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RESEARCH ARTICLE

Moringa oleifera Ethanolic Extract Prevents Oxidative Damage on Lens Caused by Sodium Valproate Used in Epilepsy Treatment

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ABSTRACT

Objective: Valproic acid/valproate (VPA) is an antiepileptic agent that is structurally a short-chain fatty acid. It triggers the generation of reactive oxidants that can affect lens tissue. *Moringa oleifera* Lam. is a prevalent plant that grows in Asia, Africa and South Africa. The plant has anti-inflammatory, hepatoprotective, nephroprotective and cardioprotective activities.

Materials and Methods: The effect of 70% ethanol extract of the *Moringa oleifera* leaves was examined on VPA-induced lens tissue damage in this study. Experimental rats were grouped into four: the control (C), *Moringa* extract (M), VPA, and VPA+M group. M extract and VPA respectively were administered orally at a dose of 0.3 and 0.5 grams per kg body weight daily for fifteen days. The lens tissues of the rats were taken after sacrifice. Oxidative stress markers including glutathione, lipid peroxidation, and advanced oxidation protein products levels, glutathione reductase, glutathione peroxidase, glutathione-S-transferase, and superoxide dismutase activities, total oxidant status, total antioxidant status, reactive oxygen species, nitric oxide levels and aldose reductase and sorbitol dehydrogenase activities were determined.

Results: Tissue homogenates showed a significant decrease in glutathione and total antioxidants, as well as an altered activity of superoxide dismutase and glutathione-related enzymes in VPA groups. Moreover, a significant rise in the concentration of nitric oxide, reactive oxygen species and total oxidants, coupled with higher aldose reductase and sorbitol dehydrogenase activities were detected. In contrast, changes in the levels of these parameters were offset in the VPA+M group by *Moringa* extract.

Conclusion: This suggests that *Moringa oleifera* leaves are an excellent nutritional composite for mitigating the damaging properties of VPA.

Keywords: Antioxidant enzymes, Lens, *Moringa oleifera*, Oxidative damage, Valproic acid.

INTRODUCTION

Valproic acid/valproate (VPA) is a broad-spectrum agent effective against generalised seizure and other related forms of neurological disorders. It is structurally a short-chain fatty acid. Despite its efficacy and wide acceptance/usage, the administration of VPA is accompanied by a wide range of adverse drug reactions and toxicity. The generation of non-reduced reactive intermediates, reactive oxygen species, as well as peroxides are implicated to be the primary causes of VPA-induced oxidative stress. These intermediates destabilise antioxidant status, deplete glucuronide and CoA levels, disrupt beta-oxidations, and hinder mitochondrial function as well.[1] In addition to the pancreas,[2] heart,[3], intestine,[4] brain,[5] liver,[6] kidney[7] and lungs[8], the functionality of lens tissue is also shown to be affected by VPA.[9] Therefore, the significance of any food-based substance capable of mitigating the deleterious effect of VPA upon co-administration cannot be over-emphasized.

Moringa oleifera Lam. (Drumstick or Horseradish) is nicknamed 'the miracle tree' due to its diverse and multipurpose benefits. The plant is indigenous to Asia, Africa, and South America-regions where epilepsy remains endemic. The leaves of *Moringa oleifera* are rich in vitamins such as vitamin A (as β-carotene), vitamin B, and vitamin C. More so, reasonable concentrations of zinc, calcium, copper, iron, magnesium, and potassium are found in the leaves.[10] Furthermore, studies have shown that *Moringa oleifera* possesses essential fatty acids and some rare essential oils. Besides these, quercetin, kaempferol and myricetin are the conspicuous flavonoids identified in the plant leaves.[11] In addition to enzyme inhibition action,[12] leaf extract of *Moringa oleifera* is verified to

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have antioxidant,[13] and anti-inflammatory action.[14] It protects hepatocytes,[15] nephrone,[16] cardiac tissue,[17] and has wound healing effects.[18] Therefore, can be meritoriously engaged in the treatment of multifarious complications and devoid of the fear of toxicity. In the current study, the action of *Moringa* extract against VPA-induced toxicity on the lens tissues of Sprague Dawley rats was investigated.

MATERIALS AND METHODS

Collection and Preparation of Plant Sample

Plant samples were collected, identified, and prepared as earlier reported.[12] Briefly, powdered shade-dried *Moringa oleifera* leaves were extracted using 70% ethanol (Merck KGaA). After boiling and a clear Soxhlet siphon was obtained, the solvent was evaporated, and the residue was weighed and stored at -20°C.

Experimental Protocol

The research protocol (11.2020.mar) for the present experiment has earlier been published.[19] The female Sprague Dawley rats utilised were provided by the Experimental Animals Research and Implementation Centre of Marmara University. Under standard conditions, the rats aged 4-5 months were divided into four experimental groups as follows: The control (C; n=8), *Moringa* extract (M; n=8), VPA (n=15), and VPA+M (n=12) group. All treatments were given orally. *Moringa* extract and VPA (dissolved in normal saline) respectively were given at a dose of 0.3 and 0.5 grams per kg body weight daily for fifteen days. Overnight fasted animals were sacrificed on day sixteen, then lens tissues were collected and homogenised in ice-cold normal saline (at 10% w/v).

Biochemical Analysis

From the homogenates of lens tissue (10% w/v), standard methods were used to determine glutathione (GSH) levels,[20] lipid peroxidation level (LPO) from malondialdehyde (MDA) concentration,[21] the activities of sorbitol dehydrogenase (SDH),[22] aldose reductase (AR),[23] glutathione reductase (GR),[24] superoxide dismutase (SOD),[25] glutathione peroxidase (GPx),[26] and glutathione-S-transferase (GST).[27] The total oxidant status (TOS),[28] total antioxidant status (TAS),[29] concentration of reactive oxygen species (ROS),[30] nitric oxide (NO) levels,[31] advanced oxidation protein products (AOPP),[32] and total protein level[33] of the homogenate were also quantified.

Statistical Analysis

Analysis of variance (ANOVA) from the data expressed as mean ± standard errors (SEM) using GraphPad Prism software version 6.0 (San Diego, CA, USA). Tukey's multiple comparisons test was used to determine significant differences at $p<0.05$.

The effect of *Moringa* extract against VPA-induced toxicity on the lens tissues of Sprague Dawley rats was further identified by principal component analysis (PCA). This was executed using OriginPro 2022b version 9.95 (Northampton, Massachusetts, USA).

RESULTS

The effect of *Moringa* extract on lens GSH, LPO, and AOPP levels of experimental animals is presented in Figure 1. Statistical analysis revealed a substantial decrease in GSH of the VPA administered group when equated to control groups ($p<0.0001$). In contrast, levels of LPO, and AOPP were markedly amplified ($p<0.0001$ and $p<0.01$ respectively). *Moringa* extract mitigated these defects, keeping GSH, LPO, and AOPP levels of the VPA+M group to a near normal; the GSH level of the VPA+M group was above that of the VPA group ($p<0.0001$), while levels LPO ($p<0.0001$) and AOPP ($p<0.001$) are below that of VPA group.

GR, GPx, GST, and SOD activities are presented in Figure 2. Compared to the control groups, sole treatment with VPA caused a significant alteration in GR ($p<0.001$), GPx ($p<0.01$), GST ($p<0.001$), and SOD ($p<0.01$) activities. The activity of these enzymes in the VPA+M group was statistically higher than those of animals treated with VPA.

The TAS, TOS, ROS, and NO levels of the experimental animals' lens tissues are depicted in Figure 3. As observed from Figure 3, the TAS of the VPA administered group was below that of the control groups ($p<0.05$). However, its levels in the VPA+M group were significantly elevated ($p<0.0001$). On the other hand, TOS, ROS, and NO levels of the VPA group were statistically elevated as compared to the control groups ($p<0.0001$). These defects were however curtailed by concomitantly administering *Moringa* extract. Thus, resulted in higher levels of TAS ($p<0.0001$), as well as lower levels of TOS, ROS, and NO ($p<0.0001$) in the VPA+M group as against the VPA group.

Lens tissue AR and SDH activities are presented in Figure 4. The activities of both AR and SDH were remarkably elevated upon administration of VPA ($p<0.0001$ and $p<0.05$ respectively). These defects were significantly reversed upon co-administration of VPA with *Moringa* extracts ($p<0.0001$) in comparison to VPA.

PCA was used to prove the relationship among biochemical results for each group (Figure 5). PCA analysis revealed that the first two components detailed around 64.23% of the total variation in the experimental data (PC1: 64.23%, PC2: 15.59%). Primarily, in the first component, NO, ROS, AOPP, LPO, TOS, SDH, and AR were collected together. These collected data were highly negatively correlated with GSH, GR, GST, GPx, TAS and, SOD (Figure 5).

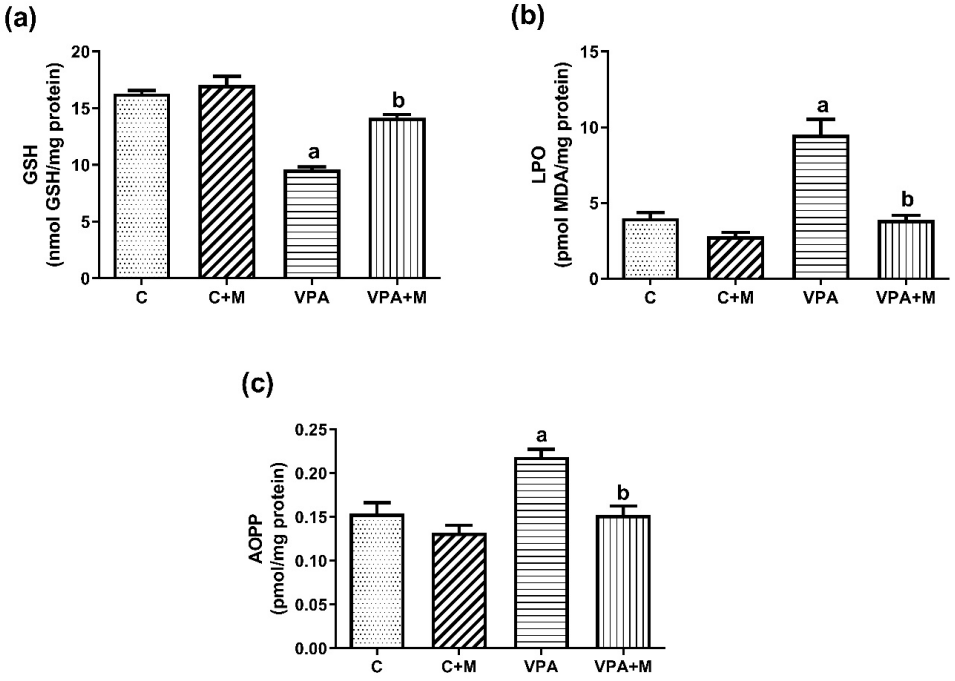

Figure 1. Effect of *Moringa* extract on lens tissue of experimental animals (a) GSH levels; ^{a}p<0.0001 vs. control; ^{b}p<0.0001 vs. VPA, (b) LPO levels; ^{a}p< 0.0001 vs. control, ^{b}p<0.0001 vs. VPA, (c) AOPP levels; ^{a}p< 0.01 vs. control; ^{b}p<0.001 vs. VPA. Values were given as mean and standard error. C: Control group; C+M: Control+*Moringa* extract group; VPA: Valproate group; VPA+M: Valproate+*Moringa* extract group.

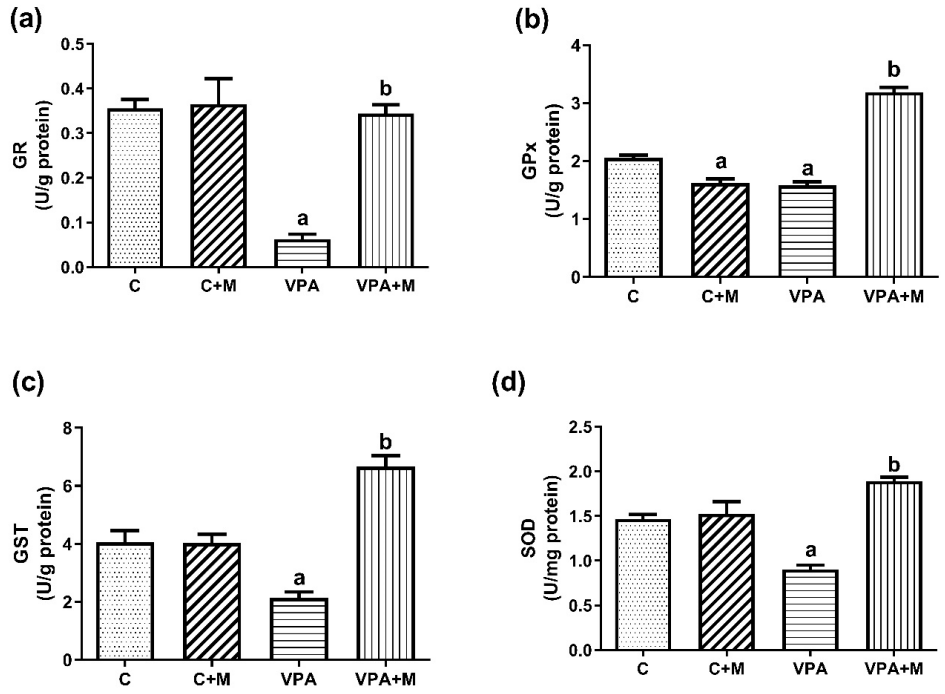

Figure 2. Effect of *Moringa* extract on lens tissue of experimental animals (a) GR activities; ^{a}p<0.001 vs. control; ^{b}p<0.0001 vs. VPA, (b) GPx activities; ^{a}p<0.01 vs. control, ^{b}p<0.0001 vs. VPA, (c) GST activities; ^{a}p<0.001 vs. control; ^{b}p<0.0001 vs. VPA, (d) SOD activities; ^{a}p<0.01 vs. control; ^{b}p<0.0001 vs. VPA. Values were given as mean and standard error. C: Control group; C+M: Control+*Moringa* extract group; VPA: Valproate group; VPA+M: Valproate+*Moringa* extract group.

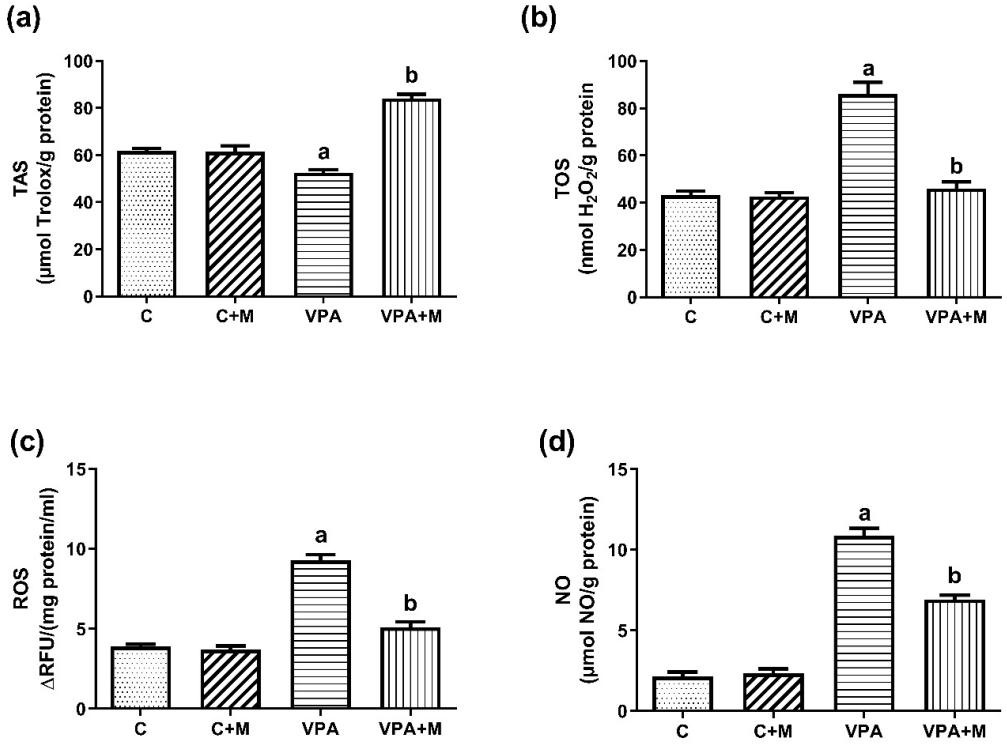

Figure 3. Effect of *Moringa* extract on lens tissue of experimental animals (a) TAS levels; ^{a}p<0.05 vs. control, ^{b}p<0.0001 vs. VPA, (b) TOS levels; ^{a}p<0.0001 vs. control; ^{b}p<0.0001 vs. VPA; (c) ROS levels; ^{a}p<0.0001 vs. control; ^{b}p<0.0001 vs. VPA; (d) NO levels; ^{a}p<0.0001 vs. control; ^{b}p<0.0001 vs. VPA. Values were given as mean and standard error. C: Control group; C+M: Control+*Moringa* extract group; VPA: Valproate group; VPA+M: Valproate+*Moringa* extract group.

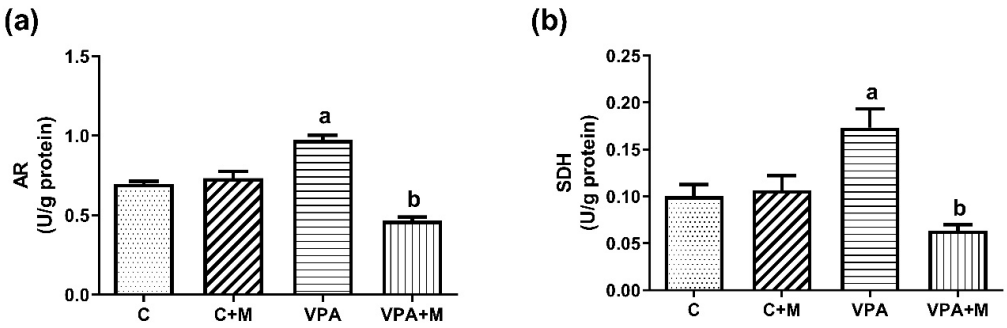

Figure 4. Effect of *Moringa* extract on lens tissue of experimental animals (a) AR activities; ^{a}p<0.0001 vs. control, ^{b}p<0.0001 vs. VPA, (b) SDH activities; ^{a}p<0.05 vs. control; ^{b}p<0.0001 vs. VPA. Values were given as mean and standard error. C: Control group; C+M: Control+*Moringa* extract group; VPA: Valproate group; VPA+M: Valproate+*Moringa* extract group.

DISCUSSION

Amongst the most widely used anti-epileptic drug is VPA and its corresponding salts. However, this drug has been proven to cause multiple organ damage and subsequently mortality.[2–6,8] Amongst the organs grossly affected is the lens tissue.[3,4] Findings have shown that VPA exhibits its side effects by destabilising oxidant/antioxidants balance, triggering inflammatory reactions, autoimmune reactions, and lipid peroxidation among other chain reactions.[1] Thus, researching and exploiting molecules as well as food-based substances capable of mitigating the deteriorative effect of VPA is of paramount significance.

The diverse pharmacological effects of *Moringa oleifera* leaves have been proven to be associated with its rich vitamins and antioxidant components. Extracts of the plant leaves are shown to have antioxidant activity,[13] anti-inflammatory,[14] and protective effect on several organs/tissues.[15–17] Consequently, prompting the present study, to evaluate the protective effect of

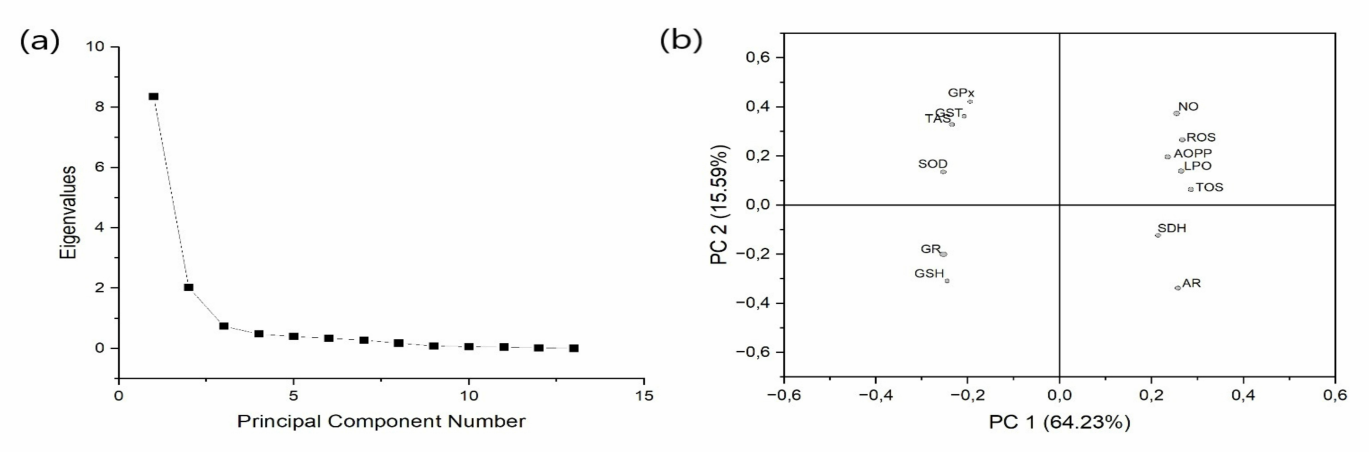

Figure 5. (a) Principal component analysis (PCA) plot, (b) PCA model of biochemical results for all groups. All biochemical results of lens tissues indicator plotted as a function of two first components, principal component 1 (PC1: 64.23%) and principal component 2 (PC2: 15.59%), explaining together 79.92% of information in the obtained dataset.

Moringa extracts against VPA induce lens toxicity in Sprague Dawley rats.

GSH is a substantial antioxidant molecule that participates in a both enzymatic and non-enzymatic process that protect tissues against oxidative stress. It is significant for the protection of proteins, lipids, and important subcellular organelle including mitochondria, and its level is usually high in lens tissue.[35] The present findings suggest that the administration of 0.5 g/kg b.w./day VPA for 15 days resulted in a diminished GSH level in lens tissue. This may be a consequence of the overproduction of free radicals and exhaustive use of the GSH in the lens tissue. Furthermore, the levels of LPO and AOPP-key markers of oxidative stress and contributing risk factors to tissue damage/necrosis were found to significantly increase in the VPA group. This finding is in agreement with the report of Tong et al.,[36] and a clear indication of increased lipid peroxidation and the oxidation proteins, following the accumulation of ROS and/or diminished GSH levels. The present outcomes are in agreement with an earlier report by and Tunali et al.[9] The concurrent administration of VPA with *Moringa* extract prevented the depletion of GSH levels, and as well downregulated the levels of both LPO and AOPP. The ability of *Moringa* extract to exhibit a positive effect on GSH, LPO, and AOPP levels is most likely linked to its antioxidant properties as earlier reported.[13]

Antioxidants enzymes including GR, GPx, GST, and SOD and play a vital role in the antioxidant system. GR is the key enzyme involved in the reconversion of oxidized glutathione (GSSG) to reduced glutathione (GSH) via utilising NADPH. GPx on the other hand is involved in the reduction of hydrogen peroxide to water, as well as the conversion of lipid peroxides to their corresponding alcohols. Thus, GPx protects against oxidative stress and cellular membrane damage.[37] GST catalyses the conjugation of GSH with xenobiotics and other potentially reactive molecules, thereby bringing about their detoxification.[38] SOD is responsible for the detoxification of superoxide into hydrogen peroxide and oxygen molecules. An alteration in the activity of any of these enzymes (GR, GPx, GST, and SOD) can significantly affect the redox state and the antioxidant mechanism. In the present study, the activities GR, GPx, GST, and SOD in lens tissue were grossly distorted upon administration of only VPA to experimental rats for 15 days. Previous findings indicate that VPA is an inhibitor GR, and chronic administration of VPA can affect the overall activities of antioxidant enzymes.[9] The co-treatment of VPA with *Moringa* extract resulted in a stabilised, non-distorted levels or higher activities of this enzyme. This can be primarily attributed to the strong antioxidant property of the plant extract.

TAS is the measure of the total antioxidants level in a biological system or sample. High TAS levels usually suggest higher antioxidant potential. On the contrary, TOS, ROS, and NO represent the levels of oxidants and oxidants species in a system. The higher their levels, the more likely a system is prone to oxidative stress. In the present study, the administration of VPA resulted in a decline in TAS, as well as a corresponding increase in TOS, ROS, and NO levels. This is a consequence of the excessive production of reactive oxygen species and depletion of antioxidant reserves due to VPA metabolism as earlier suggested.[1] In the VPA+M group, the levels of TAS were markedly elevated even beyond that of the control group, while TOS, ROS and NO levels were kept lower than that of the VPA group. This effect of *Moringa* extract on VPA administered animals is probably due to its rich vitamin composition and antioxidant power. This is in line with earlier studies that proved the ability of antioxidants vitamins to mitigate oxidative stress and mop up radicals.[39]

AR is a key enzyme of the polyol pathway that belongs to the aldoketo reductase superfamily.[40] The activity of AR involves the utilization of NADPH (as reducing equivalents) to

produce sorbitol from glucose. On the other hand, SDH catalyses the conversion of sorbitol to fructose by reducing NAD^+ to NADH.[41] Elevated activity of this enzyme will ultimately result in the depletion of NADPH reserve and increased osmotic pressure due to the accumulation of sorbitol in lens tissue. Thus, distorting both GSH levels and the activities of GR, GST, CAT, and other essential antioxidant enzymes. In general, increased tissue activity of AR and SDH could distort the overall antioxidant system by depleting NADPH and inducing osmotic pressure or tissue damage. In the present study, the activities of both AR and SDH (a marker for cellular injury) of VPA-administered rats were significantly elevated. This finding is in agreement with the reports of Tunali et al.[9] The administration of *Moringa* extract together with VPA counterpoises these defects via its antioxidant potential and possible enzyme inhibition effects.

CONCLUSION

The present findings indicate that the co-administration of VPA with *Moringa* extract could mitigate the side effect and deleterious effects of VPA on the lens tissue of experimental animals. This is a positive effect of *Moringa oleifera* leaves is likely due to its antioxidant properties, rich vitamin composition, and antioxidant phytochemical.

Ethics Committee Approval: The research protocol was approved by the Experimental Animal Local Ethical Committee of Marmara University(protocol number: 11.2020.mar. The female Sprague Dawley rats utilised were provided by the Experimental Animals Research and Implementation Centre of Marmara University.

Conflict of Interest: Authors declared no conflict of interest.

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