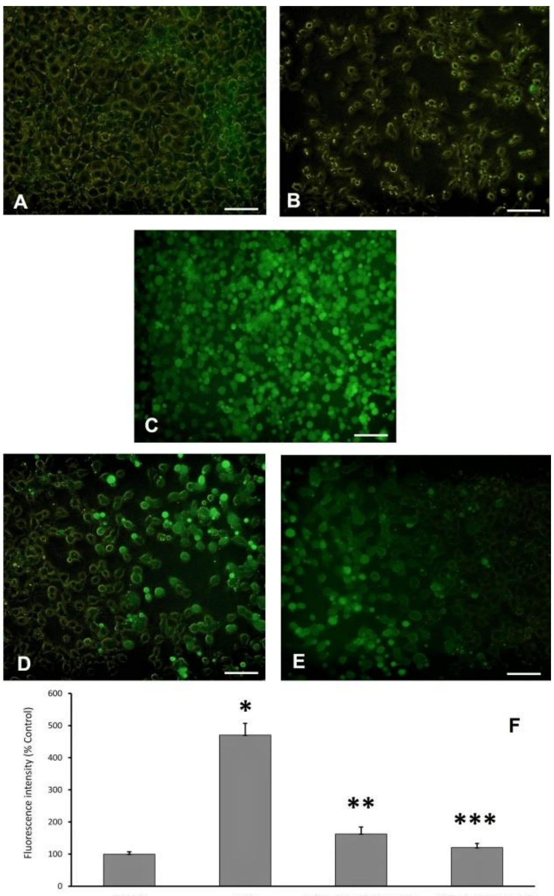

Figure-6. Evaluation of ROS generation in cells treated with methylglyoxal and quercetin.

A-Control, B- DMSO, C-MG, D- MG + Quercetin (0.1 µM), E- MG + Quercetin (1 µM), F-Fluorescence intensity (% control). MG treatment caused significantly higher fluorescence intensity compared to DMSO group. However, both 0.1 and 1 µM of quercetin prevented ROS formation in MG-treated cells (*p<0.00001 vs. DMSO, **p<0.0001 and ***p<0.00001 vs. MG). Bars=100 µM.

Quercetin decreased total oxidant stress

The total antioxidant capacity and total oxidant stress levels were measured to evaluate the relationship between MG toxicity and oxidative stress. Although there was a decrease in TAC levels in cells exposed to MG compared to the control, this effect was not statistically significant. On the other hand, when the TOS levels were evaluated, it was observed that MG group had significantly higher TOS levels compared to the control group ($p<0.005$). In the groups that added quercetin at two different doses with MG, the TOS levels were found to be significantly lower than in the MG group ($p<0.01$), (Table-1).

Table-1. Evaluation of total antioxidant capacity (TAC) and total oxidant stress (TOS).

	TAC (mmol Trolox Eq/L)	TOS (µmol H_2O_2 Eq/L)
Control	0.37 ± 0.05	4.82 ± 0.86
DMSO	0.35 ± 0.04	3.82 ± 0.26
MG	0.31 ± 0.03	9.24 ± 0.74*
MG + 0.1 µM Quercetin	0.33 ± 0.08	5.76 ± 0.87**
MG + 1 µM Quercetin	0.35 ± 0.08	5.65 ± 0.54**

Results were presented as mean ± SEM (n=8). Statistical analyses were performed by one-way ANOVA and post-hoc Tukey HSD test. *p<0.005 vs. control group, **p<0.01 vs. MG group

DISCUSSION

Methylglyoxal is one of the most effective glycation agents generated in cells (11). MG and other dicarbonyl compounds cause a toxicity called carbonyl stress in the body. MG toxicity is associated with the formation of MG-derived DNA compounds by cross-linking with DNA, contributing to mitochondrial dysfunction and free radical production, and leading apoptosis in different cell types, apart from binding to proteins and causing the formation of MG-derived AGEs (26). Thus, they cause protein and DNA modifications and epigenetic changes in the organism. At the same time, it has been observed that they can induce oxidative stress by reducing the production of antioxidants and increasing the production of mitochondrial superoxides (2).

In the current study, the toxic effect of MG on SH-SY5Y cells and whether this effect occurs through oxidative stress in cells was evaluated. First, a dose-response study was performed to determine the IC 50 of MG. When various doses of MG between 10-1000 μM were added to the culture medium, it was observed that the cell viability decreased depending on the dose. Also, morphological analysis of the cells clearly demonstrated that the intercellular connections were significantly impaired and there were shrinkage and deformations in the bodies of the cells treated with MG. Also, to investigate whether MG induced apoptotic cell death in SH-SY5Y cells, cells were evaluated with nuclear Hoechst 33258 staining. Thus, MG exposure caused a substantial enhancement in apoptotic cells compared to control cells.

It has been reported in previous studies that oxidative stress may be one of the underlying mechanisms of cell damage caused by MG. To examine whether MG causes oxidative stress in SH-SY5Y cells, the production of ROS was evaluated using DCFDA oxidation method and total oxidant status assay. According to the results, ROS production was significantly higher in the MG group than in the control group. In line with our findings, in a previous study on PC12 cells, it has been reported that intracellular ROS production and apoptotic cell death increased in cells exposed to MG for 6 hours compared to control (27). In a more recent study conducted by Chun et al., it has been demonstrated that MG treatment can induce cell death and elevate oxidative stress in neural progenitor cells through the activation of ERK signaling pathway (28).

Several lines of evidence suggest that plant-derived flavonoids have many biological and pharmacological effects such as anti-oxidative, anti-inflammatory, and anti-cancer effects. Quercetin is a polyphenol with phenolic hydroxyl groups, prevents free radical-induced cytotoxicity, and has strong antioxidant effects against oxidative stress (18, 19, 24). It has been shown to reduce cell proliferation by inducing apoptosis and cell cycle arrest in many cells (29). Quercetin exerts its neuroprotective effect through enhancing glyoxalase-1 functions in SH-SY5Y cells under chronic high glucose treatment, which may be mediated by stimulation of Nrf2/ARE pathway (30).

In the current study, the effects of quercetin on SH-SY5Y cells were tested using various doses (0.1 μM, 1 μM and 10 μM) for 24 hours. It was observed that cell viability increased at 0.1 and 1 μM doses of quercetin compared to the control, while a significant decrease in cell viability was observed at 10 μM. Therefore, 0.1 and 1 μM doses of quercetin were used in subsequent experiments in our study. The results of our study revealed a significant reduction in MG-induced loss of cell viability when 0.1 and 1 μM quercetin was added to the culture medium. In addition, morphological changes were observed to be quite low in the 0.1 and 1 μM quercetin added groups compared to the MG added group, which supported the hypothesis that quercetin had protective effects against MG toxicity. Related to these findings, there are some conflicting results in the literature reporting the effects of various doses of quercetin on cell viability. For example, Ossola et al. found that while 10, 50 and 100 μM quercetin increased cell viability in SH-SY5Y cells through 6 hours, depending on the concentration, treatment of the cells with 100 μM quercetin for 24 hours caused cytotoxicity (31). Similarly, Liu et al. have demonstrated neuroprotective effects of quercetin against HG-induced neuronal damages in SH-SY5Y cells at 0.1-50 μM, with best effect at 10 μM (30). However, in a recent study conducted by Pakrashi et al., it has been reported that pre-treatment of SH-SY5Y cells with 50 nM quercetin not only displayed significant increase in cell viability but also exhibited reduction in cell toxicity (17). These studies in the literature support that quercetin may have a dual effect depending on the dose and time used in the experiments.

Previous studies have revealed that quercetin exhibits strong antioxidant activity against free radical-mediated cellular damage by maintaining oxidative balance. In the present study, MG-induced ROS formation and TOS levels were decreased by quercetin treatment suggesting that quercetin successfully reduced oxidative stress and cellular damage. In addition to demonstrating the antioxidant properties, we hypothesized that quercetin may contribute to the protection of SH-SY5Y cells from MG-induced apoptosis. To determine whether quercetin can reduce cell apoptosis by suppressing oxidative stress, we investigated apoptotic morphological features with nuclear Hoechst 33258 staining. We observed that quercetin significantly alleviated the apoptotic cell death in MG treated cells. Consistent with the findings in our study, quercetin has been shown to significantly scavenge rotenone-induced ROS generation using DCFDA fluorescent dye in SH-SY5Y cells (19). Similarly, in a recent study, Bao et al. suggested that quercetin can inhibit ROS and lipid peroxide production and reduce apoptosis by increasing Bcl-2 and decreasing Bax expressions in H_2O_2-induced PC-12 cells (32).

CONCLUSION

In conclusion, quercetin revealed significant cytoprotecting effect against oxidative damage induced by MG in SH-SY5Y cells through its antioxidant and antiapoptotic properties. Although the results of this study suggest that quercetin, a potent herbal antioxidant, may have beneficial effects in neuronal cell damage induced by MG toxicity, further studies are needed to clarify other potential mechanisms.

Conflict of interest: The authors have no conflicts of interest.

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