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Protective Effect of β -Glucogallin on Damaged Cataract Against Methylglyoxal Induced Oxidative Stress in Cultured Lens Epithelial Cells

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Background: β -glucogallin (GG) is one of the major plant polyphenolic antioxidants that have been associated with positive effects on human health and are crucial in the developing defense mechanism against the risk of diseases. However, reports on the protective mechanism of GG in lens epithelial cells are limited.

Material/Methods: ARPE-19 cells (a human retinal epithelial cell line) were exposed to methylglyoxal (MG) with or without GG to illuminate the protective role of GG in counteracting the cataract signaling.

Results: Cells predisposed to MG demonstrated an increase in oxidative stress with augmented ($P < 0.01$) inflammatory cytokines such as cyclooxygenase (COX)-2, chemokine receptor CXCR4, interleukin (IL)-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and intercellular adhesion molecule 1 (ICAM-1) genes. In addition, the expression of aldose reductase (AR) was increased to 2-fold with accumulated sorbitol in MG exposed cells compared to control. On the other hand, cells exposed to MG evidenced a 3-fold increase in RAGE (receptor for advanced glycation end products) and a 2-fold increase in NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) expression compared to control cells. Intriguingly, lens epithelial cells pre-treated with GG attenuated the reactive oxygen species levels with improved antioxidant enzymes. Simultaneously, the levels of AR and other inflammatory cytokines were observed in the levels closer to control cells in GG pre-treated cells.

Conclusions: Thus, the results of the present investigation show that GG may be a potential drug for the prevention of cataract development and progression.

MeSH Keywords: **3T3 Cells • Glucan 1,3-beta-Glucosidase • Hypercementosis • Leukemia, Lymphocytic, Chronic, B-Cell • Photosensitivity Disorders**

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Background

Hyperglycemia in an adult is characterized by high levels of glucose in the blood, with glucose measuring 126 mg/dL during fasting or 200 mg/dL after meals [1]. Chronic effects of increased blood sugar level could be complicated by increased blood pressure, stroke, diabetic retinopathy, and degeneration of nerves that result in cataract, glaucoma, and other associated complications [2]. The chronic effects are debilitating such as the loss of eyesight due to degeneration of nerves and tissues to the cornea or lens which can cripple vision and result in socio-economic dependence. Increased degeneration of nerves to the eyes causes pressure on the nerves and can result in edema in the retina, and under such conditions can cause apoptosis in retinal epithelial cells [3]. Hyperglycemia is the key contributor to the development of neurodegenerative diseases in that elevated levels of aldose reductase (AR) expression have been implicated in the pathogenesis of cataract [4]. Also, increased production of reactive oxygen species (ROS) and sorbitol, due to enhanced activity of AR in glucose metabolism in patients with hyperglycemia, suggests the role played by AR in the progress of neurodegenerative diseases [5]. Experimental studies in diabetic predisposed mice have shown AR blockage prevents the buildup of markers for oxidative stress and the progression of tissue degeneration towards the retinal onslaught. AR inhibitors that reduce the effect of inflammatory responses due to cytokine secretion and ROS production can be used to inhibit the activity of AR and hence the ocular complications [6,7].

Methylglyoxal (MG) is a toxic aldehyde and its influence on cell proliferation and differentiation has been studied [8]. Hydrogen peroxide has been known to be a mediator in the increase of ROS and it dramatically increases the mutagenicity of MG in the secondary complications of diabetes mellitus [9,10]. Accumulation of MG happens in hyperglycemia due to non-enzymatic reactions of glucose with lens proteins, and it generates advanced glycation end-products (AGEs) of lens proteins by aggregation of crystallin towards lens opacity in cataracts [11,12], neuronal injury [13], and initiates lipid peroxidation [14,15]. With the recent search for the non-invasive and traditional method of treatment, the use of phytochemicals from plants has attracted major attention. Amongst these phytochemicals, β -glucogallin (GG), a structural analog of gallic acid, has been studied in various diseases both in *in vitro* and *in vivo* studies. Most of the plant berries studied act as sources of GG. As these phenols help the plant through protection using these molecules as a defense mechanism, most of the plants contain these phytochemicals. Such plants include Amla (*Embllica officinalis*), strawberry (*Fragaria ananassa* and *Fragaria vesca*), and raspberry (*Rubus idaeus*) which have been suggested to be major sources of GG. Moreover, GG is very well known for its AR inhibitory activity in ocular tissues and has

been observed to inhibit the activity of sorbitol in hyperglycemia patients with regards to cataract development [16,17]. However, studies have been limited in attempts so identify the oculo-protective role of GG.

Hence, this study attempted to assess the potential role of GG as an agent to be used in controlling cataract progression against MG induced oxidative stress in human ARPE-19 cells. The importance of GG in the control of ROS in ARPE-19 cells induced with stress with agents expressed in hyperglycemia [1] was the hypothesis we attempted to prove in our experiments.

Material and Methods

MG, GG, and 2',7'-dichlorofluorescein diacetate (DCFH-DA) were obtained from Sigma Aldrich, St. Louis, MO, USA. Kits for RNA isolation, cDNA synthesis, and SYBR Green/ROX master mix were obtained from Qiagen (Valencia, CA, USA). Primer sequences for polymerase chain reaction (PCR) were obtained from Eurofins MWG (Operon). Enzyme-linked immunosorbent assay (ELISA) kits for cyclooxygenase (COX)-2 (ab210574) were from Abcam, USA, chemokine receptor CXCR4 (OKEH01535) was from Aviva Systems, CA, USA, interleukin (IL)-6 (D6050), IL-8 (D8000C), monocyte chemoattractant protein-1 (MCP-1) (DCP00), intercellular adhesion molecule 1 (ICAM-1) (DCD540) were from R&D Systems Inc., MN, USA. Protein carbonyl, lipid peroxidation, superoxide dismutase (SOD), catalase, reduced glutathione (GSH), and glutathione peroxidase (GPx) assays kits were obtained from Cayman Chemicals, USA. D-Sorbitol Colorimetric Assay Kit was from BioVision, Milpitas, CA, USA. All other chemicals used were reagent grade.

Cell culture

Human retinal epithelial cell line ARPE-19 was used as a model for this study and was purchased from ATCC, USA. Cells were maintained in DMEM/F-12 (1: 1) culture medium supplemented with 10% fetal calf serum with 1 mM/L glutamine, 100 U/mL penicillin, 50 μ g/mL each of streptomycin and neomycin in a humidified incubator containing 5% carbon dioxide at 37°C. For the experiments, cells were grown in culture plates, coverslips, and flasks according to the experiment protocol, until confluence.

Experimental protocol and biochemical assays

Cells were separated into 4 groups: group 1 was non-treated control, group 2 cells were grown in the presence of MG (100 μ M) for 24 hours, group 3 cells were pre-treated with GG (100 μ M) for 2 hours prior to MG treatment, and group 4 cells were treated with GG alone as a drug control. At the end of the treatments, cells were collected by scraping and centrifuged

Table 1. Primer sequences.

Gene	Primer	Sequence (5'-3')	Annealing
AR	F	TTTGAGGCTGTGGTTTGCCT	58
	R	ACATCAAGCTAGACACGCC	
α B-crystallin	F	AAACGGCCTGGGTGGATAGA	59
	R	TGCTTGCACTGCTGATACCT	
PDGF	F	TGGGATCCCAGAGTTGGTC	57
	R	CAAACCCGAGAGACCACAA	
RAGE	F	CCTCAGGACCAGGGAACCTA	58
	R	GGGGCAGGAAATTAGAGCCT	
NF- κ B	F	CCAGACCAACAACAACCCCT	56
	R	GATCTTGAGCTCGGCAGTGT	
GAPDH	F	TTCTTTGCGTCGCCAGCC	59
	R	CTTCCCGTTCTCAGCCTTGAC	

at 1500 g for 10 minutes at 4°C. The Cayman assay kits were used for the analysis of lipid peroxidation, protein carbonyl content, the antioxidant enzymes SOD, catalase, GPx, and reduced GSH as per manufacturer's protocol. For the analysis of sorbitol content, cells (10^6 cells) were collected after the treatment, washed with cold phosphate-buffered saline (PBS) and deproteinized. The amount of sorbitol in the cells was quantified using the D-Sorbitol Colorimetric Assay Kit as per manufacturers' instruction.

Intracellular ROS release

To measure the levels of ROS produced in the cells, oxidant sensitive fluorescent probe, DCFHDA was used. About 1×10^5 cells grown in lysine-coated coverslips were treated with/without MG and GG were incubated with DCFHDA (10 μ M) at 37°C. The fluorescence released was observed in a confocal microscope and the images were captured (20 \times magnification), and the amount of fluorescence produced was measured using fluorimeter at an excitation and emission wavelength of 488 and 530 nm respectively.

Real-time (RT)-PCR

For the analysis of mRNA expression, total RNA was extracted from the cells, quantified and the first-strand cDNA was synthesized using 1 μ g of total RNA. Real-time (RT)-PCR was performed using the StepOnePlus™ Real-Time PCR System. The forward (F) and reverse (R) primers used for gene expression are given in Table 1. The PCR amplifications were done in triplicates using SYBR Green PCR Master Mix. The reaction conditions were optimized for each gene using the following cycle: the initial cycle setting was 95°C for 7 minutes; followed by 30 cycles at 95°C for 15 seconds and 60°C for 1 minute;

followed by 1 cycle at 95°C for 1 minute, 55°C for 30 seconds, and 95°C for 30 seconds for the dissociation curve. The reaction mixture without template cDNA was used as a negative control. The level of gene expression was determined by the comparative Ct method ($\Delta\Delta$ CT) using the Ct values of GAPDH as an endogenous control.

Enzyme-linked immunosorbent assay (ELISA)

For the analysis of cytokines levels, ARPE-19 cells grown with or without MG and GG were scraped off, collected, centrifuged at 1500 g for 15 minutes to remove particulates, and the supernatant was stored at 80°C until further analysis. The level of cytokines, such as COX-2, CXCR4, IL-6, IL-8, MCP-1, and ICAM-1, were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits.

Statistical analysis

For the statistical analysis, GraphPad Prism Software was used (GraphPad Software, San Diego, CA, USA). Results are expressed as mean \pm standard error (SE). Statistical significance was evaluated by one-way analysis of variance (ANOVA). The *P*-value of <0.05 was considered significant.

Results

The present study was designed to evaluate the protective role of GG against MG induced cellular damage; human ocular epithelial cells were used as a model. Initially, human epithelial cells were challenged with MG for 24 hours and demonstrated the onset of oxidative markers indicated by the increased levels of lipid peroxidation, and proteins carbonyl with suppressed

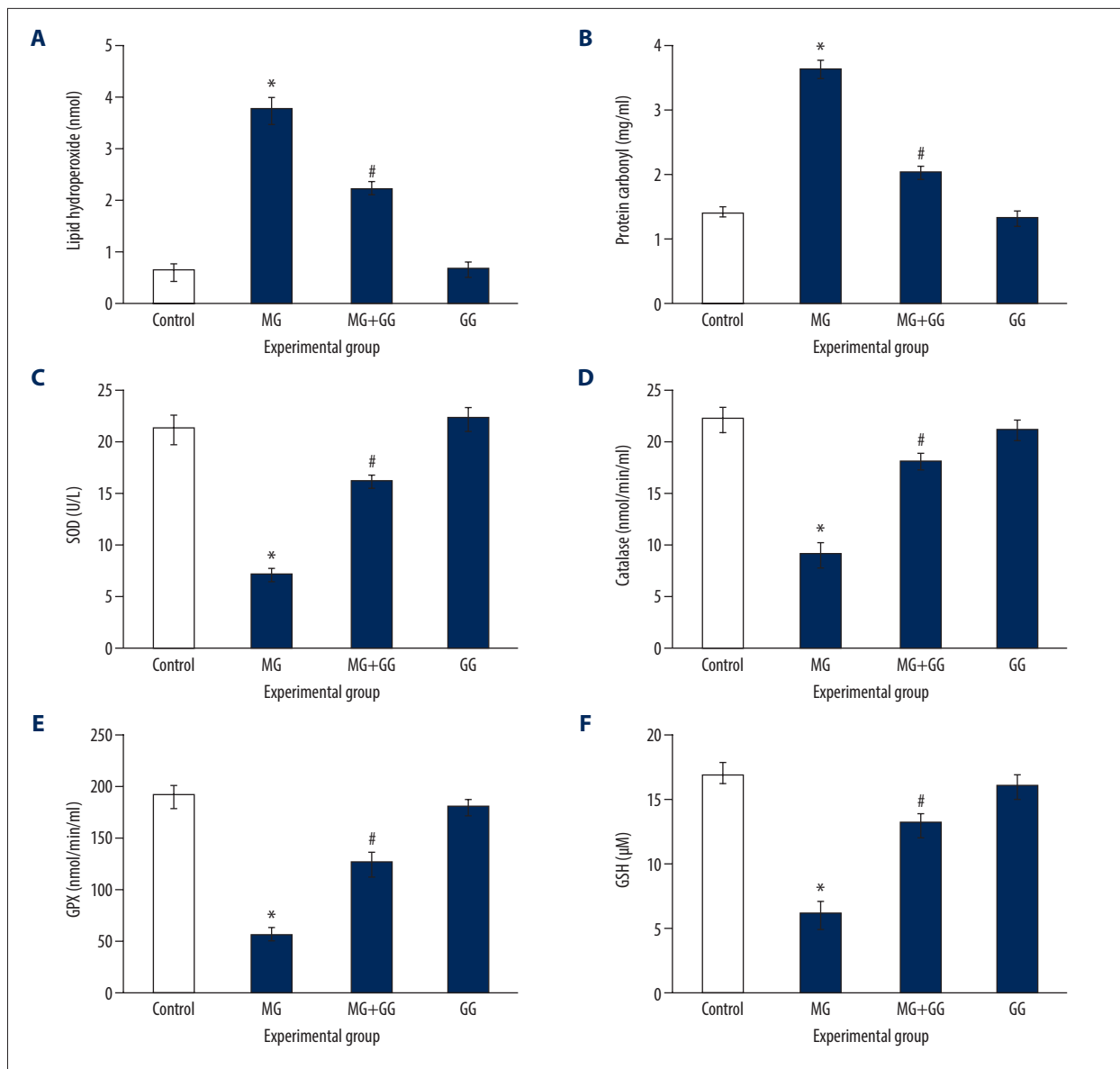


Figure 1. (A–F) Represents the levels of lipid peroxidation, protein carbonyl, SOD, catalase, glutathione peroxidase, and glutathione of control and experimental cells. Values are expressed as means \pm SE (n=6). Statistical significance expressed as * $P < 0.05$ compared to untreated controls, # $P < 0.05$ compared to MG exposed cells. MG – methylglyoxal; SOD – superoxide dismutase.

levels of SOD ($P < 0.01$), catalase ($P < 0.01$), GPx ($P < 0.01$), and GSH levels ($P < 0.01$) compared to control cells. The cells pre-treated with GG restored levels similar to that of control cells, suggesting that GG exerts protection from oxidative damage for lens cells (Figure 1).

Conversely, reports have shown that elevation of oxidant status is the major event in the cataract development and an agent that prevents this event is the key drug needed for the prevention of adverse effects in cells. In the present study, cells with MG demonstrated a 5-fold increase in ROS release evidenced by the fluorescence data. On the other hand, GG pre-treatment

prevented the onset of oxidative radical release, which further confirms its protective nature (Figure 2).

It was evidenced from earlier reports that the expression of α B-crystallin helps in maintaining the lens and retinal cells against oxidative stress conditions. Hence in the current study, the expression level of AR, α B-crystallin, and platelet-derived growth factor (PDGF) were elucidated. The study results demonstrated a significant increase in AR (2-fold), α B-crystallin (2.2-fold), and PDGF (1.5-fold) with increase accumulation of sorbitol in MG exposed cells compared to control. While cells pre-treated with GG significantly attenuated these markers of

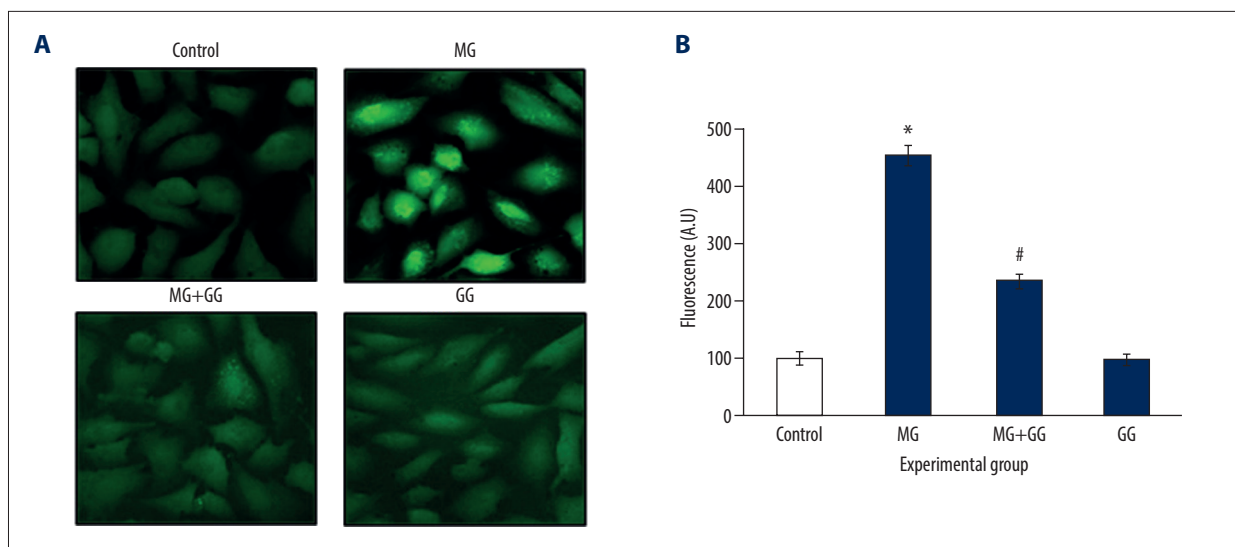


Figure 2. The effect of MG and GG on the release of ROS in ARPE-19 cells. **(A)** The confocal microscopic picture of cells emitting fluorescence is represented. **(B)** The fluorescence quantification measure at 488 and 530 nm is represented. Values are expressed as means \pm SE (n=6). Values are expressed as means \pm SE (n=6). Statistical significance expressed as * $P < 0.05$ compared to untreated controls, # $P < 0.05$ compared to MG exposed cells. MG – methylglyoxal; GG – β -glucogallin; ROS – reactive oxygen species; SE – standard error.

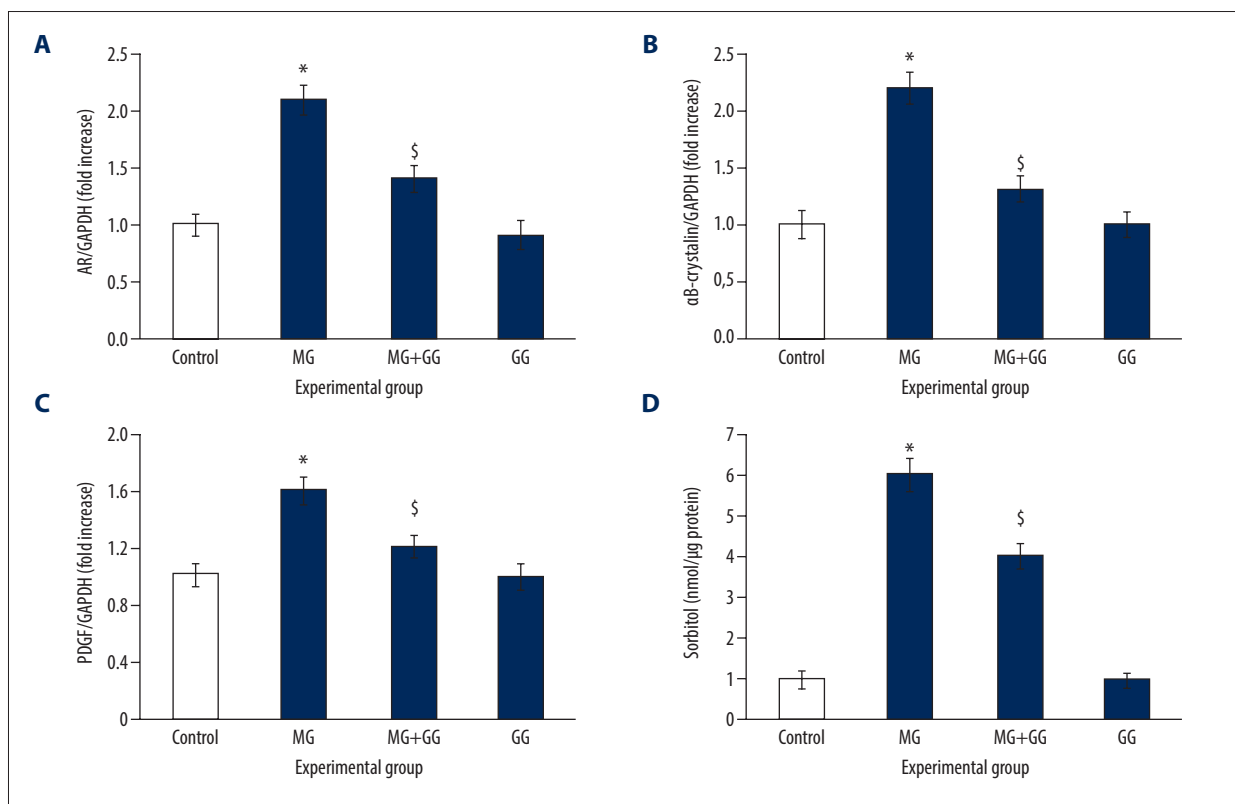


Figure 3. **(A–C)** The qRT-PCR mRNA expression analysis of AR, α B-crystallin, and PDGF normalized to GAPDH in the control and experimental group of cells. **(D)** Sorbitol levels. Values are expressed as means \pm SE (n=6). Values are expressed as means \pm SE (n=6). Statistical significance expressed as * $P < 0.05$ compared to untreated controls, # $P < 0.05$ compared to MG exposed cells. qRT-PCR – quantitative real time polymerase chain reaction; AR – aldose reductase; PDGF – platelet-derived growth factor; MG – methylglyoxal.

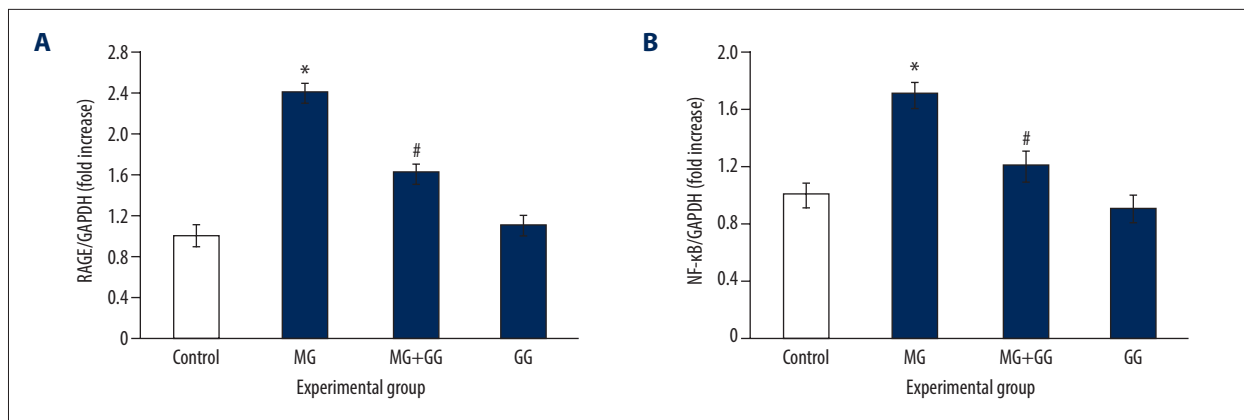


Figure 4. (A, B) The qRT-PCR mRNA expression analysis of RAGE and NF- κ B normalized to GAPDH in the control and experimental group of cells. **(B)** Sorbitol levels. Values are expressed as means \pm SE (n=6). Values are expressed as means \pm SE (n=6). Statistical significance expressed as * P <0.05 compared to untreated controls, # P <0.05 compared to MG exposed cells. qRT-PCR – quantitative real time polymerase chain reaction; RAGE – receptor for advanced glycation end products; NF- κ B – nuclear factor kappa-light-chain-enhancer of activated B cells; SE – standard error; MG, methylglyoxal.

cataract and reduced sorbitol was evidence that GG mediates the cataract prevention via attenuating AR signaling (Figure 3).

Further, the mRNA expression of RAGE (receptor for advanced glycation end products) and NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) also was elucidated in the study. The major role of MG is vitiated by the activation of RAGE and further down streamed via the NF- κ B pathway. Hence in the present study, the defensive role of GG against MG was elucidated and the results showed that the indicative decrease in the levels of RAGE (2.4-fold) and NF- κ B (1.7-fold) were observed in GG pre-treated cells exposed to MG, suggesting that aggressive cataract development is routed via key NF- κ B signaling (Figure 4).

Moreover, it was substantiated and found from PCR analysis results, that MG played a major role in lens epithelial cell derangement functioning; hence to decipher the beneficial role of GG, the levels of cytokines was unraveled using ELISA. The results clearly showed that the levels of cytokines were significantly (P <0.01) increased in COX-2 (1.5-fold), CXCR4 (2-fold), IL-6 (2.1-fold), IL-8 (1.6-fold), MCP-1 (1.7-fold), and ICAM-1 (1.3-fold) in MG group while and GG pre-treated MG exposed cells could endure the activation of pro-inflammatory cytokines (Figure 5). Thus, the results demonstrated the promising role of GG, which can contribute to the development of novel treatment strategies to protect lens epithelial cells.

Discussion

The influence of GG in MG-induced oxidative damage in mammalian cells and the cascade effect seen on antioxidant proteins and enzymes in the development of neurodegenerative

diseases has been discussed here in the context of cataracts in hyperglycemic patients. The generation of MG is majorly due to the oxidation of glucose and amino acid breakdown in cells and tissues, and it occurs at an increased rate in certain pathological conditions [18,19]. The generated MG is toxic, and we hypothesized the role played by it in the degeneration of lens epithelial cells in cataracts; we induced ARPE-19 cells with MG and then treated the induced cells with a plant AR inhibitor GG". The detrimental effects of MG and the rescuing role played by GG in attenuating the effects were analyzed at various points of action of MG.

We showed that the toxic effects of MG on the induction of ARPE-19 cells in the form of a rise in the levels of lipid peroxidation and a corresponding increase in the AGE-glycation end-products [20]. A marked increase in the concentration of lipid hydroperoxide and in the protein carbonyl as observed (Figure 1) on induction with MG. Because of this, the cells underwent oxidative stress with induction and a simultaneous increase in the enzymes and proteins that would combat the built-in oxidative stress was observed. This may be due to the free radicals produced as a result of MG that would also accelerate lipid peroxidation with the increase in lipid hydroperoxide (Figure 1).

Reports on the treatment of MG in mice and the subsequent increase in ROS observed that reacts with antioxidant enzymes in establishing oxidative stress has been studied with SOD, catalase, and reduced glutathione (GSH) [8]. The buildup of anti-oxidative enzymes is high; the corresponding act of inhibition of MG activity is observed in GG-treated cells by up-regulating the SOD, catalase, and GSH antioxidant enzymes. This indicates the level of oxidative stress due to MG activity in the cells (Figure 1). The significant results obtained with the

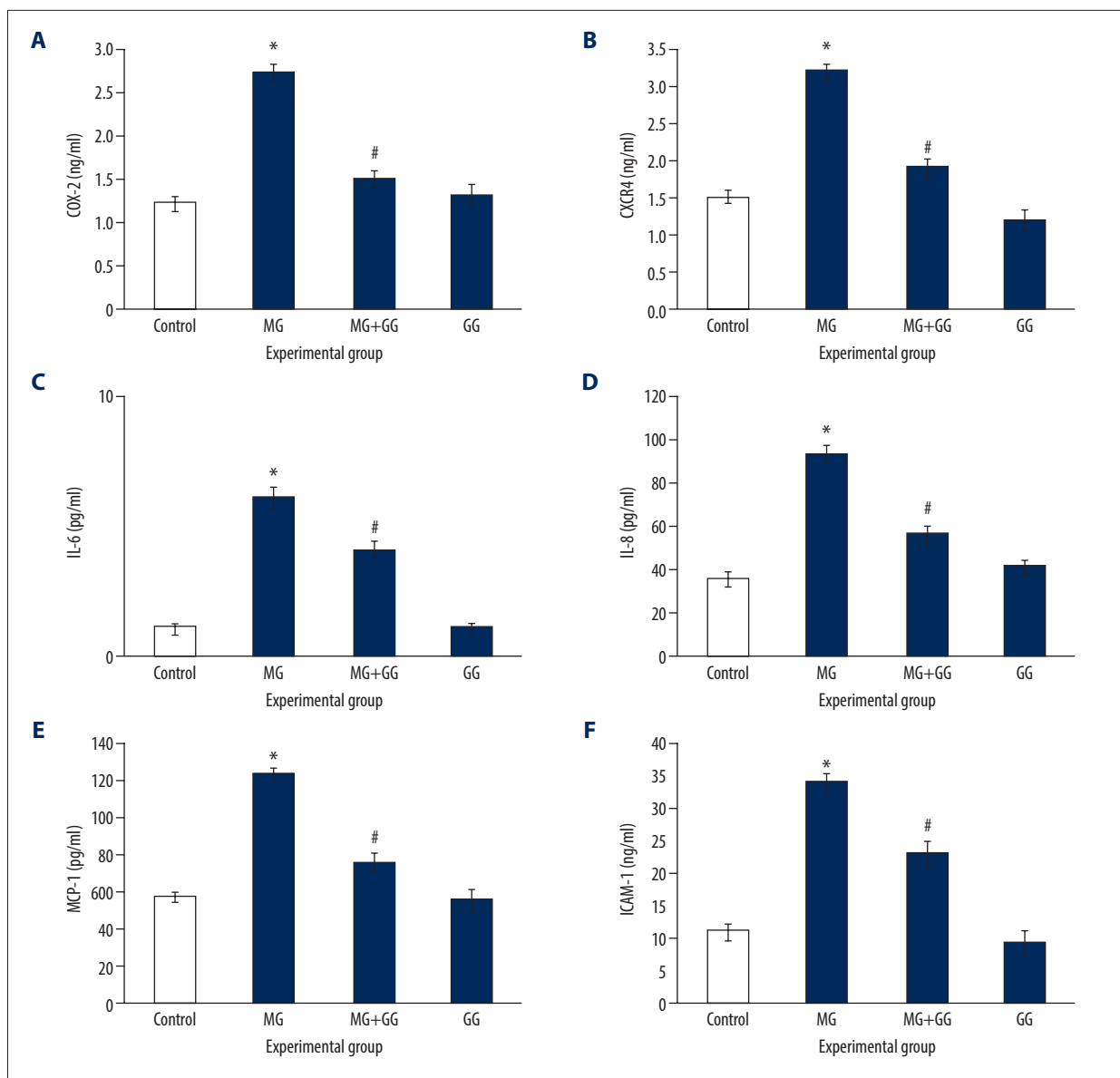


Figure 5. (A–F) Represents cytokine expression analysis of COX-2, CXCR4, IL-6, IL-8, MCP-1, and ICAM-1 in control and experimental group of cells. Values are expressed as means \pm standard error (SE) (n=6). Values are expressed as means \pm SE (n=6). Statistical significance expressed as * $P < 0.05$ compared to untreated controls, # $P < 0.05$ compared to MG exposed cells. MG – methylglyoxal.

action of GG on stress-induced cells, were in the interest of the conversion of toxic aldehydes produced as the by-products of the action of MG into non-toxic intermediates.

The decrease in the activity of antioxidant enzymes in the cells induced with MG can be explained by weakening of enzymes [8] induced by MG, while at the same time decreasing the activity of GSH as a co-factor. The observed decrease in the activity of antioxidant enzymes was proportional to the increase in the concentration of the MG used for induction. Marked decreases in GSH activity in the MG-treated cells were

observed (Figure 1) and could be recuperated with the introduction of GG and recovered significantly. However, the activity of another protective enzyme, GPx, was also significantly altered in the GG treated cells after MG induction. Hence the conversion of the toxic metabolites of glucose by MG was sufficiently activated by GSH-dependent detoxifying enzymes [8] with co-activation of GPx.

The upregulation of AR in hyperglycemic patients would catalyze the conversion of glucose to sorbitol and has been directly implicated in the secondary diabetic complication of

cataract by the accumulation of AGE in the retinal cells due to high production of ROS. The observed single fold increase in AG would correspondingly increase the AGE-related crystallins (glycated forms) [21] and a 5-fold accumulation of sorbitol due to glucose conversion in MG induced cells have been observed (Figure 3). The aggregation of modified crystallins is known to be important for cataract formation [22] and the gravity of the cataract formation is emulated in the form of improved expression of PDGF [23]. The inflammation of the damaged lens tissues and the increased opacity of the lens coincides with the increase in the expression of PDGF explains the pathogenicity of cataract [23,24]. GG, known to be an inhibitor of AR in the cataract tissues effectively reduced the accumulation of sorbitol [1] when treated and could reverse the effect of cataract (Figure 3).

Another aspect of oxidative stress in the high-glucose milieu is the increase in the expression of receptor of AGE (RAGE) (Figure 4) in cells induced by MG. Increase in RAGE indicates the increased binding of AGE to its receptor and in-turn translocates NF- κ B into the nucleus and activates the pathway leading to the expression of various inflammatory cytokines to sustain the oxidative damage to the neurons [25–27]. Hence, the observed increase in RAGE suggests that for the downstream signaling to incur, the receptor-mediated initiation of cell signaling could have been activated by MG as MG is a potent glycation initiator. Hence the results also evidenced the significant increase of RAGE expression, thus, the study findings have illuminated a light on the RAGE mechanism in the ocular epithelial cells.

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Furthermore, the observed overexpression of IL-6 and IL-8 in the MG-activated cells (Figure 5) is a direct consequence of that glucose-rich environment in the MG over-expressed hyperglycemic patients, and would face neuroinflammatory response [28] in cataracts and a similar response to the expression of COX2 in MG-activated cells [27] and a direct correlation between MG and other inflammatory cytokines such as MCP1 and ICAM-1, towards an adaptive immune response.

Conclusions

Overall, we have demonstrated in human lens epithelial cells (ARPE19), that MG could increase AGE generation and together with sorbitol could increase the oxidative damage by recruiting inflammatory cytokines like IL-6, IL-8, and MCP-1, and their effects could be counteracted by action of GG which activates the anti-oxidative defense mechanism of SOD and catalase enzymes, and reduces the neuroinflammation in lens epithelial cells of cataract. Thus, the results of the current study concluded that the protective action exerted by GG was through its role as a ROS-scavenger which warrants further investigation in downstream signaling pathways before being considered for the development of novel treatment plans for retinal cells.

Conflicts of interest

None.

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