Original Article

The Possible Protective Effect of Platelet Rich Plasma on Flouxetine-Induced Renal Cortical Changes in Male Albino Rats: Histological and immunohistochemical Study

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ABSTRACT

Background: Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. Platelet rich plasma (PRP) is an autologous derivative of the whole blood which has an important regenerative role in medicine..

Materials and Methods: Thirty adult male albino rats were used in this study. They divided into three groups: control, flouxetine and platelet rich plasma treated groups.

Results: There was statistically significant difference between the studied groups regarding creatinine level, MDA, IL6 and TNF with the highest level was reported in the fluoxetine group. The renal cortex of fluoxetine treated group showed congested glomerular capillaries. Some tubular cells had dark stained nuclei. Massive interstitial infiltration of inflammatory cells was detected in some sections. PRP treated group showed marked improvement in the histological structure of renal cortical tissue. Sections of fluoxetine treated group revealed a few PAS positive reaction at the brush border of most of PCT and the basal lamina of the tubular cells, that returned as the control group in PRP treated group. In fluoxetine treated group′ cytoplasmic positive reaction in fluoxetine treated group was seen in many epithelial lining of the tubules positive immunoreactions in few tubules PRP treated group.

Conclusion:our study found that fluoxetine causes deterioration of the kidney function and changes in histological structure of renal cortex which were improved by PRP application. which were improved by PRP application.

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Key Words: Flouxetine, kidney, platelet rich plasma, rat.

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INTRODUCTION

Depression is a serious health condition with over 264 million people worldwide sufferers. It is different from short-lived emotional and usual mood fluctuations responses in its long-lasting bad effects on daily life[1]. One of the most widely prescribed antidepressant drug is fluoxetine which is one of Selective Serotonin Reuptake Inhibitors (SSRIs) group. This drug group acts by inhibiting the serotonin reuptake into presynaptic serotonergic neurons which leads to an acute increase in serotonin concentrations at the synaptic cleft. The accumulated serotonin binds to the postsynaptic serotonin receptors and produces its effects[2]. The side effects of SSRIs are fewer than other antidepressants because of its highly spelectivity for 5-HT receptors[3]. Most of their side effects related to hyponatremia induced by SSRIs e,g headache, blurred vision, polydypsia, weakness, muscle pain, cramps, tremor, impaired gait, feeling of listlessness, tiredness, nausea, vomiting[4]. Also, fluoxetine is primarily eliminated through the kidney, which is crucial for preserving a proper level of electrolytes and water[5].

Platelet rich plasma (PRP) is the source of growth factors [GF] and cytokines which are released from α-granules and dense-granules of platelets. These growth factors participate and regulate the cellular level of tissue healing. This effect leads to proliferation and differentiation of cells involved in tissue regeneration[6].

PRP becomes trend in the medical field which is applied with a wide range from cardiovascular to eye diseases[7] Hegab *et al*.[8] stated that PRP could improve renal injury induced by adriamycin by correcting its associated proteinuria through decreasing its harmful oxidative stress, inflammatory and fibrogenic responses. The administration of exogenous growth factors enhances renal tubule cell regeneration and accelerates the recovery of renal function. Some studies demonstrated that hepatocyte growth factor (HGF) stimulates regeneration of renal tubular cells which leads to the repair of kidney structure and function after damage[9].

This work aimed to study the effect of platelet rich plasma on flouxetine induced renal cortical changes in adult male albino rats.

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MATERIALS AND METHODS

Chemicals

Fluoxetine (Prozac. Cap): was purchased from Lilly Pharmaceutical Company (Lilly, USA).) (20mag/capsule).

Experimental groups

In our study, 30 adult male albino rats (5–7 months) with an average body weight ranging from (200–250 g). They were from the breading animal house, Faculty of Medicine, Zagazig University. The research ethics committee at Zagazig University approved the experimental protocol. The approval number was (ZU-IACUC/3/F/215/2022). The animals were given free access to food and water while being housed at a standard temperature with regular dark and light cycles .They were divided into three groups 10 rats each.

Group I (control group),

- Subgroup (Ia): 5 rats (negative control) received no treatment.
- Subgroup (Ib): 5 rats injected intraperitoneally with saline for 12 weeks.

Group II, injected intraperitoneally with fluoxetine 20 mg/kg/day for 12 weeks. Each capsule (20mg/capsule) content was dissolved in 5ml saline[10].

Group III, fluoxetine was given to rats by intraperitoneal injection of 20 mg/kg/day, along with 0.5 ml of PRP that had been dissolved in PBS eliminate platelet aggregates, put in a sterile insulin syringe and administrated subcutaneously twice weekly for 12 weeks[11]. 24 hours from the last dose, animals were anesthetized by ether inhalation, sacrificed, dissected. The kidney samples were prepared for Haematoxyline and eosin, PAS, immunostaining and electron microscopic examination.

Methods

Blood sampling and PRP preparation

PRP was obtained from seven male rats. Its preparation was done at medical biochemistry department, Faculty of Medicine, Zagazig University. This was done by adapting the protocol of double centrifugation tube method[12]. Under aseptic conditions rats were anesthetized using ketamine, and 2 ml of blood from the retro-orbital plexus was taken with capillary tubes, first dipped in sodium citrate 3.2%, then collected in 0.3 mL of the anticoagulant in a tube. The blood centrifugated twice, first centrifugation at 1600 revolutions/minute (rpm) for ten minutes. After centrifugation, the tube displayed three basic layers, at the bottom red blood cells, leukocytes or buffy coat directly above, and plasma (PRP and platelet-poor plasma (PPP) at the top) in the superior layer. This plasma was pipetted, and it was centrifuged once more for ten minutes at 2000 rpm. Following this centrifugation, the tube showed two components: the platelet button at the bottom and PPP at the top. We remove the top portion of PPP, while the remainder was left in the tube with the platelet button. After being stirred, the platelet button was then re-suspended in PBS (1:1) and freezing at 80°C till used. PRP was immediately activated before use with calcium chloride (0.8mL PRP + 0.2mL 10% CaCl2), which are aggregation inducers, that used to activate PRP, and trigger degranulation and release of the GFs[12].

Biochemical study

Blood samples were taken at the end of the experiment under ether light anaesthesia in non-heparinized tubes from the retro-orbital veins. Centrifuging serum at 4000 g for 20 minutes and storing it at 20°C was the method used to separate the serum. The kidneys were removed, cleaned with ice isotonic saline (0.9 percent), and kept at -80°C for storage. They were subsequently homogenized in ice-cold 0.15 M KCl using a sonicator homogenizer to create a 10% homogenate, which was then centrifuged and utilized to estimate the levels of MDA, IL-6, and TNF in renal tissue

The levels of blood urea and serum creatinine were calculated in all animals using colorimetric kits (purchased from Bio-diagnostic Co., Giza, Egypt) following the manufacturer's information (Catalog number: EIABUN)[13].

Markers of oxidative stress in renal tissue

Colorimetric measurements of MDA, a marker of lipid peroxidation, using a readily available kit, (Biodiagnostic, Cairo, Egypt) were made in kidney homogenate. Thiobarbituric acid and MDA react in an acidic media to produce thiobarbituric acid product, which has an absorbance that can be measured at 534 nm

IL-6 and tissue tumour necrosis factor (TNF) levels measurement

The measurment of TNF and lL-6 for determining the degree of the endothelium injury which induces inflammation and increases cytokine production. The levels of TNF- and IL-6 in kidney homogenate were measured using an ELISA kit from the Glory Science Company, St. Del Rio, USA, in accordance with the manufacturer's instructions (Catalog Number: E-BC-K025-S)[14]. The values in each group were determined in the centrifuged homogenates supernatant at the Department of Biochemistry, Faculty of Medicine, Zagazig University.

Light microscope technique

The samples were processed for paraffin sections preparation that were stained with H&E and PAS for carbohydrate[15]. For immunohistochemistry, to block the endogenous peroxidase put paraffin sections in 0.1% hydrogen peroxide for 30 min, then incubated with the primary antibody at 4°C [primary antibodies: rabbit monoclonal anti-rat TLR2 antibody (ab108998; Abcam, Cambridge, Massachusetts, USA). Then the sections were washed three times in PBS and incubated with secondary antibody for 1 h. The last step of staining was incubation

with chromogen, called diamiobenzidine (DAB). Mayer's hematoxylin used as a counter stain. Negative control sections were prepared by excluding the primary antibodies[16].

Transmission electron microscope technique

The specimens were double fixed in 2.5% buffered glutaraldehyde, and 1% osmium tetroxide, then dehydrated and embedded in epoxy resins. 1% toluidine blue is used to stain semithin sections and then examined under light microscope and ultrathin sections (70-90 nm) were stained with lead citrate and uranyl acetate[17]. The sections were photographed using a JEOL JEM 2100 EXII Electron Microscope (Jeol Ltd), Faculty of Agricultural, Electron Microscope Research Laboratory, Mansoura University, Egypt.

Histo-morphometric analysis

Measurement of area percent of positive stained PAS sections and positive iNOS reaction with "Leica Qwin 500" image analyzer computer system ((Leica Ltd, Cambridge, UK) in Department of Pathology, Faculty of Dentistry, Cairo University, Cairo, Egypt. Measurements were obtained in non-overlapping ten fields of randomly chosen five rat's slides in each group X400[18].

Statistical analysis

The IBM SPSS 19.0 programme was used to conduct the analysis[19]. We expressed all obtained data as mean ± Standard Deviation (SD). ANOVA was used, followed by least significant difference (LSD) Post hoc test for comparison between groups. $P<0.05$ were considered as significant difference.

RESULTS

Biochemical results

The fluoxetine group reported the greatest level of urea, with a statistically significant difference between examined groups. Significant difference between the fluoxetine group and both control group and PRP group while there was no significant difference between control group and PRP group. Creatinine, MDA, IL6 and TNF, statistical significant difference between examined groups with the highest level in fluoxetine group. There was statistical significant difference between other groups and control group (Table 1, Histogram 1).

Histological results

H & E stained sections from control group, showed normal structure of the renal cortex which is comprised of tubules and renal corpuscles with little interstitial tissue. The renal corpuscle consisted of glomerulus surrounded by visceral and parietal layers of Bowman's capsule with Bowman's space inbetween. The renal tubules were formed of proximal and distal convoluted tubules which were lined by simple cuboidal epithelium with central rounded nuclei. The distal convoluted tubule had wider lumen than the proximal tubules (Figure 1A). The renal cortex from fluoxetine treated group raveled congested glomerular capillaries. Tubular cells with dark stained nuclei were noticed. Interstitial inflammatory cellular infiltration was seen (Figure 1B). Other sections of flouxetine treated group showed dilated tubules with flattened desqumated epithelium, atrophied glomerulus, desqumated epithelium in other tubules, interstitial hemorrhage was also noticed (Figure 1C). In the same group other sections showed partial destruction of capillary tufts, shrunken glomeruli with widening of Bowman's space (Figure 1D).

PRP treated group sections showed apparently normal histological structure, with well-formed capillary tufts. Renal tubules were nearly normal with vesicular nuclei (Figure 1E)

PAS stained sections from control renal cortex showed positive reaction at the basal lamina of most of the tubular cells and brush border of PCTs (Figure 2A). Sections of fluoxetine group showed few PAS positive reaction at the brush border of PCT and the basal lamina of the tubular cells, with complete loss of the brush border in some tubules (Figure 2B). In PRP group positive reaction at brush border of PCTs and basal lamina of tubular cells were noticed (Figure 2C).

Immunohistochemical staining for iNOS

In the control group Immunoreactions was positive in the cytoplasm of few renal tubules and glomeruli (Figure 3A). Cytoplasmic positive reaction in fluoxetine treated group was seen in many epithelial lining of the renal tubules and in the endothelium (Figure 3B) However, in PRP group, positive immunoreactions in few tubules and endothelium (Figure 3C).

Electron microscopic results

Control renal cortex showed podocyte foot processes. Glomerular blood capillaries with a thin, fenestrated endothelial lining. Glomerular filtration barrier was composed of fenestrated endothelium, secondary foot processes with filtration slit membrane and regular thin, uniform, basement membrane, (Figure 4A)

Fluoxetine treated group revealed disorganized foot processes of podocyte, glomerular filtration barrier. Glomerular basement membrane was thickened (Figure 4B). PRP treated group, showed improvement, as renal barrier seen some podocyte foot processes are still irregularly arranged. Other foot processes appeared normal, fenestrated glomerular capillaries endothelium, and regular basement membrane (Figure 4C).

Proximal convoluted tubules of the control group showed epithelial cells with euchromatic nuclei, apical closely packed luminal microvilli, basal infoldings and basal regular mitochondria (Figure 5A). Fluoxetine treated group showed irregular basal infoldings, irregular arranged mitochondria, numerous intracytoplasmic vacuolations. Electron dense granules, apical microvilli, and thickened

basement membrane were seen (Figure 5B). PCT of PRP group showed nearly normal structure. PCT had closely packed apical microvilli, euchromatic nuclei, basal infoldings and basal mitochondria (Figure 5C).

Control distal convoluted tubules raveled euchromatic nuclei, basal infoldings and basal mitochondria (Figure 6A). Flouxetine treated group revealed distal convoluted tubules irregular arranged mitochondria, and irregular basal infoldings. Thickened basement membrane was also noticed (Figure 6B). Other sections of flouxetine treated group showed pyknotic nucleus nuclei ,and other irregular nuclei (Figure 6B*). PRP group showed nearly normal structure with euchromatic nuclei, regular basal mitochondria and basal infoldings , but basement membrane is still irregular (Figure 6C).

Histo-morphometric and statistical results

Significant statistical difference among the studied groups in PAS area percent with the greatest level was the control group and the lowest level was the fluoxetine group. There was significant difference between the fluoxetine group and both control group and PRP group while no significant difference between control group and PRP group. Significant statistical difference between the examined groups concerning iNOS with the greatest level was found in the fluoxetine group. Significant difference between control group and the other groups was recorded (Table 2, Histogram 2).

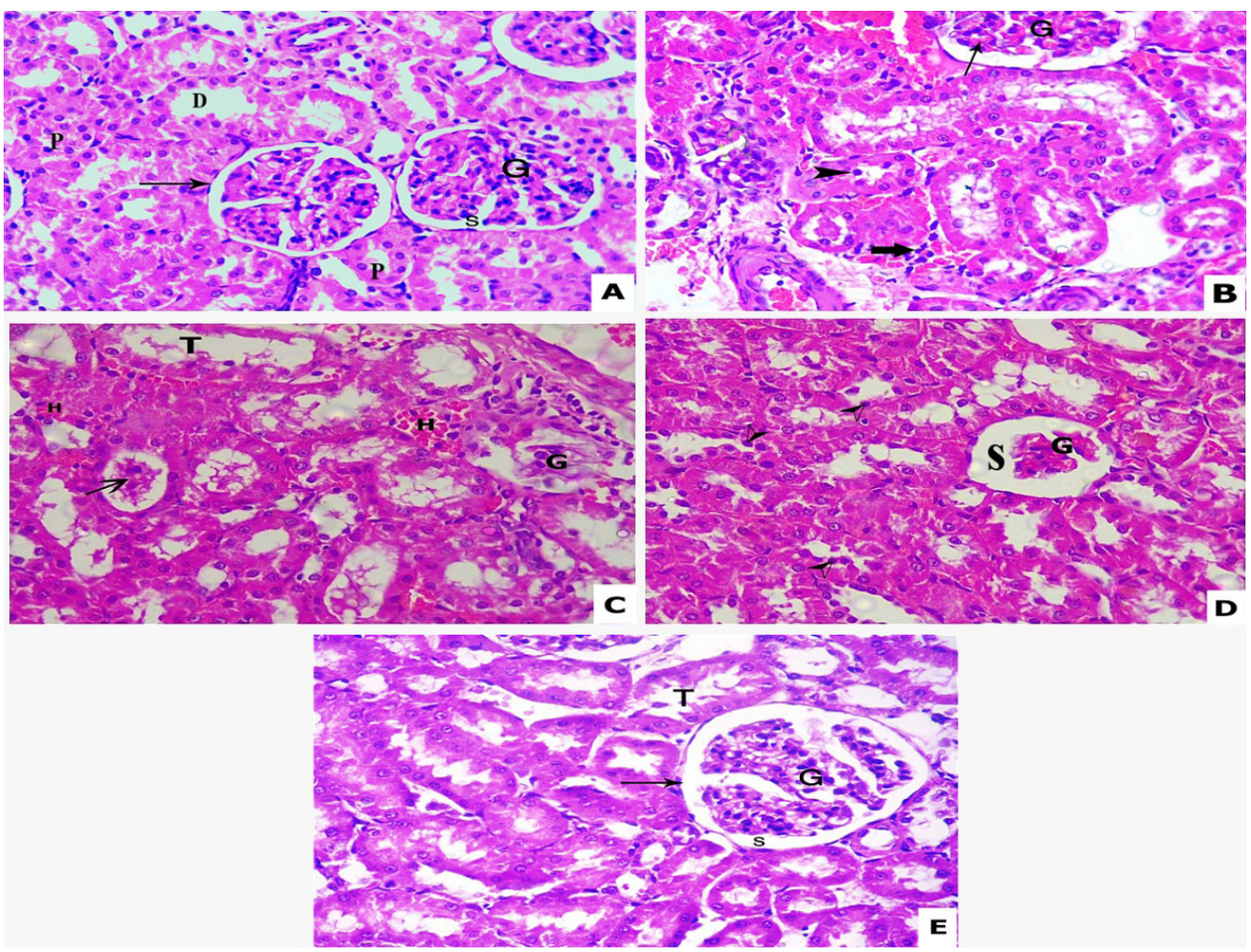


Fig. 1: H&E stained sections showing (A): the control renal cortex. The renal corpuscles (arrow) and tubules (T) with minimal interstitial tissue are seen. Each renal corpuscle consists of glomerulus (G) that is surrounded by visceral and parietal layers of Bowman's capsule enclosing the Bowman's space (S) .Proximal (P) and distal (D) convoluted tubules are also detected. (B): flouxetine treated group showing glomeruli with congested capillaries (G). Inflammatory cellular infiltrations are also noticed (thick arrow). Many cells with darkly stained nuclei are also seen (arrowhead) are seen. (C): Other sections of flouxetine treated group showing dilated tubules with flattened desqumated epithelium (T) Atrophied glomerulus (G), desqumated epithelium in other tubules (arrow), interstitial hemorrhage (H) is also noticed (D): In the same group other sections showing partial destruction of capillary tufts, shrunken glomeruli (G) with widening of Bowman's space (S), and many cells with darkly stained nuclei are also seen (arrowhead) (E): the PRP treated group showing renal corpuscle (arrow) which consists of glomerulus (G) surrounded by visceral and parietal layers of Bowman's capsule, enclosing the Bowman's space (S). Renal tubules (T) are normal with vesicular nuclei. (H and E × 400, Scale bar; 20 µm).

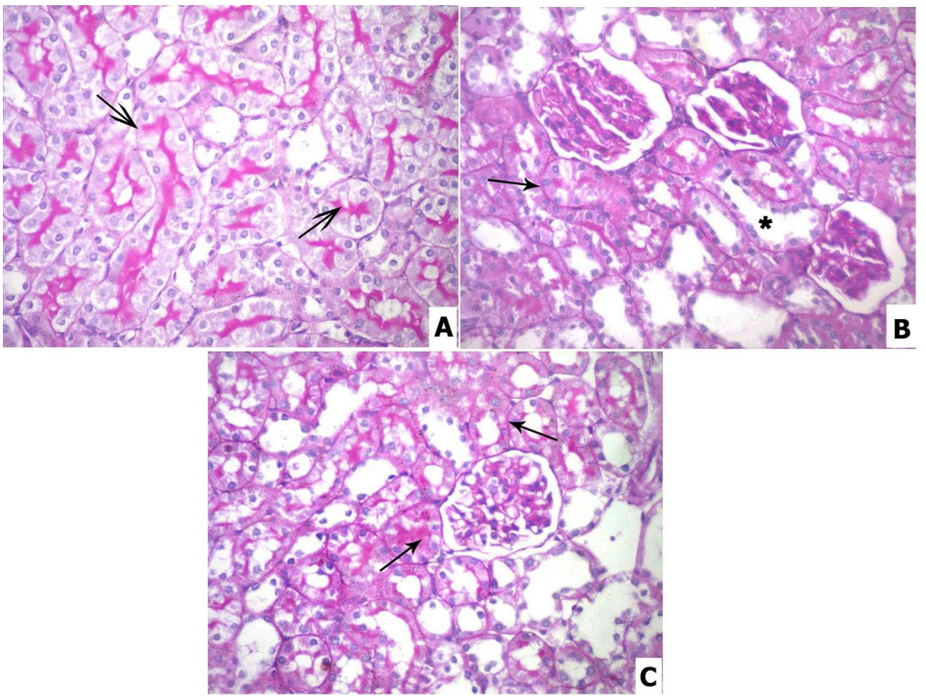


Fig. 2: Photomicrographs of PAS stained sections showing (A): the control renal cortex which reveals positive reaction (arrow) at the basal lamina of the tubular cells and the brush border of PCTs. (B): The flouxetine treated group showing few PAS positive reaction in the brush border of lining cells of PCT and the basal lamina of the tubular cells (arrows). Areas of complete loss of reaction are detected in other tubules (asterisks). (C): PRP treated group showing positive reaction (arrow) at the basal lamina of tubular cells and the brush border of PCTs. (PAS × 400, Scale bar; 20 µm).

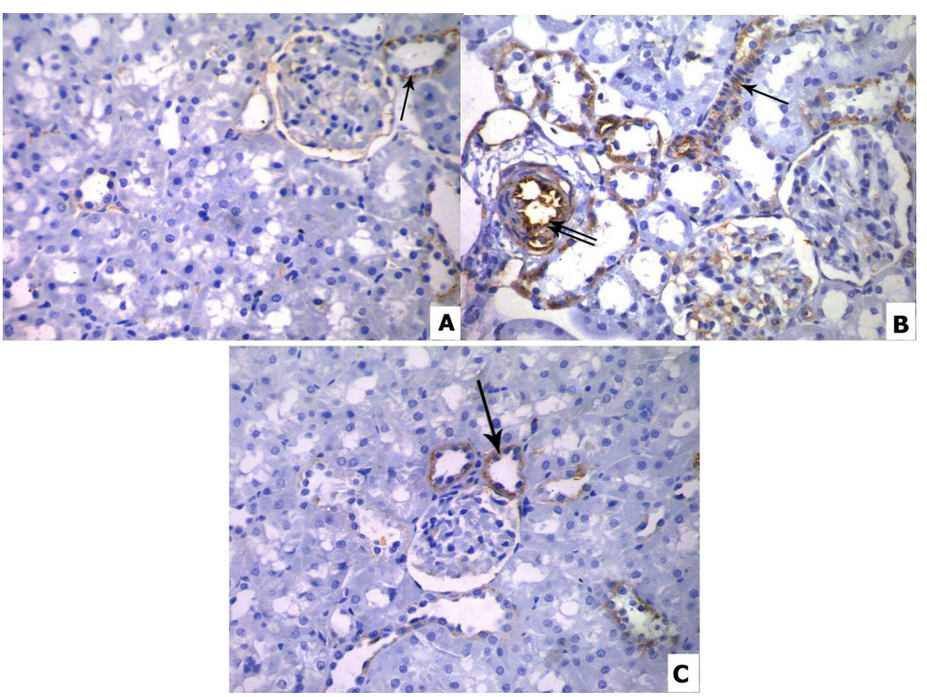


Fig. 3: Immunohistochemical staining for iNOS showing in (A): the control group, positive reaction (arrow) in the cytoplasm of few renal tubules and glomeruli. (B): the flouxetine treated group showing positive iNOS reaction in the cytoplasm of many epithelial lining of the renal tubules (arrows) and in the endothelium (double arrows). (C): the PRP treated group showing positive iNOS reaction in few tubules (arrow) and glomerulus. (Immunoperoxidase technique × 40, Scale bar; 20 µm).

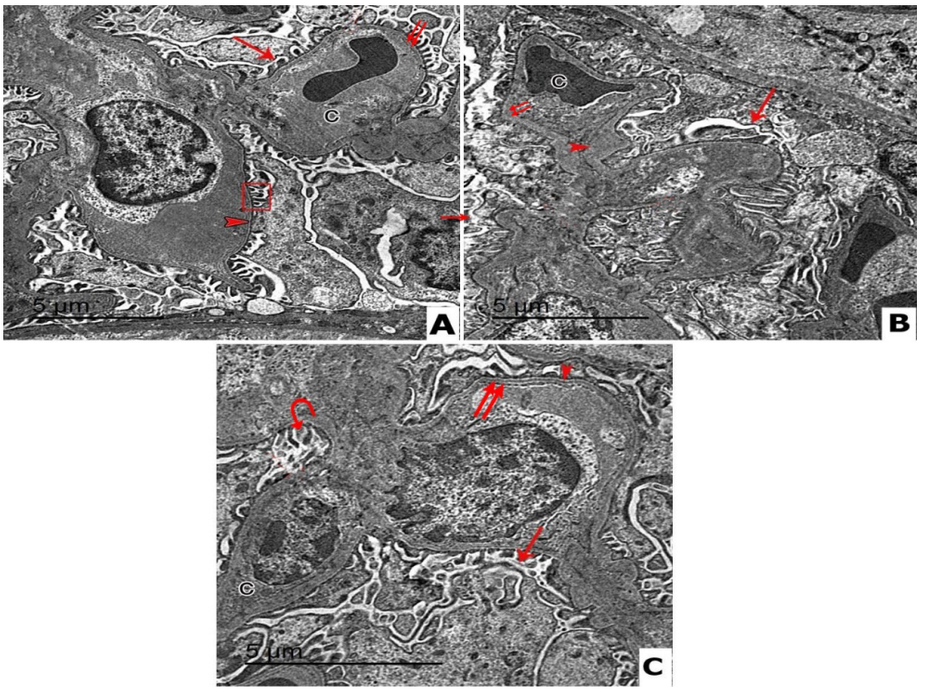


Fig. 4: Electron micrographs of renal cortex showing in (A): control group, glomerular capillaries (C) lined by fenestrated endothelium (double arrow). Glomerular filtration barrier (rectangle) .Regular glomerular basement membrane (arrow head), and podocyte secondary foot processes (arrow) with filtration slit membrane. (B): flouxetine treated group showing disorganized podocyte foot processes (arrow), glomerular capillaries (C) with distorted endothelium (double arrow) and thickened glomerular basement membrane (arrow head). (C): PRP treated group showing renal barrier with some podocyte foot processes are still irregularly arranged (arrow). Other foot processes appear partially normal (curved arrow), glomerular capillaries (C) with fenestrated endothelium (double arrow), and regular glomerular basement membrane (arrow head) are detected. (TEM, Scale bar; 5 µm).

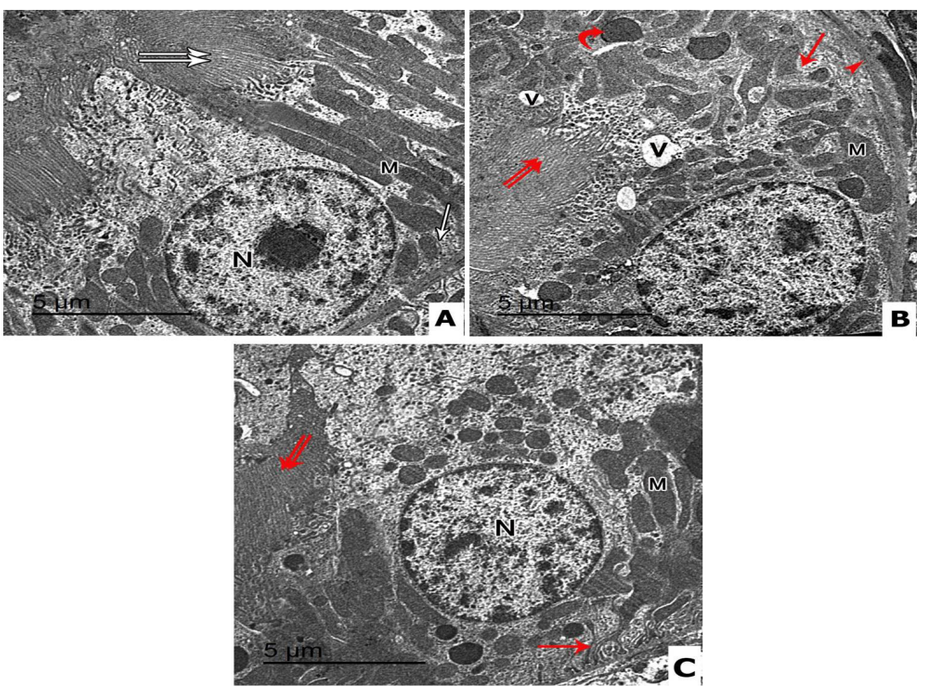


Fig. 5: Electron micrographs of renal cortex showing the proximal convoluted tubular cells in (A): control group, with euchromatic nuclei (N), luminal microvilli (double arrow). Basal infoldings (arrow) and basal mitochondria (M) are also noticed. Proximal convoluted tubules in (B): flouxetine treated group appears with irregular basal infoldings (arrow), intracytoplasmic vaculation (v), irregular arranged mitochondria (M) and electron dense granules (curved arrow). Apical microvilli (double arrow), thickened basement membrane (arrow head) are noticed. (C): PRP group showing euchromatic nuclei (N), closely packed apical microvilli (double arrow), basal mitochondria (M) and basal infoldings (arrow). (TEM, Scale bar; 5 µm).

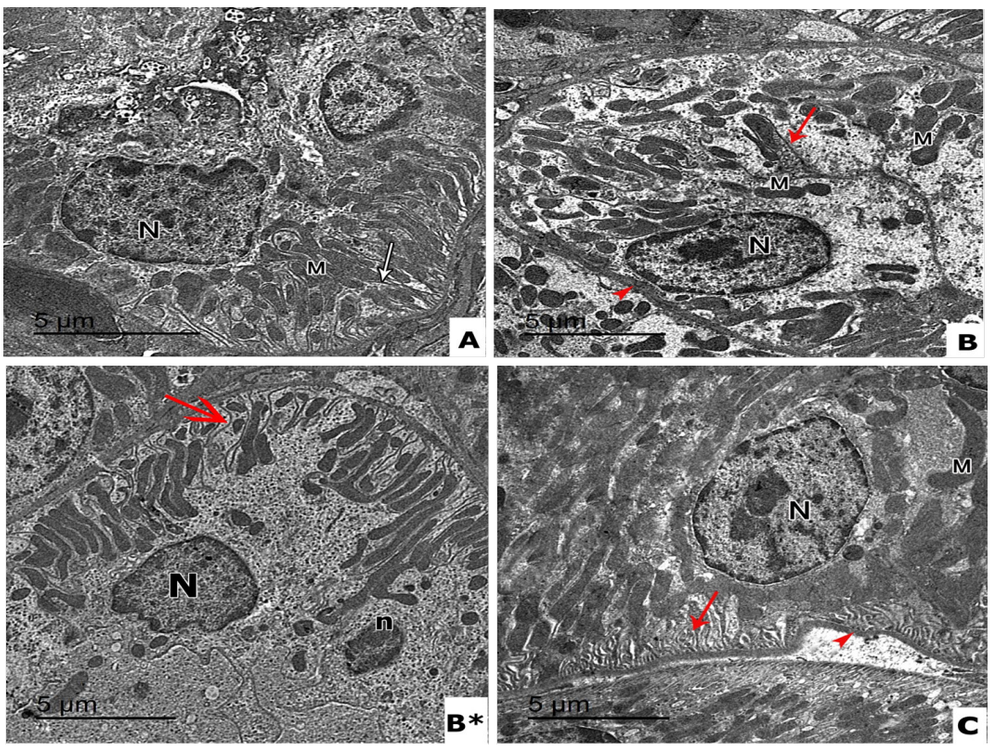


Fig. 6: Electron micrographs of renal cortex showing the distal convoluted tubular cells in (A): control group with euchromatic nuclei (N), basal infoldings (arrow) and basal mitochondria (M). In (B): flouxetine treated group, appear with dark stained nuclei (N), irregular basal infoldings (arrow) and irregular arranged mitochondria (M). Thickened basement membrane (arrow head) is noticed. (B*):Other sections of flouxetine treated group show pyknotic nucleus (n) and other irregular nuclei (N) is also seen (C): PRP treated group showing distal convoluted tubular cells with euchromatic nuclei (N), regular basal mitochondria (M) basal infoldings (arrow) with irregular basement membrane(arrow head). (TEM, Scale bar; 5 µm).

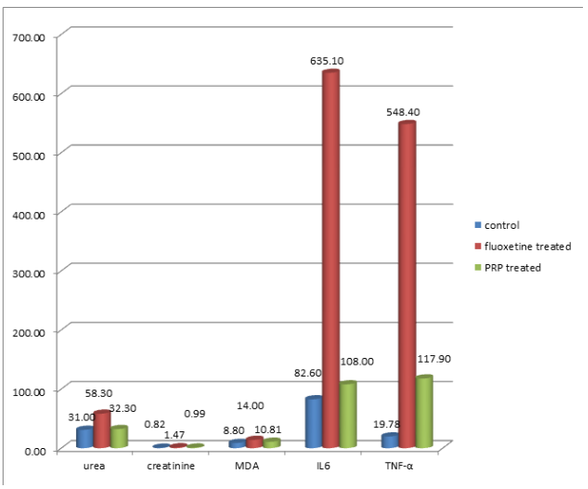
Table 1: Mean values (±SD) of serum urea, creatinine, tissue MDA, IL6 and TNF-α levels in the studied groups

Items		N	Mean±SD	F	*P value*	Post hoc
urea	control	10	31.00±1.33	363.4	<0.001*	P1<0.001* P2=0.265 P3<0.001*
	fluoxetine treated	10	58.30±2.94			
	PRP treated	10	32.30±3.02			
	Total	30	40.53±13.02			
creatinine	control	10	.823±0.07	84.7	<0.001*	P1<0.001* P2=0.003* P3<0.001*
	fluoxetine treated	10	1.47±0.15			
	PRP treated	10	.994±0.1			
	Total	30	1.095±0.29			
MDA	control	10	8.80±0.37	82.0	<0.001*	P1<0.001* P2<0.001* P1<0.001*
	fluoxetine treated	10	13.99±1.13			
	PRP treated	10	10.81±1.03			
	Total	30	11.20±2.34			
IL6	control	10	82.60±4.03	488.8	<0.001*	P2<0.001* P1<0.001* P2<0.001*
	fluoxetine treated	10	635.10±22.86			
	PRP treated	10	108.00±7.63			
	Total	30	275.23±259.38			
TNF	control	10	19.78±1.69	667.3	<0.001*	P3<0.001*
	fluoxetine treated	10	548.40±37.16			
	PRP treated	10	117.90±6.22			
	Total	30	228.69±234.4			

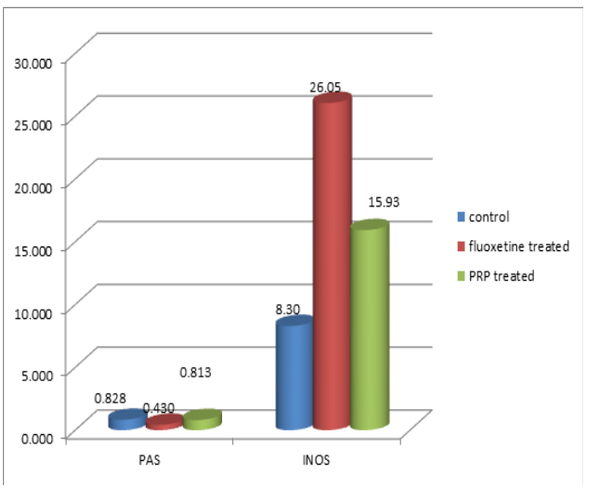
Table 1: Mean values (±SD) of serum urea, creatinine, tissue MDA, IL6 and TNF-α levels in the studied groups

Items (Area percentage)		N	Mean	F	*P value*	Post hoc
PAS reaction	control	10	0.827±0.01	351.2	<0.001*	P1<0.001* P2=0.379 P3<0.001*
	fluoxetine treated	10	0.430±0.03			
	PRP treated	10	0.812±0.05			
	Total	30	0.690±0.19			
iNOS reaction	Control	10	8.30±1.41	209.07	<0.001*	P1<0.001* P2<0.001* P3<0.001*
	fluoxetine treated	10	26.05±1.92			
	PRP treated	10	15.93±2.37			
	Total	30	16.76±7.62			

P1 control group vs fluoxetine group P2 control group vs PRP group P3 fluoxitine group vs PRP group



Histogram 1: Mean values of serum urea, creatinine, tissue MDA, IL6 &TNF In different studied groups



Histogram 2: Mean values of Area % of PAS and iNOS reaction in the different studied group

DISCUSSION

Over 264 million people are affected by depression globally, which is a prevalent disorder that can cause severe mood swings and even suicidal thoughts. Every year, over 800 000 people, mostly young adults aged 15 to 29, commit suicide[1].

Due to its accessibility and low cost, fluoxetine is frequently prescribed as an antidepressant for patients seven years of age and older. Additionally, it can be used to treat obsessive-compulsive disorder, borderline personality disorder, premenstrual dysphoric disorder, panic disorder, and adult post-traumatic stress disorder[20].

In our work, sections stained with H&E in flouxteine treated group showed disturbed cellular orientation in the PCT with cytoplasmic vacuolations in some tubules and debris-cast in others. In agreement with Aggarwal *et al*[21] who reported dilated proximal convluted tubules with debris-cast in their lumen in the flouxteine-treated group.

In group II, renal tubules appeared with desqumated glomerular and tubular epithelium. Accordingly to Frazier *et al*.2012 who reported that sloughed epithelial cells that fill lumina and lose their cellular outlines can form cellular casts. Also, they stated that tubular casts caused by increasing glomerular permeability which is associated with glomerular damage and injured tubular epithelium which fill the tubules with large amounts of protein[22].

Group II showed tubular diltation and cellular vacuolations as signs of necrosis. Flouxteine increases free radicals formation affecting Pars recta in PCT with releasing large amount of reactive metabolites. Local toxicants are generated by deconjugation of these metabolites by tubular beta-lyase and gamma- glutamyl transpeptidase[23].

In the same group H&E stained sections revealed glomeruli with congested capillaries which can explained by the inhibition effect of flouxteine in the voltage-dependent Ca2+ channels in the vascular smooth muscle cells. It attenuates resistance arteriole myogenic constriction, which may exacerbate pressure-induced microvascular damage[24].

Regarding iNOS level, significant statistical difference between the examined groups, with the fluoxetine group reporting the highest level. The control group and the other groups differed significantly. Additionally, inflammatory cells were visible in the same group's H&E stained sections. In line with Naito *et al*.[25], who reported the infiltration of inflammatory cells between renal tubules.

Fluoxetine (Flux) is a medication that contains fluorine. Exposure to fluoride (F-) has been found to increase the formation of free radicals and have an impact on the antioxidant defense system. Stępniak,[26] shown that Flux damages the liver and triggers free radical responses,

Free radicals directly damage renal tissue, especially the endothelium, which is highly susceptible to oxidative stress and changes phenotypic as ROS levels in and around blood vessels rise to an unhealthy level. The endothelium is adversely affected, which induces inflammation and increases cytokine production[27].

Small secreted proteins called cytokines are made by almost all cells to control and affect immune response. When pro-inflammatory cytokines are released, immune cells are stimulated to produce more cytokines "cytokine storm" which attract the inflammatory cells to the field and begin the inflammatory reaction[28].

Through sheddases activation and suppression of endogenous protease inhibitors, activated inflammatory cells release oxygen/nitrogen species that can promote greater shedding of the endothelium and tubular glycocalyx. Additionally, other proteins such as, neutrophil elastase, matrix metalloproteinases, thrombin, plasmin, tryptase, and cathepsin B are released in inflammatory conditions, resulting in glycocalyx shedding. It explains significant statistical difference among the studied groups in PAS area percent as the greatest level was in the control group and the lowest level was in the fluoxetine group[29].

Ultrathin sections examined with electron microscopic from flouxetine treated group showed disorganized podocyte foot processes. In several cell types, including murine and human podocytes, ROS have the ability to trigger apoptosis[30]. According to other investigations, free radicals cause podocyte loss in a nephropathy model[31].

In our study PRP was injected subcutaneous. Wasterlian *et al*[32] found that extravascular PRP injection resulted in elevated levels of IGF-1,vascular endothelial growth factor (VEGF),and BFGF. Thus supporting that extra vascular route as subcutaneous one may be responsible for systemic performance enhancing the effect of PRP

H&E stained sections of PRP group, PAS stained sections and iNOS immunological stained sections showed results near to control group. Lyras *et al*.[33] reported that in regenerative medicine, platelet-rich plasma functions as a desirable biologic tool. It contains significant amounts of growth factors (GFs), including epidermal growth factor (EGF) which is released from α-granules and dense-granules of platelets., hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), adenosine triphosphate (ATP), and adenosine diphosphate (ADP), These factors are important for angiogenesis and tissue regeneration by regulating physiological functions proliferation, differentiation, and migration of cells.

The cortical renal tubules epithelium showed pronounced regeneration after being damaged by trauma, according to Moghadam *et al*.[34]. The biological effects of platelet GFs were cited by Matsumot and Nakamura[35] as the cause of epithelial cell renewal. Epithelial cells multiply when epithelial growth factor is present. In cases of acute renal insufficiency, IGF-1 stimulates tubular cell regeneration. By promoting epithelial cell proliferation and inhibiting apoptosis, HGF aids the tubular epithelial cells survival.

The main benefit of PRP over alternative delivery methods for growth factors is that it is a low-cost, simple-to-obtain substance with no chance of immunological reaction or rejection. Leukocytes in it also reduce the chance of infection[36].

Despite the fact that PRP is often associated with encouraging tissue regeneration, some authors are opposed to it. The findings of Martn-Solé *et al*.[37] indicated that kidney quality had declined rather than tissue regeneration..

Many theories tried to explain kidney deterioration after PRP injection instead of regeneration. The creation of thrombi in intra renal blood arteries would be the first one. The second theory claimed that renal damage was brought on by PRP's high osmolality. A third theory is that the platelets that were injected, particularly those that included leukocytes, released inflammatory cytokines[38].

CONCLUSION & RECOMMENDATION

In conclusion, our study discovered that fluoxetine produces histological abnormalities in the renal cortex structure and impairment in the function of kidney, which were improved by the application of PRP as demonstrated by biochemical and structural changes.

For fluoxetine, which must only be administered under strict clinical supervision, more research is needed to ensure its long-term safety. Although PRP is utilized to alleviate tissue damage, longer-term researches are needed to determine their long-term efficacy. To change their proper safe effective dose, more studies are required

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التأثير الوقائي المحتمل للبلازما الغنية بالصفائح الدموية على التغيرات القشرية الكلوية المحدثة بالفلوكستين في ذكور الجرذان البيضاء: دراسة هيستولوجية و هستوكيميائية مناعية

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الخلفية: الاكتئاب هو اضطراب مزاجي يسبب الشعور المستمر بالحزن وفقدان الاهتمام. البلازما الغنية بالصفائح الدموية هي مشتق ذاتي من الدم الكامل والذي له دور تجديدي مهم في الطب .

المواد والطرق:. تم استخدام ثلاثين من الفئران البيضاء البالغة في هذه الدراسة. الدم والكرياتينين في الدم. وتم قياس مستويات المالونديالدهيد في أنسجة الكلى. تم تجهيز عينات من الكلى للفحص المجهري الضوئي والإلكتروني.

النتائج: كان هناك فروق ذات دلالة إحصائية بين المجموعات المدروسة فيما يتعلق بمستوى الكرياتين مع أعلى مستوى تم الإشارة إليه في مجموعة فلوكستين. أظهرت القشرة الكلوية للمجموعة المعالجة بالفلوكستين احتقان الشعيرات الدموية الكبيبية. تحتوي بعض الخلايا الأنبوبية على نوى داكنة اللون. أظهرت المجموعة المعالجة بالبلازما الغنية بالصفائح الدموية تحسنًا ملحوظًا في التركيب النسيجي للأنسجة القشرية الكلوية. كشفت أقسام المجموعة المعالجة بالفلوكستين عن عدد قليل من التفاعلات الإيجابية لـملون حمض شيف الدوري .في المجموعة المعالجة، شوهد التفاعل السيتوبلازمي الإيجابي في المجموعة المعالجة بالفلوكستين في العديد من البطانة الظهارية للأنابيب، وتفاعلات مناعية إيجابية في عدد قليل من الأنابيب في المجموعة المعالجة بالبلازما الغنية بالصفائح الدموية .

الخلاصة: وجدت دراستنا أن فلوكستين يسبب تدهور وظائف الكلى وتغيرات في البنية النسيجية لقشرة الكلى والتي تم تحسينها عن طريق البلازماالغنية بالصفائح الدموية