



Effect of Grape Seed Extract in Minimizing the Harmful Effects of Monosodium Glutamate on the Chicken Embryonic Retina to Show Scientific Miracles In the Holy Quran

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Authors' contributions

This work was carried out in collaboration between both authors. Author FAG designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author NAH managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

In 1969, a Canadian laboratory announced that its studies on synthetic alkaline (cyclamate) proved to be a carcinogen despite its use for more than twenty years in the beverage industry. There are many additives that have raised the controversy about the large extent of safety to consumers and the most famous controversy and consumption is the article of monosodium glutamate (MSG) which touched research on the negative impact on samples of research experiments. This research aims to study the effect (MSG) on the formation of retina in chicken embryos and the potential improvement effects of GSE grape seed extracts during incubation as part of the solutions provided in the event of the long term use of MSG and its accumulation in the body Human. The experimental groups were divided into 4 groups based on the injection period and the injected substances. The first control group (Injected with saline), the second group, treated with MSG, the 3rd group were treated with Monosodium glutamate and grape seed extract at days 0,1 of incubation, whereas the 4th group, was treated with MSG and then the GSE (M – G) were given

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at 3,4 days post MSG . The effect of the experimental materials on the development of the retina at the age of 14 was investigated in the current work. The results showed that the treatment of embryos with MSG dose (0.1 ml) caused many of the abnormalities at the level of tissue formation of the retina, and after the treatment of the fetus with GSE was noted to reduce the damage to the tissue of the retina. The results showed that the treatment of embryos with MSG dose (0.1 ml) caused many of the abnormalities at the level of tissue form of the retina, and after the treatment of the fetus with GSE was noted to reduce the damage to the tissue of the retina.

Keywords: Chick embryo; Monosodium Glutamate; retina; grape seed extract; developed.

1. INTRODUCTION

The use of herbal medicine represents a long history [1-3]; medicinal plants have also been widely used as medicinal and aromatic plants since ancient times [4]. There is no doubt that the modern food industries facilitated the diversity of food and availability and conservation of damage in different seasons of the year, we find that winter crops are available in the summer and spring crops are in winter, in addition to the export of foods in international trade, which requires the addition of medicinal plant extracts as food supplements to the different food products. Some of the external materials to be homogenized with the food content, whether to preserve or improve its taste. These materials are known as food additives, and with the continued technological progress in the field of food manufacturing, the number of approved additives has increased because of the multiple properties, chemical additives for food has become very large in number.

Since 1987, a certain percentage has been determined for each category of additives on a global scale, allowing consumption per person per day, but this is not enough for several reasons: The dose and its relationship to sensitive groups in society, such as children, pregnant women and the elderly, remain a neglected point when discussing the effects of chemical additives. Second, Some food labels do not specify the percentage of chemical additives in the food category and the maximum allowable intake of these chemical additives. Third, the amount of the dose consumed is one of the most important factors to reduce the risk of use. The consumer consumes many processed food products in his daily life, and the problem is not in the use of these substances or others, but the problem is the focus used and repeated use in a day, which may make the dose beyond the safe limit of health enters the body. A large amount of these substances leads to accumulation in the body beyond the safe limit.

In addition, the harmful effect of some additives may appear only in the long run, as in 1969 when a Canadian laboratory reported that its studies of the local chemical (cyclamate) proved to be a carcinogen despite its use for more than twenty years. For many years, food additives had important roles in many types of food. Our ancestors used raw materials as food additives. They used the salt as a preservative substance for meats, also they used some herbs and spices to get a better flavor of foods. Today, people prefer food that is rich in flavor and color. The advances in food technology and food additives made that easy. There are a lot of food additives used to prepare food [5]. Food additives are widespread in industrial French products and some clusters of additives frequently co-occurring in food products were identified. These results pave the way to future etiological studies merging composition data to food consumption data to investigate their association with chronic disease risk, in particular potential 'cocktail effects'[6].

The effects of food additives may be immediate or health risk in the long term of constant exposure. Sometimes immediate effects include headaches, change in energy levels, alteration in behavior, and immune response. Long-term effects of some food additives had been linked to increased risk of cancer [7,8].

One of the most famous chemical substances added to the food is called MSG, which has caused widespread debate among consumers, researchers and scientists about how safe it is for human health, So it was necessary to search for practical solutions that accompany the use of food additives and limit their effects, and when we look at the research available to us, we found that it is limited to the prevention of the impact of MSG on the tissues of rats and adult mice without addressing the protection of tissues of the fetus during the period of composition despite the MSG can cross the placenta and reach the fetus. [9;10;11]. Hence the idea of this research is

to find alternative solutions that have health benefits in the protection of fetal organs and at the same time be accessible to all categories of consumers, through the development of therapeutic mechanisms to mitigate the effects of harmful MSG on the organs of the fetus. Monosodium Glutamate (MSG) is one of the most common food additives. Several studies revealed that MSG has a toxic effect on fetal development/fetus, children, adolescents, and adults. Physiological complications associated with MSG toxicity are hypertension, obesity, gastrointestinal tract troubles, and impairment of the function of the brain, nervous system, reproductive, and endocrine system [12].

After referring many researches, we found that the fruit of grapes is consumed globally with large quantities and has different biological functions due to the components of polyphenols, which are mostly in the seeds of grapes by 60-70% and in the crust by 30%, the grapeseed contains 5% to 8% of its weight [13]. Besides, grapes were mentioned about 11 times in the Holy Book. For these reasons, grape seeds were selected as a study. The samples of chicken embryos were used generally for carrying out such experiments due to their availability with low costs, requires short incubation period and the fact that the chicken embryos of the laboratory animals good for accurate determination of the age of the fetus, and to facilitate the incubation of embryos within the laboratory and access to various genetic stages [14]. The retina was selected for study among the fetus members, for several research consensus on the retinal effect of MSG [15;16;17;18]. Although MSG and grapefruit have been studied by many researchers, the new study in this paper is to study the potential improvement effects of GSE in reducing the adverse effects of MSG on the retinal tissue structure of chicken embryos and to show the scientific miracle in this blessed fruit.

2. MATERIALS AND METHODS

2.1 Materials

Fertilized chicken eggs were obtained from Fakieh Poultry Farms. Monosodium Glutamate (MSG) was purchased as a powder from Al-Mizani medical corporation – Saudi Arabia, with a 0.1-millimeter dose [15] and Grape Seed Extract, obtained from GNC - Makkah Al Mukarramah - Saudi Arabia and used 0.3 ml according to [19].

2.2 Experimental Design

The eggs of the fertilized chicken were divided into four main groups, each containing 10 fertilized eggs that were injected once with 0.1 ml of the MSG solution (0.75mg MSG/gm. egg weight) in the air chamber before incubation.

1 - Control group: injected with 0.1 ml of distilled water during the first week of incubation in the following days (0, 1).

2 - Treated with monosodium glutamate: It was injected twice with 0.1 ml of MSG solution in the air chamber during the first week of incubation in the following days (0, 1).

3-Group treated with Monosodium glutamate and grape seed extract together: It was injected twice with 0.1 ml of MSG solution and GSE with 0.3 in the air chamber during the first week of incubation in the following days (0, 1).

4 - The group treated with MSG and then the GSE (M – G): it was injected with MSG per day (0, 1) and then injected with GSE in the following days (3, 4) (therapeutic group).

The air chamber was set in the wide part of the egg and the eggs were divided into work groups and data to the groups were written. The wide segment was sterilized and two holes were made in the wide part of the eggshell using a sterile pin [20], the groups were injected with extract or distilled water and then the holes were closed using small pieces of paraffin wax. The eggs were incubated at a temperature of 37.5°C with the special placement of eggs so that the wide part of the egg containing the air space to the top and the part of the point down. The growth process was followed through the optical examination (Fig.1).

2.3 Statistical Analysis

The mal formation in the embryos was detected by visual examination and photographed by digital camera, where as the histological examination was performed by fixing of retina in formalin(10%), processed as general technique, then stained by H&E stain. Statistically, One-way analysis of variance (ANOVA) and the Student's t-test were used, in addition to a stepwise multiple comparisons procedure was used and also we used post hoc test whenever

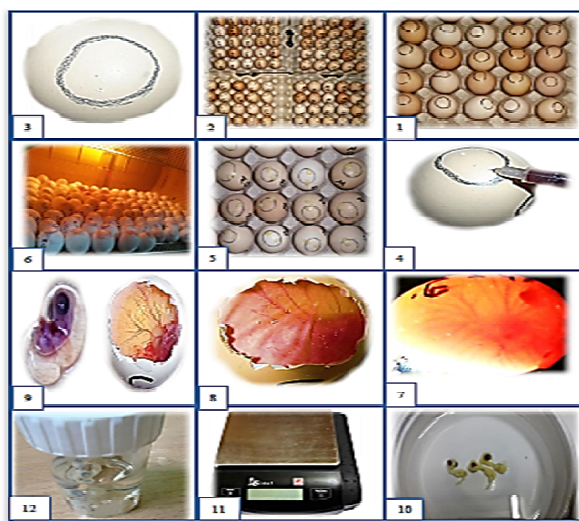


Fig. 1. The steps of the research experiment

a significant difference between three or more sample means has been revealed by an analysis of variance (Anova). Values were expressed as means \pm SE. The level of significance was set at $p < 0.05$. All statistical methods were performed by SPSS version 23.

3. RESULTS AND DISCUSSION

3.1 Congenital Malformations

The fetal examination reveals that there are clear congenital abnormalities in several embryos in the MSG treated group, which is a lack of eye, a complete congenital malformation of the fetus, a hernia in the viscera, deformation of the bones of the neck and limbs, small size of the fetus and delayed development (Fig. 2).

Al-Qudsi F, Al-Jahdali A. [21] reported that the treatment of chicken embryos with MSG caused many congenital malformations such as delayed development and bleeding under the skin at the age of 7, 10, and 14 years of incubation and abdominal hernias on days 7 and 10. Most congenital malformations of the 10th age of incubation, such as brain deformity, were seen as only one sample and deformation of the fetus's beak.

In a study conducted by [22] to investigate the effect of (MSG) on embryonic development in zebrafish, the acute toxicity of MSG was performed for 4 days and zebrafish eggs were injected with ten different concentrations of MSG. The results of the study indicated that at low concentrations Of MSG such as 10,30, 50 mg no

mutations in embryonic development were observed, and with increased MSG, various abnormalities occurred in the zebrafish embryo and at high concentrations such as 100, 150, 200, 250, 300, 400, 500 mg, and these abnormalities were delayed growth, shrinkage of the placenta, edema of the sacral sacrum, absence of pigmentation in the fetus's body, the tail.

The cause of malformations in MSG groups is due to the toxic effect of MSG on the fetus's body. [23] reported that MSG treatment disrupts the endocrine function responsible for regulating many biologic processes including metabolism. This disruption may play a role in causing deformities, including skeletal deformities, as supported by [24] where excessive use of MSG can cause metabolic disorders and biological deformities in embryonic development. The ability to cause damage to the endocrine function may be a cause of this occurrence of teratogenicity results and disrupt vital processes in the body.

The adverse effects of toxicity caused by high levels of glutamate have shown a blockage of the central artery, and the disappearance of one or both eyes may be due to the central artery occlusion of the eye [25]. It may be due to MSG's ability to induce oxidative stress [26,27] reported that embryos have a high level of O_2 consumption, making them susceptible to oxidative damage. [28] added that oxidation is a cause of congenital malformations and that the free radicals created by this oxidation may

originate from fetal metabolism or surrounding areas. Correspondingly, there were no abnormalities in the treatment group (MSG-GSE). This is consistent with [29] noting that the extract of grape seeds and folic acid is a protective factor against fetal abnormalities resulting from the use of azathioprine. The treated embryos (with artificial sweeteners; one of the food additives) were hemorrhage, abnormal brain development, growth retardation, and abnormal eye development(4). [30] and [31] added that congenital malformations caused by experimental diabetes can be prevented by antioxidants such as vitamin C and E.

3.2 Body Growth Parameters

3.2.1 The weight

There was a significant decrease in the weight of the fetus in the group treated with MSG where the mean difference of body weight was greater and showed a significant difference from the mean body weight in the control sample where $P = .002$ and the average difference between them

is 4.230, while no significant differences in the weight of other groups was observed (Table 1; Fig. 3).

3.2.2 The length

There were no significant differences in the length of embryos in experimental groups (Table 2; Fig. 3). Note that there is a significant decrease in the length of the beak in the group treated with MSG where $p=0.011$ and the difference between the mean of this group and the control sample is 0.132, and no significant differences in the length of the embryo in other groups (Table 3).

3.2.3 Neck length

There was a significant decrease in the length of the fetal neck in the MSG-treated group where $P = 0.015$ and the mean difference was 0.158. There is also a significant increase in the length of the fetal neck in the common group (M+G) where $P = .003$ and the difference between the averages is -1.96 (Table 4).

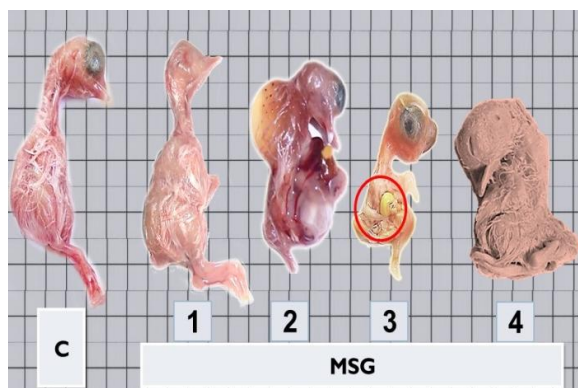


Fig. 2.The disorders that appeared at the age of 14 days:1- The disappearance of the eye. 2- Complete deformation of the shape of the fetus. 3- Hernia in the abdomen, Small size of the fetus. 4- Deformation in the limbs and neck



Fig. 3. The effect of experimental materials (GSE/MSG) on fetal weight and length at 14 days

Table 1. The statistical analysis of mean difference between groups in weight of embryos per gram

The weight	(I) groups	(J) groups	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
						Lower Bound	Upper Bound
		MSG	4.230 [*]	1.338	.002	1.595	6.865
		MIX	1.050	1.338	.433	-1.585-	3.685
		M - G	.880	1.338	.511	-1.755-	3.515

Table 2. The statistical analysis of the mean difference between groups in length of embryos per centimeter

Total length	(I) groups	(J) groups	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
						Lower Bound	Upper Bound
		MSG	.120	.335	.721	-.540-	.780
		MIX	.138	.335	.681	-.522-	.798
		M - G	-.282-	.335	.401	-.942-	.378

Table 3. The statistical analysis of the mean difference between groups in the length of the beak in centimeters

Length of beak	(I) groups	(J) groups	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
						Lower Bound	Upper Bound
		MSG	.132 [*]	.052	.011	.031	.233
		MIX	-.034-	.052	.510	-.135-	.067
		M - G	.074	.052	.152	-.027-	.175

Table 4. The statistical analysis of the mean difference between groups in neck length in centimeter

Neck length	(I) groups	(J) groups	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
						Lower Bound	Upper Bound
		MSG	.158 [*]	.064	.015	.031	.285
		MIX	-.196 [*]	.064	.003	-.323-	-.069-
		M - G	-.052-	.064	.420	-.179-	.075

3.2.4 Beak length

It is clear from the statistical studies conducted for morphological properties (Weight, length, length of beak, neck length) that the group treated with MSG alone was very detrimental to fetal organs, while the group treated with grape seed extract had no detrimental effects on fetal organs. For MSG damage on the weight of the fetus, a significant decrease was revealed in the control sample, which was in agreement with [32] that showed the administration of MSG (4 mg/g body weight) under the skin in newborn rats on day 2, 4, 6, 8, 10 led to a decrease in the weight of treated rats.[21]reported that MSG-treated embryos showed less weight than the control

group. [33] reported that treating rats with MSG daily oral doses of 30 and 60 g/kg bw for two months caused a significant increase in the weight of the mouse body.

The results of the present study showed that there was a significant decrease in the length of the beak and the length of the neck that agreed with [21], where there was a decrease in the diameter of the eye on day 10-14 of the incubation. The neck appeared shorter in the MSG group than in the control group.

The embryos treated with MSG had a small size. This is indicated [34], who reported that the treatment of embryos with MSG leads to small

embryos, as pointed out by [25] who reported that embryos injected with MSG are unable to obtain adequate food which leads to the inability of cells to grow and divide efficiently and fast enough. In addition, [35] and [12] reported that increased glutamate had a toxic effect on the hypothalamus, resulting in decreased growth hormone in the body, thus affecting fetal growth and reproduction of cells.

As for the therapeutic effect and improvement of GSE and reduction of MSG damage, we agree with this [36]. It was reported that rats with diabetes developed with STZ resulted in a decrease in body weight and after treatment with GSPE they were able to increase body weight and restore it. [37] also noted that the biologically active ingredients in grapes inhibit a wide range of chronic disorders associated with metabolic syndrome. GSE prevents oxidative stress [38]. Several studies have also indicated that melatonin, an antioxidant, plays an important role in regulating the growth hormone secretion in the body through its effect on the area of the thalamus in the brain and inhibition of the hormone peptide Somatostatin [39;40].

3.3 Histological Studies

3.3.1 Effects on the thickness of the retina in chicken embryos

The results of the analysis of the thickness of the retina for the experimental groups, which were compared with the control sample, are as follows:

There was a significant decrease in the thickness of the retina in the MSG treated group, where the statistical significance was $P = 0.000$ and the difference in mean was 0.422, while the joint group (M + G) gave a statistical significance value of $P = 0.000$ and the mean difference between the control sample, was 573 *, and there were no significant differences in retinal thickness in the treatment group (Table 5).

3.3.2 Effect on retinal tissue in chicken embryos

An examination of the cross-sections of eye Retina (R) in 14-day chick embryos in group treated with MSG showed the thickness of the Neural Retina (NR). Note that in the layer of rods and cones (R & C)1 and Inner nuclear layer (I.N.L)4 have less condensed cells with many spaces between the cells. Henle's membrane seemed to be disintegrated, Inner

plexiform layer (I.N.P) has very few widely dispersed fibers, Ganglion Cell layer (GCL), and Nerve fibers layer (N.F.L) increased compared to the control (Fig. 5).

The histological examination of groups treated with grape seed and monosodium glutamate showed that the cells began to regain their shape and the relative convergence of total retinal fish.

Tamás A. [16] agreed that the treatment of the retina with MSG resulted in severe degeneration of the retinal layers, where the thickness was equal to half the thickness of the retinal layer, and the emergence of the internal nuclear layer (INL), Inner plexiform layer (IPL) was not distinguished.

Moustafa KA, Okasha EF. [41] reported several retinal tissue changes caused by MSG treatment, including the dissociation of the PE layer, distortion, and irregularity of the photoreceptors. The degeneration of the cells of the inner nuclear layer and (G.C.L) Ganglion cells layer, the expansion and congestion of some blood vessels, and a statistically significant reduction in retinal thickness were observed.

A Japanese study concluded that a high-MSG diet for several years may increase the concentration of glutamate in the vitreous body, destroying cells in the retina. [42], and [43] suggest the reason may be that MS affects the structure and function of the retina due to the presence of glutamate receptors in most layers of the retina. High glutamate disrupts the systemic blood barrier to enter the retina, to prevent polarization, thereby motivating cell death.

An improvement was observed in the form of the tissue in GSE grape seed groups. The tissue began to regenerate its tissue form, where the degeneration of the internal nuclear layer (I.N.L), and the disappearance of the gaps in (I.P.L), and the cells regained their relative form in (G.C.L).

Sun Y. [36] reported that early treatment of GSPE may protect the retina from diabetic retinopathy by reducing cellular oxidation induced by oxidative stress by activating the Nrf2 pathway, which is responsible for protecting retinal cells from programmed cell death. The rate of programmed cell death was significantly increased in the diabetic group. After retinal treatment with GSPE, the rate of cellular death in retinal cells was observed. Several research

studies have also demonstrated the ability of Proanthocyanidin to protect nerve cells from the damage; it may be caused as a result of several diseases.

Treatment of ssdRGC-5 cells with B/G increased intracellular ROS and induced apoptosis (not

necrosis) with increasing caspase-3 activity. GSE rescued the ssdRGC-5 cells from oxidative stress-induced cell death by inhibiting both intracellular ROS production and caspase-3 activation.: GSE had a neuroprotective effect against oxidative stress-induced apoptotic death in ssdRGC-5 cells [44].

Table 5. Statistical analysis of the mean difference between groups in the thickness of the retina

Thickness Retina	(I) groups (Ctrl)	(J) groups	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
						Lower Bound	Upper Bound
		MSG	.422	.055	.000	.313	.531
		M+G	.573	.055	.000	.464	.682
		M - G	-.002-	.055	.971	-.111-	.107

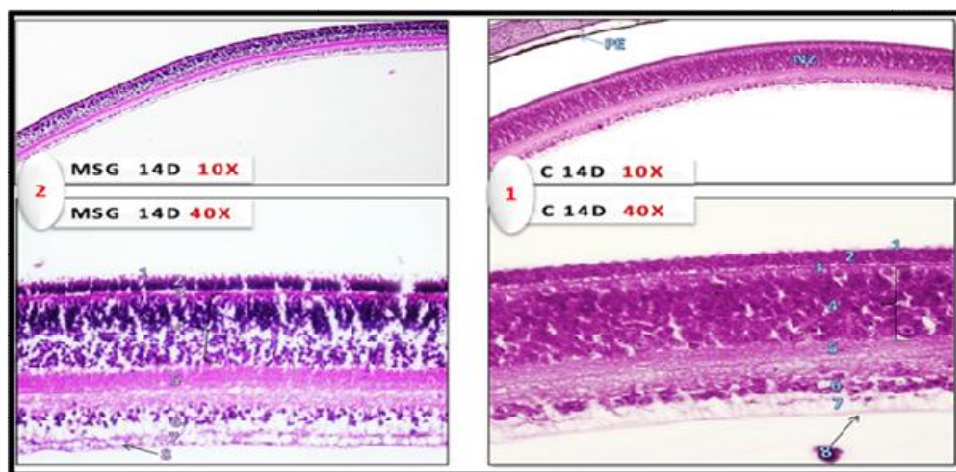


Fig. 4. Histological sections of chick embryo retinas. (10 X - 40X, H&E.)

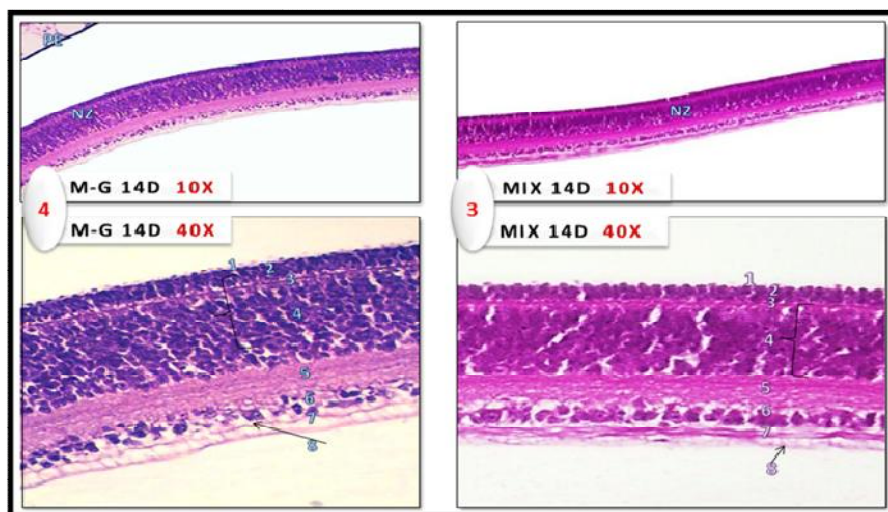


Fig. 5. Effect of retinal tissue in chicken embryos

This enhanced ability to reduce MSG damage is due to the inclusion of grape seeds in the active compounds with vital effects. They contain high concentrations of phenolic compounds known as polyphenols. These antioxidants can influence various pathological processes by the free radicals through the ability to access the cellular components (mitochondria - nucleus) with the chemical activity in the cell, where the active compound is proanthocyanidin [45;46], which has significant physiological effects, and has an antioxidant effect that is 20 times stronger than vitamin E and C [47]. Braanthocyanidine also inhibits the process of lipid peroxidation and membrane protection from oxidative damage through direct association with roots Free and inhibition of xanthine oxidase enzyme leading to a reduction of active root formation [48].

GSE revealed significant improvement in the oxidative stress markers and then the histological and morphometric picture of the cerebellum. GSE has a neuroprotective effect on the cerebellum of VPA treated rats through its potent antioxidant effect [49]. MSG decreased testosterone hormone levels and elevated oxidative stress markers [50].

- (1) Control 14 day, show the outer pigmented layer (PE) and the inner Neural layer (N.L) of the retina which is formed of 8 layers:
 1. External limiting membrane (E.L.M)
 2. layer of rods and cons (R & C)
 3. Henle's membrane (H.M)
 4. Inner nuclear layer (I.N.L)
 5. Inner plexiform layer (I.P.L)
 6. Ganglion cells layer (G.C.L)
 7. Nerve fibers layer (N.F.L).
 8. Internal limiting membrane (I.L.M).
- (2) Group treated with MSG. Note that in the layer of rods and cons (R & C)1 and Inner nuclear layer (I.N.L) 4 have less condensed cells with many spaces between the cells. Henle's membrane seemed to be disintegrated, Inner plexiform layer (I.N.P) has very few widely dispersed fibers, Ganglion Cell layer (GCL), and Nerve fiber layer (N.F.L) increased compared to the control.
- (3) Group treated with MSG + GSE. It shows that the retina consists of two main layers, the outer pigmented layer (PE) and the inner Neural layer (N.L), which consists of 8 layers as in the control sample, is observed in this

group improvement in the form of cells. It is also noticed that the total thickness of the retina is less compared to the control group with a difference in the layer of nerve fibers (7) which appear less thick.

- (4) Group treated with MSG then GSE. It shows that the retina consists of two main layers, the outer pigmented layer (PE) and the inner Neural layer (N.L), which consists of 8 layers as in the control sample, we observe a relative affinity in the total thickness of the retina with the control group.

4. CONCLUSION

It is known to us that several pathways contribute to damage in the eye, including oxidation and cellular death. The compounds derived from grape seeds, such as Brauanthocyanidin, have the ability to prevent the proteins that mediate these pathological processes, through the following:

-Prevent the enzymes associated with oxidation to become overactive and include these enzymes Xanthine and catalase oxides; help protect cell membranes from free radical damage; reduced levels of O₂ interactivity in the blood; reduced fat oxidation (fat peroxide).

The effect of GSE on the harmful effects of MSG has been demonstrated. This therapeutic effect adds to many of the benefits of the miracle grapefruit, which is mentioned in 11 topics in the Holy Quran, Through our results, we recommend more research studies to study the therapeutic and preventive effects of grape seeds using different doses and time periods.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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