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Oxidative injure occur of citalopram and floxtein in rat with embryos in different organs

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ABSTRACT

The reason of this study was investigate effects Citalopram and Floxtein for histological embryos in different organs with anatomical effects in male reproductive organs of adults rats for 90 days. The 45 rats were divided into three equal groups (control and two treated groups), and animals were treated as follow: 1- Control group (n=15) 2-Treatment group (n=15) treated each day with citalopram tablets 20mg in distal water for 80 days.3-Treatment Group (n=15)treated daily Fluoxetine capsules 20mg in distal water for 80 days. At 84 days animals sacrificed then male reproductive organs, with embryos weighted and take organs for histopathological study. The present study shows that treatment with Citalopram and Floxtein cause a significant reduce in body weight of embryos and effects on organs.

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INTRODUCTION

Citalopram is an antidepressant (selective serotonin reuptake inhibitor) used in the treatment of depression (Matsui *et al.*, 1995; Rochat *et al.*, 1995). Citalopram mechanism via a balance of normal chemicals(neurotransmitters) in the brain, next to improving mood and feelings of well (Meng and Gauthier, 2005; Juan and Zhiling, 2012). Citalopram is well use to treatment eating disorders (bulimia nervosa, anorexia nervosa,) plus mental conditions (panic disorder, obsessive-compulsive disorder) (Gutteck and Rentsch, 2003; Kollroser and Schober, 2003). Side effects lack of appetite, vomiting, drowsiness, diarrhea, Nausea, trouble sleeping, fatigue, dry mouth, muscle/joint pain (Sane *et al.*, 2010). Severe side effects: sweating, changes in sexual ability, weight changes. Alter in the regulation of menstrual periods, speed heartbeats, seizures, vision problems. Males: prolonged erection, serious allergic reaction (Eap *et al.*, 1998; Buzinkaiová and Polonský, 2000). Avoid taking citalopram in heart problems, liver disease, stomach bleeding, thyroid disease, severe kidney problems (Solomons *et al.*, 2005; Stauss *et al.*, 2000). If this medication is used through the third trimester, the infant may develop symptoms, including feeding or breathing difficulties, constant crying (Strekalova *et al.*, 2006; Mombereau *et al.*, 2010). Finally, medication passes into breast milk and may have effects on a nursing infant. Breast-feeding has not recommended when used this drug (Reymond *et al.*, 1993). Animal data have shown that citalopram induces decrees fertility and pregnancy, the decline in number in implantation and abnormal sperm (Pacher and Kecskeméti, 2014).

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) (Asnis *et al.*, 2004) used to treatment of main depression disorder; vomiting in patients with moderate-to-severe bulimia nervosa; panic disorder; premenstrual dysphoric disorder (Perez-Caballero *et al.*, 2014; Kaya *et al.*, 2000). This medication works via the balance of natural

substances (neurotransmitters) in the brain, so improving mood and feelings of comfort (Capelozzi *et al.*, 2010). Common side effect: headache, anxiety, nervousness Libido decrease Nausea, anorexia diarrhea (Gonzalez-Rothi *et al.*, 1995; Kerviler *et al.*, 1996). Avoid taking Fluoxetine mainly of liver problem, kidney disease, stomach bleeding, diabetes, seizure disorder, heart disease (Vandezande *et al.*, 1997). This medication must use when principle needed throughout pregnancy (Braun *et al.*, 2012). If this medication is used throughout the third trimester, an infant could develop symptoms involve muscle stiffness, jitteriness, feeding or breathing difficulties, (Estarriol, 2012; Bernard *et al.*, 2012) finish Fluoxetine go to breast milk and harm effects on a nursing infant, so breastfeeding when taking this drug is not recommended (Torok *et al.*, 2012).

MATERIALS AND METHODS

Forty-five adult rats were obtained from Kut Technical Institute / Middle Technical University Iraq. Animals were placed at the animal house, College of science, Wasit University and fed with pellet during experimental periods. The temperature was 25C°. Female was left in a separate cage with one male for each cage ratio 2:1. The male and female couple were kept together in a mating cage for two weeks

The rats were divided into three equal groups (one control and two treated groups), and the animals were treated as follows:

1- Treatment group. (n=15) treated daily with citalopram tablets 20mg in distal water for 80 days 2- Treatment group. (n=15) Treated daily with treated every day with Fluoxetine capsules 20mg in distal water for 80 days.3-control Group. (n=15) Not treated (Lattimore *et al.*, 2005). The body weight of the embryos detects by electrical balance. At 84 days, animals sacrificed next male reproductive organs, with embryos weighted and taken organs (liver, kidney treated with citalopram), (lung, kidney and liver treated with Fluoxetine) for histopathological study. Embryo sampling preserved in 10% formalin buffer solution until preparation of histopathological section. Tissue was cut at 7-8μm and embedded in paraffin and stained with hematoxylin and Eiosin stain(H&E) (Chambers *et al.*, 2006).

Statistical Analysis

Data were expressed as the mean + standard error of mean and were compared by one way ANOVA followed by LSD. P-value more than 0.05 was considered as statistically significant (Steel *et al.*, 2012).

RESULTS AND DISCUSSION

Table 1: Effect Citalopram on the body weight rat's embryos in 1day

Parameters	Control	Citlopram
Bodyweight (gram) of embryo	1.20+ 0.066 a	0.60 + 0.033 b

-The value represent Mean(gram) +Standard Error
-The different small letters show significant effect between different group

Table 1 showed a significant decrease of body weight in Citalopram compared with the control of the experimental periods. In embryo-fetal developmental toxicity

were observed treatment with citalopram cause vomiting, lack of appetite, diarrhea in pregnant rats, which lead decrease of body weight in embryo (P.S.M.Healthcare Limited, 2016).

Table 2: Effect of Fluoxetineon the body weight of rats embryos in 1day

Parameters	Control	Fluoxetine
Bodyweight (gram)of embryo	1.40+ 0.060+ a	0.66 + 0.028 b

-The value represents Mean(gram) +Standard Error
-The different small letters show significant effect between different group

Table 2 showed a significant decrease of body weight in fluoxtein compared with the control of the experimental periods. fluoxetine leads to reduce food intake in pregnant rats next decreased embryo body weight (Morrison *et al.*, 2005).

Table 3: Effect Citalopram on Hb (g/dl) rats in 1day after scarified

Parameters	Control	Citlopram
Hb (g/dl)	15.93 $\pm$ 0.69 a	.41 $\pm$ 0.38 7

-The value represents Mean(gram) +Standard Error
-The different small letters show significant effect between different group

Table 3 showed a significant decrease of Hb (g/dl) in Citalopram compared with the control of the experimental periods. Some of the biochemical abnormalities and impair cell-mediated immunity with elevated receptiveness to infection lead to decline Hb level occurs a state of anemia (Medsafe , 2016).

Table 4 in our study, the decrease in hemoglobin concentration because of non-regenerative anemia arising of stress occur disorder of hematopoietic

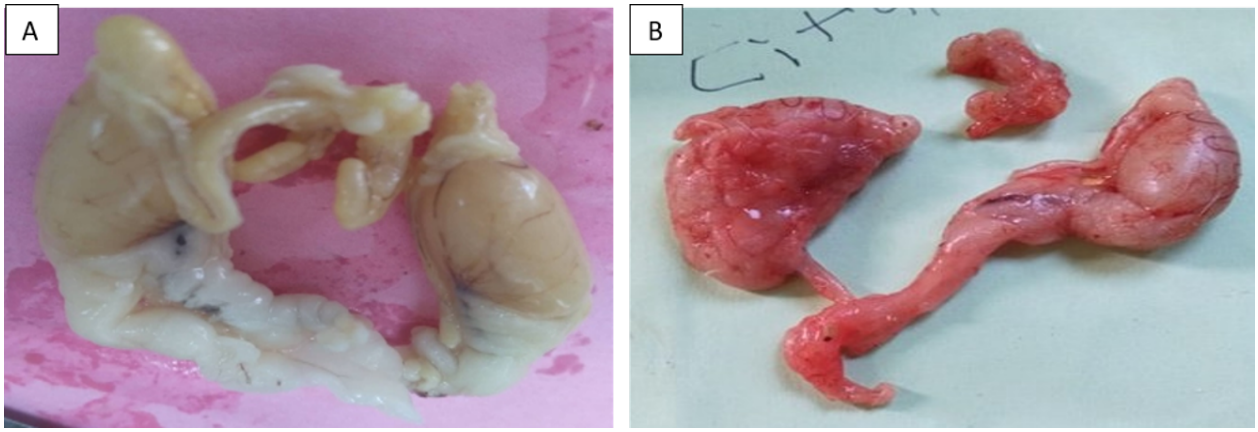

Figure 1: Cross-examination of reproductive male's rats(A) control group. (B) treated the group with citalopram tablets orally

Table 4: Effect Fluoxetine capsules oraly on Hb (g/dl) ratsin 1day after scarified

Parameters	Control	Fluoxetine
Hb (g/dl)	13.82±0.57 a	6.0±0.27

-The value represents Mean(gram) +Standard Error
-The different small letters show significant effect between different group

stem cells resulting in decline erythrocyte, leukocyte and platelet count (Sántha *et al.*, 2016).

Cross-examination of reproductive organs mals rats (Figure 1 -A control group) normal reproductive organs (Figure 1 -B treated with citalopram tablets). Citalopram caused testicular damage and dysfunctions caused by chronic stress of citalopram through restoring equilibrium of normal chemicals(neurotransmitters) in the brain, lead to degeneration of germinal epithelium, with the disappearance of spermatozoa and spermatids, then spermatocytes and finally Sertoli cells which lead testicular damage and dysfunctions (McKean and Sime, 2012).

Cross-examination of reproductive organs mals rats (Figure 1 -A control group) normal reproductive organs (Figure 1 -B treated with Fluoxetine capsules) Degeneration, atrophy and decreases weights of the testes with testicular damage as demonstrated by a decrease in the number of both primary and secondary spermatocytes and spermatids. As well the fibroblast, immature and mature Leydig (Gelenberg and Markowitz, 2010). FLX exhibit detrimental effects on male reproductive organ functions by acting both centrally on the thyroid glands and peripherally on testicular tissues (Frohlich and Meston, 2005). FLX induce acute increases in extracellular serotonin levels and chronic increases in the activity of the serotonergic system in different regions of the forebrain due to increased concentration of serotonin in the synaptic cleft without affecting other monoamine reuptake mechanisms or other neurotransmitter receptors (M.Shelby, 2014).

Effects citalopram on liver tissues. A-light microscopic picture of the normal liver show normal central vein B –normal hepatocytes. C- liver of rats treated with citalopram (e) pointed degeneration in some hepatocytes (f) pointed congestion of central vein.

Ingestion of citalopram raise in the activity of free radical produce enzyme, xanthine oxidase (XO), with an increased level of nitric oxide (NO) in the liver causing oxidative tissue to injure. The oxidative tissue damage leads to a reduction in the action of liver sorbitol dehydrogenase plus elevating in liver serum marker enzymes, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase. These changes lead to liver damage (Azaz-Livshits *et al.*, 2012).

Effects of citalopram on Kidney Tissues. A-light microscopic picture of normal kidney shows normal tubules (B) showing also severe degenerative change in tubules. These results show that ingestion of citalopram produces an increase in the action of free radical produce enzyme, xanthine oxidase (XO), in addition, increased of nitric oxide in (Azaz-Livshits *et al.*, 2012). The increment of such oxidative stress markers with increased MDA (index of lipid peroxidation) and elevation of serum markers of creatinine and uric acid in the kidney causing Oxidative tissue damage.

In Figure 5 Control group (A) normal alveolar wall. (B) But, these cells in fluoxetine – treated change in the alveolar wall. In that study, HoxB5 gene of the alveolar epithelium. Increased of HoxB5 expression in the mesenchymal cells and not in the alveolar type I cells, which explain a decreased differentiation in

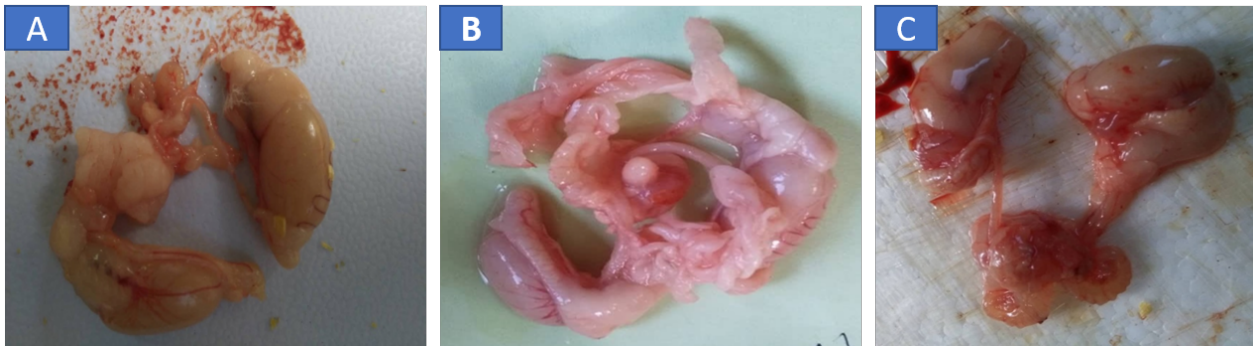

Figure 2: Cross-examination of reproductive male's rats (A) control group. (B,C) the treated group with Fluoxetine capsules orally

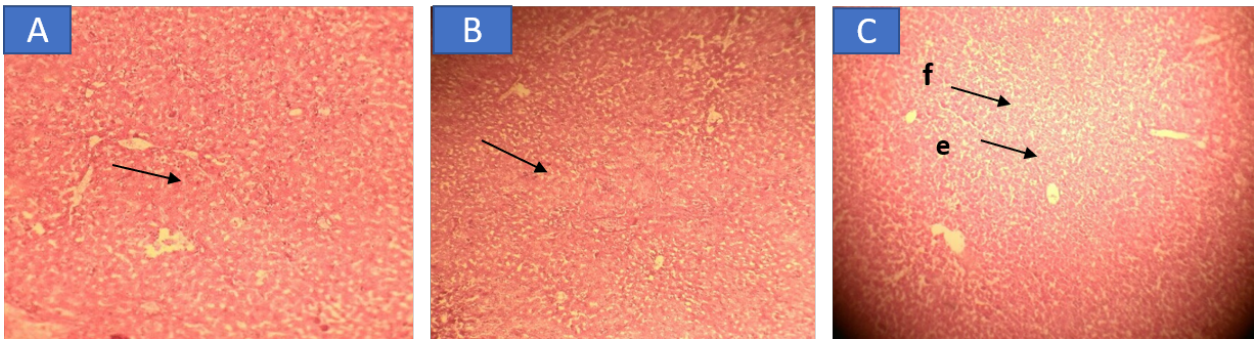

Figure 3: The slides of the fetal liver treated the groupwith citalopram tablets oraly were examined via light microscopy in two stains:hematoxylin and eosin. (H&E).(10*0.25)

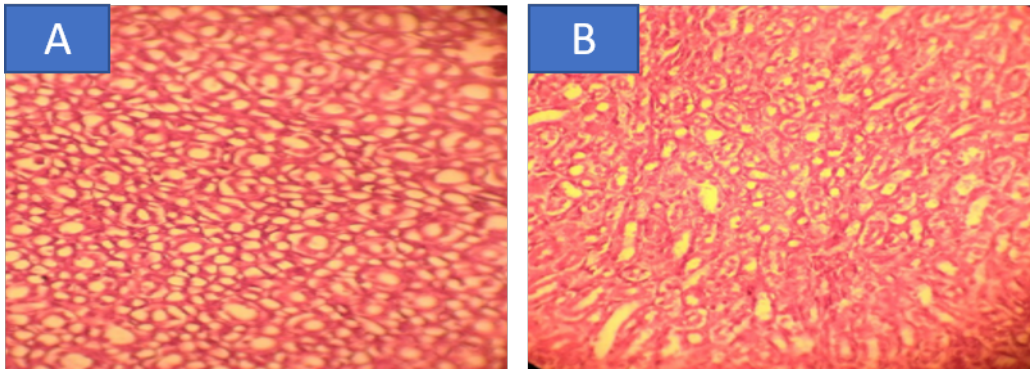

Figure 4: The slides of the fetal kidney treated group with citalopram tablets oraly were examined via light microscopy in two stains: hematoxylin and eosin. (H&E).(10*0.25)

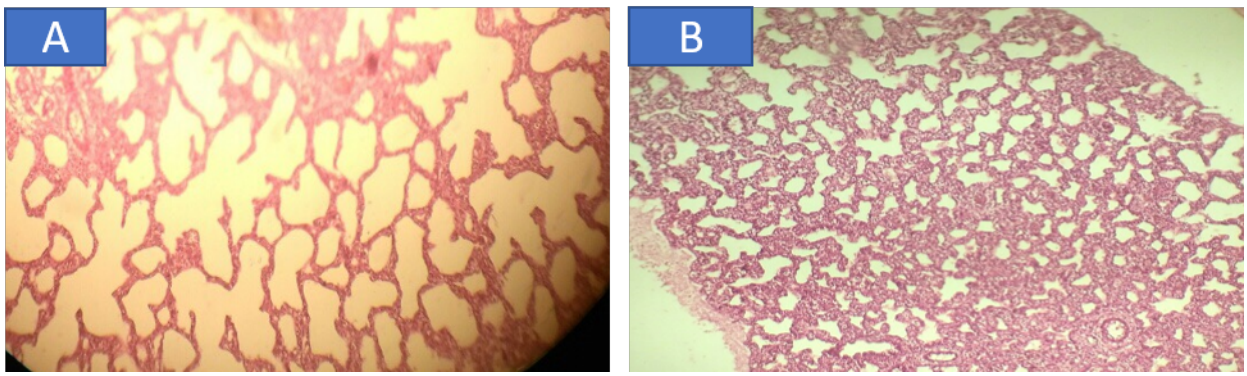

Figure 5: The slides of the fetal Lung treated the group with Fluoxetine capsules oraly were examined via light microscopy in two stains: hematoxylin and eosin. (H&E).(10*0.25)

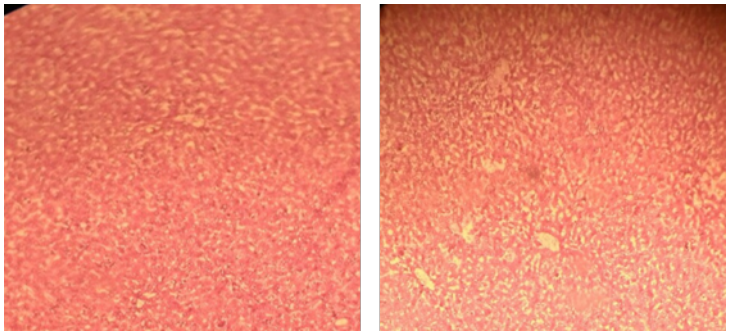

Figure 6: The slides of the fetal liver treated the group with Fluoxetine capsules oraly were examined via light microscopy in two stains: hematoxylin and eosin. (H&E)

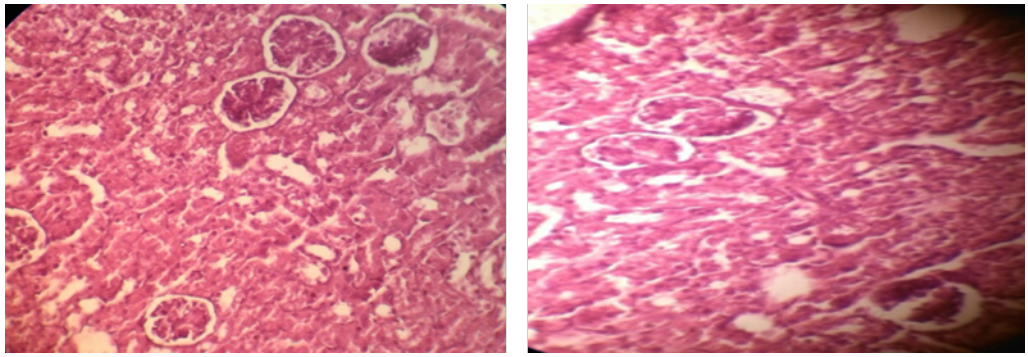

Figure 7: The slides of the fetal kidney treated group with Fluoxetine capsules oraly were examined via light microscopy in two stains: hematoxylin and eosin. (H&E).(10*0.25)

mesenchymal tissue (Tripathi, 2010).

A-light microscopic picture of control liver showed normal sinusoids B – liver of rats treated with Fluoxetine show sinusoids are not visible. Hepatic maker enzymes, for example, alkaline phosphatase and acid phosphatase assist in diagnose hepatotoxicity. Histological damages due to a rise in the blood biochemical parameters, namely alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase (Alzahrani, 2012).

In Figure 4, the kidney of natural and treated groups has been shown. In the control group, (A) glomerulus orderly is completely clear and normal. In the treated group, (B) the glomerulus is abnormal, and it seems that there is no enough development. Throughout the development, the kidney is originated from the ureteric bud, and the metanephric mesoderm in the fluoxetine group, the development of metanephric tissue was less than the control group. Fluoxetine can change the serum sodium level, leads to hyponatremia in the kidney (Aggarwal *et al.*, 2012). Studies indicate that using fluoxetine pregnancy may be associated with cystic kidney or kidney agenesis and tissue damage (Reeve *et al.*, 1999).

CONCLUSION

The present study shows that treatment with Citalopram and Floxtein cause a significant reduce in body weight of embryos and effects on organs.

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