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Original Research Article

The Combined Effect of Coenzyme Q10 and Magnesium Ion on Advanced Glycation End Products Formed by Methylglyoxal in Rabbits

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ABSTRACT

Methylglyoxal (MGO) is a poisonous and highly reactive alpha-oxoaldehyde with increased levels during oxidative stress in various disorders. MGO is generated from glyceraldehyde-3-phosphate and dihydroxyacetone phosphate during glycolysis. Continued exposure to Methylglyoxal causes Advanced Glycation End products (AGEs), implicated in different diseases, such as the early stages of diabetes, and affects male fertility, reducing sperm count and quality. This study aimed to evaluate the combined effects of coenzyme Q10 and Magnesium ion on oxidoreductase and liver enzymes due to the toxicity of MGO in experimental animals. Twenty-four rabbits (male and female) weighing 750-2100 mg, divided into four groups, were used for this experiment. Group one was used as the positive control (without treatment). Group two (negative control) received an intraperitoneal dose of 0.1 ml (20 mg/kg) per kg body weight of Methylglyoxal. Animals in group three received 0.1 ml (20 mg/kg) methylglyoxal intraperitoneally and Magnesium 5 mg/kg orally per kg body weight. Group four animals received 0.1 ml (20 mg/kg) methylglyoxal intraperitoneal, a combination of 5 mg/kg Magnesium, and 2.5 mg/kg coenzyme Q10 orally to evaluate the effect of the metal ions and antioxidants on liver enzymes activity and uric acid and other endogenous antioxidant markers (SOD and GSH). Results from our study showed that methylglyoxal exerted toxic effects on some biochemical parameters of the animals. However, the administration of CoQ10 and Magnesium ions significantly increased the levels of liver and antioxidant enzymes such as SOD and glutathione levels to resist oxidative overload.

***Keywords*:** Methylglyoxal, AGEPs, Advanced glycation end products, Glutathione, Magnesium, Ubiquinone.

Introduction

Methylglyoxal (MGO) is a toxic and highly reactive alpha-oxoaldehyde produced during glycolysis enhanced in disorders characterized by increased oxidative stress.[1] Methylglyoxal is a somewhat viscous clear yellow liquid with a strong odour. It was discovered first as a critical step in mammalian glucose metabolism. Its discovery in 1913 in plants and microorganisms, MGO has been found in a wide range of meals high in carbohydrates (80%), lipids, and fermented drinks.[2] The production of advanced glycation end products (AGEs) has been linked with diabetes and cancer, with MGO serving as a precursor, keeping a vicious loop. Diabetic hyperglycemia promotes the development of MGO and AGEs, which creates an environment conducive to tumour growth and metastasis. On the one hand, it leads to disease progression and therapeutic resistance, and on the other, chronic diabetes complications.[3] MGO has been shown to promote the production of ROS, proinflammatory cytokines, and peroxynitrites. MGO increases oxidative stress by lowering cell antioxidant capacity and detoxification mechanisms. In addition to promoting free radical generation,[4,5] it leads to oxygen poisoning, which affects living cells. Cellular toxicity is enhanced by ROS, superoxide anion radical (O_2), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH) like (OH^-).[6]

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The Glyoxalase system is the mechanism for MGO detoxification. It consists of two enzymes: Glyoxalase 1 (Glo1) and Glyoxalase 2 (Glo2), as well as glutathione (GSH), other enzymes like aldehyde dehydrogenases (ALDH) and Aldo-keto reductases (AKR), catalyze the conversion of MGO to D-lactate and metabolize MGO to pyruvate and hydroxyacetone.[7] This highly reactive endogenous chemical mediates the progress of neurological disorders and cell death. Endogenous increases in MGO amounts lead to diabetic neuropathies. Also, MGO interferes with behavioural endpoints in autism models, ageing problems, and Alzheimer's disease.[8] In the breast cancer MCF-7 cell line, MGO combined with creatine increased apoptosis and cytotoxicity compared to MGO alone.[9] Although the significance of circulating MGO levels in liver cirrhosis is uncertain, AGE binding to its receptor (Receptor for Advanced Glycation End-products) (RAGE) initiates and maintains severe inflammation. The development of liver cirrhosis is aided by systemic inflammation.[10] Increased levels of MGO lead to further loss of equilibrium between reactive oxygen/nitrogen species (ROS/RNS), described as oxidative stress, and the ability of the organism's antioxidative defence mechanisms to counteract their effects. These harmful oxidative processes are attributed to oxygenated reactive species.[11] MGO may cause apoptosis in different methods, and increased levels of MGO in the cells can lead to an increase in intracellular reactive oxygen species, oxidative DNA damage, or the build-up of advanced glycation end products (AGES).[12]

Various researchers suggest that MGO acts either as a direct toxicant or a precursor to advanced glycation end-products (AGES) and contributes to cell failure. MGO interacts with RAGE to elicit the harmful effects of AGES in distinct cell types. MGO toxicity is linked to free radical overproduction, GSH depletion, mitochondrial dysfunctions, DNA crosslinking, and death.[13] MGO forms persistent adducts with arginine, lysine, and cysteine residues in proteins, causing the impairment of proteins' function. It reacts with superoxide dismutase-1 (SOD1) in proteins and affects glycation. Also, AGEs are

synthetic nucleotides and phospholipids that form stable adducts.[14] AGEs are the insoluble end product of purine digestion in DNA, RNA and nucleotides.[14,15] GSH helps detoxify lipid metabolites like glyoxal and methylglyoxal. Non-enzymatic lipid breakdown generates dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-Phosphate. And methylglyoxal synthase enzyme in bacteria is known to convert DAHP to methylglyoxal.[16] Furthermore, Coenzyme Q10 (CoQ10) is an antioxidant found in plasma membranes and lipoproteins and is a component of the mitochondrial electron transport chain. It is produced in all cells by a mitochondrial multiprotein complex through a finely regulated mechanism.[17] On the other hand, Mg is a critical cofactor for approximately 300 enzyme processes, making it crucial for the biochemical functioning of multiple metabolic pathways. Inadequate magnesium levels could cause havoc on physiological systems that rely on the metal.[18] This study evaluates the ameliorative effects of the combination of coenzyme Q10 and magnesium ions on advanced glycation end products in methylglyoxal challenged rabbits.

Materials and Methods

Chemicals
Magnesium oxide (MgO) tablets 187.5 mg and CoQ10 tablets 100 mg were bought from the pharmacies in Basrah city.

Animals care
Twenty-four (male and female) rabbits weighing 750-2100 gm sourced from a local market in Basrah city were used for this experiment. The animals were housed in standard plastic cages in the animal house of the College of Pharmacy, University of Basrah, Iraq, to acclimatize for one and a half weeks. They were exposed to 12 hr light/dark cycle in an air-conditioned room (25.0±0ºC) and were handled according to standard protocols for the use of experimental animals. They were divided into four groups of six animals each and allowed access to water and standard rodent feed *ad libitum* augmented with bread and lettuce. Ethical approval (no. 2022/198) was obtained from the Institution's Animal Ethics committee before the commencement of the study.

Drug administration
The animals were divided into four groups of six animals each. Group 1: Positive control (untreated), received food and dist. Water. Group 2: negative control group were injected with 0.1 ml (20mg/kg) Methylglyoxal intraperitoneally. Group 3 (treated group 1). The animals in this group received 0.1 ml (20mg/kg) intraperitoneal Methylglyoxal plus 5 mg/kg of oral Magnesium. Group 4 (treated group 2). The animals in this group received a combination of intraperitoneal 0.1 ml (20 mg/kg) Methylglyoxal, 5 mg/kg of oral Magnesium, and 2.5 mg/kg of oral CoQ10.

Preparation of drugs
Magnesium Oxide tablets and CoQ10 tablets were dissolved in distilled water prior to administration for each dose.

Induction of methylglyoxal toxicity
In all groups, the rabbits were injected with methylglyoxal intraperitoneally every day for 30 days at 10 am, except for group 1 (positive control Group). Table 1 shows the groups and dose administration.
Blood samples from all the groups of animals were collected separately by direct withdrawal from the heart at zero time, after 10 days (draw 1) and then after 30 days (draw 2). In each case, 3 ml of blood was collected into a gel tube and centrifuge at 6000 rpm for 15 minutes to obtain the serum. The serum was collected using a micropipette and then stored in a deep freezer at -20 C for further analysis.

Biochemical Parameters Assayed
The blood samples were analyzed for levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) to determine the activity of liver enzymes. While the antioxidant effects parameters assayed, include uric acid, superoxide dismutase (SOD) and glutathione (GSH) levels.

Table 1: Animals grouping and drug administration

Groups	Treatment	Duration
Group1 (positive control)	No treatment	One day to 30 days
Group2 (negative control)	Methylglyoxal	Once daily for 30 days
Group3 (first treated)	Magnesium + methylglyoxal	Once daily for 30 days
Group4 (second treated)	Magnesium + Q10 + methylglyoxal	Once daily for 30 days

Also, the body weight and physical activity of the animals were evaluated.

Statistical Analysis
Data were expressed as Means ± standard deviation (SD) of samples, and further analysis was done using the Kruskal Wallis test, with statistical significance set at $p \leq 0.05$.

Results and Discussion

Table 2 shows a significant increase in the AST levels in the negative control group (methylglyoxal) after the 1st and 2nd sampling (draw 1 and 2) on days 10 and 30, respectively, indicating the effects of methylglyoxal on the AST enzyme. The activities of ALT and AST, as well as the amounts of pyruvate and extracellular glucose content, are significantly affected by active carbonyl compounds from studies.[19] While in the first treatment group from the second sampling (day 30), there were increased levels of the AST enzyme with the administration of Mg. Magnesium (Mg^{2+}) is a vital mineral for human health. It is known to regulate glucose homeostasis and insulin activities[20] and is shown to affect the expression of methylglyoxal in the experimental animals in our study. In a study, after four weeks of treatment of rats with CoQ10, it was shown that CoQ10 substantially reduced the spike of liver markers (LDH, AST, and ALT) produced by Acrylamide ($p<0.05$).[21] Table 3 shows a few changes in the ALT level in the negative control, which may be due to the short period of the study and fewer dosing. Some research shows that alterations in ALT levels require a more prolonged methylglyoxal exposure or a larger dosage.[10] There was an increase in ALT and AST plasma levels, while there was GSH depletion by methylglyoxal in the liver. It has been shown that methylglyoxal caused considerable cell damage in hepatocellular carcinoma HepG2.[22] Table 4 shows a significant change in ALP levels between the negative control and the treated groups. This is suspected to result from the injection of methylglyoxal. However, the administration of Mg^{2+} alone appears to have little or no effects on ALP levels but was significantly enhanced by the co-administration of CoQ10. CoQ10, an antioxidant, is found in the inner mitochondria membrane and helps transport electrons from complexes I and II to complexes III in the mitochondria respiratory chain. In the process, energy is provided for intracellular proton transfer. Table 5 demonstrates an increase in uric acid levels in the negative control group after ten days of administration with methylglyoxal. There was, however, no significant difference in its value after 30 of administration. Saleh *et al*. found that accumulation of methylglyoxal can cause nephrotoxicity in rats.[21] Table 6 shows a change in SOD levels after ten days and the effect of methylglyoxal on the SOD enzyme with an increase in the amounts as treatment time increases. We observed a clear improvement in the second treated group with sampling on day 30, which may be due to the antioxidant effect of CoQ10. CoQ10 is essential for maintaining cellular redox balance.[23] Table 7 reveals an increase in glutathione concentrations, indicating the enzyme's activity in protecting the cell from the oxidative effects produced by methylglyoxal. For example, eliminating toxic compounds is considered a strategy for developing salt stress tolerance in plants. The antioxidant system and glyoxalase system against ROS detoxify MGO.[24]

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Table 2: The AST levels

Blood sample (Time)	AST in U/L.				P value
	Positive control	Negative control	First treated	Second treated	
0 (1 day)	49.89 ± 11.14	46.7 ± 13.85	64.748 ± 28.45	61.65 ± 10.03	-
1 (10 days)	50.84 ± 14.33	46.81 ± 11.31	31.55 ± 22.25	40.78 ± 6.41	0.043
2 (30 days)	56.34 ± 15.73	92.46 ± 24.78	33.91 ± 11.30	44.16 ± 15.73	0.013

Table 3: The ALT levels

Blood sample (Time)	**ALT in U/L.**				**P value**
	Positive control	**Negative control**	**First treated**	**Second treated**	
0 (1 day)	77.247 ± 15.65	61.41 ± 16.16	86.15 ± 20.59	82.46 ± 13.51	-
1 (10 days)	66.07 ± 10.97	63.27 ± 14.64	51.21 ± 8.04	54.97 ± 11.33	0.003
2 (30 days)	82.73 ± 20.33	81.821 ± 15.72	61.15 ± 2.08	57.55 ± 9.19	0.001

Table 4: The ALP levels

Blood sample (Time)	**ALP in U/L.**				**P value**
	Positive control	**Negative control**	**First treated**	**Second treated**	
0 (1 day)	22.307 ± 4.48	24.19 ± 15.88	27.29 ± 14.23	28.91 ± 18.79	-
1 (10 days)	41.805 ± 14.63	27.7 ± 14.37	39.98 ± 13.048	26.041 ± 15.67	0.953
2 (30 days)	27.285 ± 13.38	48.29 ± 14.84	24.72 ± 4.97	29.096 ± 9.07	0.048

Table 5: The uric acid levels

Blood sample (Time)	**Uric acid in mg/dL.**				**P value**
	Positive control	**Negative control**	**Negative control**	**Second treated**	
0 (1 day)	0.16 ± 0.082	0.134 ± 0.037	0.134 ± 0.037	0.196 ± 0.016	-
1 (10 days)	0.2375 ± 0.063	0.151 ± 0.32	0.151 ± 0.32	0.22 ± 0.11	0.017
2 (30 days)	0.188 ± 0.051	0.173 ± 0.067	0.173 ± 0.067	0.197 ± 0.115	0.045

Table 6: The SOD levels

Blood sample (Time)	**SOD in U/L.**				**P value**
	Positive control	**Negative control**	**First treated**	**Second treated**	
0 (1 day)	4.48 ± 2.58	8.23 ± 2.91	4.29 ± 2.16	3.20 ± 2.43	-
1 (10 days)	2.21 ± 2.27	14.30 ± 2.58	5.46 ± 2.41	9.13 ± 6.85	0.025
2 (30 days)	4.29 ± 2.83	17.38 ± 2.89	110.02 ± 26.94	56.42 ± 16.27	0.034

Table 7: The glutathione levels

Blood sample (Time)	**Glutathione in ng/ml.**				**P value**
	Positive control	**Negative control**	**First treated**	**Second treated**	
0 (1 day)	1.510 ± 0.278	2.292 ± 0.328	1.436 ± 0.059	1.73 ± 0.254	-
1 (10 days)	0.122 ± 0.017	0.122 ± 0.015	0.379 ± 0.037	1.16 ± 0.175	0.033
2 (30 days)	0.139 ± 0.042	0.125 ± 0.018	0.15 ± 44.22	2.239 ± 1.855	0.01

The results were analyzed using the Kruskal test due to the randomized and small population of the specimens. The results show a change in the oxidative system in the first and the second treatment, and p-values appear significant after the first and second withdrawal. There was also an improvement in AST levels, which means that the antioxidant (CoQ10) influences methylglyoxal metabolism, which affects the redox system, and this enzyme is vital in the respiratory chain. When CoQ10 enters the respiratory system, it supplies the cells with energy through electron transport from the protein I unit (NADH dehydrogenase) to the protein II complex (succinate dehydrogenase) and also from complex II

to complex III (bc1 complex).[11,25] Farsi *et al*. previous study indicated that receiving a daily dose of 100 mg CoQ10 resulted in a considerable reduction in hepatic aminotransferases AST.[26] Maheshwari *et al*. reported that Magnesium oxide has no antioxidant effect.[27] However, most studies on Magnesium oxide show only antibacterial and antifungal activity.

The increase in uric acid at second withdrawal in the second treated rabbits group may be due to resistance to methylglyoxal or an increase in their appetite. In the treatment with Q10 and Magnesium, we observe that the stimulation of glycolysis may be due to increased oxidative stress.[27] The coenzyme Q10 alone resulted in a considerable decrease in uric acid levels (table 5). Furthermore, in the case of SOD from the first withdrawal, there was an increase in its concentration. The MGO can react with the metalloenzyme superoxide dismutase 1 (SOD1), causing the loss of enzymatic activity. Polykretis *et al*. demonstrated that glyoxal, another strong oxidizing dialdehyde capable of forming AGEs, may combine with SOD1 to produce persistent adducts due to the liberation of the positive charge from the Cu, Zn-SOD1 catalytic site.[28]

The results show a change in antioxidant enzyme level. Especially in the second withdrawal, due to the glyoxalase pathway primarily responsible for MGO detoxification. The above phase started with the complex formation of MGO with glutathione (GSH), obtaining a hemithioacetal product, which is then transformed into D-lactate and GSH by the glyoxalase enzymes. As a result, glutathione will enhance as methylglyoxal levels rise.[29] Some researchers show that using antioxidants in the diabetic group did not significantly affect blood glucose levels in the treated groups. The impact of antioxidants in lowering blood glucose levels may vary depending on the amount and duration of therapy with antioxidants.[30]

Conclusion

Methylglyoxal is an oxidizing agent that can react with macromolecules like proteins. Using antioxidants and metal ions can prevent the toxic effects of methylglyoxal. Therefore, using antioxidants in this study improved liver and antioxidant enzymes such as SOD and glutathione levels to resist oxidative overload. On the other hand, there was no significant effect on uric acid levels due to insufficient antioxidants in the blood. However, using antioxidants combined with metal ions can prevent the influence of methylglyoxal.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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