SMJ- Sohag Medical Journal, Vol. 29 No(1) 2025

Print ISSN 1687-8353 Online ISSN 2682-4159

Original Article

The Possible Neuroprotective Effect Of Sesame Oil On Cerebellar Cortex Of The Offspring Against Prenatal Ingestion Of Tartrazine In Pregnant Albino Rats

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Abstract:

Background: Tartrazine is used worldwide as a food colorant, some of its metabolites are toxic, carcinogenic, and mutagenic. Sesame oil, derived from Sesamum indicum; contains fatty acids and phenolic compounds which are known for their antioxidant and anti-inflammatory properties.

Aim of the work: Our research aimed to study the possible protective effect of Sesame oil on the cerebellar cortex of the offspring of pregnant albino rats that received oral tartrazine during pregnancy.

Materials and methods: 24 pregnant albino rats were used. The animals were equally divided into three groups, each of them consisting of 8 rats. Group **A:** "control" Animals were not subjected to any treatment. **Group B**: were given tartrazine. **Group C**: were given tartrazine and sesame oil. The cerebellum of their offspring was collected for histological study at different ages.

Results: ingestion of tartrazine during pregnancy affects neurodevelopment, evidenced by histological changes in the cerebellar cortex of the offspring. Co- ingestion of Sesame oil could reduce these histological effects of the tartrazine.

Conclusion: Sesame oil ingestion has protective effects against tartarazine -induced cerebellar damage in developing rats.

Keywords: cerebellum, tartrazine, sesame oil, pregnant Rats

DOI : 10.21608/SMJ.2025.361971.1542 **Received:** February 19 , 2025 **Accepted:** March 12 , 2025

Published: May 30, 2025

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Citation: **Mena Nagy Zaher Faheem , The Possible Neuroprotective Effect Of Sesame Oil On Cerebellar Cortex Of The Offspring Against Prenatal Ingestion Of Tartrazine In Pregnant Albino Rats** **SMJ,**2025 Vol. 29 No (2) 2025 13 - 26

Introduction:

The cerebellum considered as second biggest part of the central nervous system, histologically adult cerebellar cortex has three distinct layers; molecular, Purkinje cell, and internal granular cell layer.[1] It is an ideal organ for studying the development of the nervous system because it has special morphology and distinct histological features in each stage of development. [2] Early developmental stages are characterized by an external granular layer which disappear later**.** [3]

Tartrazine (TZ) is an artificial orange-colored azo dye derived from coal tar. It is water-soluble, stable, and resistant to degradation by light and heat so as It is used worldwide as a food colorant [4, 5] and to color pharmaceuticals, and other hair products. [6, 7] After its metabolism in the body some Tartrazine (TZ) metabolites are toxic, mutagenic and carcinogenic. [8, 9] Studies showed that Ingestion of tartrazine during pregnancy resulted in cell damage in the kidneys, ovaries and testicles of the rat offspring. [10, 11]

Sesame oil, which is derived from Sesamum indicum; contains fatty acids and phenolic compounds, including lignans and phenolic acids which are known to have antioxidant and anti-inflammatory properties. [12, 13]
Previous studies reported that sesame oil has neuroprotective effects of against neurodegenerative diseases, ischemic stroke, and neurotoxicity induced by various hazardous agents. This effect is achieved by alleviation of neuronal damage, reducing oxidative stress, and preserving cognitive function. [14, 15]

Aim of the work: our work aimed to study the suggested protective effect of Sesame oil (SO) on the cerebellar cortex of the offspring of pregnant albino rats who received oral tartrazine during pregnancy.

Material and methods:

Chemicals and Drugs: Tartrazine (TZ): brought from the chemical store with CAS number (1934-21-0) as powder and each 10g dissolved in 1000ml distilled water, so that each ml contains 10mg. Sesame oil: brought from the local market.

Animals: In this research a total of 36 adult albino rats; 24 female with a weight range from 200-250g and 12 males were used. The animals were brought from the animal house of the Sohag Faculty of Science. They were kept under-the ideal circumstances of feeding, light/dark ratio and temperature, in animal house of Sohag Faculty of Science.

Experimental Design: Rats were reared in cages of plastic in a ratio of 2:1 females and males. Females were examined for the presence of sperm in the vagina (vaginal plugs) and grouped according to the protocol of our experiment and their days of pregnancy were recorded.

Then rats were divided equally into 3 groups:
Group A: The Control group: 24 male offspring of 8 control mothers received no chemicals.
Group B: (Tartrazine group): 24 male offspring of 8 mothers received TZ (5 mg/kg/day) via oral gavage from the fifth day of the pregnancy till labor. [16]
Group C: (sesame oil group): 24 male offspring of 8 mothers received TZ (5 mg/kg/day) via oral gavage from the 5th day of pregnancy till labor as mentioned before ,with oral administration of Sesame oil at a dose of 5 ml/kg /day in the same days. [17]
In each group rats subdivided in to two groups. In each; 12 rats were taken postnatal (two weeks and 4 weeks). The rats used were anesthetized, sacrificed, and then dissected and samples from the cerebellum were taken.

Histology by light microscope: Sample preparation for light microscopic study: fixation done using 10% neutral buffered formalin, then specimens were washed using running water, immersion in alcohol at serial dilutions for dehydration then Impregnation and Embedding in paraffin, cutting slices of 5-7 μm thickness and examination done with a light microscope after staining with Hematoxylin and Eosin (H&E). [18, 16]

Electron microscopic examination:
Small cuts were taken, fixed using glutaraldehyde 2.5% and processed to be examined by transmission

electron microscopic, toluidine blue was used to stain semi-thin sections then examined by an Olympus light microscope when certain areas were selected. Then ultrathin cuts, 50–80 nm, were taken from these areas and examined in the unit of transmission electron microscope, Assuit University**.** [19]

Statistical analysis:

Morphometric and Statistical analysis

Stained sections with H & E of the cerebellar cortex of the three groups at the two ages (at magnification×200) were morphometrically analyzed using software Image J (version 1.53).The following measures were taken: The external granular layer thickness, the molecular layer thickness, and the number of normal Purkinje cells in fixed area;200×300Px (fig. 1 A and B). For each section, 10 non-overlapping fields were taken. The mean± SD (Mean ± standard deviation of the mean) was measured by SPSS program version 16. The one-way analysis of variance (ANOVA) test was done for comparison between the three groups. [20]

The degree of significance (P value) was determined as follows:

P > 0.05 (NS) → Not significant.

P≤0.05 (*) → Significant.

P≤ 0.00l (**) → Highly significant.

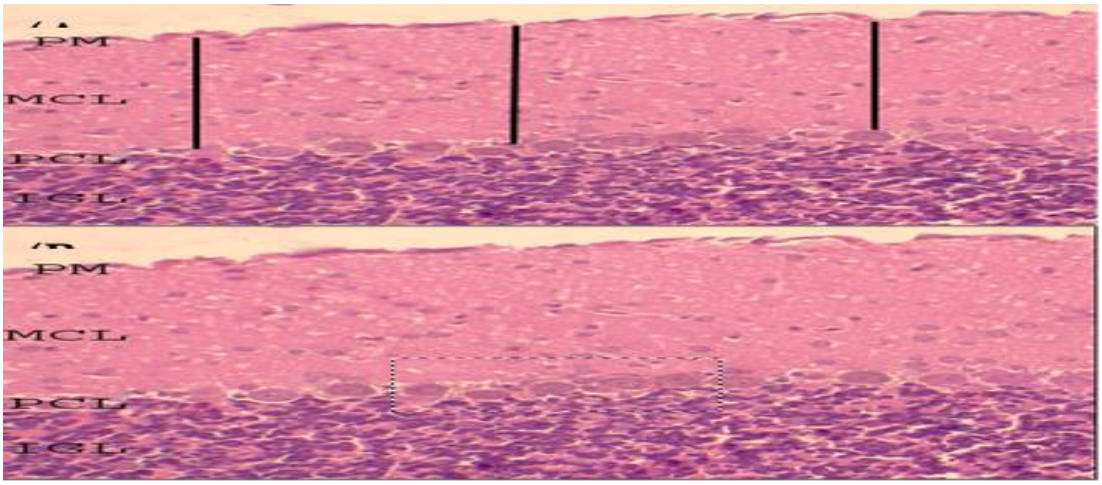

Figure 1: demonstrating how measurements taken ;(A) Measuring layer thickness. (B) Counting purkinje cell number in fixed area.

Results:

A-General observations

As regards the pregnant rats of control (group A), tartrazine (group B), or sesame (group C) there was no mortality till the end of the study. However pregnant rats treated with tartrazine (group B) showed some aggressive behavior; eating their offspring and attacking each other's.

B- Histological results:

Light microscopic Results by Hematoxylin and Eosin stain:

At the age of 2 weeks (figure 2)

The Control group (Group AI): the normal appearance of the cerebellar cortex at this age was noted; the cortex had four layers from outer to inner; external granular layer (EGL), molecular layer (ML), Purkinje cell layer (PCL) and internal granular layer (IGL). EGL appeared as a thin layer of small granule cells oval in shape. The molecular layer appeared as a distinct wide layer superficial to the Purkinje cell layer containing superficial stellate and deep basket cells. The Purkinje cell layer showed well-differentiated flask-shaped cells with large less stained nuclei and prominent nucleoli arranged in one row. The cells of the internal granular layer were condensed and appeared dark blue stained.

Tartrazine group (Group BI): The external granular layer showed areas of vacuolations. The thickness of the molecular layer was reduced when compared to control with areas of vacuolations. The Purkinje cell layer showed marked cell loss; with cells smaller in size and a lot of degenerated and dead cells. The cells of the internal granular layer were aggregated as follicles, with edematous spaces

and vacuolations in between the cells. Also there was extravasated hemorrhagic blood in all layers.

Sesame oil group (Group CI): The four layers appeared nearly similar to that of the control **(AI)**, but still there were some degenerated Purkinje cells and minimal vaculations.

At the age of 4 week (figure 3)

The Control group (Group AII): the cortex formed of a molecular layer, Purkinje cell layer and inner granular layer. The molecular layer thickness and density were increased in comparison with the cortex of 2 week-old offspring and showed superficial stellate and deep basket cells. The Purkinje cell layer was still formed of a single row of Purkinje cells. The cells were spherical and pear in shape and nuclei were large, vesicular, and intensely stained with prominent nucleoli. The granular cell layer was formed of deeply stained granular cells, round or oval in shape, and closely packed together.

Tartrazine group (Group BII): The molecular layer thickness appeared less than that of the control, and also showed a hazy and edematous appearance with areas of vacuolation. Most of Purkinje's cells were degenerated with some deeply ill-defined stained cells, other cells appeared completely degenerated. In The internal granular layer degenerated granule cells appeared aggregated with edematous spaces in between aggregations.

Sesame oil group (Group CII): all layers appeared nearly similar to control group **(AII),** but the molecular layer still showed areas of vacuolation and degenerated basket cells. Also, some Purkinje cells appeared degenerated.

B- Electron microscopic results of Cerebellar cortex at the age of 4 weeks:

The Control group (Group AII): The Purkinje cell appeared large and had invaginated euchromatic nucleus with a large nucleolus surrounded by well- demarcated nuclear envelope. The cytoplasmic membrane is well-defined and their cytoplasm showed a lot of cytoplasmic organelles; rough endoplasmic reticulum, mitochondria, and free ribosomes (Figure, 4).

The granular cells appeared more or less uniform in size and oval in shape, each cell showed a large nucleus surrounded by a thin layer of cytoplasm. Few organelles as mitochondria were noted (Figure, 5).

Tartrazine group (Group BII): Purkinje cell appeared irregular and destructed, had heterochromatic electron dense irregular nucleus, and the cytoplasm showed hardly differentiated organelles as dilated rough endoplasmic reticulum **(Figure 4).**

Most of the Granular cells were irregular, shrunken, had heterochromatic nucleus with condensed chromatin and poorly-defined nuclear envelope, and cytoplasm nearly had no clear organelles. But still, there were few normal granular cells. Also, vacuoles appeared in between cells. (Figure 5)

Sesame oil group (Group CII): The Purkinje cells appeared more or less the same as those of the control group. However, few mitochondria appeared degenerated and few vaculations still were presented inside and outside cells **(Figure 4).**

The granule cells appeared more or less the same as the control group, except for a few granule cells were shrunken and had irregular heterochromatic nuclei, more condensed chromatin, and an ill-defined nuclear envelope with cytoplasm containing no clear organelles. Also, few vaculations appeared in between cells (Figure 5).

C-Morphometric results and statistics

1. The thickness of the external granular layer

At the age of 2 weeks, The mean value of the thickness of EGL is described in Table (1). Comparison between the three groups using a one-way ANOVA test showed a significant difference (P≤ 0.000). Bonferroni Post Hoc Test showed a significant decrease in **Group (BI)** compared to the control **group (AI)** (P≤ 0.000) and that of **group (CI)** (P≤ 0.000), while there was no significant difference between the control **group (AI)** and **group (CI)** (P=1.00) **(Table 1, figure 6).**

At the age of 4 weeks, The EGL completely disappeared in the three groups **AI, BI, and CI.**

2. The thickness of the molecular layer

At the age of 2 weeks, The mean value of the thickness of ML is described in Table (2). Comparison between the three groups using a one-way ANOVA test showed a significant difference (P≤ 0.000). Bonferroni Post Hoc Test showed a

significant decrease in **Group (BI)** compared to the control **group (AI)** (P≤ 0.000). (P≤ 0.000), also there was a significant difference between the control **group (AI)** and **group (CI)** (P=1.00) **(Table 2, figure 7).**

At the age of 4 weeks, The mean value of The thickness of ML is described in Table (2) Comparison between the three groups using one way ANOVA test showed significant difference (P≤ 0.000). Bonferroni Post Hoc Test showed a significant decrease in **Group (BII)** compared to the control **group (AII)** (P≤ 0.000) and that of the **group (CII)** (P≤ 0.000), also there was a significant difference between the control **group (AII)** and **group (CII)** (P=1.00) **(Table2, figure 7).**

3. Number of normal Purkinje cells in fixed area

At the age of 2 weeks, The mean Number of normal Purkinje cells in a fixed area is described in Table (3). Comparison between the three groups using one way ANOVA test showed a significant difference (P≤ 0.001). Bonferroni Post Hoc Test showed a significant decrease in **Group (BI)** compared to the control **group (AI)** (P≤ 0.000) and that of the **group (CI)** (P P= 0.026), also there was a significant difference between the control **group (AI)** and **group (CI)** (P=1.00) **(Table3, figure 8).**

At the age of 4 weeks, the mean number of normal Purkinje cells in a fixed area is described in Table (3). Comparison between the three groups using one way ANOVA test showed a significant difference (P≤ 0.001). Bonferroni Post Hoc Test showed a significant decrease in **Group (BII)** compared to the control **group (AII)** (P≤ 0.000) and that of the **group (CII)** (P P= 0.026), also there was a significant difference between the control **group (AII)** and **group (CII)** (P=1.00) **(Table3, figure 8).**

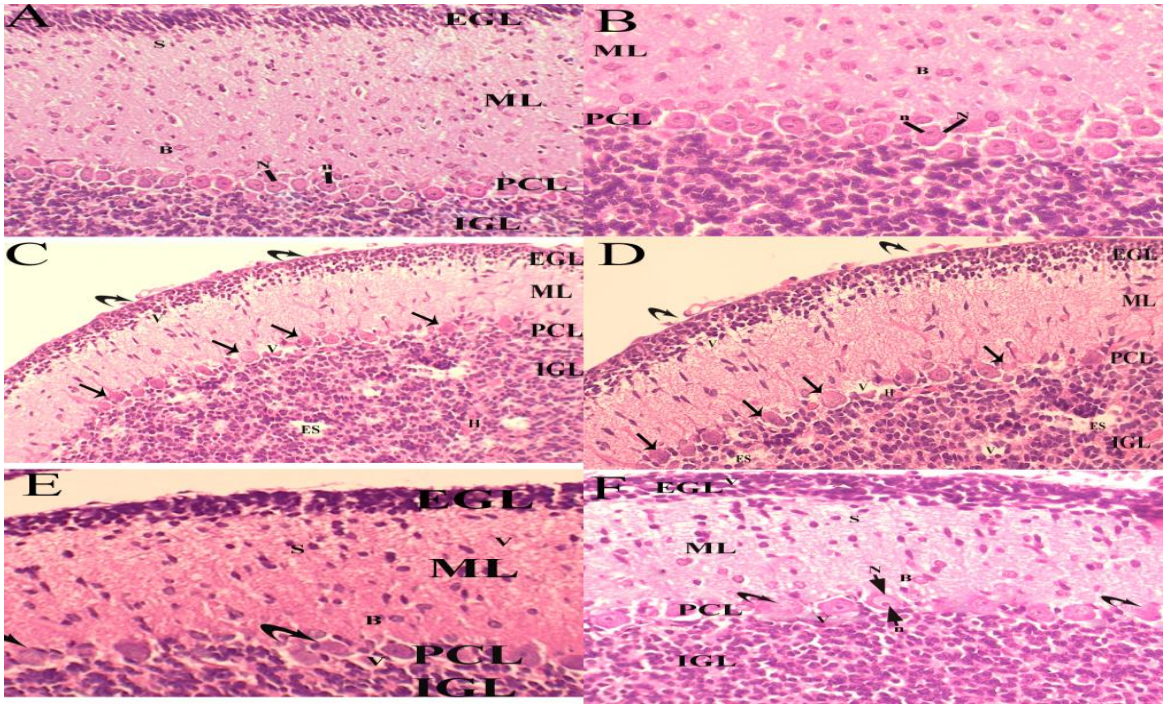

Figure 2: **photomicrographs** of sections of the cerebellar cortex of albino rats at 2 weeks of age showing the four layers of the cortex; external granular layer (EGL), molecular layer (ML), Purkinje cell layer (PCL) and internal granular layer (IGL). **A** (HX& E X 200)**, B** (HX& E X 400) **control group AI**; Molecular layer (ML) shows superficial stellate(s) and deep basket (B) cells. The Purkinje cell layer is arranged in one row of cells each has large less stained nuclei (N) and prominent nucleoli (n). The cells of the internal granular layer are condensed and appear dark blue stained. **C** (HX& E X 200)**, D** (HX& E X 400) **group AII**; the PM appears with tissue loss (curved arrow). The EGL shows vacuolation (V). The molecular layer (ML) shows a reduction in size in comparison to group AI with vacuolations (V). Most PCs are dead (arrows), with marked cell loss; decrease number of PCs. The IGL cells appear fewer in number; with edematous spaces (ES) and vacuolations (V) in between the cells. Also, there is some extravasated

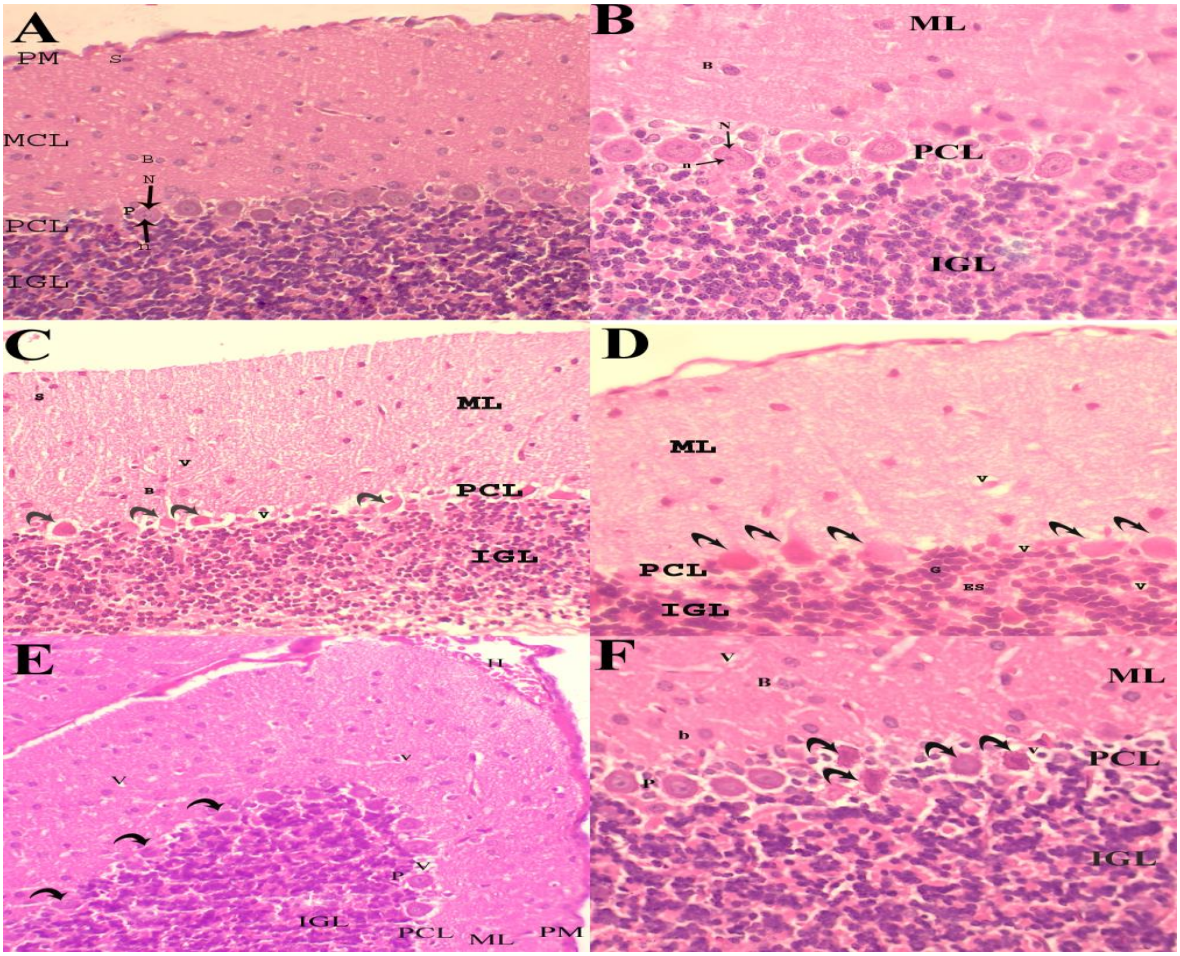

Figure 3: **photomicrographs** of sections of the cerebellar cortex of albino rats at 4 weeks of age showing; pia matter (PM), molecular layer (ML), Purkinje cell layer (PCL), and internal granular layer (IGL) with complete absence of EGL. **A** (HX& E X 200)**, B** (HX& E X 400) **control group BI**; Molecular layer (ML) thickness is increased as compared to that of 2 weeks age with superficial stellate(s) and deep basket (B) cells. PCL arranged in a single row with cells (P) spherical and pear in shape and nuclei (N) are large, vesicular, intensely stained with prominent nucleoli (n). The granular cell layer is formed of deeply stained granular cells, round or oval. **C** (HX& E X 200)**, D** (HX& E X 400) **group BII**; the molecular layer appears hazy and edematous with a reduction in its size and areas of vacuolation (V). Most PCs are destructed (arched arrows) with some PCs appearing deeply stained with ill-defined features, others appear completely degenerated. Cells of the internal granular layer (IGL) are aggregated and show degenerated granules (G) and edematous spaces (ES) in between. **E** (HX& E X 200)**, F** (HX& E X 400) **group BIII**; all layers appear nearly similar to the control group, but still there are areas of vacuolation (V) and degenerated basket (b) cells in ML. Also, PCL still shows degenerated PC (arched arrows). A small area of hemorrhage in the pia matter (H).

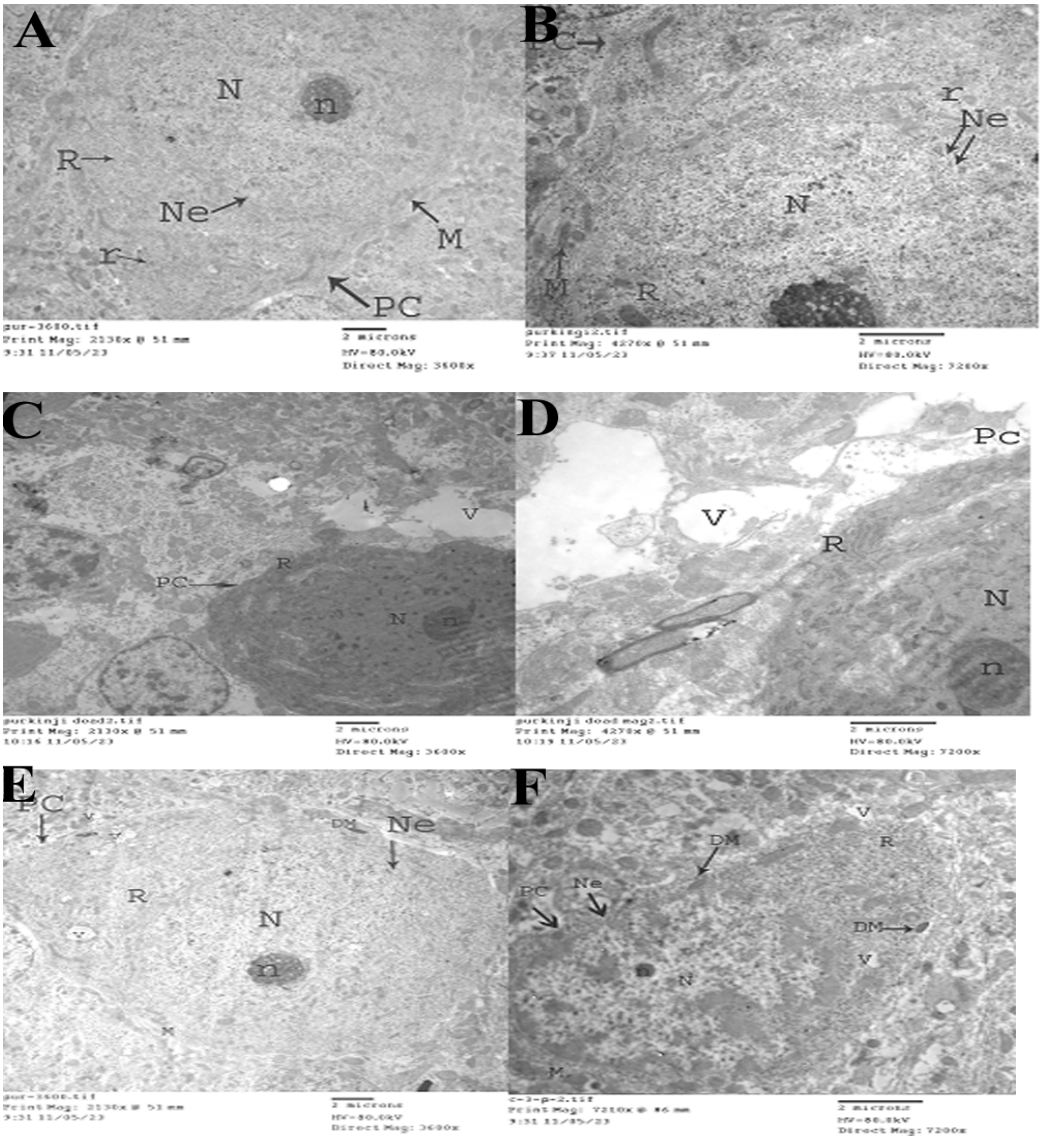

Figure 4: **Electron micrographs** of Purkinje cells at 4 weeks of age. **Control group BI (A)** viewed at ×3600 and **(B)** viewed at ×7210; showing its characteristic shape; oval large cell with a clear-demarcated cell envelope (PC), euchromatic nucleus (N) appears with distinct nuclear envelop (Ne) and prominent nucleolus (n), the cytoplasm contains clear organelles; the mitochondria (M), ribosomes(r) and Rough endoplasmic reticulum (R) appears healthy. **Group BII (C)** viewed at ×3600 and **(D)** viewed at ×7210; the cell membrane (PC) appears irregular, the heterochromatic nucleus (N) appears with an unclear nuclear envelope (Ne) and prominent nucleolus (n), there are no clear organelles; except some dilated Rough endoplasmic reticulum (R). Vacuoles (V) were noted within the cytoplasm and outside the Purkinje cell. **Group BIII (E)** viewed at ×3600 and **(F)** viewed at ×7210; PC appears nearly similar to the control group, except few mitochondria appear degenerated (DM). Vacuoles (V) appear within the cytoplasm and outside the Purkinje cell.

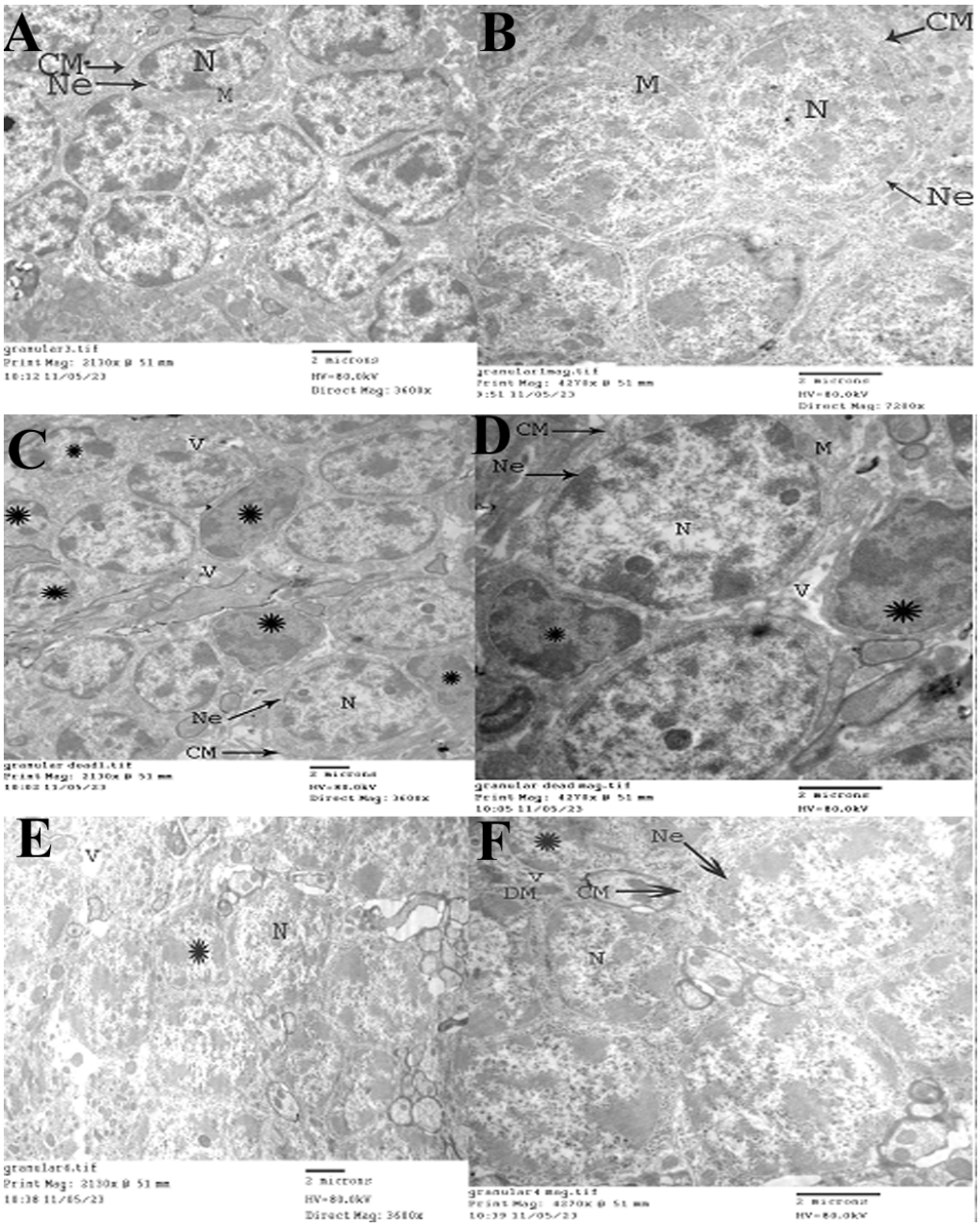

Figure 5: **Electron micrographs** of the granular cells of 4 weeks. **Control group BI (A)** viewed at ×3600 and **(B)** viewed at ×7210; granular cells show large size euchromatic nucleus (N) which shows well demarcated nuclear membrane (Ne) and a thin rim of cytoplasm with clear cell membrane (CM) the cytoplasm contain multiple mitochondria(M). **Group BII (C)** Viewed at ×3600. **(D)** Viewed at ×7210; many granule cells are shrunken (*) with irregular shrunken heterochromatic nucleus, with condensed chromatin and poorly-defined nuclear envelope. Their cytoplasm contains no clear organelles. vaculations appear in between cells (V). **Group BIII (E)** Viewed at ×3600. **(F)** Viewed at ×7210; most of the granular cells are more or less similar to the control group, except a few cells appear degenerated with Vacuoles (V) noted within and outside the cytoplasm.

Table 1: Statistical analysis of thickness of EGL in the three groups using one way ANOVA test

Postnatal age	Thickness of EGL	Group 1	Group 2	Group 3	P*	P1*	P2*	P3*
2 week	Mean ± SD Quartile(Range)	55.37±13.51 52(36:91)	33.06±7.24 32(23:59)	58.23±31.2 51(27:162)	<0.001	<0.001	1	<0.001

Table 2: Statistical analysis of thickness of ML in the three groups using one way ANOVA test

Postnatal age	Thickness of ML	Group 1	Group 2	Group 3	P*	P1*	P2*	P3*
2 week	Mean ± SD Quartile(Range)	214.2±49.66 213(153:340)	113.86±35.33 103(72:206)	122.31±31.76 111(83:200)	<0.001	<0.001	<0.001	0.1
4 week	Mean ± SD Quartile(Range)	253.43±60.24 267(159:373)	177.2±27.83 177(127:236)	215.83±60.97 227(112:309)	<0.001	<0.001	0.009	0.007

Table 3: Statistical analysis of number of Purkinje cells in the three groups using one way ANOVA

Postnatal age	Purkinje cells NO	Group 1	Group 2	Group 3	P*	P1*	P2*	P3*
2 week	Mean ± SD Quartile(Range)	5.49±1.27 5(4:9)	2.46±1.04 3(0:5)	4.2±1.43 4(2:8)	<0.001	<0.001	<0.001	<0.001
4 week	Mean ± SD Quartile(Range)	3.74±1.29 3(2:6)	1.74±0.70 2(1:3)	2.77±1.09 3(1:6)	<0.001	<0.001	0.001	<0.001

P comparing between the three groups using Oneway ANOVA

P1 comparing between group1& group2 using Post Hoc Bonferroni Tests
P2 comparing between group1& group3 using Post Hoc Bonferroni Tests
P3 comparing between group2& group3 using Post Hoc Bonferroni Tests
*: Significant if P≤0.05 & highly significant if (P≤0.001).

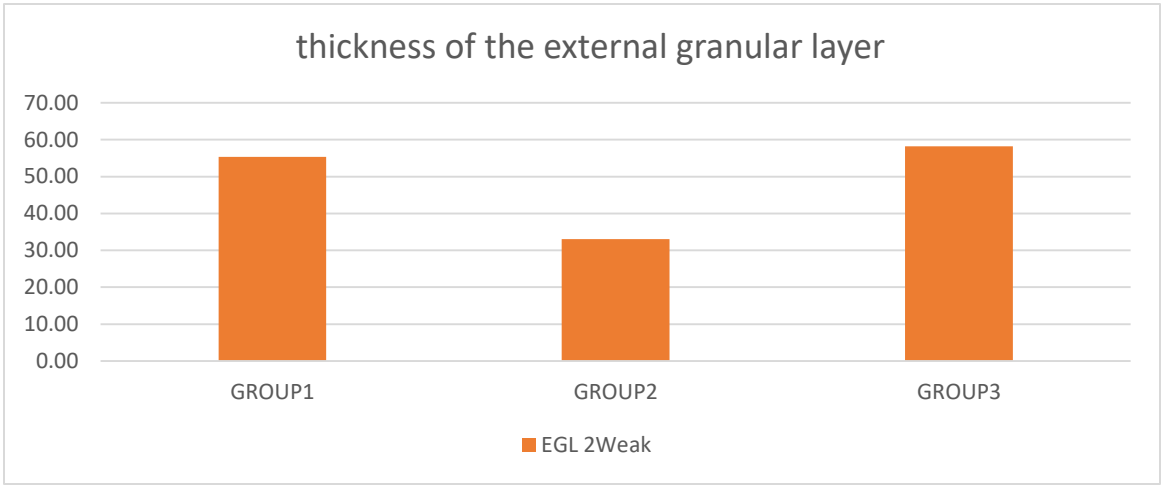

Figure 6: Chart showing statistical analysis of thickness of external granular layer of the three groups at 2weeks of age

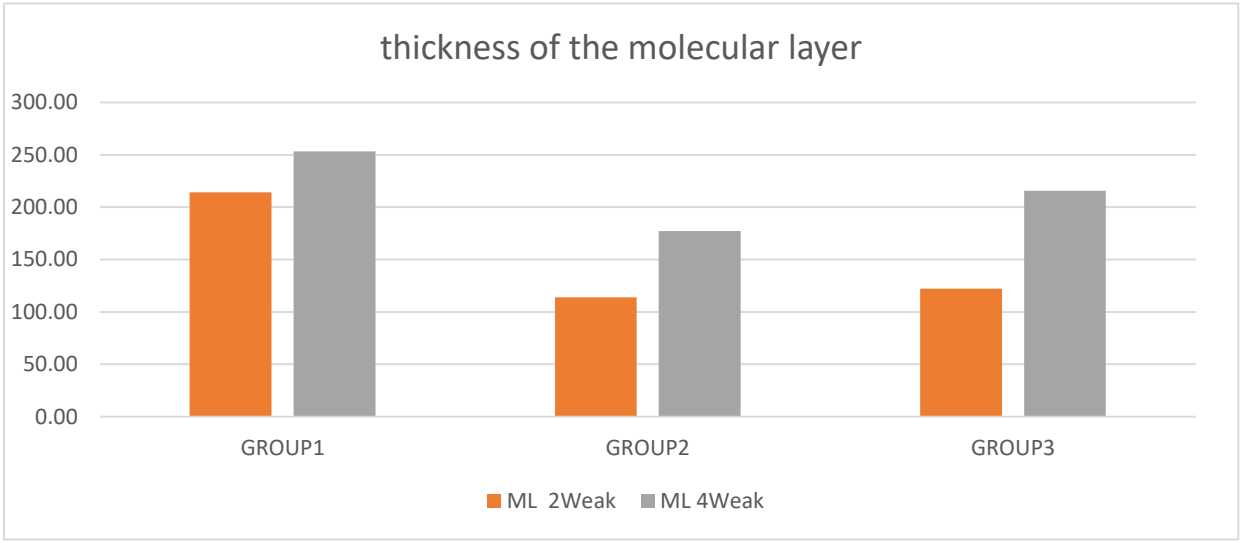

Figure 7: Chart showing statistical analysis of thickness of Molecular layer of three groups at 2weeks and 4weeks of age

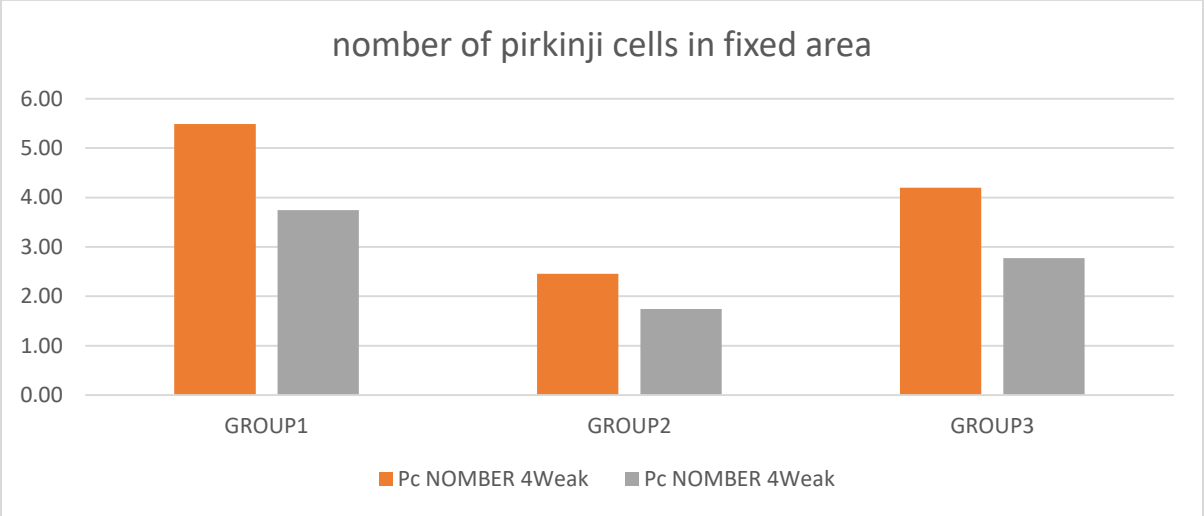

Figure 8: chart showing statistical analysis of No. of Purkinje cells in the three groups at 2weeks and 4weeks of age.

Discussion

The use of azo dyes; like tartrazine can result in certain diseases such as anemia, lesions in the brain, liver, kidney, and spleen; tumors and cancer; delay and lack of growth and mental abnormalities in the offspring. [6,21]

Our study demonstrated that administration of tartrazine to pregnant rats affects the development of cerebellum of the offspring; which was histoologically observed by a decrease in the diameter of the external granular layer, decreased diameter of the molecular layer and decreased number of normal Purkinje cells. Also electron microscope showed apoptosis of cells. These histopathological changes were observed in all ages.

Also, **Biswas et al.** [22] reported that ingestion of azo dyes (tartrazine) and their mixture interfere with learning and memory, enhanced oxidative stress, decreased acetylcholinesterase activity, and disrupted neuronal structure, which may be due to effects on the electron transport chain and increased oxidative stress which could affect behavior and cognitive performance.

Similarly, **S Mahmoud et al.** [23] mentioned that tartrazine ingestion induced neurotoxicity cleared histologically by vacuolar degeneration and swelling of the cerebellar cortex with decreased numbers of Purkinje cells and increased number of apoptotic cells.

Moreover, **Ovalioglu et al.** [24] investigated the effects of tartrazine exposure on development of the neural tube, in early-stage chicken embryo. The results reported that tartrazine could cause neural tube defect NTD in the chicken model of embryo development.

However when tartrazine was administered within the adequate daily intake to pregnant and lactating mice; teratogenic effects and neurobehavioral changes were noticed in their offspring. Confirmed by histological changes in different parts of the brain. [16]

Also, **Miller et al.** [25] who conducted a systemic study on tartrazine's effect on activity and attention in children, found that human and animal clinical trials toxicology literature confirmed an association between synthetic food colors and behavioral impacts in children.

Erickson et al. [26] studied the consequences of exposure to artificial food dye (tartrazine), and they suggested that tartrazine ingestion at least contributes to motor hyperactive behaviors, whatever underlying stress-induced programming.
On the other hand, an older study mentioned that when pregnant Rats were exposed to the artificial

food dye during pregnancy lactation didn't affect fetal development or the postnatal mortality rate of the newborn. The sole effect on the postnatal development of the central nervous system (CNS) was a tiny temporary alternation in the neuromotor clinging ability of female newborns. [(27)]

Also, another study noted that artificial food dyes which are used commonly have no bad effects on hippocampus-dependent spatial learning and memory when ingested as a mixture in adequate daily amounts. Only mild significant effects on locomotor activity were noted. [(28)]

The current study suggested that concurrent oral administration of sesame oil together with tartrazine to pregnant rats has a protective effect on the cerebellum of their offspring proved by the prevention of apoptotic effect on cerebellar cortical cells mainly Purkinje cells.**Ahmed et al.**[(29)]

Evaluated the neuroprotective effect of sesame oil after drug-induced Parkinson's disease model in mice. They suggested that sesame oil may have a good neuroprotective effect due to the presence of potent antioxidants such as sesamolin, sesamin, and sesamol in sesame oil.

Hussien et al. [(30)] concluded that Sesame oil significantly improved the oxidative stress of cypermethrin on the brain suggested by protected histological changes, improved fragmentation of genomic DNA, and return of the plasma triacylglycerol and cholesterol to normal levels.

Asle Iranifam et al. [(31)] mentioned that a diet with 10% sesame oil during conception and lactation elevates the passive ″avoidance memory learning after 48 hours" in mice at the age of 30 days.
Moreover, a study of the suggested health-promoting effects of sesame revealed that sesame oil could manage oxidative stress-related diseases such as atherosclerosis and neurodegenerative diseases such as Alzheimer's disease. [(32)]

Also, **Shuaib and Doaa.**[(33)] screened the neuroprotective role of sesame oil hippocampal damage caused by energy drinks, and they concluded that drinking Energy drinks induced morphological and morphometric changes. However, Sesame oil administration ameliorates these adverse changes mostly because it has antioxidant and anti-inflammatory effects.
Moreover, an investigation of natural plant resources' oral administration preventive effect against dementia, cleared that ingestion of sesame seeds may protect against dementia by sesamin and sesamolin, found in sesame seeds. [(34)]

Conclusion:

- Ingestion of tartrazine during pregnancy in daily regular doses could affect the development of the cerebellum of the offspring, thus neurodevelopment.
- Sesame oil ingestion in daily doses could have a protective effect against that of tartrazine.

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