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Moringa oleifera improves liver and kidney functions in Valproic Acid autistic-like rat model

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Moringa oleifera improves liver and kidney functions in Valproic Acid autistic-like rat model

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ABSTRACT

Autism is a neurological disease that affects social reciprocity and communication throughout life. Autism has been on the rise at an alarming rate over the last three decades, while the frequency appears to vary by country. The present study was designed to investigate the effect of *Moringa oleifera* leaves on sodium valproate (VPA) induced autistic-like rat model on the liver and kidney function and histopathology changes in rats compared with the synthetic drug risperidone. 40 pregnant females rats, 5 of them were used as control and the other 35 received a single oral dose of 800 mg/kg valproic acid (VPA) on the 11th day of gestation then their offspring after weaning were randomly distributed into equal groups (n=8) and treated for 25 days as group 1: (Cont-) offspring of control mothers, (Cont+) VPA injection served as control positive, group 3: VPA+ moringa(400/mg/kg b. wt, p.o), group 4: VPA+ RIS (1 mg/kg b. wt, p.o), and group 5: VPA+ moringa + RIS. The rats were sacrificed at the end of the experiment and serum was used for the estimation of serum aspartate transaminase (AST), alanine transaminase (ALT), urea, and creatinine in addition to the histopathological study of the liver and brain. The results showed improvement in the weight, liver, and kidney function by moringa and/or risperidone treatment in comparison with VPA treated group**.** Therefore, it may be concluded that *Moringa oleifera* extract had a protective effect due to its impact on liver and kidney function.

Keywords: Moringa, Autism, Risperidone, Liver, Valproic acid

INTRODUCTION

Autism spectrum disorder (ASD) is a lifetime neurological illness characterized by social impairments. as well as social and repetitive behaviors. The gender ratio is four males to one female. The ASD cause is unknown, however environmental, and dietary factors influence the disorder **(Bjørklund et al., 2019).** Valproic Acid (VPA) is an anticonvulsant

medication that is mostly used to treat epilepsy, resistant depression, and migraine prevention. The VPA was used to produce an animal model of ASD which is the best model for autism because of defective neuronal development in the cerebellum and other brain parts with disruption in synaptic connections. Furthermore, rats prenatally exposed to VPA exhibited behavioral characteristics comparable to the nature of human beings. It certainly constitutes a robust autism model, displaying face, concept, and predictive validity. The VPA animal model is a tool for investigating the neurological alterations underlying autism behavior and searching for new therapeutics **(Arafat & Shabaan, 2019).**VPA treatment might cause both reversible and permanent liver damage. Several mechanisms have been postulated to explain VPA-induced hepatotoxicity, including the formation of reactive VPA metabolites, suppression of fatty acid oxidation, oxidative stress, disruption of lipid metabolism, and genetic variants **(Guo et al., 2019)**.

Moringa oleifera (MO) is a highly valuable plant that is found in many tropical and subtropical areas. This tree has recently been promoted as an exceptional indigenous source of highly digestible protein, Ca, Fe, vitamin C, and carotenoids appropriate for use in many of the world's so-called developing regions where malnutrition is a serious issue. In terms of vitamins and minerals, moringa leaves are superior to carrots in terms of vitamin A, milk and eggs in terms of calcium, spinach in terms of iron, oranges in terms of vitamin C, and bananas in terms of potassium.MO is particularly significant for its therapeutic contents. In addition to its powerful water-purifying abilities and high nutritional content **(Melo et al., 2013).**

MO leaves' mechanism of action is most likely due to their high concentration of polyphenols and other antioxidative chemicals, which give neuroprotection by scavenging free radicals or activating the cellular antioxidant system. **(Luqman et al., 2012)** There are several studies on the use of MO to treat diabetes, hyperlipidemia, hypertension, hypoglycemia, and other conditions, but there is currently very little information on pure compounds derived from MO that have been successfully used to treat neurodegeneration, neurological, or related conditions**(Igado & Olopade, 2016)**. While ASD has a neurological and behavioral range, the connection between food and nutrition should be addressed. Reports on the nutritional consumption of children with ASD have yielded contradicting results **(Meguid et al., 2017).**

The intake of 200 and 800 mg/kg of MO leaf extract reduced liver damage that is made by acetaminophen-induced, as measured by reductions

in aspartate transaminase(AST), Alanine transaminase(ALT), and *alkaline phosphatase* (ALP) and elevations in hepatic glutathione. **(Fakurazi et al., 2008)** These investigations were extended and indicated that intraperitoneal administration of 200 and 400 mg/kg body weight of hydroethanolic extracts of MO leaf and flower protected against acetaminophen-induced liver damage. The extracts reduced hepatic lipid peroxidation, improved glutathione levels, and enhanced the antioxidant enzymes superoxide dismutase and catalase. It has been shown that an extract of *M. oleifera* leaves can reduce gentamicin-induced nephrotoxicity. **(Fakurazi et al., 2012)** The leaf extract dramatically reduced histological alterations, lipid peroxidation, and blood urea and creatinine levels, all of which are indicators of gentamicin-induced kidney damage. **(Stohs & Hartman, 2015)**

Risperidone (RIS) Antipsychotic medicines are routinely administered to children with ASD. The Food and Drug Administration (FDA) has authorized RIS for the treatment of irritability in children with autism disorder, including aggression toward others, self-injuriousness, temper tantrums, and mood swings. Antipsychotic medicines have been demonstrated in tests to minimize behavioral difficulties and increase the contextual adaptation of autistic patients. **(Hesapcioglu et al., 2020)** Because RIS works on serotonin and dopamine, it can be used to treat negative symptoms of schizophrenia while also decreasing positive symptoms **(Pajonk, 2004)** and mild autistic behavior such as mood swings, self-injury, and hostility toward others, especially at low doses. **(Kirino, 2014)**

Thus, the main aim of this work was to investigate the possible improvement of MO ethanolic extract with/without Risperdal on Liver and kidney functions such as ALT, AST, urea, and creatinine. The improvement of neurological and hepatic histopathological changes associated with autism may also be considered.

Materials and Methods

1-Animals

At the animal house national research center (NRC), Giza, Egypt, forty female albino rats weighing 180–200 g were obtained. The rats were kept in plastic cages, four pregnant female rats per cage. Throughout the experiment, animals were maintained at a constant temperature of 25 2 °C and under a 12-hour light/12-hour dark cycle. During the trial, a commercial mouse pelleted food was given. Before the trial started, the animals were given two weeks to get used to the lab environment. Ad libitum access to food

and water was provided, and weight gain was monitored biweekly. The state authorities approved the experimental techniques and procedures, and they conformed to ethical guidelines for animal protection at the faculty for women for Arts, Sciences and Education, Ain Shams University. At 25 days old, the rat's offspring were sacrificed, and the tissues were removed and kept at −70 °C until the assays were performed. serum was extracted for biochemical study, and liver and brains were isolated and presented in 10% formalin for the histological study.

2-Drugs

Sodium valproate: VPA Sodium Salt 98% was purchased from, Sigma, St. Louis, MO, USA, and Risperidone oral solution was purchased from JANSSEN CILAC. *Moringa oleifera*: the Ethanolic extract prepared at the Agricultural Research Centre (ARC), Giza, Egypt. Extraction and analysis of the total phenolic, total flavonoids, and total antioxidant capacity was analyzed according to **(Su & Silva, 2006)** and**(Ivanova et al., 2010)**.

3-Experimental design

The female rats were mated overnight, and vaginal lavage was the way to check for the existence of the sperm. The first day of gestation was chosen to be the day when the smear was sperm positive. On the 11^{th} day of gestation, the rats were divided into two main subgroups: the first one included 5 animals treated with the vehicle. While the rest 35 animals were treated with VPA (800 mg/kg, orally) **(Ali & Elgoly, 2013).** On the 25th day of birth, the offspring male was randomly distributed into five groups**: Group 1 (control -):** These include 8 male offspring of the mother group who received oral saline. **Group 2 (VPA - Control +):** These include 8 male offspring of the mother group who received oral VPA **Group 3 (VPA+ Moringa):** These include 8 male offspring of the oral VPA mother group who were orally gavaged 400 mg/kg/day of the *Moringa oleifera* extract **(Mohamed et al., 2019)**. **Group 4 (VPA+Risperdone):** These include 8 male offspring of the oral VPA mother group who were orally gavaged with 1gm/kg/day(**Ali et al., 2020) Group 5 (VPA+Moringa+ Risperidone):** These include 8 male offspring of the oral VPA mother group who received the MO and RIS with the dosage mentioned in the previous groups**.**

Biochemical assay:

Alanine aminotransferase activities (ALT) were measured in serum using the modified kinetic. **(Reitman & Frankel, 1957)** Chemical kits purchased from Bio Diagnostics Egypt, CAT No: AL 10 31 (45). Aspartate amino Transferase (AST) activities were measured in serum using the modified kinetic methods. **(Reitman & Frankel, 1957)** kits purchased from Bio Diagnostics Egypt, CAT No: AS 10 61 (45). Urea was determined in serum using the modified kinetic method or liquid color. **(Fawcett & Scott, 1960)** kits purchased from Bio Diagnostics, Egypt, CAT No: UR 21 10. creatinine was measured using a modified kinetic method. **(Bartels et al., 1972) (Larsen, 1972)** kits purchased from Bio Diagnostics, Egypt, CAT No: CR 12 51.

Histopathology Examinations:

Small specimens of the liver and brain organs were taken from each experimental animal, fixed in neutral buffered formalin 10%, cleared in xylene, and embedded in paraffin. Sections of 4- 6 mm thicknesses were prepared and stained with hematoxylin and eosin.

Statistical analysis:

Values are shown as means ± SE. the Statistical analysis was performed by one-way ANOVA. The difference between treatments post hoc Duncan's at ($P \leq 0.05$) was considered significant. The Statistical package for the social science “SPSS” for Windows software, Release 20.0(SPSS, Chicago, IL, USA) was used.

RESULT

The data presented in Fig (1) show the growth weight chart of different treated groups of offspring rats during the period of the experiment. The data showed a significant decrease in all treated groups as compared to the control group in the first, 14^{th}, and 24^{th} days after weaning.

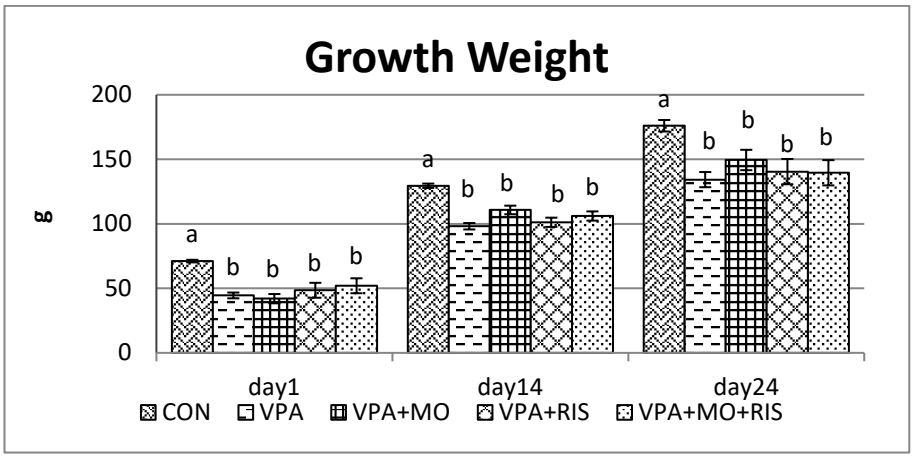

Fig (1): the growth weight chart of different treated groups during the period of treatment. Data represented as means± SE of eight rats, groups with the same symbols are not significantly different at $p< 0.05$ at the same time. CON= Control, VPA= Valporic acid , MO= Moringa and RIS= Risperidone.

Figure (2): A significant increase in the serum AST activity in VPA-treated rats was noted, compared to the control and VPA+ MO group. While the VPA group did not show significance with VPA+RIS and VPA+MO +RIS. Moreover, the VPA+MO group exhibited anon significant decrease when compared to the VPA+RIS and VPA+MO+RIS and control group (figure 2).

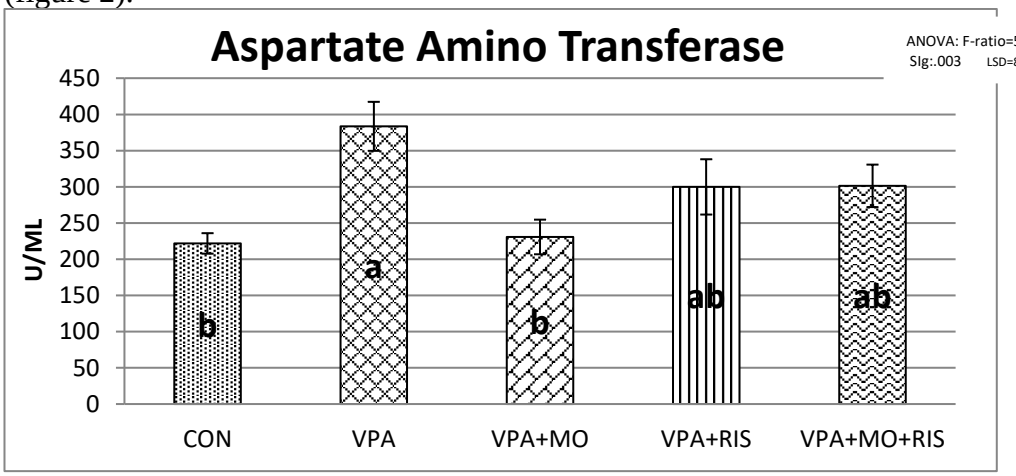

Fig (2): the Serum level of AST in different treated groups. Data represented as means± SE of eight rats, groups with the same symbols are not significantly

different at p< 0.05. CON= Control, VPA= Valporic acid , MO= Moringa and RIS= Risperidone.

Figure (3) illustrates a significant increase in serum ALT activity in VPA-treated rats when compared to the control and VPA+MOR and VPA+MO+RIS groups. While VPA+RIS and VPA+MO+RIS and VPA+MOR-treated rats exhibited a non-significant increase when compared to the control group

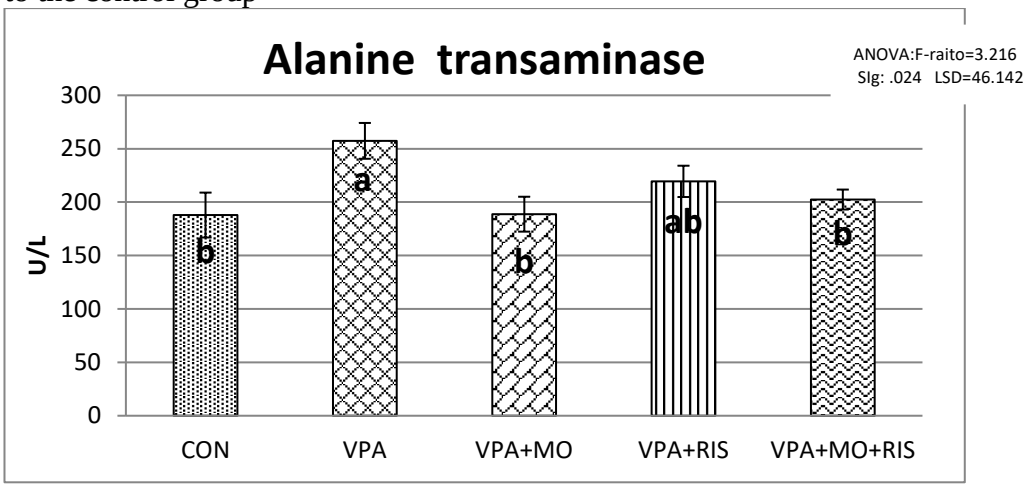

Fig (3): the Serum level of ALT in different treated groups. Data represented as means ±SE of eight rats, groups with the same symbols are not significantly different at p< 0.05. CON= Control, VPA= Valporic acid , MO= Moringa and RIS= Risperidone.

The VPA-treated rats exhibited a significant increase in serum creatinine activity when compared to the control and VPA+MO group (**Fig.** 4). While VPA+MO+RIS showed a significant increase in creatinine level in comparison with VPA+RIS and control group and not sig to VPA and VPA+MO groups. On the other side, the VPA+RIS group showed a significant decrease in comparison with the VPA, VPA+MO, and VPA+MO+ RIS. Also, VPA+ MO rats exhibited a significant increase in creatinine levels in comparison with control, and VPA + RIS, and an increase was noticed in creatinine levels in the VPA group.

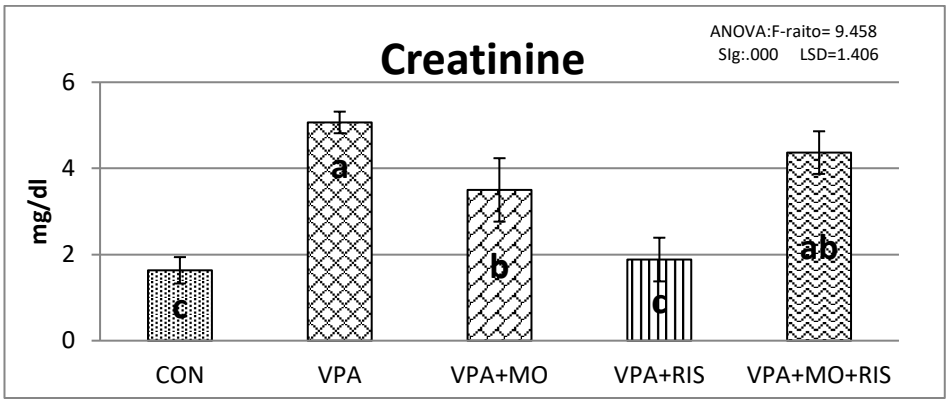

Fig (4): serum levels of creatinine in different treated groups. Data represented as means± SE of eight rats, groups with the same symbols are not significantly different at p< 0.05. CON= Control, VPA= Valporic acid , MO= Moringa and RIS= Risperidone.

The data depicted in Figure (5) shows the effect of different treatments with VPA (positive control), MO, RIS, and MO in combination with RIS. Also, both MO and RIS enhance the urea values add these are in order: VPA+MO+RIS, VPA+RIS, VPA+MO then VPA as a positive control.

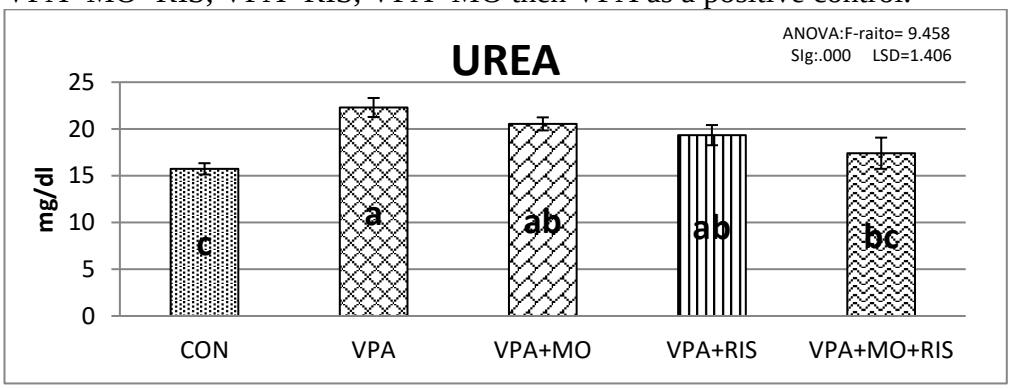

Fig (5): the serum level of in UREA different treated groups. Data represented as means± SE of eight rats, groups with the same symbols are not significantly different at p< 0.05. CON= Control, VPA= Valporic acid , MO= Moringa and RIS= Risperidone.

Histopathological results:

Hematoxylin and eosin-stained sections

The histological presence of the liver tissue of the control group is shown in the plate (1-A), It showed a typical lobular architecture and liver cells spreading normally from the central vein. As shown, hepatocytes retained eosinophilic granular and well-delineated vesicular basophilic nuclei. In diseased Liver tissue in the group administered (VPA) showed the hepatocytes in some areas lost their cell integrity, which appears fused, while other areas manifested a totally necrotic region as a damaged zone, in addition of that the lymphocytic infiltration pointed to inflammatory features all over hepatic tissue (the plate 1-B). The kupffer cells increased in number in the blood sinusoid regarding their activity against hepatic tissue injury. The congested central vein negatively affects the cells around it, while another region seems near to normal. The VPA + MO treated Liver tissue in (the plate 1-C) showed rarely improved hepatic cells with other fragmented and released cellular depress, highly Kupffer cells activated, and congested central vein. Liver tissue of VPA+RIS treated rats (the plate 1-D) showed markedly improved cell architectures, dilated and congested hepatic portal vein with fibrotic bands around portal triads, with bile duct hyperplasia. Finally, in the VPA+MO+RIS treated group, the Liver tissue (the plate 1-E) illustrated significantly improved hepatic cell arrangement and dilated hepatic vein.

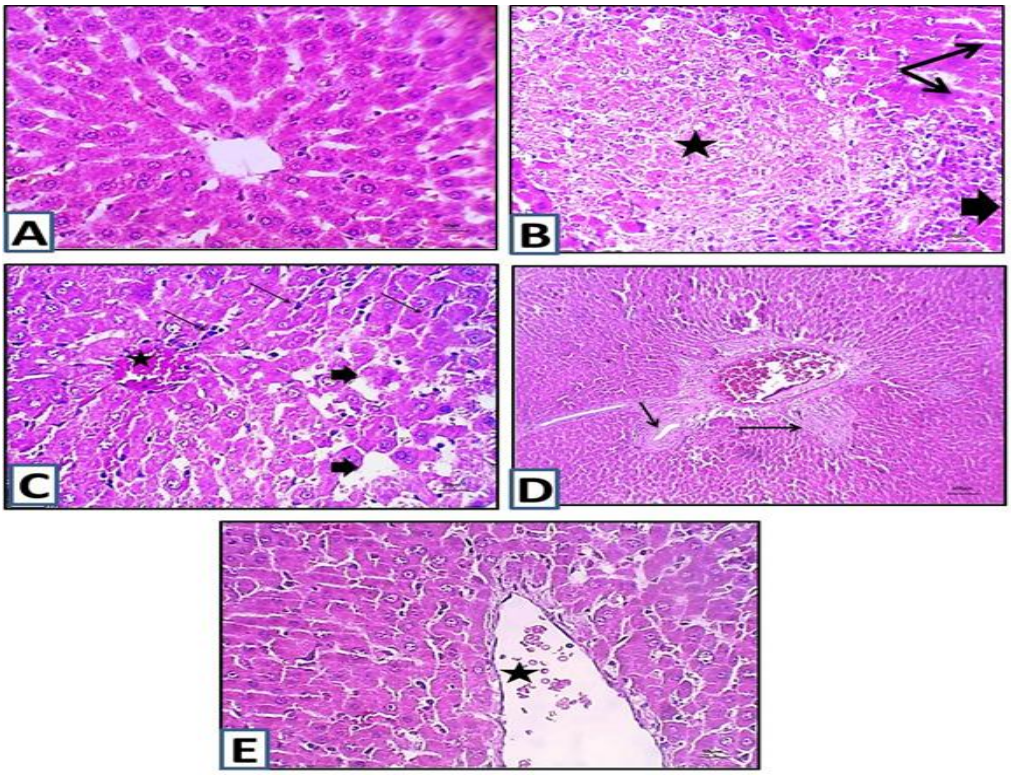

Plate (1) The Photomicrographs of Liver tissues

Plate (1) The Photomicrographs of Liver tissues (A): control group revealed the normal structure of hepatocytes revealed normal lobular architecture with normal hepatic cells radiating from the central vein while Liver tissue (B) of the VPA group illustrates the hepatocytes' necrotic large area (star), dilated blood sinusoid (2 arrows), and scattered inflammatory lymphocytes infiltration (head arrow). The treated Liver tissue in (C) the VPA+MO group showed rarely improved hepatic cells with other fragmented and released cellular depress (head arrow), highly Kupffer cells activated (3 arrows), and congested central vein (star). In the other treated group by VPA +RIS, the Liver tissue (D) showed markedly improved cell architectures, dilated, and congested hepatic portal vein with fibrotic bands around portal triads, with bile duct hyperplasia (2 arrows). Finally, in the VPA+MO+RIS treated group, the Liver tissue (E) illustrated significantly improved hepatic cell arrangement and dilated hepatic vein. (H&E-X400 a, b, c, e) (H&E-X100, d).

Plate 2 displays the photomicrographs of the cerebral cortex that were stained with HE. The control group (plate 2-A) revealed a normal structure,

with the molecular layer (mo) covered by pia matter (P) that was regularly attached and rich in invaded blood capillaries (bc), external granular layer (eg), external pyramidal layer (ep), internal granular layer (Ig), internal pyramidal layer (Ip), and polymorphic layer (pm). While the VPA group's cerebral tissue (plate 2-B) showed a lack of plexus, a necrotic region that was widely dispersed and had big vacuoles, additional pyknotic nuclei in the exterior granular layer, and dilated congested blood capillaries, the VPA group's brain tissue did not. However, the cerebral tissue in (plate 2-C) in the VPA+MO-treated group seldom displayed better distribution with scattered vacuoles and pyknotic nuclei of each glial and nerve cell, often giving the fabric a scrawny appearance. The cerebral tissue in (plate 2-D) in the VPA+RIS treated group exhibited noticeably improved cerebral tissue, although capillary blood vessels were dilated and had shrinking cells with pyknotic nuclei in the molecular layer. The cerebral tissue in (plate 2-E) shows that both the external and internal layers of the cortex in the group that received treatment with VPA+MO+RIS show many normal cell bodies and only a small number of neuronal cell bodies appear dark shrunken with pyknotic nuclei (P). Deeply stained glial cell nuclei (G), along with what appear to be normal blood capillaries, as well as sporadic small vacuoles (V) in the detected layer.

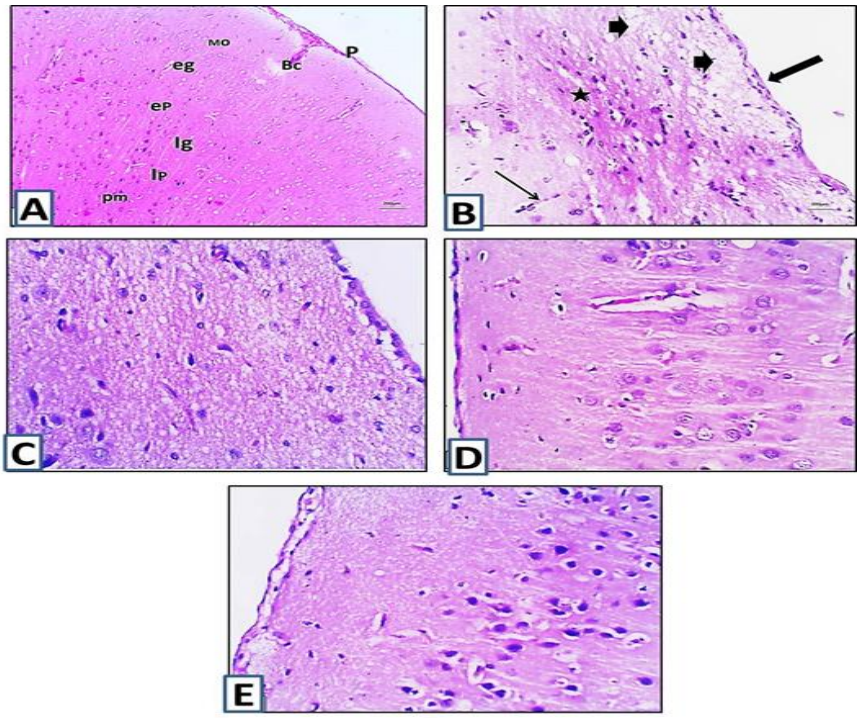

Plate (2)the Photomicrographs of brain cerebral cortex tissue.

Plate 2 showed the Photomicrographs of cerebral cortex tissue in (A) the control group revealed normal structure, showed the molecular layer (mo) was covered with regularly attached pia matter (P) rich by invaded blood capillary (bc), external granular layer (eg), external pyramidal layer (ep), internal granular layer (Ig), internal pyramidal layer (Ip), and polymorphic layer (pm). While the cerebral tissue (B) in the group administered VPA case illustrates a loss of plexus, necrotic area widely distributed with large vacuoles, (heads) other pyknotic nuclei in the external granular layer (star), and dilated congested blood capillary (thin arrow). But in the treated group by (VPA +MO) the cerebral tissue in (C) showed rarely improved distribution with distributed vacuoles, and pyknotic nuclei of each of the glial and nerve cells, generally the fabric appears scrawny. In the group treated by (VPA+RIS), the cerebral tissue in (D) showed markedly ameliorative cerebral tissue was observed, but capillary blood vessels were dilated and manifested shrinking cells with pyknotic nuclei in the molecular layer. In the group treated by (VPA+MO+RIS), the cerebral tissue in (E) illustrates both external and internal layers of the cortex display many normal cell bodies and few

neuronal cell bodies appear dark shrunken with pyknotic nuclei (P) Deeply stained nuclei of glial cells (G) together with apparently normal blood capillaries besides sporadic small vacuoles (V) in the detected layer. (H&E-X400)

Hematoxylin and eosin-stained slices used for histologic examination of plate 3 revealed the distinctive hippocampal formation sections. These are the hippocampus proper, the dentate gyrus, and the subiculum. The hippocampi are unique and vital regions found in each of the cerebral hemispheres. Most often, the dominant left hippocampus facilitates language learning and memory whereas the non-dominant right side handles non-verbal memory. Because bilateral hippocampal lesions result in amnesia. The normal hippocampus proper is formed of Cornu Ammonis CA1 and CA2 formed of the zone of small pyramidal cells, and CA3 and CA4 formed of the zone of large pyramidal cells. CA4 projects into the concavity of dentate gyrus that is formed of small granule cells. The subiculum is an outward continuation of the CA1 region. Areas in between compact zones of cells comprise the molecular layer which consists of neuronal processes / (axons and dendrites), glial cells, and scattered nerve cells (Plate 3-A). In the VPA group, the hippocampus section (Plate 3-B) demonstrated decreased thickness of the layer of small pyramidal cells of CA1 and marked affection of large pyramidal cells of CA3 with vesicular nuclei, granular cells presented marked retraction of processes with vacuolations, and molecular layer (ML) demonstrated enlarged neurons and enlarged glial cells, as well as dilated blood capillaries in their cells. In the VPA+MO treated group the hippocampus section (Plate 3-C), showing rarely improved in some granular cells with a decreased thickness of the layer of small pyramidal cells of CA1, collapsed, clumping, and compact granular cells area with dark nuclei and dilated capillary. The hippocampal portion (Plate 3-D) showed a considerable reduction in the size of the big pyramidal cells in the VPA+ RIS treated group, along with a relatively better side of the molecular layer (ML) granular cells. Intense vacuolations were also visible in granular cell layers. A few of the pyramidal cells are shrunken with pyknotic nuclei in the VPA+MO+RIS treated group, but overall, the hippocampal portion (Plate 3-E) exhibits a remarkable improvement with an almost normal pyramidal cell size that seems relatively consistently distributed and loosely packed.

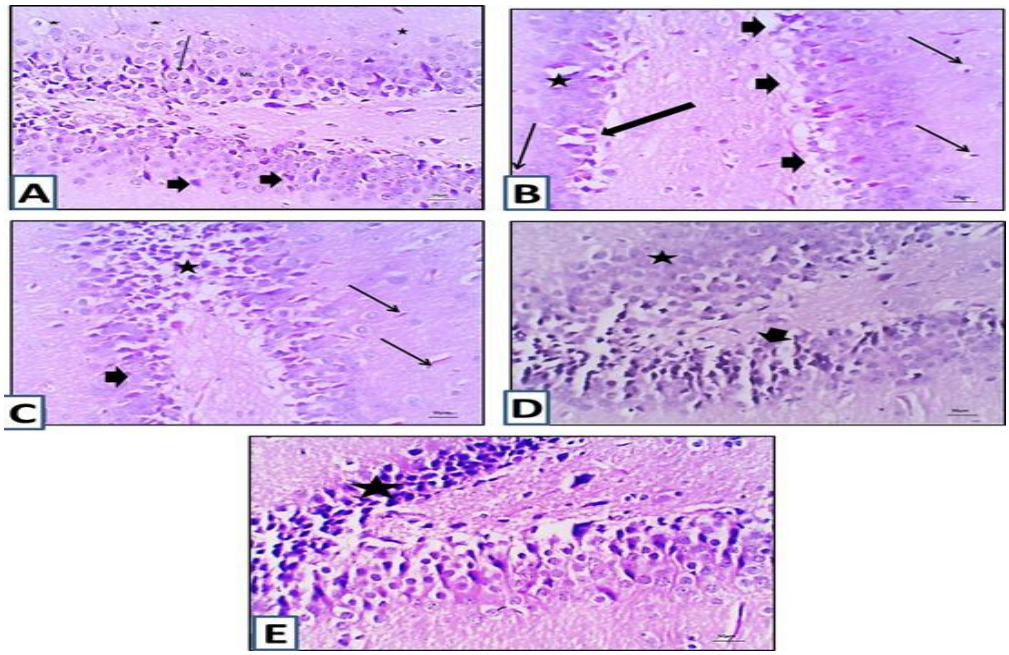

Plate (3) The Photomicrographs of brain hippocampus tissue.

Plate (3) The Photomicrographs of a section from the normal hippocampus in (A) control group showing more than 5–6 compact layers of small pyramidal cells of the CA1 area, most with vesicular nuclei (arrow) in the molecular layer (ML) and illustrations many glial cells (*), in addition to pyramidal cells (head). In the VPA group the hippocampus section (B) presented decreased thickness of the layer of small pyramidal cells of CA1 and marked affection of large pyramidal cells of CA3 with vesicular nuclei (long arrow), granular cells performance marked retraction of processes with vacuolations (heads), and molecular layer (ML), enlarged neurons and enlarged glial cells (arrow), with dilated blood capillaries (star) In the group, treated VPA+MO the hippocampus area (C), presentation rarely enhanced in some granular cells with a decreased thickness of the layer of small pyramidal cells of CA1 (head), collapsed, clumping and compact granular cells area with dark nuclei (star) dilated capillary (arrows). In the group treated with VPA+RIS the hippocampus area (D), manifested a relatively enhanced side of the molecular layer (ML) granular cells (star) with marked shrinkage in the size of large pyramidal cells (head) Granular cell layers also presented marked vacuolations. Finally, In the group treated with VPA+MO+RIS the hippocampus section (E), demonstrations significantly improved with a

nearly normal pyramidal cell size that appears somewhat regularly arranged and loosely packed, a few of them are shrunken with pyknotic nuclei (star). (H&E-X400)

Discussion

Autism Spectrum Disorder is a neurodevelopmental disorder caused by a lack of verbal and nonverbal communication, social skills, and relationships**(Wei et al., 2014)**. The underlying cause of ASD is still unidentified. As a result, the current study was carried out to better understand the relationship between the biochemical and histological aspects of autism. We concentrated on the way of performing the ASD animal models. Despite the significant evidence for genetic links to ASD, an early environmental injury is still an increasing worry, especially given the recent increase in autism prevalence **(Fombonne, 2005).** This model, which represents one of the environmental causes of autism, may more accurately represent idiopathic autism than transgenic mice that have mutations in specific autism-associated genes **(Nicolini & Fahnestock, 2018).** Due to its ability to cause ASD when administered early in pregnancy, we considered valproic acid (VPA) as a useful model of autism**(Stadelmaier et al., 2017)**.

Newborns exposed to prenatal VPA had delayed maturation as seen by reduced body weight, a minor decrease in brain weight, and delayed eye-opening, suggesting potentially altered neurodevelopmental consequences**(Al-Askar et al., 2017).** The rodent model of autism was created by exposure of rat fetuses to VPA on the 12.5^{th} day of gestation (VPA rats). The model and human data show strong anatomical, pathological, and etiological parallels, Furthermore, VPA rats displayed slower maturation and reduced body weight **(Schneider & Przew\locki, 2005).**

Valproic acid was linked to several significant side effects in the blood, pancreatic, hepatic, and renal function. It has been established that VPA is a teratogen that induces abnormalities in the neural tube. The research mentioned that VPA may harm the liver and induce pancreatitis. Additionally, it has been suggested that one of the frequent adverse effects of VPA therapy is liver impairment. Research has shown that the VPA impact led to liver biopsy findings of cholestasis, significant bile duct loss, and portal inflammation. Uncertainty persists regarding how VPA alters the metabolism of lipids to lead to fatty liver. Additionally, it has been shown that VPA has a critical function in the degenerative alterations that occur in pregnant rats' kidneys **(Al-Amoudi, 2017).**

Long-term treatment medications, such as RIS, should consider the risk of hepatotoxicity and renal impairment in addition to severe metabolic and inflammatory consequences**(Papatriantafyllou et al., 2022)**. According to the study, rats given RIS exhibited hepatotoxicity, including zonal necrosis and partial obstruction of the central vein **(Bariweni et al., 2022)**. Additionally, a severe case of hepatic damage can progress into acute or chronic liver failure, showing signs of cellular swelling and lysed cells that leak intracellular fluid into the environment, finally triggering an inflammatory response **(Guicciardi et al., 2013)**.

The mechanism behind risperidone-associated metabolic abnormalities and hepatic and kidney side effects requires additional investigation. Recent data show that risperidone can raise blood ALT and AST levels (a liver inflammation indicator) in mice. Upon that, serum ALT and AST levels were determined. Long-term therapy with risperidone-inducing visceral obesity linked with cholestatic hepatitis and hepatic steatosis resulted in similar findings in mice and people. Furthermore, an analysis of liver enzymes demonstrated that risperidone caused liver damage in rats by increasing free radical damage and decreasing plasma total antioxidant activity. Risperidone's actions finally resulted in hepatic adverse effects due to the stimulation of hepatic lipogenesis **(Tsai et al., 2021)**.

According to our research, rats with chemically induced acute liver damage may benefit from the curring benefits of MO extracts. The prevention of lipid peroxidation by-products as well as increased antioxidant enzymes are most likely what causes MO extracts to have therapeutic/hepatoprotective benefits**(Sharifudin et al., 2013)**. These findings may be due to the flavonoid, and phenolic in the extracts, and a significant amount of b-carotene and all necessary amino acids It has been suggested that *M. oleifera's* b-carotene is what gives it its hepatoprotective properties. B-Carotene may have effective antioxidant action that traps free radicals. If taken along with modern medicine, MO could very well be helpful **(Pari & Kumar, 2002).**

Moringa seemed to provide defense and preserve the hepatocellular membrane's structural integrity. This was clear from the substantial decrease in AST and ALT levels, which showed that treated rats were protected against antitubercular medication toxicity. Our results agreed with a study that reported that a moringa extract has lower levels of AST and ALT in hepatotoxicity **(Pari & Kumar, 2002)**. The study found that blood urea levels in cadmium-treated rats significantly increased as compared to serum urea levels in control rats and rats that had received MO extract as a pretreatment.

The amount of urea is used to measure renal function and won't increase until at least half of the kidney's nephrons have been destroyed. The antioxidant qualities of the plant may have prevented oxidative damage to the kidney's microstructure, which may have contributed to the near-normal urea content shown in the rats pretreated with an extract of MO in this study. Rats exposed to cadmium developed liver and renal damage, while an extract of MO had significant promise for protection**(Ajilore et al., 2012).**

An earlier study discovered that MO extract enhanced the healing of liver cells. The capacity of MO and silymarin to cure the hepatic damage was equivalent, there was demonstrated by the histological observation. The study of the liver and kidney tissues was supported by hepatoprotective investigations. The advancement of the hepatocellular damage seen in histological investigations was effectively prevented by the MO extracts. The effects of the extract treatments significantly decreased the number of necrotic hepatocytes and inflammatory cell infiltration, which prevents further liver damage. These results point to the tissue-protective properties of MO extracts in rats exposed to toxic chemicals. The hepatoprotective impact of the MO leaf extract on liver damage has shown a significant protective function of its influence on the levels of aspartate aminotransferase, alanine aminotransferase, and lipid peroxidation in the liver**(Sharifudin et al., 2013).**

In contrast, the hepatic tissues taken from the group which received VPA indicated significant alterations in intrahepatic blood vein congestion. Furthermore, quantities of the leukocyte inflammatory cells were seen infiltrating this area of the group which received VPA. It is worth noting that following VPA exposure, most of the hepatocytes had cytoplasmic vacuolation with pyknotic nuclei, congestion, fibrosis, and bile duct necrosis surrounding the portal tract, as well as fatty infiltrations in the VPA group. Microscopical examination of the kidney cortex of VPA-treated rats revealed congested and enlarged renal veins, as well as vacuolar degeneration in certain tubular epithelial cells and cell debris, dispersed in tubular lumina. The renal tubules had cytoplasmic vacuolation of the epithelial lining and proteinaceous casts in their lumen. In addition, an edematous lesion was seen between the tubules. The renal tubules seemed seriously damaged, with fractured and degraded glomeruli**(Al-Amoudi, 2017).**

In addition, the groups who had received MO as a pretreatment showed notable preservation of liver histology. The return of the enzyme levels to normal after MO treatment revealed that moringa extract may play some functions in maintaining the structural integrity of the hepatocellular

tissue and preventing enzyme leakage into the bloodstream. The commonly held belief that transaminase levels will recover to normal is supported by our findings. This study also revealed that therapy with MO decreased the levels of elevated blood urea and creatinine, which suggests that the MO's components not only preserved the kidney's structural integrity but also enhanced its ability for regenerative and reparative processes**(Mansour et al., 2014)**.

No synergism was observed in VPA+MO+RIS treated group in comparison with VPA+ MO treated group which showed an improvement in body weight, serum aspartate aminotransferase activity, and serum creatinine content. This improvement could probably be due to the desirable healing compounds in the moringa (**Chhikara et al., 2020)**.

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مستخلص المورينجا اوليفيرا يحسن وظائف الكبد والكلى فى نموذج الجرذان المشابه للتوحد المحدث بحمض الفالبورك

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الملخص العربى

التوحد هو اضطراب عصبى مزمن يؤثرعلى السلوك والقدره على التواصل الاجتماعى وقد تزايد المرض انتشارا فى العقود الثلاثه الاخيره وتهدف هذه الدراسه الى معرفه تاثير مستخلص نبات المورينجا اوليفيرا على التغير فى وظائف الكى والكبد فى نموذج الجرذان المشابه للتوحد المحدث بحمض الفالبورك ومقارنته بعقار الريسبيردون . تم اعطاء مجموعه من اناث الجرذان الحوامل جرعه واحده من حمض الفالبوريك بتركيز ٨٠٠ مجم / كجم فى الفم وبعد فطام النسل تم توزيعه عشوئيا الى خمس مجموعات متساويه (ن=٨)عولجت لمده ٢٥ يوم على النحو التالى : المجموعه الاولى الضابطه السالبه تلقت محلول ملحى المجموعه الثانيه ناتج الامهات المحقونه بحمض الفالبوريك ولم تتلقى علاج ,المجموعه الثالثه ناتج الامهات المحقونه بحمض الفالبوريك وتلقت علاج باستخدام مستخلص المورينجا اوليفيرا(اليسر) بتركيز (٤٠٠ ملجم/كجم /فمويا),المجموعه الرابعه ناتج الامهات المحقونه بحمض الفالبوريك وتلقت الريسبردون بتركيز (١ملجم/كجم/ فمويا), المجموعه الخامسه ناتج الامهات المحقونه بحمض الفالبوريك وتلقت مستخلص المورينجا اوليفيرا + الريسبردون بتركيز (١ملجم/كجم /فمويا), تم التضحيه بالجرذان فى اليوم ٢٥ من الولاده وتم تقيم ظائف الكبد والكلى من خلال سيرم الدم بالاضافه الى التشريح النسيجى للكبد والمخ وقد اظهرت النتائج ان العلاج بالمورينجا اوليفيرا يحسن وظائف الكبد والكلى بالمقارنه بالمجموعات المعالجه بحمض الفالبوريك ونستخلص من ذلك ان مستخلص المورينجا اوليفيرا لديه القدره على حمايه وتحسين وظائف الكبد والكلى وحاله الانسجة وذلك مع او بدون الريسبردال بالمقارنه مع المجموعه المصابه بالتوحد .

الكلمات المفتاحيه : المورينجا,التوحد ,حمض الفالبوريك ,الريسبيردون ,الكبد .