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BENEFICIAL EFFECTS OF *CARICA PAPAYA LINN* SEEDS AGAINST ESCITALOPRAM OXALATE HEPATOTOXICITY IN FEMALE MICE

Laila A. Hummdi, Aisha D. Alalwani, Emtenan A. Arishi
Faculty of Sciences, Biology Department
University of Jeddah,
Kingdom of Saudi Arabia

Bushra Abd Nehme
Agricultural sciences,
Engineering Plant protection Department
Baghdad University

ABSTRACT

The aim of this study was to report the protective effect of aqueous extract of carica papaya Linn seeds against antidepressant drug (Escitalopram oxalate) histopathological impairment. Fifty adult female mice weighing 25.88 ± 27.89g were randomly assigned into five groups 10 mice each, control group G_1 *and four treated groups. Mice in groups* G_2 *and* G_3 *treated daily with low dose 10mg/kg body weight, and high dose 20 mg/kg body weight of Escitalopram oxalate drug (EOD) up to 8 weeks. whereas mice in* G_4 *and* G_5 *treated with doses 10,20 mg/kg body weight of EOD in combination to100mg and 200mg/kg body weight of Carica Papaya seeds (CPS) extract respectively. The results showed that the EOD caused a significant reduction in the mean values of body weight as well as increased in absolute and relative liver weights of mice in the tested groups* G_2 *and* G_3 *compared to control,* G_4 *and* G_5.

*However, highly significant increased (**p < 0.01**) in serum ALP, AST, and ALT enzymes in groups **G_2** and **G_3** was observed, and there was no a visible increase in these enzymes level in mice groups **G_4** and **G_5** that received both EOD and papaya seeds extract. While EOD caused marked histopathological changes in the liver tissue of mice in groups **G_2** and **G_3** which were manifested by congestion of central and portal veins, inflammatory infiltrate hepatocytes vacuolation, focal necrosis, blood sinusoid disruption and kupffer cells necrosis. The liver sections of mice in groups **G_4** and **G_5** showed reduction in liver injury compared to EOD -treated and control mice in group **G_1**, **G_2** and **G_3**. It could be concluded that the present results point out that the liver is sensitive to the adverse effects of EOD and the influence of the aqueous extract of Carica Papaya Linn seeds is time and dose dependent.*

Key words : Hepatotoxicity – Escitalopram- Lexapro- liver - *carica papaya*.

Introduction

The liver is one of the most vital organs among all of the organs in the human body. It performs some 500 bodily functions. It is plays a role in lipid, carbohydrate and protein metabolism, detoxify and the body's immune defense, as well as produce and excrete bile, albumin, coagulation factors, cholesterol, steroid hormones, and xenobiotic drugs **(Jevas, 2017; Franciscus, 2018).**

Voican *et al.*, (2014) found that the all antidepressants can induce hepatotoxicity, especially in elderly patients, liver damage is in most cases idiosyncratic and unpredictable. **(Diogo *et al.*, (2017)** reported that the drug-induced liver injury is the 4th most important cause of liver disease in Western countries. Antidepressant medications are used to treat a variety of conditions, including depression and other mental/mood disorders **(Goldberg, 2017).** Depression is a common and invalidating mental illness affecting approximately 2.5% of the general population **(Serafini, 2012).** Based on the World Health Organization surveys; depression has been suggested to become the second leading cause of disability by 2020 **(Ahmed *et al.*, 2014).** On the other hand, **Biour *et al.*, (2014) and Diogo *et al.*, 2017)** studies indicated that the drugs used in psychiatry and neurology are the second most important group of drugs can cause serious liver damage, after anti-infectious drugs. **Carrier *et al.*,(2016)** revealed that the patients with psychiatric disorders are usually more exposed to multiple somatic illnesses, including liver diseases.

Escitalopram oxalate drug (Lexapro) has been used as an antipsychotic drug in humans **Saxena *et al.,* (2017)** reported that the Escitalopram oxalate classified as selective serotonin reuptake inhibitors (SSRIs). The SSRIs are the most commonly prescribed class of antidepressants and are considered as the first for the treatment of depression and anxiety. It works by increasing levels of a neurotransmitter serotonin in the brain. which can lead to an improved mood.

Voican *et al.,(*2014) and Friedrich *et al.,* (2016) found that the all serotonin reuptake inhibitors are metabolized in liver by cytochrome P450 enzymes system for reason they competitively inhibit these hepatic enzyme and increase the levels of other medications metabolized by these enzymes, and leading to hepatic dysfunction. According to the World Health Organization, 75% of the world's populations are using herbs for health purpose **(Pan *et al.,* 2014).** A critical review of the existing data on the widely used herb appear to be has offered an effective medicine for the treatment of illnesses, and the pharmacological effects depending on the season, climate, geographic locations, and the harvesting methods **(Sharma *et al.,* 2010 ;Pan *et al.,* 2014; Kumar *et al.,*2017).** Pawpaw ***(Carica Papaya** Linn***)*** occupies a prominent place among the most important tropical fruit grown in the world, and is used as medical applications in worldwide in different ways **(Tarun and Prashar,2015; Barrosoa *et al.,* 2016).** It is consumed as ripe fresh fruit or young leaves, shoots and fruits cooked as a vegetable **(Oduola *et al.,* 2007).**

Tarun and Prashar,(2015) established that the Carica papaya *Linn* is used as processed product, and the whole plant parts including fruit, root, bark, peel, seeds and pulp are known to have medicinal properties, as well as, **Oduola *et al.,* (2007),** proved the fruit latex is used to remove freckles, proteolytic enzyme from fruit is used in treatment of dyspepsia, digestive disorders and reducing enlarged tonsils, the root infusion is used for syphilis, asthma relief, flowers have been used for jaundice and sore throat, extracts of the twigs of the pawpaw tree inhibition of cancer proliferation as these extracts inhibit enzymes necessary for metabolic processes in tumour cells, and the extract of unripe pawpaw has been possess antisickling properties. **Owoyele *et al.,* (2009)** established that the leaves of *Carica papaya Linn* have anti-inflammatory and antifertility activity.

Furthermore, **Udoh and Udoh,(2005) Olagunju *et al.,* (2009)** proved the seeds have no nutritive value, but in herbal medical practice, they have been used to treat a variety of

ailments such as typhoid fever and malaria fever, hypertension, diabetes mellitus, wound healing, and hypercholesterolaemia. Also**, Olagunju *et al*., (2009)** and **Yogiraj *et al.*, (2014)** pointed that the hot infusion of the seeds of the unripe or mature fruits of *Carica papaya Linn* is used in the treatment of renal and hepatic disorders. However, **Barrosoa *et al.*,*(*2016)** reported that the many benefits of papaya are due to high content of vitamin A, B and C, proteolytic enzymes which have antiviral, antifungal, antibacterial and anthelmintic activity.

In view of this, the present study was performance to establish the protective effect of the aqueous extract of mature *Carica Papaya Linn* seeds (CPS) against the toxic manifestations of Escitalopram oxalate drug on the mice liver cells.

Materials and Methods

The Drug

Generic Name: Escitalopram oxalate.
Common Brand Name: Lexapro (Forest Laboratories – U.S.) was purchased from the pharmacy of king faisal specialist hospital.

Drug Solution: Drug was dissolved in (distilled water) immediately before use. The dose of Escitalopram oxalate drug was selected according to **(Cimen *et al.*, 2015).**

Aqueous extract of *Carica Papaya Linn* seeds:

Papaya fruits was purchased from local grocery market in Jeddah, KSA. The papaya seeds taken from fresh papaya fruits were washed under tap water, air dried, powdered and a suspension was prepared in distilled water in Laboratory of faculty of pharmacy king Abdul-Aziz university. The dose was selected according to **(Diogo *et al.*, 2017 ;Saxena *et al.*, 2017)**

Animals

The present work carried out on the 50 female Swiss albino mice of 12 weeks old, with an average weighing 25.88 ± 27.89g. They were obtained from the animal house of faculty of pharmacy, King Abdulaziz University in Jeddah. Mice were maintained within the room well ventilated range temperature between 20-21 º C and an appropriate lighting on a 12 h light/dark cycle and 50 ± 10% humidity and fed dry balanced meal for experimental animals provided by the General Organization for Grain Silos and Flour Mills in Jeddah, with a

constant source of water , and left several days to adapt. All experimental procedures were performed in according to **OECD (2010a,b)** guideline on the design and conduct of chronic toxicity, and the **Council of Europe, (2006)** recommendations of Laboratory Animal Care. The animals were categorized into five groups each consisted of 10 mice as follows:

Group 1(G_1) : Served as a control group and daily orally given the drug and Papaya seeds carrier (distilled water) for 8 weeks.

Groups G_2 and G_3: Drug treated mice and daily oral administered 10 mg and 20mg/kg body weight of Escitalopram oxalate drug respectively for 8 weeks with equivalent to the cumulative human therapeutic doses according to **Brunton*, et al*., (2017)** and calculated to mice according to **(Paget and Barnes, 2004).**

Groups G_4 and G_5 : Drug and papaya seeds treated mice daily given 10 mg and 20mg /kg body weight of Escitalopram oxalate drug respectively and after an hour orally received 100 mg and 200mg /kg body weight of aqueous extract of *Carica Papaya* seeds respectively for 8 weeks. .

Biochemical analysis:

At the end of experiment 8 weeks the blood samples from all mice groups was immediately collected from the retro-orbital (eye vein) of a mouse **Schermer,(1997)** into sterilized ETDA tubes for serum separation and were kept for subsequent evaluation of biochemical parameters activities of serum alkaline phosphatase (ALP), aspartic aminotransferase (AST), and alanine aminotransferase (ALT) enzymes according to **Varley *et al*., (1980)** method by using commercial kits (Bio Merieus,France)**.**

Histological study:

For histological studies the mice in all groups were killed by cervical dislocation the liver specimens of each animal group were fixed in 10% buffered formalin solution and the pathologic changes were evaluated on the hematoxylin and eosin (H&E) stained sections which carried out hematoxylin according to **(Suvarna *et al*., 2018),** coded, and examined.

Statistical analysis

Statistical evaluation was performed to evaluated the Differences among groups using student's test and analysis of variance. The difference was considered significant when $p<0.05$. Calculations were performed with SSPS 20.0.statistical software.

Results

As presented in **(Table 1)** there were differences in the mean bodyweights among the treated groups (G_2,G_3,G_4,G_5) as compared to control group G_1. There was a significant ($p<0.05$, $p<0.01$) and dose dependent reduction in the mean bodyweights of mice in groups G_2,G_3. While, the extract offered a significant ($p<0.05$) protection of bodyweights depressed in the mice treated with EOD in combination by papaya seeds extracted. In contrast, showed a significant ($p<0.05$, $p<0.01$) rise in the mean absolute and relative liver weights of mice in groups G_2,G_3 received 10mg and 20 mg/kg of EOD. These elevations were significantly ($p<0.05$), attenuated in mice groups G_4,G_5 combination treated with the extract.

Likewise, administration of the EOD to mice in groups G_2,G_3 in doses of 10mg and 20mg/kg, caused significant ($p <0.05$) elevated in serum level of ALP, AST and ALT with respect to control in dose related fashion. Oral given of the papaya seeds extract to mice in doses of 100 ml and 200 ml/g groups G_4,G_5 reduced the concentration of serum enzymes (ALP,AST and ALT) compared with G_2 and G_3 , and they slightly higher than normal levels **(Table2).**

In the present investigation the liver sections of control mice **G_1** revealed the normal hepatic architecture and the typical hexagonal hepatic lobules, each consists of regularly plates of polygonal hepatocytes with eosinophilic cytoplasm and the basophilic nuclei is centrally located with one or two nucleoli centered around a hepatic vein and with portal tracts situated at the corners. The hepatocytes enclosing the blood sinusoidal network which lining with endothelial cells and tissue resident macrophage (kupffer cells) located within the sinusoid **(Figure 1a,b).**

Regarding to liver sections of 10mg/kg EOD-treated mice **G_2** showed mild central veins congestion **(Figure 1c)**, hepatocytes necrosis and blood sinusoids stasis **(Figure 1d),**vacuolated hepatocytes in areas surrounding the central vein **(Figure 2a).** However, liver sections from mice treated with 20mg/kg of EOD **G_3** indicated marked alterations included,

congested of central, portal areas and blood sinusoids associated with hepatic tissue edematous **,(Figure 2b)**, necrosis of hepatocytes with pyknotic and deformed nuclei, infiltration of inflammatory cells in the areas display clear haemolysis and around the necrotic cells **(Figure 2c)**, vacuolar cytoplasmic degeneration of hepatocytes, kupffer cells necrosis with agglomeration of red blood cells in disrupted sinusoids were observed **(Figure 2d)**.

On the other hand, The sections of liver of mice G_4 and G_5 injected with drug and given papaya seeds extract were more or less normal configuration in comparison with that of the control. **Figure 3 (a,b)** indicated normal liver histoarchitecture with slight red blood cells lysis in central vein and blood sinusoid in the mice liver **G_4** received 10mg/kg of EOD in combination with 100ml of aqueous extract of *Carica Papaya Linn* seeds. Whereas, examination the liver sections of mice in **G_5** given 20mg/kg of EOD with 200ml of papaya seeds extract revealed very mild lesions in liver tissue as necrotic of some hepatocytes, small occasional foci of lymphocytes cells aggregates around central veins were still observed, **(Figure 3c,d).**

Table (1): Mean body weighs , absolute and relative liver weight of control and experimental adult female mice at the beginning and end of experimental period (8 weeks).

Experimental Groups						
Weights		**(G1) Control**	**(G2) EOD**	**(G3) EDO**	**(G4) EOD/CPS**	**(G5) EOD/CPS**
Zero Day	**M**	**25.88**	**26.120**	**28.641**	**27.990**	**28.357**
	±SEM	**7.89**	**7.614**	**2.496**	**6.83**	**5.558**
	P	**-**	**0.600**	**0.542**	**0.643**	**0.744**

Body Weigh	M	34.18	24.09	26.95	32.550	33.340
	±SEM	6.17	3.104	1.476	2.261	4.371
	P	-	0.02*	0.021*	0.030*	0.023*
Zero Day	M	8.940	9.541	9.763	9.436	8.886
	±SEM	0.626	0.3947	0.4301	0.919	0.709
	P	-	0.501	0.466	0.601	0.721
Absolute liver weight	M	9.221	10.422	13.58	9.740	10.634
	±SEM	0.827	.59447	0.248	0.39573	0.512
	P	-	.0157*	0.00**	0.047*	0.041*
Zero Day	M	4.655	4.841	4.785	4.877	4.786
	±SEM	0.332	0.281	0.127	0.433	0.294
	P	-	0.564	0.576	0.583	0.622
Relative liver weight	M	4.737	4.963	5.128	4.810	4.921
	±SEM	0.425	0.245	0.245	0.476	0.250
	P	-	0.036*	0.00**	0. 315	0.024*

- P> 0.05 not Significant, *P < 0.05 Significant ; or ** p < 0.01 high Significant

S.E : Standard Error of Mean.

Table (2): Serum level of ALP, ALT and AST enzymes of experimental and control groups at the end of experimental period (8 weeks).

Experimental Groups						
Liver Bio parameter		(G1) Control	(G2) EOD	(G3) EDO	(G4) EOD/CPS	(G5) EOD/CPS
ALP mg/dl	M	198.00	220.12	510.20	211.80	226,25
	±SEM	±2.09	±8.19	±14.23	±17.37	±24.07
	P	-	0.053*	0.00**	0.113	0.013*
ALT mg/dl	M	34.38	45.00	62.00	35.80	39.22
	±SEM	±9.06	±7.73	±35.17	±27.22	±15.33
	P	-	0.00**	0.00**	0.446	0.024*
AST mg/dl	M	38.17	48.71	59.80	39.97	44.40
	±SEM	0.84	2.33	2.80	1.28	1.53
	P	-	0.00**	0.00**	0.230	0.019*

- **P> 0.05 not Significant, *P < 0.05 Significant ; or ** p < 0.01 high Significant**

S.E : Standard Error of Mean.

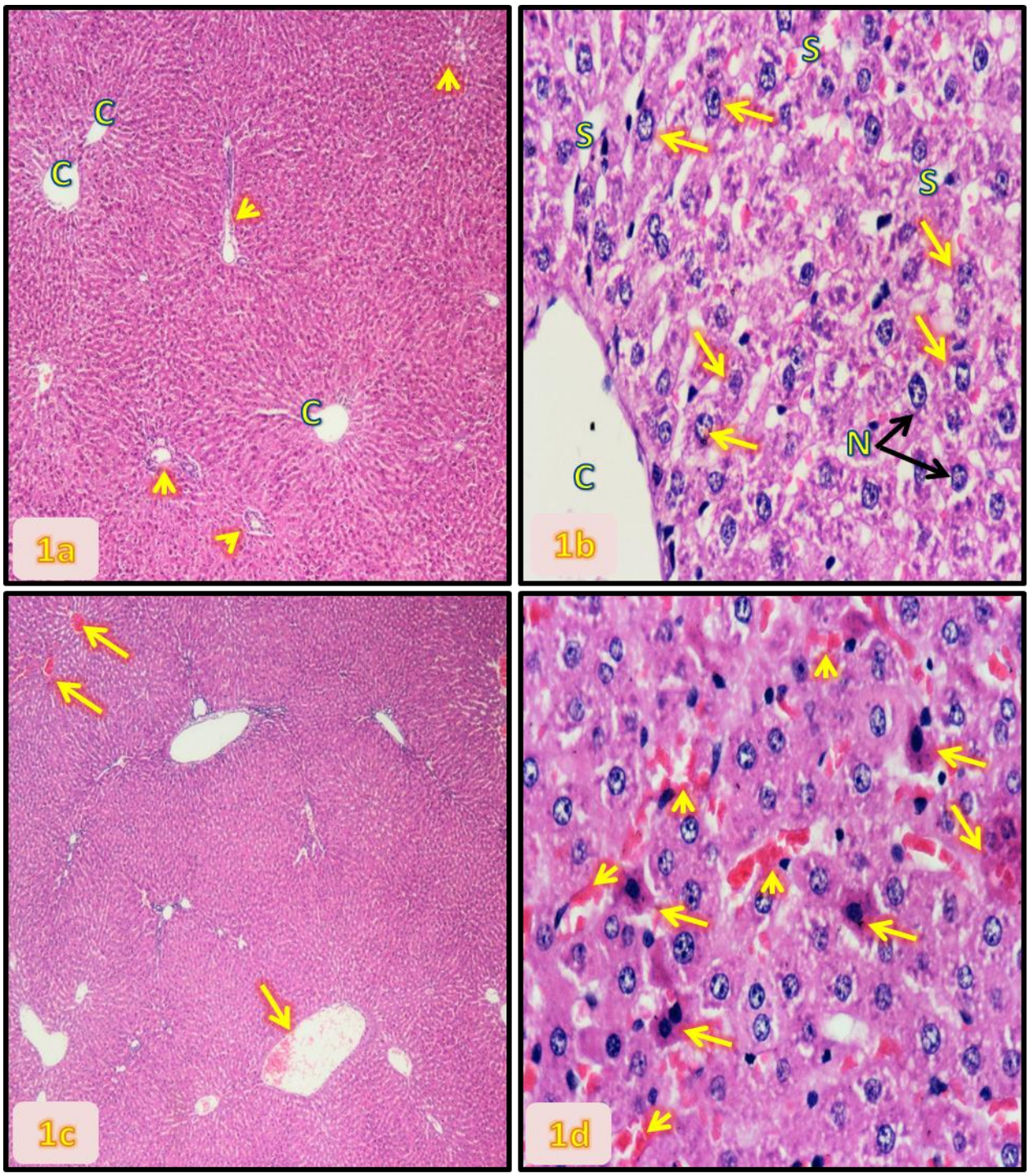

Figure 1. (a-d) :(a,b) Cross sections of control mice liver showing normal architecture pattern of hepatic tissue, central veins(C). portal area (arrow heads),hepatocytes (arrows) with central nuclei (N) and blood sinusoids (S) (H & E. x100,400).(c) mice liver received

10mg/kg of EOD showing mild central veins congested (arrows) (H&E x400). (d) hepatocytes necrosis (arrows) and blood sinusoids stasis (arrow heads) (H&E x400).

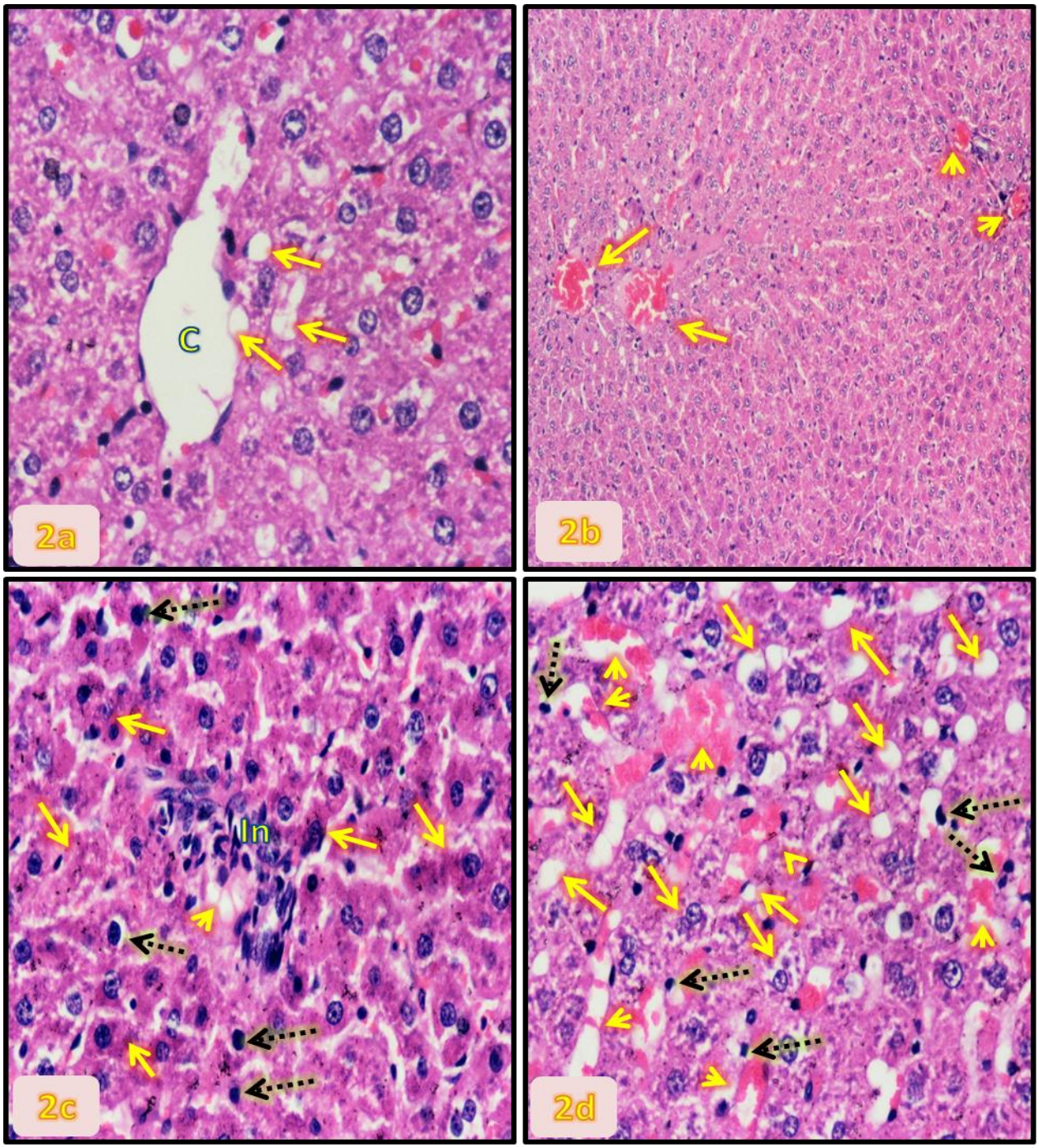

Figure 2. (a-d): (a) mice liver received 10mg/kg of EOD showing hepatocytes vacuolated (arrows) around the central vein (C) areas (H&E x400). (b-d) liver of mice treated with

20mg/kg of EOD, (b) showing marked congested of central veins (arrows) and portal veins (arrow heads) (H&E x100). (c) showing marked necrosis of hepatocytes (arrows), pyknotic nuclei (dot arrows), inflammatory cells infiltration (In) , haemolysis with edematous (arrow heads) of hepatic tissue (H&E x400). (d) showing vacuolar cytoplasmic degeneration (arrows), kupffer cells necrosis (dot arrows), and red blood cells agglomeration in disrupted sinusoids (arrow heads) (H&E x400).

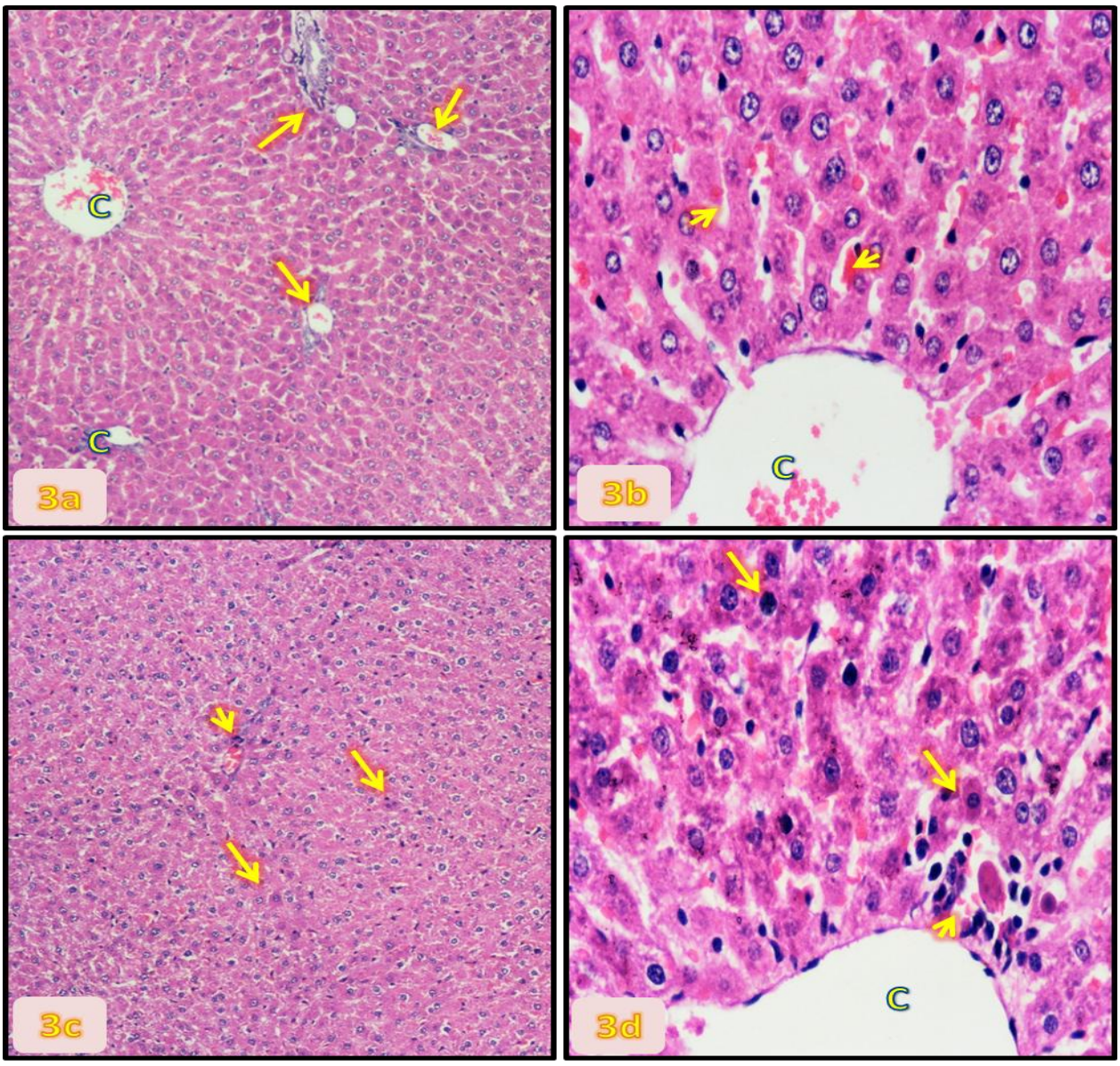

Figure 3. (a-d) :(a,b) Cross sections of liver of mice treated with 10mg/kg of EOD and given 100 ml papaya seeds extract, showing normal architecture of hepatic tissue with slight red blood cells lysis in central vein (C) , portal vein (arrows) and blood sinusoid

(arrow heads) (H&E. x100,x400).(c,d) mice liver received 20mg/kg of EOD and 200 ml papaya seeds extract showing very mild hepatocytes necrosis (arrows), small foci of lymphocytic infiltration (arrow heads) around central vein (N), (H&E x100,x400).

Discussion

The present study showed a significant and dose dependent reduction in the mean bodyweights as well as increase in the mean absolute and relative liver weights of animals in groups given 10mg and 20mg /kg of Escitalopram oxalate drug. Similarly, **Zhang *et al.*,(2009)** observed that body and organ weights were found to be insensitive to antidepressant drug effect. Also**, Friedrich, *et al* ., 2016** pointed similar findings, loss of appetite occurred during treatment with selective serotonin reuptake inhibitors especially escitalopram, citalopram, and fluoxetine in patients. However, **Boyda *et al.,* (2010)** demonstrated that the most commonly reported side effect of antipsychotic drugs in humans, mice and rats is weight gain. These results are commonly associated with metabolic side effects. **Smith *et al.,* (2008)** confirmed the primary site of increased glucose output to be the liver, and the antidepressant drugs clozapine and olanzapine caused acute elevations of glucose production which lead to liver weight gain. Conversely, **Hosch and Svestka ,(2008) ; Revel *et al.,* (2012)** revealed that the Escitalopram oxalate and Clomipramine not cause a change in body weight in rodents. In accordance to that found in this work **Ismail *et al* ., (2014)** recorded no significant difference in body weight changes was noted between the control and tested rats groups receiving C. papaya leaf extract. Thus, treatment at various dose regimens of C. papaya seeds extract daily for 52 weeks did not cause a significant alterations in body weight and organs weight **(Goyal *et al.,* 2010).**

Previous literature **Olagunju *et al.,* (2009)** indicated that enzymatic systems was progressing by the cell to ride with oxidative stress that is associated with reactive oxygen species generated. Similar findings were reported in **Voican *et al.,* (2015)** study that all antidepressant drugs are associated with a risk, of metabolic activation to reactive oxygen free radicals. Our results are in agreement with **Seykans, (2017); Diogo *et al.,* (2017)** observed that the use of Escitalopram oxalate drug has induced hepatotoxicity and is associated with abnormally high serum ALT and AST with less increase in (ALP). Thus, in patients during psychotropic treatment **(Friedrich, *et al.,* 2016).** However, the present study showed the efficiency of aqueous extract of *Carica Papaya* seeds against Escitalopram

oxalate drug effects by reduction in the level of ALP,AST, and ALT. These observations agree with those previously mentioned by **Sadeque *et al.*, (2012)** in liver rats treated with CCL4 in combination with Aqueous extract of *Carica papaya*. Evidence suggests that preventive role of papaya seeds help detoxify the liver and have different properties such as antioxidant and free radical scavenging activity **(Yogiraj et al., 2014).** These enzymatic disruption were promoted histological findings. Thus, **Adachi *et al.*, (2007)** reported that liver impairment was confirmed by a significant increase in liver enzyme activity and uric acid concentration in liver of treated rats providing an evidence for the pathological role of antidepressant drugs in inducing oxidative liver injury. In addition to, **Voican *et al.*, (2015) ; Friedrich, *et al* ., 2016** studded found that the latency period between medication initiation and appearance of liver injury symptoms is generally between a few days and 6 months, with particular concerning to the length of use, the dose, and the time.

The histological investigation in present study are consistent with those found in a **Ahmed *et al.*, (2014)** study that the antidepressant drug fluoxetine induced hydropic degeneration in the hepatocytes of rats, and supported by **Pniak, (2011)** who showed hepatocellular changes and acute hepatitis in the liver of both patients and animal models as an adverse effects of fluoxetine exposure. Moreover, **Suen *et al.*, (2013)** noted mild inflammation around central veins portal tract with vacuolated degeneration of hepatocytes, lipofuscin pigmentation accumulation in the liver of patients used sertraline in the treatment of depression. It has been stated that the cytoplasmic vacuolation in mammalian cells occurs in early stages of toxic disease after exposure to bacterial or viral pathogens as well as to various medications **Shubin *et al.*, (2016).** The present results were coinciding with those of **El-Banhawy *et al.*, (1993)** who described the vacuolation of hepatocytes as ballooning degeneration and interpreted it as a kind of cellular defensive mechanism against injurious substances. At the same time, **Aki *et al.*, (2012)** concluded that the formation of the vacuoles due to equilibration of osmotic pressure by water diffusion across organelle membranes. Thus, osmotic effects associated with disturbed ionic balance in the organelles leads to accumulation of ions and cytoplasm water wich rapidly passes through leaky membranes of cell organelles. Vacuolization often causes necrotic death rather than apoptoic **(Shubin *et al.*, 2016).**

Active studies established that the necroptosis is a type of programmed necrosis developed after the activation of death receptors when caspases and the inhibitor of apoptosis protein are deficient, the receptor interacting protein kinases 1 and 3 as well as pseudokinase are the main regulators of necroptosis **(Han *et al.*, 2009; Feoktistova *et al.*, 2015).** In relation to these finding it has been evidenced that the degenerative changes appeared earlier in the cytoplasm than in the nuclei of hepatocytes this suggested that the nuclear damage is a sequence of cytoplasmic damage **(Hummdi, 2007).**

The obtained results were agree with those stated by **Edrees and Hummdi ,(2011)** studies, revealed that the hepatic centrilobular zone is known to be particularly susceptible to ischaemic damage. Also, reactive metabolites are usually formed first in the centrilobular hepatocytes and cause damage to these cells. **Riviere and Papich (2013)** proved that the haloperidol drug activation of DA receptors located on blood vessels causes vasodilatation. The present work was similarly achieved by **(Hummdi, 2007; Edrees and Hummdi, 2011)** who documented that the Kupffer cells were presumably actively engaged in phagocytosis of cells debris arise as a sequence of the resultant hepatocellular degenerative process. It was found that Kupffer cells are involved in case of hepatotoxicity.

On other side, the animals in groups (**G_4,G_5**) witch administered aqueous extract of papaya seeds showed significant reduction in liver tissue deterioration induced by Escitalopram oxalate. These findings run in harmony with several studies **Olagunju *et al.*, (2009) ; Sadeque *et al.*, (2012)** have been indicated that oral treatment with aqueous extract *Carica Papaya* seeds prevented marked renal histological lesions of hydropic degeneration of the glomerular and tubular cells, liver necrosis and fatty degeneration in CCl4- treated rats. Also, recent study match with those suggested that the, extract of unripe pawpaw has no adverse effect on liver functions**(Oduola *et al.*, 2007).** As well as **Ismail *et al* ., (2014**) revealed no significant histological changes in liver of male and female rats received *C. papaya* leaf extract .

In addition to, the current results match with the results obtained by other authors, pointed that the protective role of *Carica Papaya* seeds could be due to the presence of potential medicinal properties as detoxify the liver, antioxidant, antiflammatory agents, and this protective effect of the extract is mediated through antioxidant and hydroxyl, superoxide anion and hydrogen peroxide radical scavenging activity (**Olagunju *et al.*, 2009 ;**

Abdelgadir *et al.*, 2014). Subsequently, their protection via antioxidant and/or free radical scavenging activities due to the high concentration of flavonoids and alkaloids they contain (**Olagunju *et al.*, 2009 :Adeneye and Benebo, 2008).** However, **Yogiraj *et al.*, (2014)** reported the papaya seeds seem to have more potent medicinal values than the flesh. Moreover, our results confirm those previously reported by **Udoh, and Udoh, (2005)** who recorded that the extent of liver cell damage at low doses of C. papaya seeds 10 and 50 mg/kg was not significant. Therefore, proper dose regimens should be designed to avoid toxicity when the dosage is abused.

Conclusion:

On the light of the present study it could be concluded that the aqueous extract of *Carica Papaya Linn* seeds as an important natural medicinal plant, it found have therapeutic efficiency and safety in decreased the hepatotoxicity induced by EOD, and the variation in the efficacy degree of aqueous extract of *Carica Papaya Linn* seeds is time and dose dependent.

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