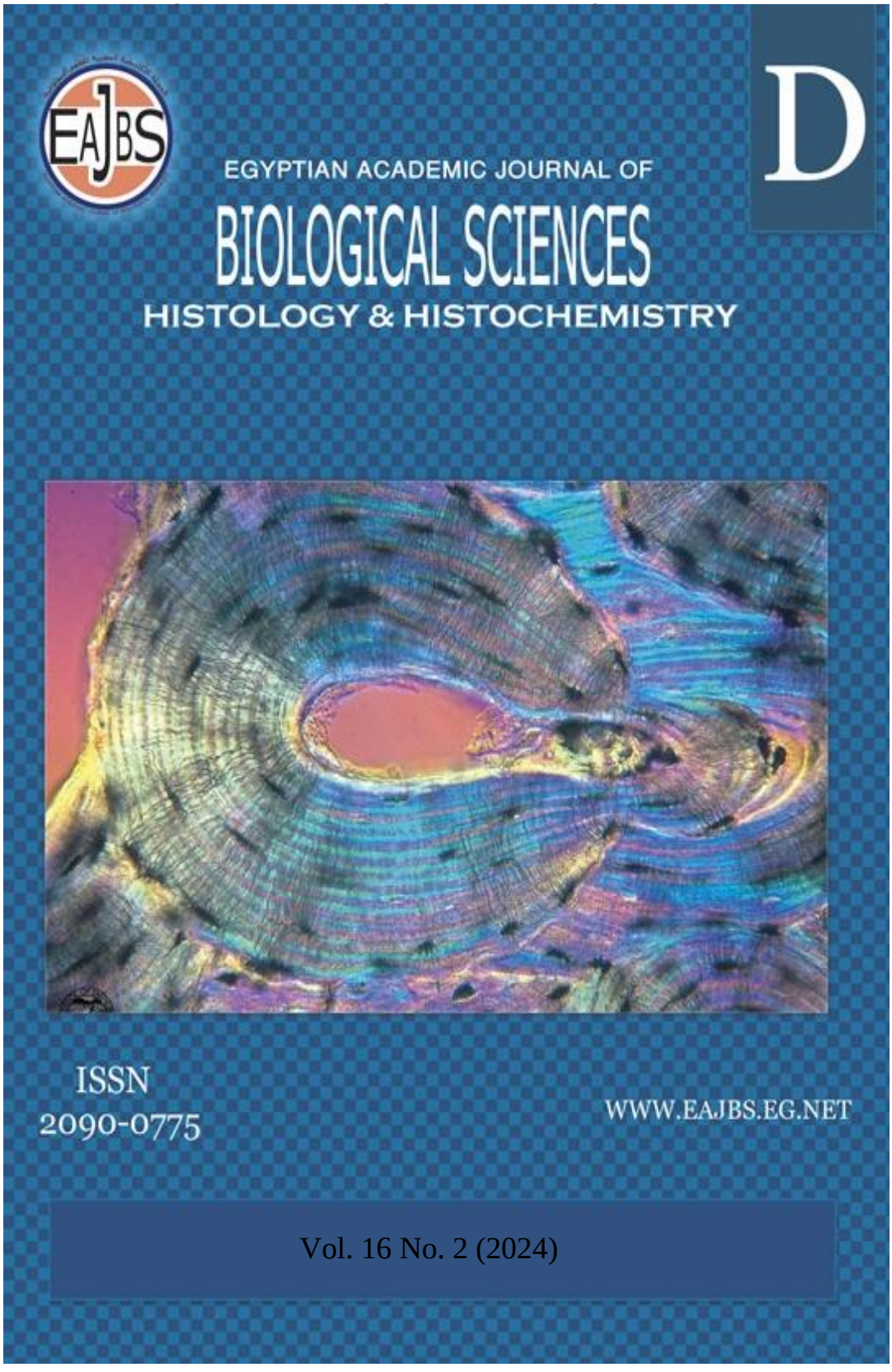

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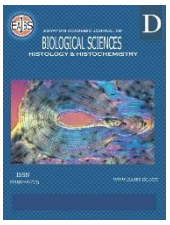

A comparative Study of The Antidepressant Effect of *Datura stramonium* Leaf Extract against Seroxat in Pregnant Albino Rats and Their Offspring: Light and Electron Microscope Study

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ABSTRACT

Postpartum depression is a severe psychiatric disease that affects 10-30% of moms worldwide. Elucidating the possible antidepressant role of *Datura stramonium* by mitigating the harm to the brain frontal cortex caused by maternal depression in both the mother as well as offspring in comparison to the antidepressant drug (Seroxat) is the aim of the current work. A hydroethanolic extract of *Datura stramonium* is prepared and analyzed phytochemically utilizing Fourier transform infrared spectrophotometry. Twenty-five rats were separated into five groups (each with five mothers and offspring rats): I (Control non-pregnant), II (Control pregnant), III (Postpartum), IV (*Datura* treated) groups in which mothers administered with 50 mg of D. stramonium extract orally, and V (Seroxat treated group) in which mothers administered with 0.36 mg/100g body weight of paroxetine orally. After a week following the delivery, every treated mother rat and offspring were slaughtered and dissected for brain extraction, preparation and staining with haematoxylin and eosin, Congo red, and SERT immunoreaction for light microscopic examinations. The brain's frontal cortex was taken and prepared for observation of cellular ultrastructure. Ultimately, it was analyzed and imaged using a transmission electron microscope. Overall results of *Datura* treatment showed mild improvement in most mothers and offspring groups but an antidepressant drug (Seroxat) showed some ameliorated effects on mothers but not offspring.

We can conclude that Datura leaf extract can be used as an antidepressant for pregnancy-related brain damage as an alternative to the well-known treatment of Seroxat, but it should be taken with caution under medical supervision.

INTRODUCTION

Depression constitutes a widespread neuropsychiatric disorder that affects a large number of people. The most prevalent neurological symptoms in depressed patients include sleep issues, memory loss, dizziness, and headaches (Liu *et al*., 2022). Depression represents an international health issue that is considered one of the main causes of disability. Depression becomes significantly more stressful in women when it happens throughout gestation; many writers believe that the neuroendocrine alterations happening during pregnancy promote the emergence of depression-related conditions (Vieira *et al*., 2013).

Depression after delivery constitutes a severe psychiatric disease that affects 10-30% of moms worldwide. Its etiology and pathophysiology are not fully known as of today, although numerous ideas on the interaction of hormones, genetics, epigenetics, nutrition, neurotransmitters and socio-environmental variables have been proposed (Rupanagunta *et al*., 2023).

Depression as well as other stressful feelings throughout pregnancy, like anxiety, can be damaging to the mother's, fetuses, and newborn's health. Thus, it is crucial to examine potential risk along with the incidence of prenatal depressive disorders throughout pregnancy (Al-abri *et al*., 2024). Examples of risk factors comprise young age, previous experiences of depression, experiencing familial violence, higher life pressures, a lack of social help, unplanned pregnancy, having a lower income, poorer learning, smoking cigarettes, unmarried position, and bad relationship qualities (Hamel *et al*., 2019).

Pregnancy is distinguished by hormonal swings that outnumber any other neuroendocrine event in a woman's lifespan (e.g., menstruation, puberty, and menopause) (Deems & Leuner, 2020). Pregnancy is marked by a significant rise in circulating steroid hormones such as estradiol, progesterone, and cortisol (Galea & Frokjaer, 2019). These constantly growing chemicals are considered to affect the brain by crossing the blood-brain barrier in humans as well as animals during pregnancy (Sacher *et al*., 2020). Among humans, no less than two independent studies have established that pregnancy causes considerable reductions in the size of the brain (Oatridge *et al*., 2002) as well as grey matter size (Hoekzema *et al*., 2017). Furthermore, alterations in the endocrine system are connected with alterations in the cerebral hemisphere, such as decreases in the brain or grey matter volume (Luders *et al*., 2018). A range of depression treatments have previously been tried (Cuijpers & Karyotaki, 2021). For example, SSRIs that denote selective serotonin reuptake inhibitors are the first-line pharmaceutical treatments. In women suffering from moderate to severe postnatal depression, SSRIs have demonstrated improvement and remission (Brown *et al*., 2021). Paroxetine is a popular antidepressant that is often used to treat anxiety and depression. It belongs to the class of drugs known as SSRIs (Fernandes *et al*., 2020).

Medicinal herbs contain bioactive compounds designed to mitigate chemotherapy-induced harmful effects (Mahmoud *et al*., 2018). *Datura stramonium* appears as a medicinal herb in the Solanaceae family that occurs in the tropics and temperates of the world; it developed in America and currently exists in India, Ethiopia, Australia, Nigeria and China (Céspedes-Méndez *et al*., 2021). *Datura stramonium* is a leafy, tall, robust, smooth, pale yellow-green plant that may reach 1.2 m in height (Cherie Melaku & Amare, 2020). *Datura stramonium* has anti-cancer, anti-oxidative, and anti-inflammatory properties (Nasir *et al*., 2020; Sharma *et al*., 2021). *Datura stramonium* was additionally employed to treat asthma and epilepsy (Mohammed *et al*., 2021). Alkaloids found in *Datura stramonium* include hyoscyamine, atropine, apo atropine, scopolamine, tigloidin, aposcopolamine, and N-oxide (Batool *et al*., 2020). *Datura stramonium* has been employed in conventional medicine for centuries to treat pain, shortness of breath, fevers, and other symptoms. It is a strong deliriant and hallucinogen. However, because alkaloids have significance for both therapeutic and hallucinogenic qualities, greater doses are harmful. It possesses sedative and hypnotic properties (Sa, 2018).

The purpose of this study is to compare the antidepressant effects

regarding *Datura* stramonium within the frontal cortical tissue of pregnant female rats' brains to those produced by antidepressant medicines.

MATERIALS AND METHODS

Collection and Extraction of *Datura stramonium*:

Datura stramonium leaves were gathered from the Ornamental Plants Department, Faculty of Agriculture, Cairo University, and extracted at the Botany Department, Faculty of Science, Helwan University. Freshly harvested leaves were air-dried in a well-ventilated environment. Clenched dried leaves weighing 655 g were submerged in 2 L of distilled water and 70% ethanol in a 1:1 ratio for 72 hours. It was then extracted and filtered via muslin sheets and Whatman filtration paper. To ensure maximum extraction, the residue was resoaked twice. The filtrates were dried (evaporated) at decreased pressure at around 40°C to get the solid extract (8.7% yield) (Akindele *et al*., 2015). The required dose of the extract was (50 mg/kg b. wt.) dissolved in purified water, which was administered to the group treated with *Datura stramonium* daily by gastric gavage every day during pregnancy (Ogunmoyole *et al*., 2019).

Phytochemical Analysis:

Using the technique of Pakkirisamy *et al*., (2017). PerkinElmer Fourier transform infrared spectrophotometry (FT-IR) spectrometers, Instrument Model: Spectrum Two, Instrument Serial Number: 109979 were used to perform FTIR for *Datura stramonium* leaves in the central laboratory, Faculty of Science, Helwan University. The transmittance range for scanning was 4000 to 400 cm1 (Mid-IR region).

Chemicals and Drugs:

A therapeutic dosage of an antidepressant medication (Seroxat) is used. GlaxoSmithKline Company, Cairo, Egypt, manufactures Seroxat (paroxetine hydrochloride, tablets). It is a phenylpiperidine hydrochloride salt. Paroxetine hydrochloride is a white powder with no odor. The paroxetine dosage was 40 mg each pill. It was powdered and mixed with distilled water. According to EL-Gaafarawi *et al*. (2005), the animals in the paroxetine group were given a daily oral dose of 0.36 mg/100g b.w. In 0.5 mL of pure water, each dosage was dissolved.

Experimental Animals and Design:

The study was done at the Zoology Department, Faculty of Science, Helwan University. The study included twenty adult female as well as ten male albino rats measuring 120-150 gm, as well as five female albino rats measuring 70-90 gm. All the rats came from the animal facility of the Egyptian Organization for Biological Products and Vaccinations. All animals were housed in standard cages, five every cage, in a controlled-temperature area (22ºC) with a 12-hour light/12-hour dark cycle. The animals were provided an unrestricted supply of food and water.

The Helwan University Institutional Animal Care and Use Committee for Laboratory Animals (HU-IACUC/Z/SR0604-43) gave its approval to the experiment. The Zoology Department at the Faculty of Science at Helwan University has received permission.

Twenty-five rats were separated into five distinct groups: I, II, III, IV, and V (each including five mothers and offspring rats).

I- The control non-pregnant rats group comprised five mature female rats measuring 70-90 grams (non-pregnant) and received no medication.

II-Control pregnant rats group: comprised of five pregnant rats and their fetuses for two weeks; they received no medication.

III-Postpartum rats group: comprised of five mom rats and their offspring, who received no medication.

IV- *Datura* treatment rats group: Composed of five mom rats and their offspring, every mother rat was given 50 milligrams of *Datura stramonium* extract by mouth on the first day after fertilization till parturition.

V-Seroxat treatment rats group comprised 5 mother rats and the offspring they produced. Every mother rat was given 0.36 mg/100g of body-weight of paroxetine in an oral form on the first day after fertilization until parturition.

Light Microscope Study:

Within seven days after delivery, both treatment mother rats and pups were sacrificed under 6% isoflurane anesthesia and separated for brain surgical removal, and preparation, along with staining with haematoxylin and eosin (H&E) (Bancroft & Layton, 2019), Congo red and SERT (serotonin transporter) immunoreactions during light microscopic assessments will be performed (Rajamohamedsait & Sigurdsson, 2012).

Immunohistochemistry:

Paraffin-embedded lung tissue slices were stained utilizing diaminobenzidine (DAB) staining kits (Maxin-Bio, Fuzhou, China). The main rabbit polyclonal antibody to the SERT protein (bs-1893R, Biosynthesis Biotechnology, Beijing, China) was diluted 1:300. As a negative control, samples were treated with 0.01 M phosphate-buffered saline (PBS) rather than the primary antibody. Immunohistochemical staining was performed using a standard indirect approach that employed citrate antigen retrieval.

Electron Microscope Study:

The frontal part of the brain cortex was removed and processed for cellular ultrastructure analysis (Afifi & Embaby, 2016).

The sections were studied by JEOL-JEM-1010 transmission electron microscope in an electron microscopic examination unit at the Regional Center for Mycology and Biotechnology (rcmb), al-Azhar University to perceive the ultrastructural changes.

Morphometric Analyses:

ImageJ analysis software (Fiji ImageJ; 1.51 n, NIH, USA) was used in the Zoology and Entomology Department of Helwan University.

The area % of the thickness of the cortex in frontal sections by H&E stain plus percentage of positive serotonin transporter immunoreaction were assessed in ten separate fields at a ×400 magnification.

Statistical Analysis:

The results are reported as mean ± SD. Data for several variable comparisons were analyzed using one-way ANOVA in the statistical package program (SPSS version 20). To compare group significance, the "Tukey" post-hoc analysis was used. P-value ≤ 0.05 was considered statistically significant (Petrie & Sabin, 2005).

RESULTS

The FTIR assessment of the leaf extract indicated the existence of Aldehyde, Alkane, Amine, alkyl halide, and alkenes, with prominent peaks at 3012.88, 2928.01, 2908.58, 2852.65, 1742.51, 1267.16, 1236.3, 1147.57, 1020.41, 877.68 (Table 1).

Table 1: Fourier-transform infrared assessment of main function groups in *Datura stramonium* leaf extract

Peak (Wave number cm-^{1})	Transmittance %	Appearance	Group	Compound class
3012.88	15.862	Medium	=C-H Stretch	Aldehyde
2928.01	15.415	Strong	C-H Stretch	Alkane
2908.58	15.313	Strong	C-H Stretch	Alkane
2852.65	15.018	Strong	C-H Stretch	Alkane
1742.51	9.174	Strong	C=O Stretch	Aldehyde
1267.16	6.671	Medium	C–N Stretch	Amine
1236.30	6.508	Medium	C–N Stretch	Amine
1147.57	6.041	Strong	C-F Stretch	alkyl halides
1020.41	5.372	Strong	C-F Stretch	alkyl halides
877.68	4.620	Strong	=C–H Bending	Alkenes

The microscopic analysis of Hematoxylin & Eosin- stained sections in the cortical frontal part of non-pregnant control revealed the cerebral cortex's well-known normal structure. From the outside in, they discovered six layers of grey matter including molecular then external granular then external pyramidal then interior granular then internal pyramidal and multiform layers. Inside these layers, neurons, particularly pyramidal and granular cells, as well as neuroglia cells, are prevalent. These layers were concealed from the exterior by thin pia matter (Fig. 1A). Few neurons were seen in the molecular and exterior granular layers, as well as granule cells having spherical vesicular nuclei and conspicuous nucleoli, and glial cells with robust nuclei and pericelllar haloes. A blood vessel can also be seen (Fig.1B). The frontal part of brain cortex of a pregnant woman revealed deformation and layers disorganization as well as thick fibrous pia matter, decreased cortical thickness, and a reduction in the number of blood vessels (Fig. 1C). Few neurons contain darkly stained nuclei were seen in the molecular and external granular layers, additionally to smaller pyramidal-shaped neurons with darkly pigmented nuclei and basophilic cytoplasm, as well as smaller granular cells having round vesicular nuclei (Fig.1D). The Postpartum group's frontal brain exhibited normal retinal layers. A molecular layer is bordered by thin pia matter and a thicker cortex than while pregnant (Fig.1E). The molecular and exterior granular layers revealed a few neurons with normally labeled nuclei in the molecular layer. Pyramidal cells containing basophilic cytoplasm along with vesicular nuclei and granule cells with round vesicular nuclei are located in the outer granule layer (Fig. 1F).

The molecular and external granular layers of the *Datura*-treated mother revealed few neurons with normal-coloured nuclei, granule cells have spherical vesicular nuclei, while pyramidal cells have basophilic cytoplasm plus vesicular nuclei. Blood vessels were also observed (Fig. 2A). The molecular and external granular layers of the Seroxat-treated mother revealed a few neurons with typically labeled nuclei, granule cells having round vesicular nuclei, and pyramidal cells having vesicular nuclei. There are dilated blood vessels (Fig. 2B). The pregnant group's fetus' brain cortex had typical layer histological features. Normal neurons along with neuroglia were also present (Fig. 2C). The postpartum offspring group had normal granule cells having central nuclei, regular pyramidal cells having vesicular nuclei, as well as neuroglia cells (Fig. 2D). The layers showed granule cells featuring complete degeneration, smaller pyramidal cells having darkly stained nuclei with cytoplasmic vacuolation, along with some apoptotic cells in the Seroxat -treated progeny (Fig. 2E). The layers in the *Datura* -treated offspring showed typical granular and pyramidal cells (Fig. 2F).

The Congo red stain indicated a minor accumulation of amyloid plaques within the frontal part of the brain cortex of non-pregnant rats (Fig. 3A). The Congo red dye indicated significant amyloid plaque deposition in the pregnant control group's frontal part of brain cortex (Fig. 3B). The Congo red dye indicated modest quantities of plaques of amyloid in the frontal part of brain cortex of a postpartum lady (Fig. 3C). *Datura*-treated mothers developed large deposits of plaques of amyloid in their frontal part of brain cortex (Fig. 3D). Seroxat-treated mothers showed mild plaques of amyloid in their frontal part of brain cortex (Fig. 3E). Congo red staining revealed no amyloid plaques throughout the frontal brains of postpartum *Datura* and Seroxat-treated children (Figs. 3F, 3G, and 3H).

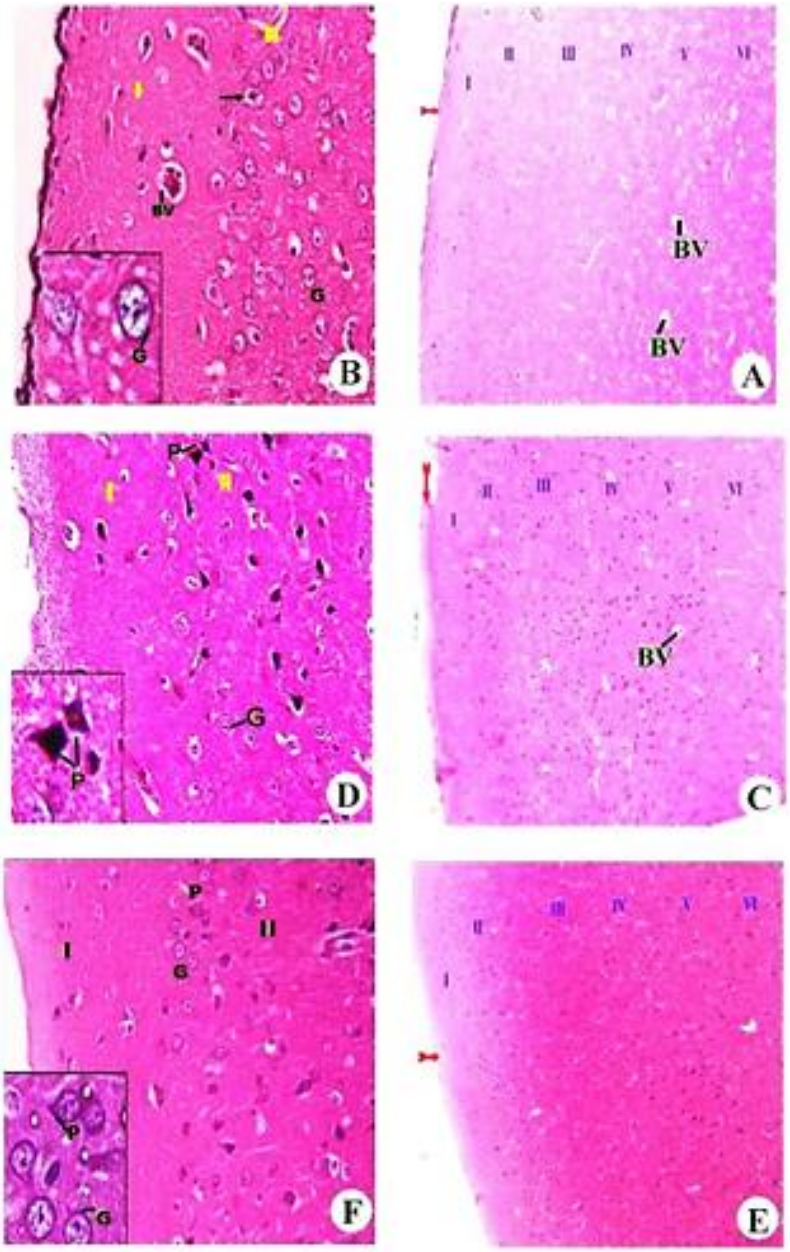

Fig. 1: A photomicrograph of the frontal brain taken from non-pregnant control (A-B), pregnant (C-D), as well as postpartum (E-F). (A) The cerebral cortex displays intact cortical layers with a layer of pia matter (red-tailed arrow) covering the molecular layer visible. Note the existence of blood vessels (BV) (×100). (B) The upper two layers reveal few neurons in the molecular layer and granule cells (G) with round vesicular nuclei and significant nucleoli in the outer granule layer. A blood vessel (BV) is also seen. Note: - glial cells with dense nuclei and pericellular halos (→) (×400; inset, ×1000). (C) Cortex shows distorted cortical layers, thickened fibrous pia mater (red-tailed arrow) covers the molecular layer, whereas cortical thickness decreases. Observe the reduction in the number of blood vessels (BV) (×100). (D) Upper two layers exhibit a few neurons containing darkly stained nuclei in the molecular layer. The outer granular layer reveals shrunken granule cells (G) with rounded vesicular nuclei and shrunken pyramidal neurons (P) with basophilic cytoplasm and darkly colored nuclei (×400; inset, ×1000). (E) The Cortex has typical retinal layers, thin pia matter, or red-tailed arrows, and a thicker cortex envelops the molecular layer (×100). (F) Upper two layers reveal small plenty of neurons in the molecular layer with a normally stained nucleus, the pyramidal cell (P) with basophilic cytoplasm along with vesicular nuclei and the granule cell (G) with rounded vesicular nuclei are visible in the outer granular layer (×400; inset, ×1000). (H &E stain).

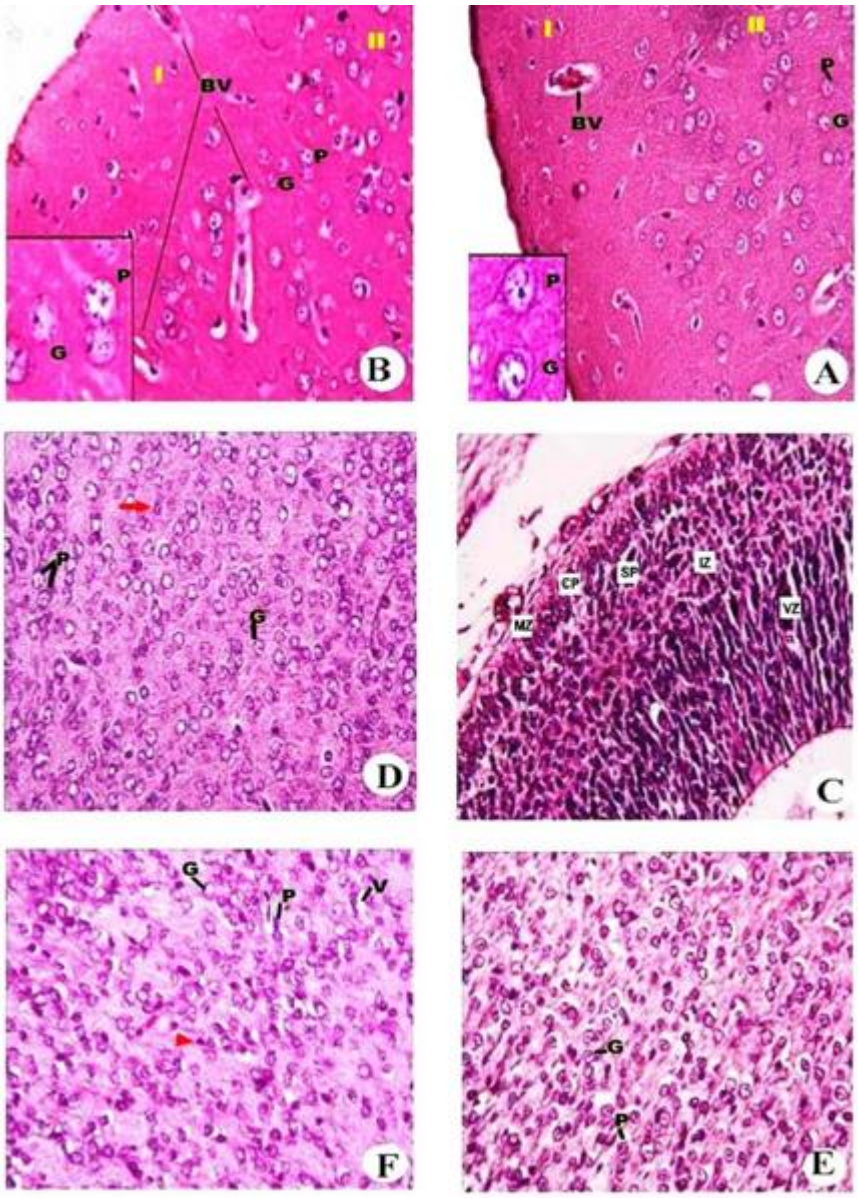

Fig. 2: Photomicrograph of the frontal part of the cerebral cortex of Datura and Seroxat treated mother (A-B), fetus (C), postpartum offspring (D), Datura and Seroxat treated offspring (E&F). (A) Molecular (I) and external granular (II) layers of Datura treated mother show few neurons with normal stained nuclei in the molecular layer. The outer granular layer shows a granule cell (G) with rounded vesicular nuclei and a pyramidal cell (P) with basophilic cytoplasm along with vesicular nuclei. Blood vessels (BVs) were further seen (×400; inset, ×1000). (B) Molecular (I) and external granular (II) layers of Seroxat treated mother show few neurons with a normal stained nucleus in the molecular layer. The outer granular layer shows granule cell (G) with rounded vesicular nuclei and Pyramidal cells (P) have vesicular nuclei. Dilated blood vessels (BV) have been seen (×400; inset, ×1000). (C) The fetal frontal part of the cerebral cortex has typical histological layers, including VZ, SP, CP, and MZ. Observe normal neurons alongside neuroglia cells (×400) (D) The postpartum offspring group's frontal part of the cerebral cortex demonstrates normal granule cells (G) with central nuclei, cells with pyramidal shape (P) with vesicular nuclei, plus neuroglial cells (arrow) (×400). (E) The frontal part of the cerebral cortex of Datura-treated offspring exhibits normal G cells with central nuclei and P cells with vesicular nuclei (x400). (F) Seroxat-treated offspring's frontal cortex, displaying G cells with full degeneration, diminutive P cells with darkly pigmented nuclei and cytoplasmic vacuoles, and some apoptotic cells (arrowhead) were detected. (×400) (H &E stain).

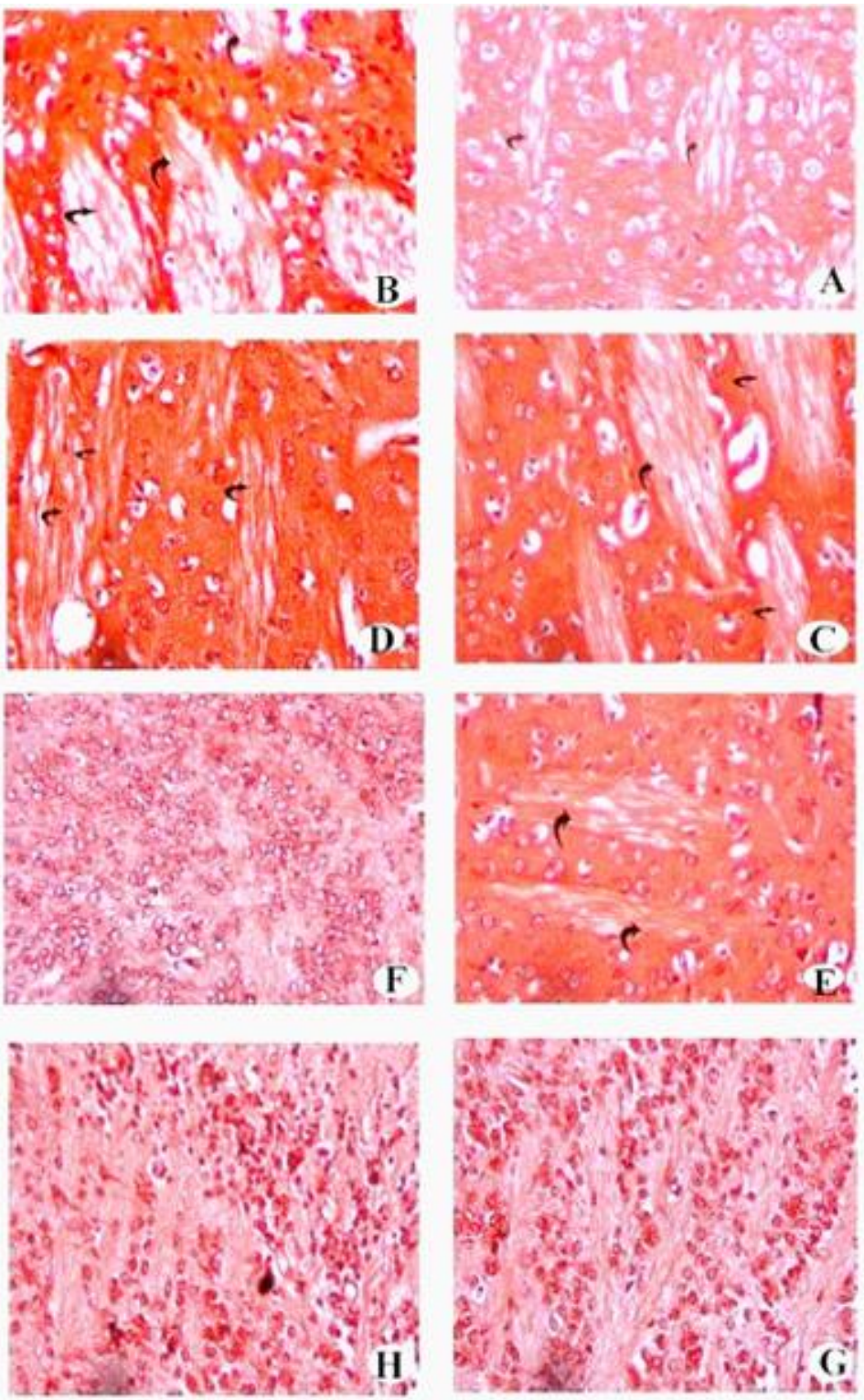

Fig. 3: Photomicrograph of amyloid in the cerebral frontal part of brain cortex of moms (A-E), offsprings (F-H). (A) Non-pregnant control frontal part of brain cortex with modest amyloid plaque deposits (curved arrows). (B) A pregnant woman's cortex of the frontal part with significant amyloid plaque deposits (curved arrows). (C) The postpartum group's frontal part of the brain cortex shows substantial amyloid plaque deposition (curved arrows). (D) The cortex of the frontal part of a *Datura*-treated mother shows significant amyloid plaque deposition. (E) Seroxat-treated mother's frontal part of brain cortex revealing minor plaques of amyloid (curved arrows). (F, G, and H) The cortex of the frontal part of postpartum, *Datura* and Seroxat-treated children revealed a minor quantity of plaques of amyloid (Congo red ×400).

In general, anti-serotonin transporter antibodies were used to confirm serotonin transporter positivity in the frontal part of brain cortex neurons and axons. In the cortical frontal area of the non-pregnant control rats, neuron and axon staining was moderate (Fig. 4A). In the brain's cortical frontal area of the pregnant control rats, neuron and axon immunoreaction was severe (Fig. 4B). In the postpartum group's frontal cortex, neuron and axon staining was modest (Fig. 4C). In the frontal brain of a *Datura*-treated mother, neuron and axon staining was modest (Fig. 4D). In The brain's frontal part of brain cortex of a Seroxat treated mother, neuron immunoreactivity was weak (Fig. 4E). Immunohistochemical staining revealed modest immunoreaction in neuron plus axon in postpartum and *Datura* treated offspring's frontal part of brain cortex (Figs. 4F&4G), while Seroxat treated offspring, it demonstrated negative immunoreaction in neuron plus axon (Fig. 4H).

An electron microscopic analysis of the frontal brain cortex of the non-pregnant control group revealed an adequate nucleus with consistently scattered chromatin, normal mitochondria having prominent cristae, and regular RER (Fig. 5A). Brain’s frontal part of the cortex of the control pregnant group showed a normal nucleus, some damaged mitochondria, and some fractured RER, along with vacuolated cytoplasm (Fig. 5B). The frontal brain of a postpartum woman exhibited a normal nucleus, normal mitochondria, and a properly structured RER (Fig. 5C). Frontal part of the brain cortex of a *Datura* treated mother revealed reduced nucleus with fragmented nucleolus, wavy chromatin, and vacuolated cytoplasm (Fig. 5D). The frontal cortical brain of a Seroxat treated mother showed a cell nucleus having well-distributed chromatin, healthy mitochondria, along with fragmented RER (Fig. 5E).

The cortex of a pregnant fetus exhibited a normal nucleus with properly dispersed chromatin material and an intact nuclear membrane, but fragmented RER-degraded mitochondria and vacuolated cytoplasm were seen (Fig. 6A). The cortex of postpartum youngsters exhibited normal nucleus with properly dispersed chromatin, normal mitochondria, normal nuclear membrane, and an RER rich by free ribosomes (Fig. 6B). The cortex of *Datura* treated offspring had a disintegrating nucleus, degraded mitochondria, some Rhode-like mitochondria, fragmented RER, and vacuolated cytoplasm (Fig. 6C). The cortex of Seroxat treated children displayed broken chromatin, degraded mitochondria, fractured RER, and vacuolated cytoplasm (Fig. 6D).

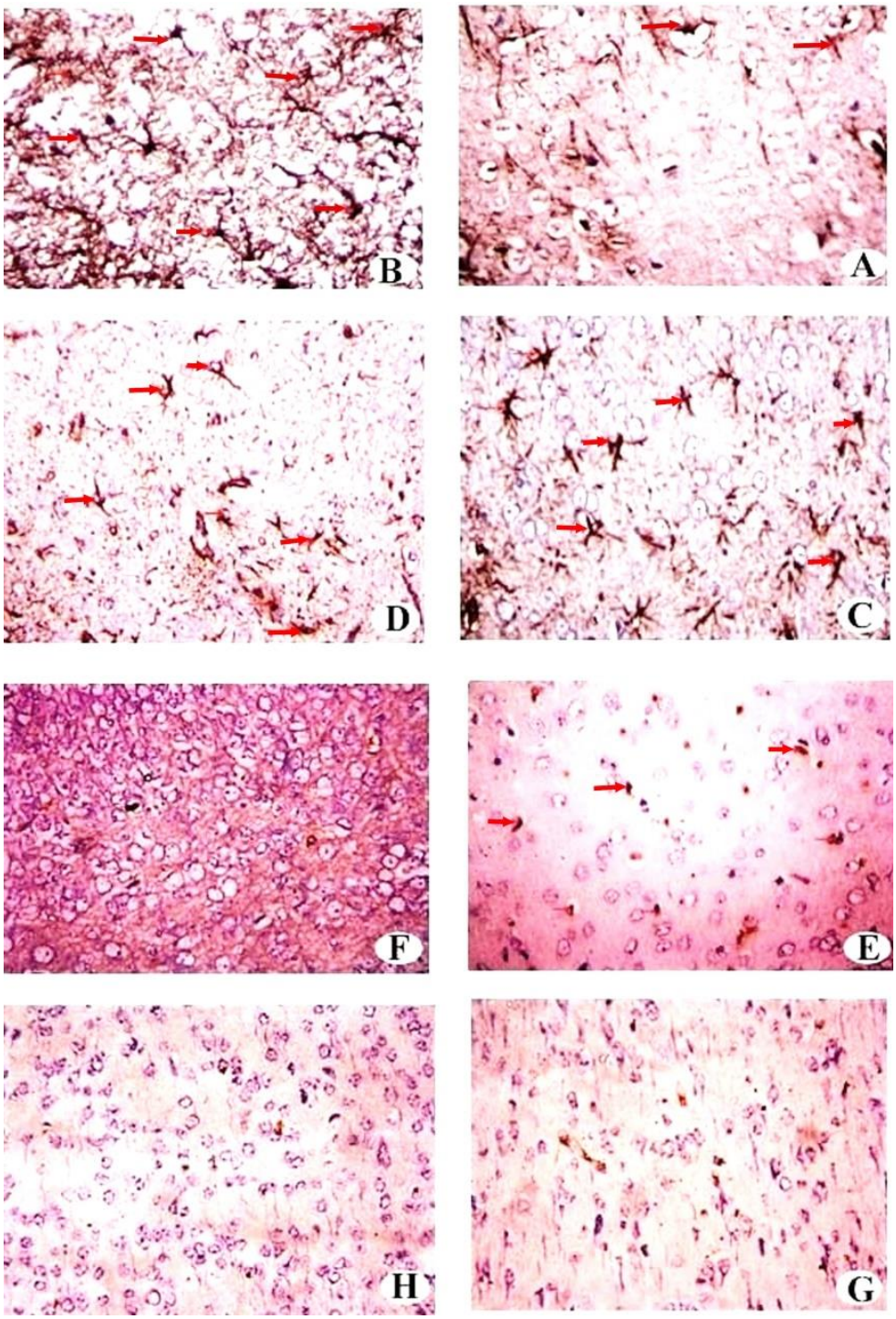

Fig. 4: Photomicrograph of SERT in mothers' (A–E) and youngsters (F–H) frontal cortex. (A) A non-pregnant control's frontal part of the brain cortex displays significant positivity in its neurons as well as axons (arrows). (B) Severe positivity in neurons as well as axons (arrows) in the frontal part of brain cortex of a pregnant control's brain. (C) The frontal part of brain cortex of the brain following childbirth; arrows indicate mild staining in the neurons along with axons. (D) A mother receiving *Datura* treatment has mild immunoreaction in her brain's frontal part of the brain cortex in both her neurons and axons (arrows). (E) The frontal part of the brain cortex of the mother receiving Seroxat exhibits little neuronal immunoreaction (arrows). (F & G) Youngsters treated with *Datura* and those with the postpartum frontal part of the brain cortex have mild immunoreactivity in neurons and axons. (H) Youngsters receiving Seroxat showed negative immunoreactivity in their brain's frontal cortex, which includes neurons as well as axons (SERT immunostain, ×400).

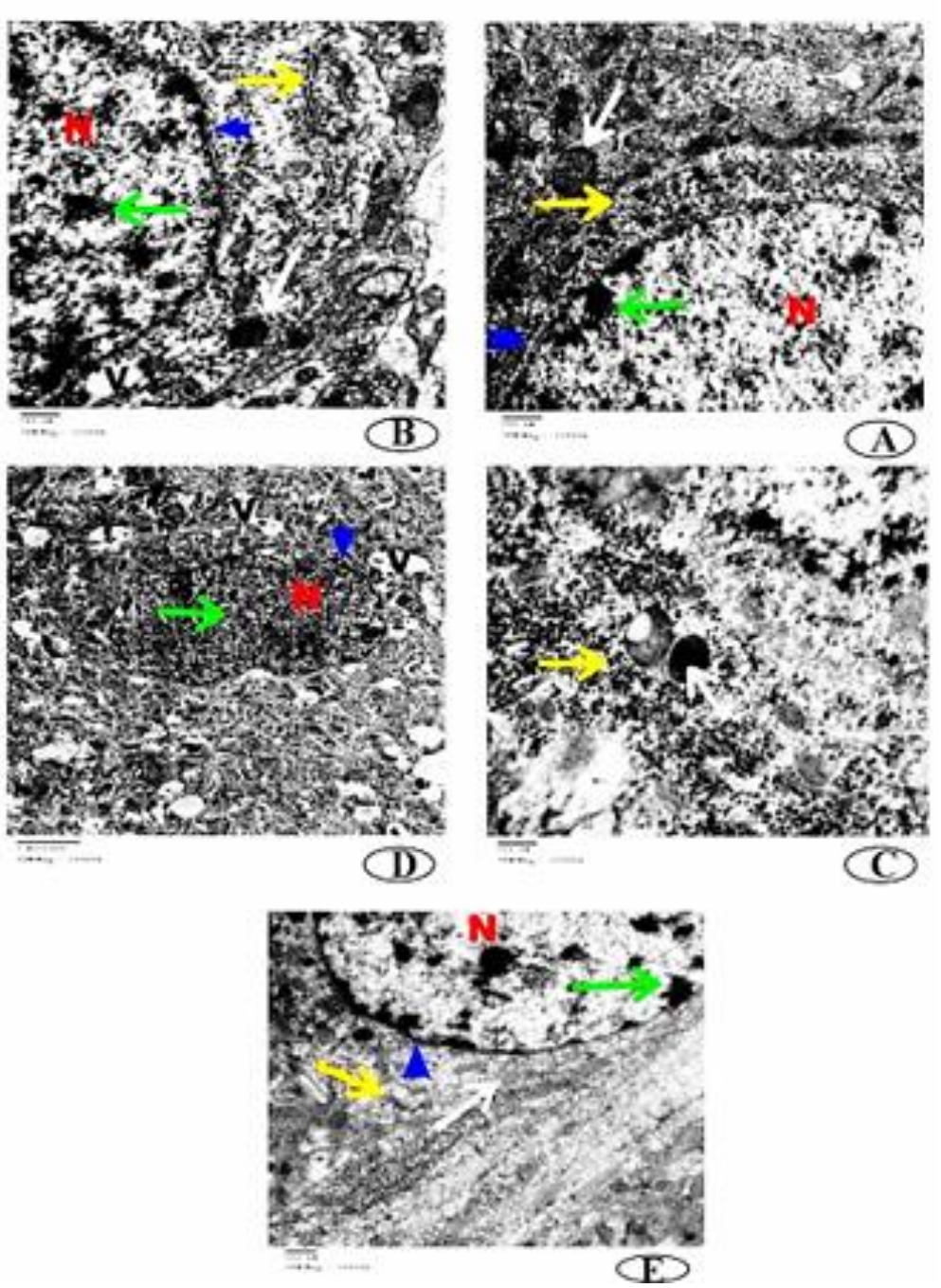

Fig. 5: (A) Electron micrograph of control non-pregnant frontal part of the cerebral cortex displaying intact N with uniformly distributed chromatin (green arrow), intact nuclear membrane (➤), typical mitochondria (white arrow), alongside apparent cristea, and typically arranged RER (yellow arrow) with free ribosomes. (B) The Cortical frontal brain area of a control maternal group shows an intact N with regularly scattered chromatin (green arrow) and an intact nuclear membrane (➤), some degraded mitochondria (white arrow), normal RER (yellow arrow), some fragmented rER, plus vacuolated cytoplasm. (C) frontal part of the cerebral cortex of postpartum rats demonstrating clearly evident appropriately constructed RER (yellow arrow) having ribosomes as well as normal mitochondria (white arrow) containing intact cristae (D) Cortical frontal brain area of Datura treated mother showing shrunken N, disintegrated nucleolus and chromatin (green arrow), wavy nuclear membrane (➤) and vacuolated cytoplasm (V). (E) The brain's frontal part of the cerebral cortex of the mother treated with Seroxat showed intact N with dispersed chromatin (green arrow), nuclear membrane (➤) and normal mitochondria (white arrow) having cristae, and fragmented RER (yellow arrow).

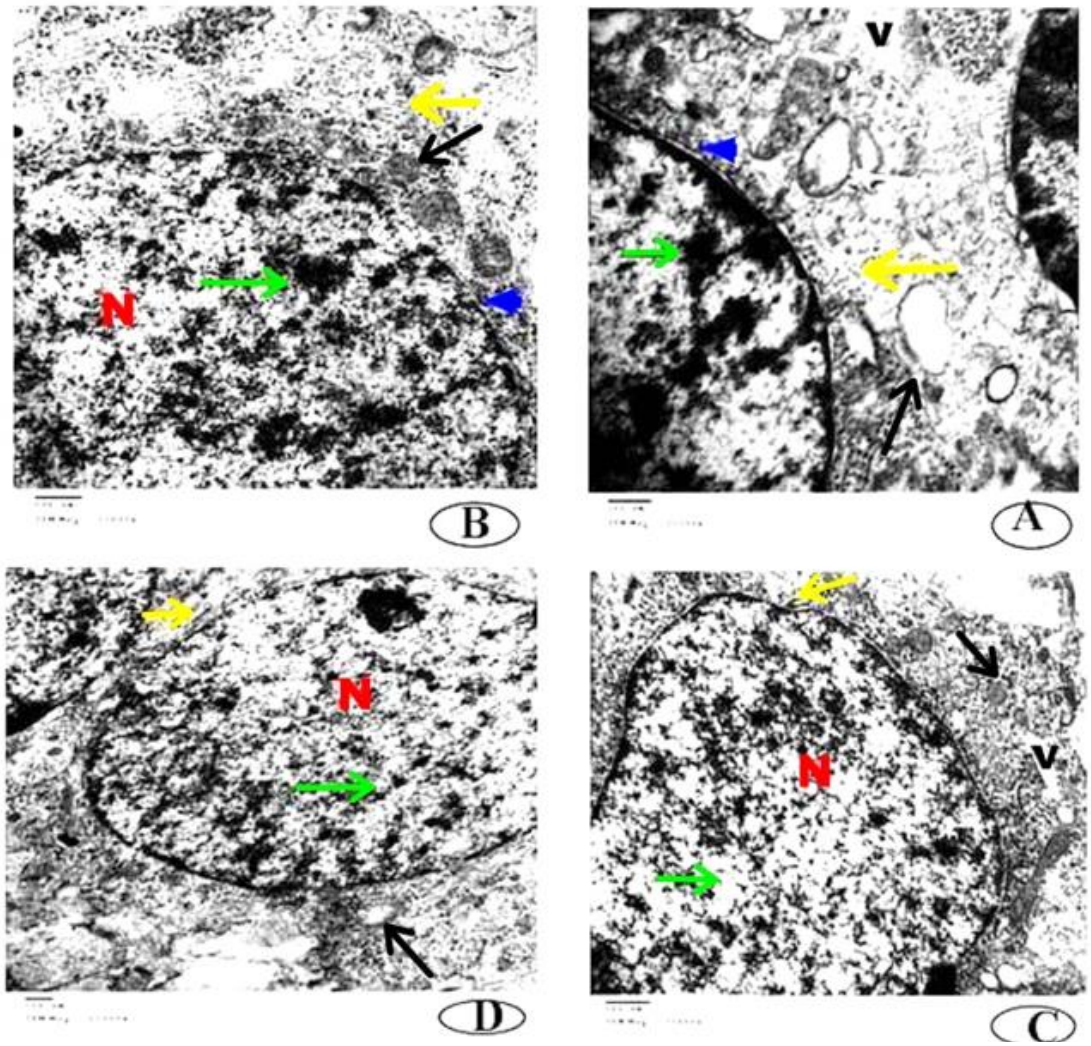

Fig. 6: Electron micrograph of the brain's frontal part of the cerebral cortex of rat youngsters (A-E). (A) The fetal frontal part of the cerebral cortex shows an organized nucleus having properly dispersed chromatin (green arrow) and nuclear membrane (➤), fragmented RER (yellow arrow), degraded mitochondria (black arrow), and cytoplasmic vacuolation (V). (B) The cortex of postpartum offspring shows a normal nucleus and chromatin (green arrow), nuclear membrane (➤), and RER (yellow arrow) stuffed with free ribosomes, and normal mitochondria (black arrow). (C) The cortex of Datura-treated offspring reveals N with disintegrated chromatin (green arrow), some Rhode as mitochondria, fragmented RER (yellow arrow), degenerated mitochondria (black arrow) and vacuolated cytoplasm (V). (D) The cortex of Seroxat-treated offspring shows N with fragmented chromatin (green arrow), fragmented RER (yellow arrow) degraded mitochondria (black arrow) and cytoplasmic vacuolation (V).

The morphometric results regarding the thickness of the cortex in frontal sections by H&E stain are summarized in Figures (7&8) while the morphometric results of the area % for positive serotonin transporter immunoreaction are summarized in Figure 9.

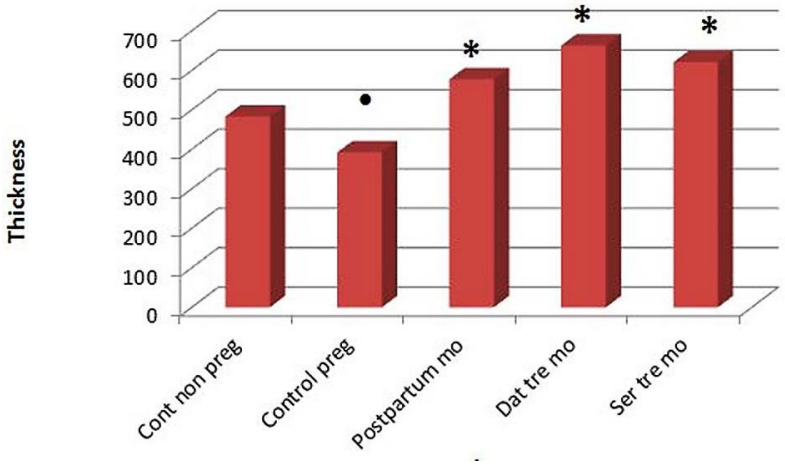

Fig. 7: Mother groups' average frontal cortical distance. (●) indicates statistical significance when compared to the control non-pregnant group ($P < 0.05$). (*) indicates a statistically significant difference from the control pregnant group ($P < 0.05$).

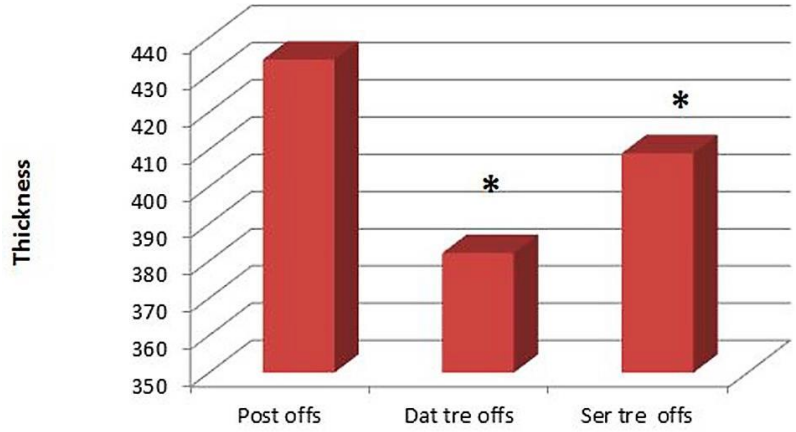

Fig. 8: The mean distance between the postpartum, *Datura*, and Seroxat-treated offspring's brain's frontal cortex. (*) Significant alteration is in relation to postpartum offspring at $P < 0.05$.

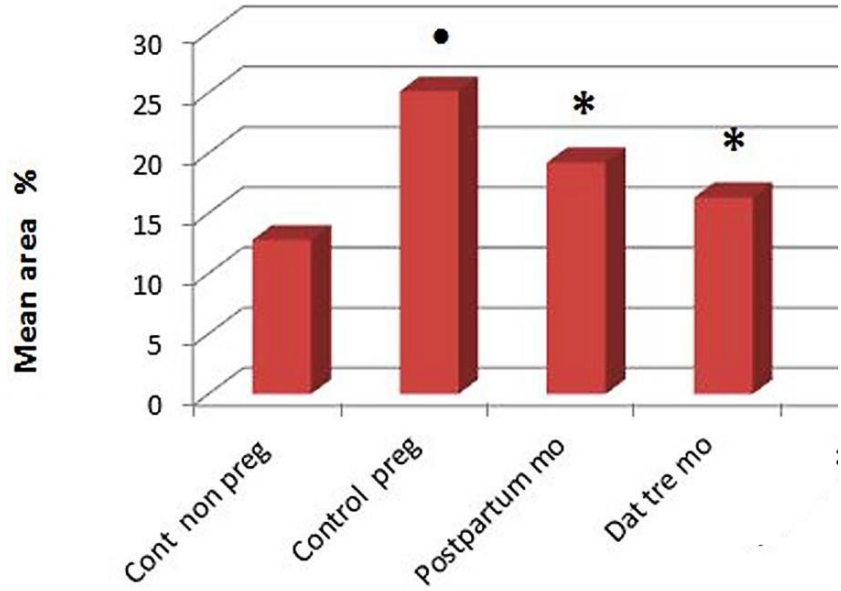

Fig. 9: Mean area per cent of positive serotonin transporter immunoreaction in the frontal part of brain cortex of mother groups and its statistical significance. (*) indicates a statistically significant difference from the control pregnant group ($P < 0.05$).

DISCUSSION

The research found histopathological abnormalities in the frontal brains of both pregnant rats and their offspring. The moms became better following taking *Datura* and an antidepressant. Depression in pregnant women has been discovered to have an inverse correlation with social support; exactly, women who have less social assistance report greater depressive symptoms versus women having more social support (Milgrom *et al*., 2019). The frontal part of the brain cortex of a pregnant rat includes decreased thickness of the frontal cortex, disorganized layers, distortion of some neurons, increased thickness of pia substance, and shrunken neurons with dark-colored nuclei. These findings are comparable to those of Oatridge *et al*. (2002) that found that the brain's size reduces throughout gestation, and these findings were consistent with Hoekzema *et al*. (2017) who showed that grey matter volume decreases significantly during pregnancy. Pregnancy-related changes might be caused by Sundström *et al*. (2017) that revealed extensive endocrine alterations in women during gestation. A majority of the hormonal alterations that take place throughout gestation, progesterone, estrogen, testosterone, Corticotropin-releasing hormone (CRH), prolactin and cortisol essentially follow this temporal plasma profile Jung *et al*. (2011) and De Souza Duarte *et al*. (2017) reported CRH being widely created throughout pregnancy, which is cut off shortly after birth. This can contribute to postpartum depression, which is associated with plasma hormone levels (increases throughout the 3rd trimester of gestation). These alterations are also inconsistent with Liu *et al*. (2017) discovered similar changes in cortical prefrontal tissue throughout depression, including degradation and degeneration of neurons plus glial cells. Changes in depression can result from a drop in hormonal dysregulation and neurotransmitter imbalance. Csaszar *et al*. (2014) observed that depressive disorders are connected with lower levels of neurotransmitters and hormonal disruptions associated with macroscopic brain alterations, which could support this finding.

Oxidative stress is also considered a causative agent for gestation depression. This can be agreed with by Samir (Samir, 2018), who discovered that pregnancy does offer too many difficulties, possibly due to the change in oxidative stress, which is also related to numerous illnesses during gestation, and Vaváková *et al*. (2015) who found oxidative stress contributes considerably to the causes of depression through the action of free radicals. The reductions in blood vessels in this study were elucidated by Chechko *et al*. (2022) who indicated a decrease in blood flow in brains and possibly volume during gestation.

Oral treatment of *Datura stramonium* produced degeneration of neurons in the hippocampus, including cellular hypoplasia along with dendritic arborization loss, according to Igben *et al*. (2023). Furthermore, they discovered a substantial increase in oxidative stress in a dose-dependent manner and antioxidant depletion in all treated experimental animals.

The Congo red staining also revealed significant amyloid accumulation throughout gestation. The greater deposition of plaques of amyloid in the cortex during gestation is congruent with the results of Ziegler-Waldkirch *et al*. (2018) who suggested that gestation alone increases levels of amyloid-β (Aβ) plaques, these amyloid deposits could be an outcome of Serotonin imbalance and a maladaptive stress response (Conejero *et al*., 2018).

Ultra-structural aspects of the brain's cortical frontal area during gestation revealed fragmented RER, mitochondrial degradation, along cytoplasmic vacuolation. Increased accumulation of amyloid plaques can promote mitochondrial degeneration, a

result similar to Reddy and Beal (Reddy & Beal, 2008) who reviewed Gathered Aβ can cause dysfunction in mitochondria in Alzheimer's disease (AD) brains. Mitochondrial malfunction leads to the development of neural illnesses. A mitochondrial failure increases the formation of ROS along with apoptosis, contributing to neurodegeneration (Zhao *et al*., 2019).

During gestation, SERT immunoreactivity also revealed intense staining in the neuron alongside the axon. Pregnancy-related increase of SERT in the brain is comparable to Kundakovic *et al*. (2022) study that found that fluctuating sex hormones are a critical biological factor that increases women's risk of depression along with anxiety. Comparable evidence in human beings and rats that the structure, as well as function of the brain, naturally vary with circulating ovarian hormones is elucidated. This can be supported by the study of Frimer and Overgaard (2015), who found that ovarian hormones affect essential elements of the serotonergic network. Postnatal rats showed remarkable enhancements such as enlargement of the frontal area of the brain cortex, normal layers, normal neuron dimension, moderate immunostaining, decreased amyloid depositing, and the microscopic examination revealed normal mitochondria along with rough endoplasmic reticulum.

According to an ancient study, the cerebral volume decrease starts following placental implantation and gradually increases following delivery. Conversely, because nutrients or metabolic substrates that were initially given to the fetus might be transferred to the newborn while breastfeeding or to the mother's tissue after birth, the metabolic alterations that occur during pregnancy may continue for several months following delivery, causing cellular degeneration (Oatridge *et al*., 2002).

In *Datura stramonium*-treated mothers, cells were intact, and highly vascularized, with heavy amyloid deposits, weak immunoreactivity, and ultra-structural features showed a shrunken nucleus with degraded nucleolus and chromatin plus vacuolar cytoplasm. This study agrees with a researcher (Soni *et al*., 2012) who found that *Datura stromonium* was administered internally to cure epilepsy, madness and depression. Also, Ekanem *et al*. (2016) stated that cytoplasmic vacuolization, neuron death and axonal atrophy in the neurons of frontal cortices of *Datura-treated* rats. The result corroborates the report of Etibor *et al*. (2015) who found the formation of amyloid content in *Datura*-treated animals. They are unique to neurodegenerative illnesses like Alzheimer's disease. They primarily contain insoluble aggregates of amyloid-beta peptide along with cellular debris around of and inside neurons.

Kocsis *et al*. (2014) concluded that scopolamine increases cerebral blood flow in the cortical prefrontal area. The decline in SERT positivity in *Datura*-treated moms is analogous to that described by Mateo *et al*. (2004) that found that cocaine interacts with SERT. These can be induced by cocaine; *Datura* contains tropane alkaloid that disrupts SERT.

Mothers who received treatment with Seroxat had some normal cells, and severely expanded blood vessels with moderate levels of plaques containing amyloid. This revealed minimal immunoreactivity in the neuron. Electron examination revealed the typical nucleus along with mitochondria plus fragmented rER. In this effort, the expansion of blood vessels may be discussed by Wang *et al*. (2015) who said that antidepressants improve cerebral blood flow. In addition, SSRIs have a direct vasodilator effect of this increased serotonin on the small cerebral vessels of the treatment group, which probably also contributes to the improvement of blood flow through the direct action of vasoactive monoamines (Elzib *et al*., 2019). These outcomes align with Severino *et al*. (2018) who found that paroxetine treatment

attenuates amyloid-β pathology in Alzheimer's disease.

Also, von Linstow *et al*. (2017) noted that administration of paroxetine to AD-like mice was shown to minimize Aβ. This may be connected to Fisher *et al*. (2016) who said that SSRIs increased α-secretase enzymatic activity while β-secretase activity remained unchanged. Serotonin receptors that enhance PKA then trigger ERK to elevate the enzymatic activity of α-secretase. This triggered activity split APP in the Aβ sequence to reduce brain ISF-Aβ levels. This result was supported by Brummelte *et al*. (2017) who said SSRIs (Paroxtine) mainly operate by inhibiting SERT within the presynaptic neuron, which modulates the external 5-HT level.

The current study discovered that the frontal brain cortex of fetuses and postpartum offspring had normal histological features for conventional layers.

Regarding the transmission electron microscopy (TEM) results, the fetus demonstrated mitochondrial damage in addition to rER fragmentation. Concurrently, the postpartum pups exhibited normal nuclei, mitochondria, and also rER. Pregnancy depressive disorders change the mom's environment and have serious effects on both the mom's and the juvenile's health (Vieira *et al*., 2013).

In this work, the frontal part of the brain cortex of pups underwent treatment with *Datura* and Seroxat revealing roughly around harmful outcomes in contrast to the control postnatal pups group. *Datura*-treated offspring exhibited granule cells that had completely degenerated, shrunk pyramidal cells having darkly pigmented nuclei, cytoplasmic vacuolation, as well as certain apoptotic cells, they exhibited low immunoreactivity. Seroxat-treated offspring included typical granules in addition to pyramidal cells. At the transmission electron microscopy level, they had similar negative effects on the nucleus, and mitochondria, in addition to rER. They demonstrated negative immunoreactivity. The findings are in line with Alizadeh *et al*. (2014) reported consumption of black henbane during gestation becomes unsafe because atropine in addition to alkaloids rapidly navigates the placenta, Because the fetus is opposed to both tachycardia along hyperthermia.

Gaukler *et al*. (2015) reported that paroxetine is considered a Class-D drug (positive risk to the human fetus) and warned that exposure to paroxetine in the first trimester could cause birth defects. Antidepressants are prescribed to pregnant women, and SSRIs readily cross the placenta and enter the fetal circulation (Rampono *et al*., 2009). Depression is recognized as a prevalent illness impacting approximately 20 percent of pregnant women. As a result, more than 10% have been prescribed antidepressants, primarily serotonin reuptake inhibitors plus selective serotonin and norepinephrine reuptake inhibitors. We believe that antidepressants change serotonin level homeostasis in the fetoplacental unit by suppressing SERT as well as organic cation transporter 3 at the maternal-fetal placental membrane (Horackova *et al*., 2021). There is additionally considerable evidence that all psychiatric medications easily pass through the placenta before reaching the fetus and can be produced in the milk of the baby. Drugs in the fetus may have a higher unbound free fraction and are capable of penetrating the cortex of the brain (EL-Gaafarawi *et al*., 2005).

CONCLUSION

To conclude, the data given in this paper suggest that *Datura* treatment has a remedying effect against pregnancy-induced brain damage, thus they must be taken carefully under medical supervision because alkaloids are accountable for both medicinal and hallucinogenic effects, and greater doses are harmful.

Declarations:

Ethical Consideration: The Helwan University Institutional Animal Care and Use Committee for Laboratory Animals (HU-IACUC/Z/SR0604-43) gave its

approval to the experiment. The Zoology Department at the Faculty of Science at Helwan University has received permission

Conflict of Interest: The authors declare that they have no conflict of interest.

Author contribution: Each author took part in the design of the study, contributed to data collection, and participated in writing the manuscript. The manuscript is neither being published nor being considered for publication elsewhere until a decision is reached by this journal.

Data availability statement: The collection of data developed and/or assessed throughout the present work is available through the corresponding author upon reasonable request.

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