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Effect of Sertraline and Fluoxetine on Some Biochemical Parameters and Histological Changes in Male and Female Laboratory Rats *Rattus norvegicus*

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Abstract:

The current study was designed to determine the effect of sertraline and fluoxetine drugs on some biochemicals and histologicals change of male and female rats. The animals were divided into five groups (each group consisting of 5 males and 5 females), the first group (control) was injected with the physiological solution Nacl 0.9%, second group was injected with10 mg / kg of Sertraline, third group was injected with 20 mg / kg of sertraline, fourth group was injected with 5 mg / kg of fluoxetine and fifth group was injected with10 mg / kg fluoxetine. The results showed that a significant increase ($P \leq 0.05$) in the concentration of urea and creatinine (except for the second group of females) in all treated group compared with control. In the liver enzymes, the results showed that a significant decrease in the concentrations of aspartate transaminase enzyme, Alanine transaminase and alkaline phosphatase in all treated groups compared with the control group($P \leq 0.05$). The kidney tissue showed histological changes such as infiltration of inflammatory cell, congestion, hemorrhage, renal glomerular distraction and loss, renal tubular hypertrophy.

Keywords: Sertraline, Fluoxetine, Kidney, Liver.

Introduction

The disorder of depression is increasing among communities, drug therapy is the best way to cure it (Sadock and Sadock, 2000). Selective Serotonin reuptake inhibitors (SSRIs) are drugs that are used for short and long term treatment of mental illnesses. Most prevalent psychiatry illnesses are depression, and SSRIs are the first line drugs in the treatment of these disorders (Bystritsky *et al.*,2013). Selective Serotonin reuptake inhibitors (SSRIs) inhibit serotonin reuptake, so it will increase in synaptic cleft (Porter and Brums,2000). SSRIs are extensively metabolized in the liver by group of enzymes cytochrome P-450 (CYP) which consists of a family of closely , Coad ministering the drugs which either inhibit or induce CYP enzymes with these antipsychotic agents may result in higher plasma level with adverse effects or lower plasma level with compromised therapeutic effects (Shastry *et al.* ,2013).Hence care must be taken while choosing antipsychotic drugs in combination with other drugs which are also metabolized by these

hepatic enzyme. Antidepressant drugs (tricyclic agents or selective serotonin reuptake inhibitors) and mood-stabilizing agents have been extensively coprescribed with antipsychotic agents in treatment of psychosis with bipolar affective disorders, generalized tonic clonic seizures, obsessive compulsive disorders, and depression. These combination are implicated in clinical hepatotoxicity (Dumortier *et al*.,2002) .Sertraline and fluoxetine are the most selective Serotonin reuptake inhibitors that are used to treat depression and anxiety, SSRIs differ in their pharmacokinetics ,Fluoxetine has the longest half-life (2days) and sertraline has half –life approximately one day (Lu S *et al.*,2009 ; Sanchez *et al.*,2014 ;Davies *et al* .,2016).

2-Material and method

1-2- Animals preparation

Fifty health rats both gender, it ages are between12-14 week weighting approximately 190-210g were obtained from Science Collage /Thi-Qar University. The animals were housed in controlled temperature room (22-25) under a 12h- light /12h –dark cycle . The animals given pellet diet and tap water *ad libitum*

2- **Study design**

The animals were assigned randomly into five group (each group contain 5 males and 5 females):

1-First group (control group) : injected with 0.2 ml of normal saline 0.9% NaCL.

2-Second group : injected with 0.2ml (10 mg/g) /day of sertraline .

3-Third group : injected with 0.2ml (20mg/g) /day of sertraline .

4-Fourth group : injected with 0.2ml (5mg/g) /day of fluoxetine .

5-Fifth group : injected with 0.2ml(10mg/g) /day of fluoxetine .

all Members of these groups were injected through the intraperitoneal membrane for 4 weeks, after the end of experimental period animals were anaesthetized and pull the blood directly from the heart by cardiac puncture .

3-2-Estimation of serum urea concentration

Wills and Savory's method (1981)was used by Using of kits were supplied by Biomerieux to determination the effect of sertraline and fluoxetine in serum urea concentration .

4-2-Estimation of serum creatinine concentration

To determination the effect of sertraline and fluoxetine in serum creatinine concentration, Tietz's method (1999) was used by using kits were supplied by biolabo (France).

5-2-Estimation of serum aspartate transaminase enzyme(AST),Alanine transaminase (ALT) & alkaline phosphatase (ALP)concentrations

Reitman and Frakel's method(1957) was used to estimation of ALT &AST concentrations, Belfied & Goldberg (1971) and Kind and King's method (1954) was used to estimation of ALP concentration.

6-2-Histological study

The Bancroft and Gamble's method (2008),Luna's method (1968) was used to prepare tissue sections (kidney and liver) .

7-2-Statistical analysis

The data were analyzed by using ANOVA to determine mean and standard error, $p \leq 0.05$ was considered as significant in this study .

3- The results

1-3-Effect of sertraline and fluoxetine on the kidney function in male rats

The results showed a significant increase in the concentration of creatinine in all treated groups compared with the control group at the probability level (P≤0.05) . The results showed a significant increase in the third group when compared with the second group and a non -significant increase in the fifth group comparison with the fourth group as shown in Table (1).

The results of the comparison between the effects of sertraline and fluoxetine, showed a non- significant increase in the fourth group compared with the second group and in the third group compared to the fifth group at the level of probability (P≤0.05) The concentration of urea ,the results showed a significant increase in all treated groups compared with the control group at the level of probability (P≤0.05) . The results showed a significant increase in the third group when compared with the second and the fourth group when compared with the fifth group at the probability level (P≤0.05). The results of the comparison between the effects of sertraline and fluoxetine, showed a significant increase in the fourth group compared with the second and the third group compared to the fifth group at the level of probability (P≤0.05).

Table 1: Effect of sertraline and fluoxetine on the kidney function in male rats (mean ±standard error)

kidney functions / groups	Creatinine (mg/dl)	±standard error	Urea (mg/dl)	±standard error
first group (control)	.72 a	± 0.02	32.80 a	± 1.92
second group (10mg/g sertraline)	.89 b	± 0.008	36.00 b	± 1.87
third group (20mg/g line)	1.08 cd	± 0.16	53.40 c	± 2.50
fourth group (5mg/g tine)	.97 b	± 0.08	53.40 dc	± 2.40
fifth group(10mg/g tine)	1.02 bd	± 0.08	45.60 e	± 1.34
L.S.D	0.11		2.71	

The differences of letters indicate significant differences at(P≤0.05)

Effect of sertraline and fluoxetine on the kidney function in female rats

The results showed a significant increase in the concentration of creatinine in the sertraline and fluoxetine groups, except for the second group, where this increase did not reach to the significance level compared to the control group at the probability level (P≤0.05) . The results showed a significant increase in the third group when compared with the second group and in the fifth group when compared with the fourth group as shown in Table (2). The comparison between the effects of sertraline and fluoxetine, the results showed a significant increase in the fourth group compared with the second and the fifth group compared with the third group at the level of probability (P≤0.05). The concentration of urea, the results showed a significant increase in all treated groups compared with the control group at the probability level (P≤0.05) . The results

showed a significant increase in the third group when compared with the second and the fifth group comparison with the fourth group. The comparison between the effects of sertraline and fluoxetine, the showed a significant increase in the fourth group compared to the second group and a non – significant increase in the fifth group compared with the third at the level of probability (P≤0.05)

Table 2: Effect of sertraline and fluoxetine on the kidney function in female rats (mean ±standard error)

kidney functions / groups	Creatinine (mg/dl)	±standard error	Urea (mg/dl)	±standard error
first group (control)	.82 a	± .02	31.00 a	± 2.23
second group (10mg/g sertraline)	.88 a	± .01	38.20 b	± 1.30
third group (20mg/g line)	1.08 b	± .08	49.60 c	± 1.51
fourth group (5mg/g tine)	.99 b	± .07	48.20 d	± 2.38
fifth group(10mg/g fluoxetine)	1.35 c	± .10	51.60 c	± 1.81
L.S.D	0.08		2.50	

The differences of letters indicate significant differences at P≤0.05)

Effect of sertraline and fluoxetine on the liver enzymes in male rats

The results showed a significant decrease in the concentration of aspartate transaminase (ALT) in all treated groups compared with the control group at the probability level (P≤0.05). The results also showed a significant decrease in the third group when compared with the second and the fifth group when compared with the fourth group as shown in Table (3).

The results of the comparison between the effects of sertraline and fluoxetine, showed a significant decrease in the fourth group compared to the second and the fifth group compared to the third group at the probability level (P≤0.05) . The results showed a significant decrease in the concentration of AST in all treated groups compared to the control group at the probability level (P≤0.05) , the results showed a significant decrease in the third group when compared with the second and fourth group when compared with the fifth group . The results of the comparison between the effects of sertraline and fluoxetine, showed a significant decrease in the fourth group compared with the second group and a non- significant decrease in the fifth group compared with the third group at the level of probability (P≤0.05). The results showed a significant decrease in the concentration of the ALP enzyme in the third and fifth groups and a decrease not reach to the level of significance in the second and fourth group compared with the control group at the probability level (P≤0.05) . The results also showed a significant decrease in the third group when compared with the second and the fifth group when compared with the fourth group .The results of the comparison between the effects of sertraline and fluoxetine, showed a non-significant decrease in the second group compared with the fourth group and in the fifth group compared to the third group at the probability level (P≤0.05) .

Table 3: Effect of sertraline and fluoxetine on the liver enzymes in male rats

liver enzymes / groups	U/l)	ndard error	U/l)	ndard error	U/l)	ndard ror
first group (control)	11.68 a	±.43	18.66 a	± .40	115.40 a	± 11.97
second group (10mg/g sertraline)	8.84 b	± .29	11.02 b	± 1.62	109.94 a	± 4.58
third group (20mg/g line)	7.08 c	± .21	9.88 b	± .92	95.00 b	± 6.04
fourth group (5mg/g tine)	7.22 d	± .21	6.79 c	± .29	112.60 a	± 2.07
fifth group(10mg/g tine)	5.26 ± .49 e	± .49	9.50 b	± .37	94.30 b	± 11.09
L.S.D	0.45		1.15		10.6	

The differences of letters indicate significant differences at P≤0.05)

Effect of sertraline and fluoxetine on the liver enzyme in female rats

The results showed a significant decrease in the concentration of ALT in all treated groups compared with the control group at the probability level (P≤0.05). The results also showed a significant decrease in the second group when compared with the third group and a non-significant decrease in the fifth group comparison with the fourth group as shown in Table (4). The results of the comparison between the effects of sertraline and fluoxetine, showed a significant decrease in the fourth group compared with the second and the fifth group compared with the third group at the level of probability (P≤0.05). The results showed a significant decrease in the concentration of AST enzyme in all treated groups compared with the control group at the probability level (P≤0.05). The results showed a non -significant decrease in the third group when compared with the second group and a significant decrease in the fifth group when compared with the fourth group. The results of the comparison between the effects of sertraline and fluoxetine, showed a significant decrease in the fourth group compared with the second and the fifth group compared with the third group at the level of probability (P≤0.05). The results showed a significant decrease in the concentration of ALP in all treated groups compared with the control group at the probability level (P≤0.05) . The results also showed a non- significant decrease in the second group when compared with the third group and a significant decrease in the fifth group when compared with the fourth group. The results of the comparison between the effects of sertraline and fluoxetine, showed a significant decrease in the second group compared with the fourth group and in the fifth group compared with the third group at the probability level (P≤0.05).

Table 4: Effect of sertraline and fluoxetine on the liver enzymes in male rats

liver enzyme / groups	U/l)	ndard or	U/l)	ndard or	ALP (U / l)	ndard error
first group (control)	9.54 a	± .45	14.68 a	± .43	133.20 a	± 4.96
second group (10mg/g sertraline)	7.44 b	± .29	10.40 b	± 1.09	89.40 b	± 5.72
third group (20mg/g sertraline)	8.20 c	± .48	11.04 b	± .28	91.52 b	± 4.26
fourth group (5mg/g fluoxetine)	2.80 d	± .76	7.75 d	± .49	110.60 c	± 2.60
fifth group(10mg/g fluoxetine)	2.18 d	± .40	3.84 e	± .60	69.16 d	± 7.21
L.S.D	0.65		0.84		7.5	

The differences of letters indicate significant differences at P≤0.05)

Effect of sertraline and fluoxetine on kidney damage (male and female)

The results of the histological study of the control group showed that the kidney is composed of the cortex, which contains the renal glomeruli and the renal tubules and the other region of kidney called medulla. The results of the histological study of the sertraline and fluoxetine kidneys showed a number of histopathological changes, including infiltration of the inflammatory cells, congestion, renal glaucoma, loss of renal glomerular, hemorrhage, renal tubular hypertrophy, necrosis, degeneration of glomerulus wall as shown in Figures (1-9).

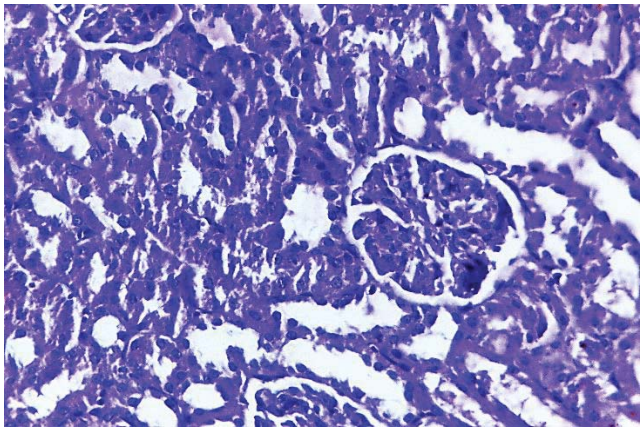
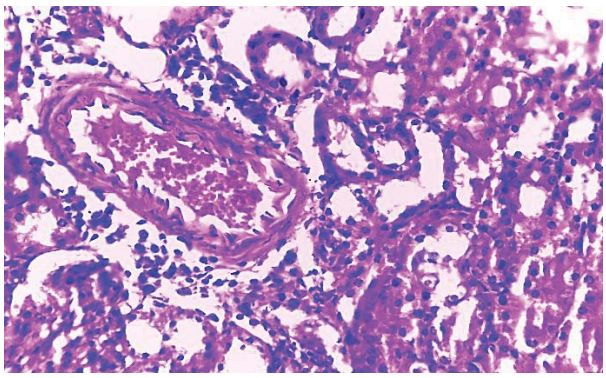
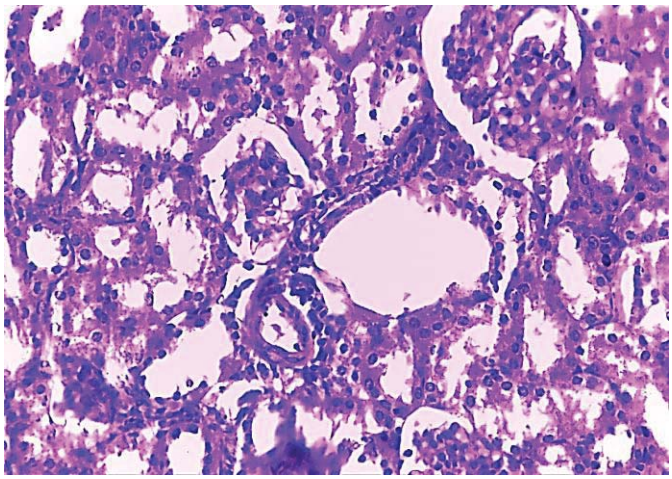


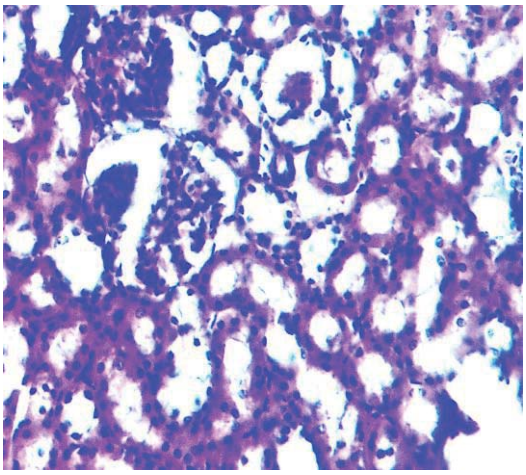
Fig (1) C .S .of kidney from control group shows A-renal glomerulus, B-renal tubules (400XH&E)



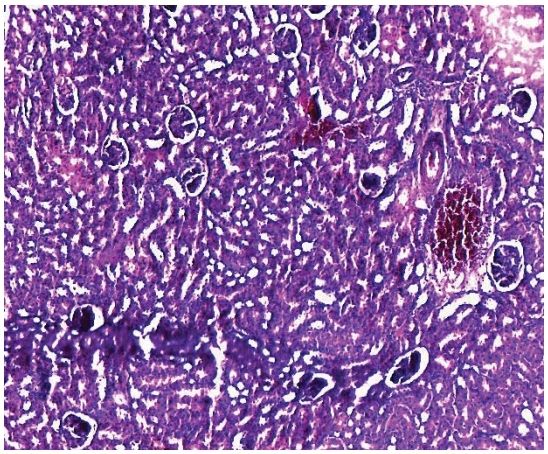
Fig(2) C.S. of kidney from second group shows A- bloody congestion, B-cellular infiltration (400XH&E)



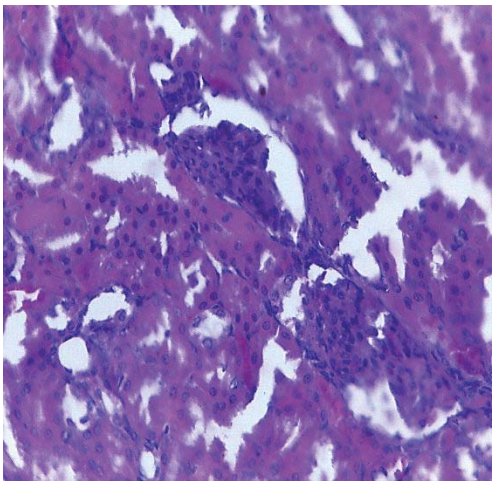
Fig(3) C.S. of kidney from second group shows A- expansion of renal tubule(400XH&E)



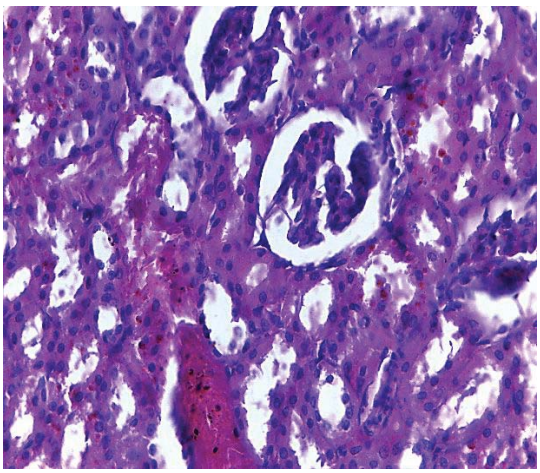
Fig(4) C.S of kidney from third group shows A-atrophy of glomerulus ,B- necrosis ,C-degeneration of glomerulus wall , D- renal tubular hypertrophy(400XH&E)



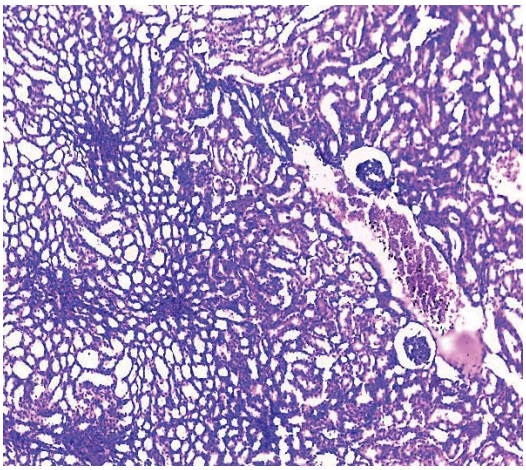
Fig(5) C.S of kidney from third group shows A- bloody hemorrhage ,B- cellular infiltration(100XH&E)



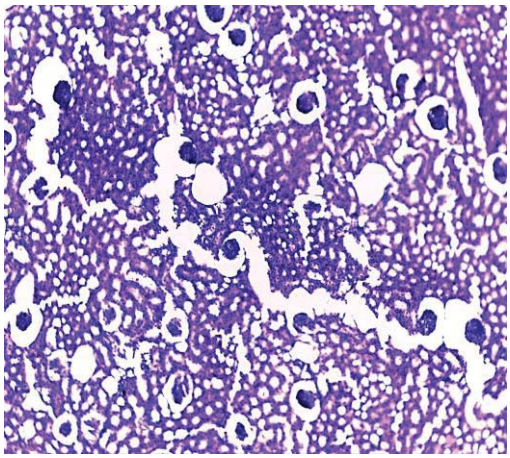
Fig(6) C.S of kidney from fourth group shows A- loss of normal shape of glomerulus ,B- renal tubulysis (100X H&E)



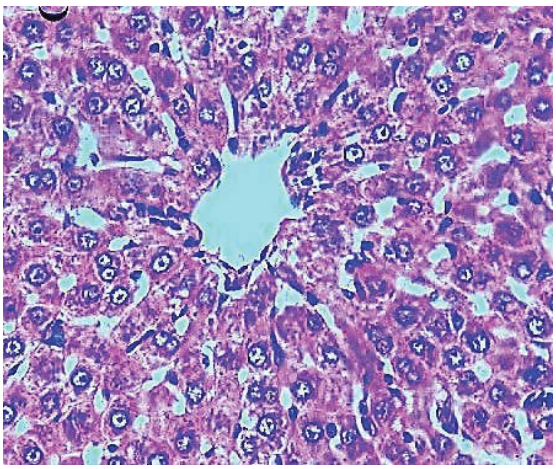
Fig(7) C.S of kidney from fourth group shows A- bloody hemorrhage,C-hyperplasia(100XH&E)



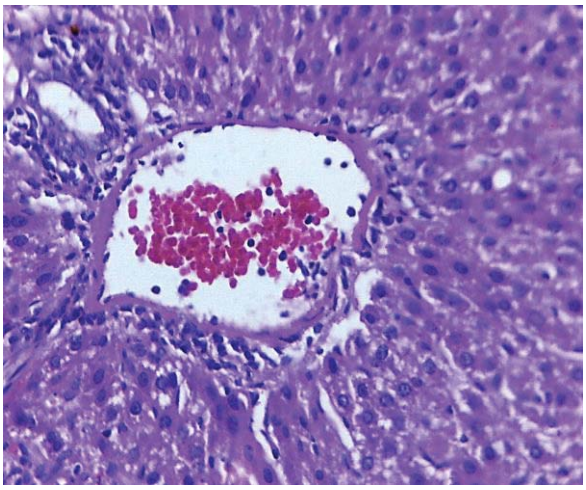
Fig(8) C.S of kidney from fifth group shows A- bloody congestion ,B- cellular infiltration(40XH&E)



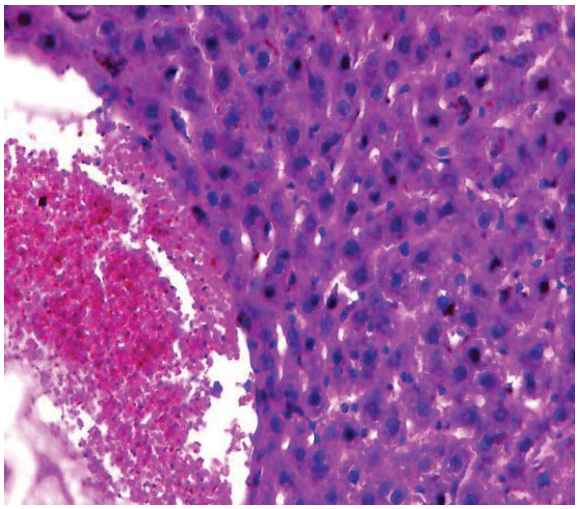
Fig(9) C.S of kidney from fifth group shows A- loss of glomerulus ,B- cellular infiltration(40XH&E)



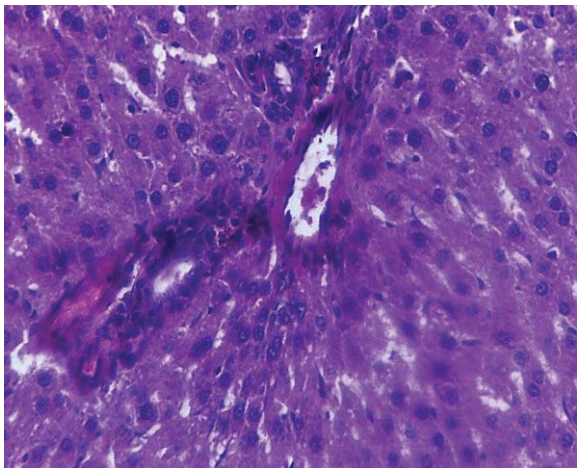
Fig(10) C.S of liver from control group shows A- central vein ,B-hepatocyte(400XH&E)



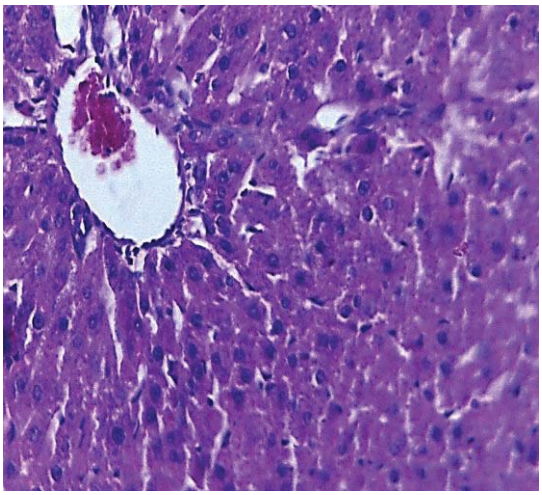
Fig(11) C.S of liver from second group shows A- bloody congestion, B- cellular infiltration (400XH&E)



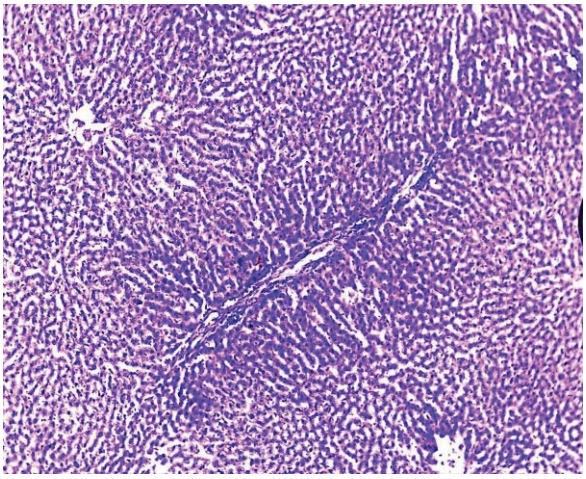
Fig(12) C.S of liver from third group shows A- congestion ,B- increased number of Kupfer cells (400XH&E)



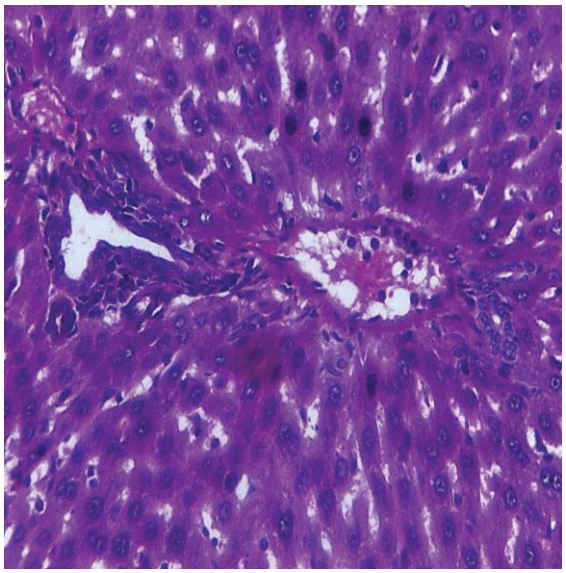
Fig(13) C.S of liver from third group shows A- edema , B- cellular infiltration (400XH&E)



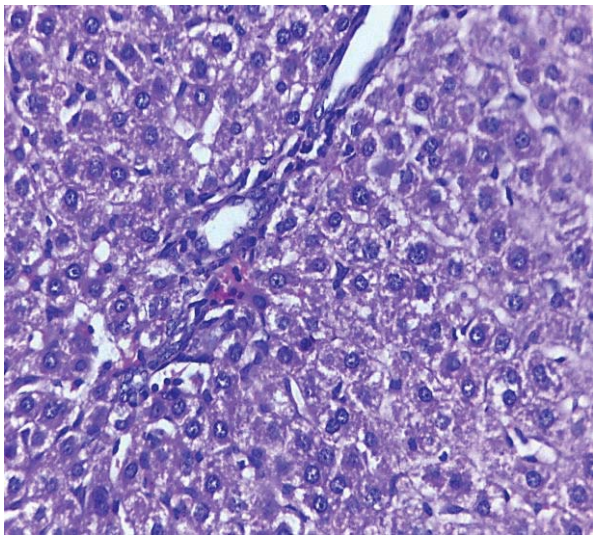
Fig(14) C.S of liver from fourth group shows A- bloody congestion ,B- necrosis (400XH&E)



Fig(15) C.S of liver from fourth group shows A- cellular infiltration B-necrosis (100XH&E)



Fig(16) C.S of liver from fifth group shows A- bloody hemorrhage ,B- cellular infiltration ,C-hyperplasia (400XH&E)



Fig(17) C.S of liver from fifth group shows A- di-nuclei cells ,B- necrosis C-cellular infiltration (400XH&E)

4-Discussion

1-4-Effect of sertraline and fluoxetine on the kidney function

The results of the statistical analysis of the present study showed a significant increase in the concentration of creatinine and urea in the groups treated with sertraline and fluoxetine(except the second group of female rats in creatinine concentration) compared to the control group.

Several studies have shown that increasing the concentration of creatinine and urea is often a sign of kidney function disorder (Gowda *et al.,* 2009).

Glomeruli integrity is an indicator of the efficiency of the filtration process for which it is responsible. any damage caused by glomerular due to the use of antidepressants causes low glomerular filtration, Rajapaske and his colleges (2010) and Thanacoody (2012) have shown that antidepressants affect on glomeruli and thus reduce the filtration rate, which leads to the retention of nitrogen wastes and thus increase the concentration of creatinine and urea supported by the tissue sections of the kidney in the current study of glomerular loss and shrinkage.

High level of urea and creatinine may be due to kidney tissue damage and kidney failure, Rose (1985) suggests that high level of creatinine is one of the most important indicators of renal failure due to the influence of functional units (nephrons).

High concentration of urea may be due to the effect of these drugs in the liver which is the site of urea manufacturing. Tan *et al*. (2007) found that urea is made in the liver from ammonia and then transferred to the kidneys by blood circulation to be discarded through the bloodstream. Histological sections showed clear effects in the liver. Tak and Firestein (2001) showed that cytokines caused numerous kidney damage, reduced their ability to function, and increased creatinine and urea concentrations due to the inability of the kidney to get rid of them, histological section showed inflammation in the kidney tissue.

2-4-Effect of sertraline and fluoxetine on the liver enzymes

The results of the present study showed a significant decrease in the concentration of liver enzymes (AST, ALT, ALP) in animals treated with sertraline and fluoxetine compared with control group.

Liver enzymes are an indicator of the pathological changes that occur in hepatocytes, especially the AST enzyme, the liver produces them (Gutierrez and Navarro, 2010).

Studies have shown that the reduction or rise of liver enzymes is an indicator of liver function disorder or dysfunction, or lack of proteins necessary to produce these enzymes (Obeten *et al*., 2013), and that AST and ALT enzymes are a predictor of liver toxicity(Rahman *et al.,* 2001) and cytolysis (Yakubu *et al.*, 2005).

The decrease in the concentration of these enzymes may be due to the effect of antidepressants on mitochondria of the liver of rats, this imbalance disrupts the generation of ATP and results necrosis and programmed cell death that will weaken the level of liver enzymes in blood(Li Y *et al*., 2012; Kalogeris and Korthuis, 2014).

The decrease may be caused by oxidative stress(Erdemer *et al* ., 2014) which leads to increase free radicals production and the lack of antioxidants that cause self-oxidation of the fatty acids that make up the hepatocellular membranes, resulting in cell damage and inability to function(Ferrari, 2000). These factors are reflect negatively on the activity of the liver and these increase the inability to produce enzymes, which causes low concentration in the blood.

3-4-Effect of sertraline and fluoxetine on the kidney damage

Medicines are one of the most common causes of renal damage, which are different depending on the type of used drug. Some of them are harmful to a particular member, and others treat it (Loh, 2009). The results of the histological sections of the kidneys of the treated rats showed satisfactory effects, including the breakdown of the renal glomeruli and their shrinkage and loss in other sections, due to the effect of free radicals. Alisia *et al*. (2011) and Dhanaskara and Ganapathy (2011) found that free radical cause oxidation lipid cell membranes, Sudhir (2004) also found that oxidants act to break down the renal glomeruli and necrosis them and damage them . It was also observed that inflammation of the kidney tissue, caused by free radicals, stimulates a nuclear factor that mediated in many inflammatory pathways (Meyer *et al*., 1993), which stimulates the expression of inflammatory cytokines (Sanchez *et al.,* 2009) and this explains the cause of the infiltration of cells. As for the atrophy of the cells of the tubules may be a means of defense to get rid of the toxicity of the drug and thus expansion of cavities as the chemical life mechanism of this process is to increase the state of protein degradation in the cells at the expense of the manufacture of cellular proteins and this leads to the weight of the case of demolition, (Kumar *et al.,* 2007).

4-4-Effect of sertraline and fluoxetine on the liver damage

The results of the microscopic examination of the treated rats showed satisfactory
effects including central vein congestion, infiltration of inflammatory cells and hemorrhage, as well as the appearance of de nuclei cells.

These histological changes in the liver may be due to the fact that chemical drugs strongly induce hepatotoxicity by increasing the generation of liver peroxidation (Yuce *et al.*, 2007), which destroys the cellular structure of cell membranes and their nuclei. The generation of ROS induced drugs interacts with the immune system which cause anti-toxic in the liver. Causing oxidative damage in tissues, where it interact with the group of thiol in the glutathione and proteins, leading to liver dysfunction.

The cause of damage to the liver tissue may be the reduction in the concentration of glutathione. which is a good antagonist of ROS in the enzyme antioxidant immune system . Gokcimen *et al.* (2002) found that

glutathione protects hepatic cells from oxidative stress. As for the case of bloody congestion, it may be due to the fact that the drugs cause acute inflammation leading to changes in the bloodstream (Robbins and Kumar, 1987). The presence of a number of di nuclei cells can be due to the division of hepatic cells as an adaptive response when the liver is infected with chronic or acute disease and when the breakdown and inflammation of the liver cells to show the cell division and then replace the cells with other new cells and thus maintain the performance of the liver function (Apte *et al*., 2004).

References:

Apte, U. M ., Mcree, R ., & Ramaiah, S. K.(2004) . Hepatocyte proliferation is the possible mechanism for the transient decrease in liver injury during steatosis of stae alcoholic liver disease. *Toxicologic pathology*, *32*(5),567-576 .

Alisi, C . S. , Ojiaka,A.O. ,Onyeze,G.O. & Osuagwu, A.(2011) . Normalization of lipoprotein phenotypes by *Chromolaena odorata* –Linn-in carbon tetrachloride hepatocyte toxicity - induced dyslipidemia . *Am . J .Drug ,Discov . Dev , 1 (4) pp: 209- 219.*

Bancroft, J.D. & Gamble, M.(2008) . Theory and practices of histological technigue .2 nd ed . *Churchill Elsevier . London ., P : 56.*

Belfield, A. & Goldberg, D.M.(1971). Revised assay for serum phenyl phosphatase activ ty using 4- amino-antipyrine . Enzyme 12(5) Pp: 561-573.

Bystritsky, A . , Khalsa,S.S., Cameron,ME. & Shiffman, j .(2013). Current diagnosis and treatment of anxiety disorders . *Pharm Ther . pp30-57.*

Davies, S., Mulsant, B., Flint, A., Meyers, B. & Rothschild, A.(2016). SSRIs antipsyochotic combination in psychotic depression ; sertraline pharmacokinetic in the presence of olanzapine , a brief report from the stopped study. Hum psychopharm acol ;31pp 5-281.

Dhanaskara, J. & Ganapathy, M .(2011). Hepatopretective effect of *Cassia auri*culate L. leaf extract on carbon tetrachloride intoxicated liver damage in wistar albino . Asian . J. Biochem . 6 (1) Pp : 104-112.

Dumortier G, Cabaret W, Stamatiadis L, Saba G, Benadhira R, Rocamora JF.(2002). Hepatic tolerance of atypical antipsychotic drugs. Encephale;28:542–51

Erdemir, F. , Atilgan, D. , Firat, F. , Markoc, F. , Parlaktas, B. S. & Sogut, E. (2014). The effect of sertraline, paroxetine, fluoxetine and escitalopram on testicular tissue and oxidative stress parameters in rats. *International braz , J , urol , 40(1_,100-108.*

Ferrai,C .(2000). Free radical ,lipid peroxidation and antioxidants inapoptosis : implication in cancer ,cardiovascular and neurological diseases .Biol Bratislava ; (6) pp:581 -590.

Gokcimen, A . , Ozguner, F. , Karaoz, E. , Ozen, S. & Aydin, G.(2002). The effect of melatonin on morphological changes in liver induced by magnetic field exposure in rats . Okajimas Folia . Anat . Jpn . 79(1) Pp : 25-31.

Gowda, S. , Desai, P.B., Hull, V.V., Math, A.A.K., Vernekar, S.N.& Kulkarni, S. S .(2009). "A review on laboratory liver function tests." The Pan African Medical Journal 3.

Gutierrez, R . M. & Navarro, Y. T.(2010). "Antioxidant and hepatoprotective effects of the methanol extract of the leaves of Satureja macrostema.pharmacognosy magazine ,6(22),125".

Kalogeris, T., Bao, Y., & Korthuis, R. J.(2014). Mitochondrial reactive oxygen species : A double edged sword in ischemia/reperfusion vs preconditioning. *Redox biology*, *2*, 702-714. *Pharmacognosy magazine 6(*22): 125-231.

Kind, P . R. & King, E .J.(1954). Estimation of plasma phosphatase by determination of hydrolyzed phenol with amino-antipyrine. Journal of clinical pathology 7(4) Pp: 322 -326.

Kumar, V., Abbas, A., Fausto, N., & Mitchell,R.N.(2007) . Robbins Basic Pathology.8th ed. Saunders Elseevier.8,345-355.

Li,Y.,Couch,L.,Higuchi,M.,Fang,J.L.&Gue,L.**(2012).**Mitochondrial dysfunction induced by sertraline, an antidepressant agents. *Toxicological science, 127(2)* 582591.

Lu , S., Zhao , Y., Hu, H.& Zhang, H.(2009). Combined use of phosphodiesterase -5 inibitors and selective serotonin reuptake inhibitors for temporary ejaculation failure in couple undergoing assisted reproductive technologies . Fertil Steril ;91pp8-1806 .

Loh, A. H., & Cohen, A. H.(2009). Drug-induced kidney disease–pathology and current concepts . *Ann Acad Med Singapore*, *38*(3), 240-250.

Meyer, M., Schreck, R., & Baeuerle, P. A . (2009).H2O2 and antioxidants have opposite effects on activation of NF-kappa B and AP-1 in intact cells : AP-1 as secondary antioxidant-responsive factor. *The EMBO journal*, *12*(5).

Obeten, K . E. , Uruakpa, K . C. & Isaac, V. (2013).The evaluation of the effect of *Sida acuta* leaf extract on the microanatomy and some biochemical parameters on the liver of wister rats . IOSR Journal of Applied Physics (IOSR-JAP) 4(1): 60-66. *Therapy*, *18*(1), 84- 112.

Porter, M .& Brums, J.(2000) . Effect of prolactin on follicle-stimulating hormone receptor binding and progesterone production granulosa cells .University of Vermont collage of medicine ,Burlington USA 73:99-105.

Rahman, M . F. , Siddiqui, M . K & Jamil, K .(2001). "Effects of Vepacide (Azadirachtra Indicans) on aspartate and Alanine Amino Transferase profiles in a subchronic study with rats .Human & experimental toxicology 20(5): 243-249.

Rajapakse,S.,Abeynaike,L.&Wickramarathne,T.(2010). Venlafaxine-associated serotonin syndrome causing severe rhabdomyolysis and acute renal failure in a patient with acute renal failure in a patient with idiopathic Parkinson disease .*Journal of* disease. *Journal of clinical psychopharmacology*, *30*(5), 620-622.

Reitman, S . & Frankel, S . A.(1975). colorimetric method for the determination of serum glutamic oxaloacetic and glutamic pyruvic transaminases. Am . J .Clin . pathol .28 (1) pp :56 – 63.

Robbins, S . L. & Kumar, V.(1987). Basic pathology .4th ed .W.B. Sunders company ..philadelphia ,London , 29(31) ,50-53.

Rose, D . B .(1985) . Pathophysiology of renal disease Sunders W.B. company Philadelphia . 55-77.

Sadock, B . J .& Sadock, V. A(2000) . Comprehensive text book of psychiatry . 7th ed .Baltimor lipincott Williams and Wilkins , pp:1441-1503.

Sánchez-López, E. , Rayego, S., Rodrigues-Díez, R . , Rodriguez, J. S., Rodrigues-Diez, R . , Rodríguez-Vita, J. & Ortiz, A.(2009). CTGF promotes inflammatory cell infiltration of the renal interstitium by activating NF-κB. *Journal of the American Society of Nephrology*, *20*(7), 1513-1526.

Sanchez, C . , Reine, E . H . & Montgomery,S.A . (2014). AComparative review of ecitalopram , paroxetine and sertraline : are they all alike ? Int Clin Psychopharacol :pp 96- 185.

Shastry, C. S., Shafeeque, A. A., & Ashwathnarayana, B. J. (2013). Effect of combination of aripiprazole with carbamazepine and fluvoxamine on liver functions in experimental animals. *Indian journal of pharmacology*, *45*(2), 121.

Sudhir, V .(2004). Oxidants and iron in chronic kidney disease . Kidney Int. Suppl . (66) pp : 50- 55.

Sunmonu,T.O ., Oloyede , O. B.,Owolarafe ,T.A., Yakubu ,M.T. & Dosumu ,O.O. (2014) "Toxicopathological evaluation of *Picralima nitida* seed aqueous extract in wistar rats." Turk J Bioch 39(2): 119–125.

Tak, P.P. & Firestein, G.C .(2001). Nf-KB : a key in inflammatory disease . Journal of clinical investigation 107(1)pp:7-11,2001.

Tan, E. H. , Ma, F. J. , Gopinadhan, S., Sakban, R. B., & Wang, N. D. (2007).C/EBPα knock-in hepatocytes exhibit increased albumin secretion and ureaproduction. *Cell and tissue research*, *330*(3), 427-435.

Tietz, N.W.(1990). Text book of clinical chemistry. 3rd Ed. C.A. Burtis, E . R. Ashwood , W.B. Saunders . Pp: 819- 861.

Thanacoody, R.(2012). Serotonin syndrome. *Medicine*, *40*(2), 63-64.

Wills,M.R. & Savory,J.(1981). Biochemistry of renal failure . Ann . clin . lab. Sci . 11(4) PP : 292 - 299.

Yakubu, M.T., Akanji, M .A.& Oladiji , A.T.(2005)."Aphrodisiac potentials of the aqueous extract of *Fadogia agrestis* (Schweinf. Ex Hiern) stem in male albino rats .Asian Journal of Andrology, **7**(4): 399-404.

Yuce, A . , Atessahin, A . , Ceribasi, A ., & Akasakal, M .(2007). Ellagic acid prevents citplatin 10 mg kg^{-1} planin- induced oxidative stress in liver and heart tissue of rats.Basic clin.pharmacol.Toxicol,101,345-349.