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Protective Effect of Aerial Parts of *Portulaca oleracea* and *Ficus carica* Leaves Against Diclofenac-Sodium Induced Hepatotoxicity in Rats

Mohamed Abd El-Ghany El-Sayed[1, *], Omayma El-Sayed Shaltot[2], Mokhtar Ibrahim Yousef[3], Entisar Abd El-Mohsen El-Difrawy[2]

[1]Food Technology Department, Institute of Agriculture Research Center, Giza, Egypt

[2]Food Science Department, Faculty of Agriculture Saba Basha, Alexandria University, Alexandria, Egypt

[3]Department of Environmental Studies, Institute of Graduate Studies & Research, Alexandria University, Alexandria, Egypt

Email address:

mohamed_abdoo3621@yahoo.com (M. A. El-Sayed), omayma.shaltot@gmail.com (O. El-Sayed S.), yousefmokhtar@yahoo.com (M. I. Yousef), Entisar41@gmail.com (E. A. El-Mohsen El-Difrawy)

[*]Corresponding author

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Abstract: The present experiment is aimed to evaluate the hepatoprotective effects of purslane (PuE) and fig leaves (FlE) extracts on diclofenac-sodium (DS) induced hepatotoxicity in rats. Adult male rats were pretreated orally with PuE and FlE extracts at a dose of 10ml/kg and 200mg/kg body weight, respectively for 14 days. Co-treatment of DS 16mg/kg body weight was given orally for 7days. The present results demonstrated that the treatment with PuE and FlE combination with DS induced a marked improvement in the studied parameters. Data indicated that there were no significant differences in relative liver weight (RLW) and relative kidney weight (RKW) in group treated with PuE and FlE and /or their combination as compared to control. Plasma liver enzyme activities as well as bilirubin levels were increased in the groups receiving diclofenac only or in combination as compared with control group. However, the administration of PuE and FlE ameliorated DS induced hepatotoxicity by improving antioxidant status, decreasing inflammation, lowering TBARS and weakening the adverse effect of diclofenac on hepatic tissues. Liver injury was confirmed by the histological changes. Taken together, the present study concluded that enhancement of antioxidants and promising activity against diclofenac-induced hepatotoxicity may a result for the effect of PuE and FlE.

Keywords: Antioxidant Activity, *Portulaca oleracea* (Pursalne), *Ficus carica* (Fig Leaves), Diclofenac-Sodium, Hepatotoxicity

1. Introduction

The major role of the liver is regulating metabolism, detoxification, secretion of bile and storage of vitamins. Thus, to maintain a healthy liver is a critical factor for good health and well-being [1]. Treatment of diseases associated with the liver is crucial, and must be done with proper and extensive care. There are few conventional drugs that can enhance liver function and offer hepatic protection or help in the regeneration of hepatic cells but they are considered to be hepatotoxic at certain dose [2]. Fifty percent of all acute liver failures and 5% of all hospital admissions are associated with drug-induced hepatotoxicity [3].

Diclofenac Sodium (DS) is a non-steroidal anti-inflammatory drug that is used for the treatment of mild-to-moderate pain, fever, and inflammation [4]. Normal therapeutic doses of DS is safe however, increased doses for longer interval leads to a broad spectrum of liver damage ranging from asymptomatic, transient, hyper-transaminasemia to fulminant hepatic failure [5, 6].

Studies have indicated that the metabolites of DS are capable of inducing hepatocytes apoptosis by mitochondrial dysfunction and generation of oxidative stress [7]. Therefore, potential therapeutic agent that could arrest any of the pathological pathways activated by DS could be used to arrest or reverse its cytotoxic action. Natural antioxidants are classified as secondary plant metabolites which play an important role in prophylaxis against many diseases. Recently, increasing attention has been focused on the application of natural products to improve human health [8].

Common purslane (*Portulaca oleracea* L.) is a member of *Portulacaceae* [9]. It is consumed as vegetable, especially in the Mediterranean region. As a matter of fact, purslane contains numerous bio-protective compounds such as antioxidants and vitamins, omega-3 fatty acids, essential amino acids and several minerals [10]. It has been observed that purslane had a wide range of pharmaceutical importance. Research reports indicated the powerful pharmaceutical activities of purslane being anti-inflammatory, protects against the reproductive toxicity, hypolipidemic effect, antioxidant and lots of other accounted natural manners [11, 12, 13].

Figs (*Ficus carica* L.), family *Moraceae*, is a plant cultivated and grows in Egypt and many other countries. All parts of this plant possess nutritive value and medicinal properties [14]. Reports showed that fig leaf contained a considerable amount of flavonoids [15]. Leaf juice is used for treatment of a variety of diseases, hypoglycaemic and hepatoprotective activity [16, 17, 18]. The present research was undertaken to evaluate effect of purslane and fig leaf extracts in diclofenac-sodium induced hepatotoxicity rats using biochemical parameters.

2. Materials and Methods

2.1. Purslane Identification, Plantation and Extraction

Purslane seeds (*Portulaca oleracea* L.), were obtained from Sabahia Horticulture research station in May 2018. Taxonomic identification was performed by botanists in Department of the herbarium of flora and phytotaxonomy Research (Horticulture research Institute, Agriculture research Center). Ten 25 cm plastic pots were filled with soil Day and night temperatures were set in the greenhouse at 27 and 19°C, respectively. The seeds germinated fully within 3-7 days, with excellent subsequent seedling growth. The plants were watered and fertilized as needed throughout the growing period, and at approximately 6 inches in height, the seedlings were thinned to ten uniform plants per pot. Samples were taken after Fifty-nine days after emergence according to Mohamed & Hussein with some modification [19].

The parts stems and leaves of the purslane suitable for consumption were used. Extraction was performed according to Dkhil *et al.* with some modification [20]. Fresh purslane, free of blemishes or obvious defects, was collected and an aqueous juice was prepared from the herb by mashing it in water in a proportion of 1:30.04 (w/v) and then leaving the mixture for about 24 h at 4°C. After mashing, the resulting crude extract was filtered and the filtrate was then kept at 4°C for future use.

2.2. Fig Leaves Collection and Extraction

Ficus carica leaves were collected from May to August 2017from Alexandria-North Coast, The leaves were dried in shade at ambient temperature until completely dehydrated, finely powdered with an electric mill and become ready for extraction process. The Plant extract was prepared according to Nebedum *et al.* with 70% ethanol (v/v) by cold extraction for 48 hours. The extracts were evaporated to dryness at 40°C in a water bath [21].

2.3. Experimental Animals

Fifty-four male Wister albino rats, 10weeks old weighing 180-195g were used in the present study. Animals were obtained from Faculty of Medicine, Alexandria University, Alexandria, Egypt. The local committee approved the design of the experiments, and the protocol conforms to the guidelines of the National Institutes of Health (NIH). After an acclimatization period of one week in the animal experimental research laboratory, the animals were randomly divided into six groups. Rats were housed in a temperature controlled room (22–23°C) with a 12h dark and 12h light cycle. Food and water were available *ad libitum*. The study complies with the Institute of Graduate Studies and Research.

2.4. Experimental Protocol

Animals within different treatment groups were maintained on their respective diets for 21 days as follows: control (C) which received saline 10ml/kg B.W/day (n= 6), DS group treated orally with Diclofenac-sodium (purchased from Sigma Chemical Company, St. Louis, MO, USA) last seven days of the experiment i.e. day 15-21 (n= 12), PuE group treated orally with Purslane Extract (n= 6), FlE group treated orally with Fig leaves Extract (n= 6), PuE+DS group treated orally with Purslane Extract for 14days prior to purslane extract plus Diclofenac-sodium for another 7days(n= 12) and FlE+DS group treated orally with Fig leaves Extract for 14days prior to fig leaves extract plus Diclofenac-sodium for another 7days (n= 12). Purslane extract was orally administered in a dose of 10ml/kg B.W/day according to Dkhil *et al*. fig leaves extract was orally administered in a dose of 200mg/kg B.W/day according to Nebedum *et al*. with some modification and Diclofenac was orally administered at a dose of 16mg/kg [20, 21].

2.5. Blood Samples Collection and Tissue Preparation

Body weights of all group rats were measured on day 1 and 21using top weighing balance. At the end of the experiment the rats were starved for 12h and then sacrificed under diethyl ether. The whole bodies of the rat were weighted immediately on the balance and blood was collected by cardiac puncture into heparinized tubes which were centrifuged at 860 Xg for 20 min, -4°C for the separation of plasma, using a cold centrifuge (Bench top

centrifuge, K3 Series, Centurion Scientific, United Kingdom). The separated plasma samples were collected into separate plain tubes. Liver samples were dissected out and washed immediately with ice-cold saline to remove as much blood as possible; one part of the liver samples and separated plasma were immediately stored at -80°C until analysis, and other part was excised and fixed in 10% formalin solution and stored in 70% ethyl alcohol until they were processed for histopathologic analysis.

2.5.1. Biochemical Parameters

Stored plasma samples were analyzed for total protein (TP), albumin (A), total bilirubin, urea, creatinine by using commercial kits (Biodiagnostic, diagnostic and research reagents, Giza, Egypt).

The activities of plasma and liver alanine aminotransferase (ALT), aspartate aminotransferase (AST), acid phosphatase (ACP), alkaline phosphatase (ALP) were assessed using the appropriate biochemical commercial kits.

2.5.2. Antioxidant Enzymes and Free Radicals in Liver

Glutathione reduced (GSH) was determined according to the method of Jollow *et al*. [22]. Superoxide dismutase (SOD) activity was measured according to Mishra and Fridovich [23]. Catalase (CAT) activity was determined using the Luck method involving the decomposition of hydrogen peroxide [24]. The activity of glutathione peroxidase (GPx) was assayed by the method of Chiu *et al*. [25]. Glutathione S-transferase (GST) activity was determined according to Habig *et al*. [26]. Thiobarbituric acid reactive substances (TBARS) were measured by the method of Tappel and Zalkin [27]. The assay was done strictly according to the procedure given along with the kits.

2.6. Histopathological Studies

The fixed tissues were dehydrated through a graded series of ethanol and embedded in paraffin blocks and rolled in slices of a thickness of 5 μm according to standard Hematoxylin & Eosin procedures [28]. The slides were examined microscopically for histopathological changes.

2.7. Statistical Analysis

Results were expressed as the mean ± standard error of the mean (SEM) from at least three independent tests. Data for multiple variable comparisons were analyzed by one-way analysis of variance (ANOVA). For differentiation between means, Duncan's test was used a post hoc test according to the statistical package program (SPSS version 16.0). The significance level was set at $P < 0.05$.

3. Results and Discussion

3.1. Body Weight and Relative Liver and Kidney Weight

Table 1 show final body weight (FBW), relative liver weight (RLW) and relative kidney weight (RKW) of male rats treated with PuE, FlE and DS or their combination. Data indicated that there was a decrease in FBW of group with DS, whereas, both PuE and FlE exhibited an obvious increased. The addition of PuE+DS and FlE+DS increased FBW. On the other hand, there was a significant increase in RLW and RKW in the group treated with DS compared with the control which similar to obtained data of Ratnasooriya *et al.* [29] who reported that toxic chemicals showed signs of toxicity reduction in food intake, diarrhea, and suppression in body weight gain. Data also showed that there were no significant differences in RLW and RKW in group treated with PuE and FlE and /or their combination compared with the control. It was obvious that the treatment with DS alone is more toxic on liver and kidney compared with their combinations.

Table 1. *Changes in FBW, RLW and RKW of male rats treated with Purslane Extract, Fig leaves Extract and Diclofenac Sodium or their combination.*

Groups	FBW	RLW	RKW
C	241 ±16.8 bc	3.22 ± 0.1cd	0.62 ± 0.01b
DS	212 ± 6.44 c	3.82 ± 0.11a	0.71 ± 0.01a
PuE	272 ± 6.63 a	3.20 ±0.01cd	0.61 ± 0.01b
FlE	245 ±10.00 ab	3.05 ± 0.01d	0.60 ± 0.02b
PuE+DS	230 ± 5.47 bc	3.51 ± 0.13b	0.63 ± 0.02b
FlE+DS	234 ± 6.20 bc	3.40 ± 0.07bc	0.64 ± 0.01b

Means in a columns not sharing the same letters are significantly different at ($P<0.05$).
C: Control, DS: Diclofenac Sodium, PuE: Purslane Extract, FlE: Fig leaves Extract.
FBW= final body weight (g); RLW= relative liver weight (%); PKW= relative kidney weight (%).

3.2. Liver Marker Enzymes

The estimation of enzymes in the plasma is a useful quantitative marker of the extent and type of hepatotoxicity. The ALT, AST, ACP and ALP activities of the groups are shown in Table (2). There were increases in plasma ALT, AST, ACP and ALP activities in the DS group, this indicate hepatotoxicity and loss of structural integrity. Darbar *et al.* showed that the administration of DS caused a dramatic elevation in serum AST and ALT, indicating sub-chronic hepatotoxicity with severe damage to hepatic tissue membranes during DS intoxication and the release of these enzymes into circulation [30]. However, pre-treatment with PuE and FlE along with DS significantly suppressed liver toxicity resulting in less release of these markers from liver tissues into blood. Results showed that there was no significant difference between PuE, FlE and control group of all tested parameters.

Table 2. *Changes in plasma ALT, AST, ACP and ALP level of male rats treated with Purslane Extract, Fig leaves Extract and Diclofenac Sodium or their combination.*

Groups	ALT	AST	ACP	ALP
C	21± 0.95 c	40.2± 0.39 c	38.4± 0.41 c	155± 0.8 c
DS	40.7 ±1.27 a	67± 1.07 a	50.8± 0.39 a	200±0.9 a
PuE	20.4± 0.91c	37.6 ±1.42 c	36.7± 0.78c	152± 0.7 c
FlE	19.2± 0.77 c	39.50± 1.56 c	38.3± 0.39 c	154± 0.9 c
PuE+DS	28.4 ±1.41 b	45.4 ±1.08 b	43.2± 0.33 b	170±0.8 b
FlE+DS	25.9± 0.47 b	44.3± 0.74 b	41.9 ±0.88 b	173± 0.7 b

Means in a columns not sharing the same letters are significantly different at (P<0.05).
C: Control, DS: Diclofenac Sodium, PuE: Purslane Extract, FlE: Fig leaves Extract.
ALT = Alanine transaminase (U/ml); AST = Aspartate transaminase (U/ml); ACP=Acid phosphatase (U/L); ALP= Alkaline phosphatase (IU/L).

3.3. Protein Profile and Kidney Functions Tests

Data represented in (Table 3) shows the changes in plasma total protein, albumin, globulin, total bilirubin, urea and creatinine. Data showed that treatment with DS significantly decreased plasma levels of total protein, albumin and globulin whereas significant increases in plasma total bilirubin, urea, and creatinine were comparable to control group. The increase in the level of plasma bilirubin is in agreement with Adeyemi and Olayaki [31] who demonstrated that oral administration of DS induced significant increase in bilirubin level. Treatment with PuE and FlE, resulted in no significant differences compared to those in the control group of all tested parameters excepted albumin and globulin when treated with PuE. Whereas, rats treated with PuE+DS and FlE+DS exhibited a significant decrease in total protein and albumin and a significant increase in plasma total bilirubin, urea, and creatinine compared to control group. Globulin exhibits no significant difference between combination and control group.

3.4. Oxidative Stress Marker

To evaluate the degree of cellular damage in hepatocytes, lipid peroxidation (LPO) in tissue homogenate was measured by estimating the formation of thiobarbituric acid reactive substances (TBARS). The estimation of GSH from tissue homogenate was done by the method of Jollow *et al.* [22]. A marked increase in TBARS levels was found in the hepatic tissue homogenate of DS, on the other hand, a decrease in GSH was obvious when compared to the control group (Figure 1 and Figure 2). These could result from the formation of excess free radicals generated by DS metabolites that overwhelm the antioxidant status system and cause peroxidation of lipids. This finding is in agreement with the work of Alabi *et al.* who administrated that diclofenac caused a significant decrease in activity of reduced the glutathione (GSH) levels when compared with those of the control group [32]. However, the combination groups showed a significant regained the increase in GSH as compared to the control group. The presence of PuE and FlE with DS partially minimized the toxic effect of DS compared to DS alone. Generally, treatment with PuE and FlE alone increased the activities of GSH and decrease the levels of TBARS in liver compared to control group.

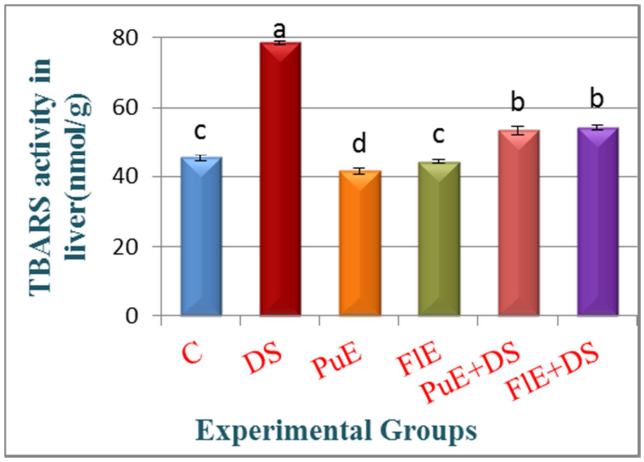

Figure 1. *Changes in liver TBARS levels of male rats treated with Purslane Extract, Fig leaves Extract and Diclofenac Sodium or Values are expressed as mean ±SE; letters indicates significant difference (P < 0.05) compared to control Group. C: Control, DS: Diclofenac Sodium, PuE: Purslane Extract, FlE: Fig leaves Extract. TBARS= Thiobarbituric acid reactive substances (nmol/g tissue).*

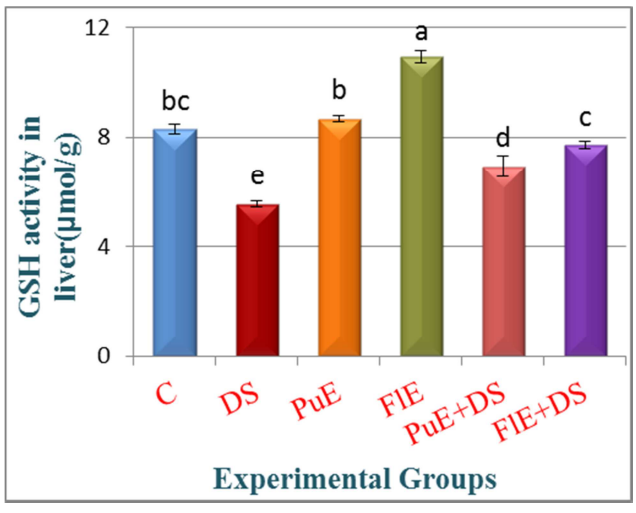

Figure 2. *Changes in liver GSH activities of male rats treated with Purslane Extract, Fig leaves Extract and Diclofenac Sodium or their combination. Values are expressed as mean ±SE, letters indicates significant difference (P < 0.05) compared to control Group. C: Control, DS: Diclofenac Sodium, PuE: Purslane Extract, FlE: Fig leaves Extract.*

Table 3. *Changes in plasma Total protein, albumin, globulin, urea, creatinine and bilirubin levels of male rats treated with Purslane Extract, Fig leaves Extract and Diclofenac Sodium or their combination.*

Groups	Total protein	Albumin	Globulin	Urea	Creatinine	Bilirubin
C	8.56 ± 0.214ab	5.28 ± 0.084b	3.29 ± 0.194a	45.7± 0.63d	0.352 ± 0.0153c	0.750 ± 0.0258bc
DS	3.28 ± 0.101d	1.33 ± 0.085d	1.95 ± 0.134c	61.1 ± 0.90a	1.07± 0.040a	2.27 ± 0.108a
PuE	8.68 ± 0.115a	6.05 ± 0.057a	2.63 ± 0.158b	46.1 ± 0.63d	0.340 ± 0.0309c	0.684 ± 0.0467c
FlE	8.51 ± 0.193ab	5.27 ± 0.091b	3.24 ± 0.131a	44.2 ± 0.70d	0.318 ± 0.0182c	0.622 ± 0.0693c
PuE+DS	8.18 ± 0.107bc	4.67 ± 0.041c	3.51 ± 0.141a	51.5 ± 0.83b	0.610 ± 0.0054b	0.886 ± 0.0302b
FlE+DS	7.77 ± 0.124c	4.69 ± 0.073c	3.07 ± 0.197ab	48.6 ± 1.26c	0.576 ± 0.0174b	0.924 ± 0.0160b

Means in a columns not sharing the same letters are significantly different at (P<0.05).
C: Control, DS: Diclofenac Sodium, PuE: Purslane Extract, FlE: Fig leaves Extract.
Total protein (g/dl); Albumin (g/dl); Globulin (g/dl); Urea (mg/dl); Creatinine (mg/dl); Bilirubin (mg/dl).

3.5. Antioxidant Enzymes

Activities of antioxidative enzyme in tissues have always been used as a marker for tissue damage [33]. Liver enzyme like SOD, CAT, GPX and GST were dramatically reduced in DS group compared to control group Table (4). However, pre-treatment with PuE and FlE along with DS significantly decrease SOD, CAT, GPX and GST compared to control group. The presence of PuE and FlE combination with DS increased the activities of antioxidant enzymes and partially minimized their toxic effect of DS compared to DS alone. Treatment with PuE and FlE showed no significant differences in GPX and GST whereas, significant increase was observed in CAT and SOD when compared to control group. In general the activities of antioxidants enzymes did not reach the control values of all combination groups treated with PuE+DS and FlE+DS but significantly suppressed the toxic effect of DS.

Table 4. *Changes in liver SOD, CAT, GSH, GPX and GST activities of male rats treated with Purslane Extract, Fig leaves Extract and Diclofenac Sodium or their combination.*

Groups	SOD	CAT	GPX	GST
C	7.14±0.200b	127±0.8c	43.2±1.03a	15.0±0.40ab
DS	3.58± 0.146d	83.7±0.77e	29.6±0.79c	8.54±0.388c
PuE	7.15±0.148b	130±0.3b	43.7±0.91a	15.5±0.58a
FlE	8.08±0.291a	132±0.5a	44.26±0.78a	15.3±0.57a
PuE+DS	5.90±0.239c	117±0.6d	35.65±0.71b	14±0.48ab
FlE+DS	6.16±0.320c	116±0.8d	37.2±0.87b	13.6±0.31b

Means in a columns not sharing the same letters are significantly different at (P<0.05).
C: Control, DS: Diclofenac Sodium, PuE: Purslane Extract, FlE: Fig leaves Extract.
SOD= Superoxide dismutase (U/g tissue); CAT =Catalase (U/g tissue); GSH= Reduced glutathione (µmol/g wet tissue); GPX= Glutathione peroxidase (IU/g wet tissue); GST= Glutathione S-transferase (µmol/hr).

3.6. Liver Histopathological Examination

From all the six experimental group histopathological liver sections of rats are shown in Figure. 2a-f and they provide supportive evidence of biochemical analysis. It's aimed to understand how tissues are organized at all structural levels, including the molecular and macromolecular, the entire cell and intercellular substances and tissues and organs.

Histological examination of sections stained of rat livers in C, in treated rats with PuE and with FlE groups, respectively revealed normal structure of hepatocytes, arranged cords of hepatocytes which extend from a central vein to the periphery of the hepatic lobules at which the portal tracts appears (Figure. 3a-c). There also revealed liver cords which are separated from each other by narrow blood sinusoids lined with endothelial cells and von kupffer cells. In contrast, liver sections in treated rats with DS showed hepatotoxicity manifested by moderate atrophied, cytoplasmic vacuolization of hepatocytes, many foci of apoptotic cells in the hepatic lobule, mild to moderate inflammatory cells, an increased in the Kupffer cells numbers, inflammatory cell infiltrations around the portal areas and mild congested blood sinusoids (Figure. 3d).

Liver sections in treated rats with PuE+DS showed mild to moderate hepatocytes improvement with modulate congested sinusoidal space, mild cellular infiltrations, hepatocellular cells have a granulated cytoplasm with mild focal or multifocal hepatocellular vacuolation (Figure 3e). On the other hand, liver sections in treated rats with FlE+DS showed a normal hepatocytes structure except a few vacuolation in hepatocytes with normal blood vessels in the periportal area and sinusoids did not show a few dilatation (Figure. 3f).

4. Conclusions

On the basis of our work, results demonstrate the mechanism of DS toxicity-induced liver dysfunction and (PuE and FlE) pre-administration had a protective effect against that toxicity. Liver sections in treated rats with FlE+DS showed a normal hepatocytes structure and (PuE+DS and FlE+DS) administration include attenuation of hematological test by decreasing the oxidative stress, increasing the activity of the endogenous antioxidant system, preserving the structure of hepatic cells. In light of such

known facts, PuE and FlE should be regarded as a new and promising agent with a high potential in the prevention and treatment of drug-induced liver injury and liver disease.

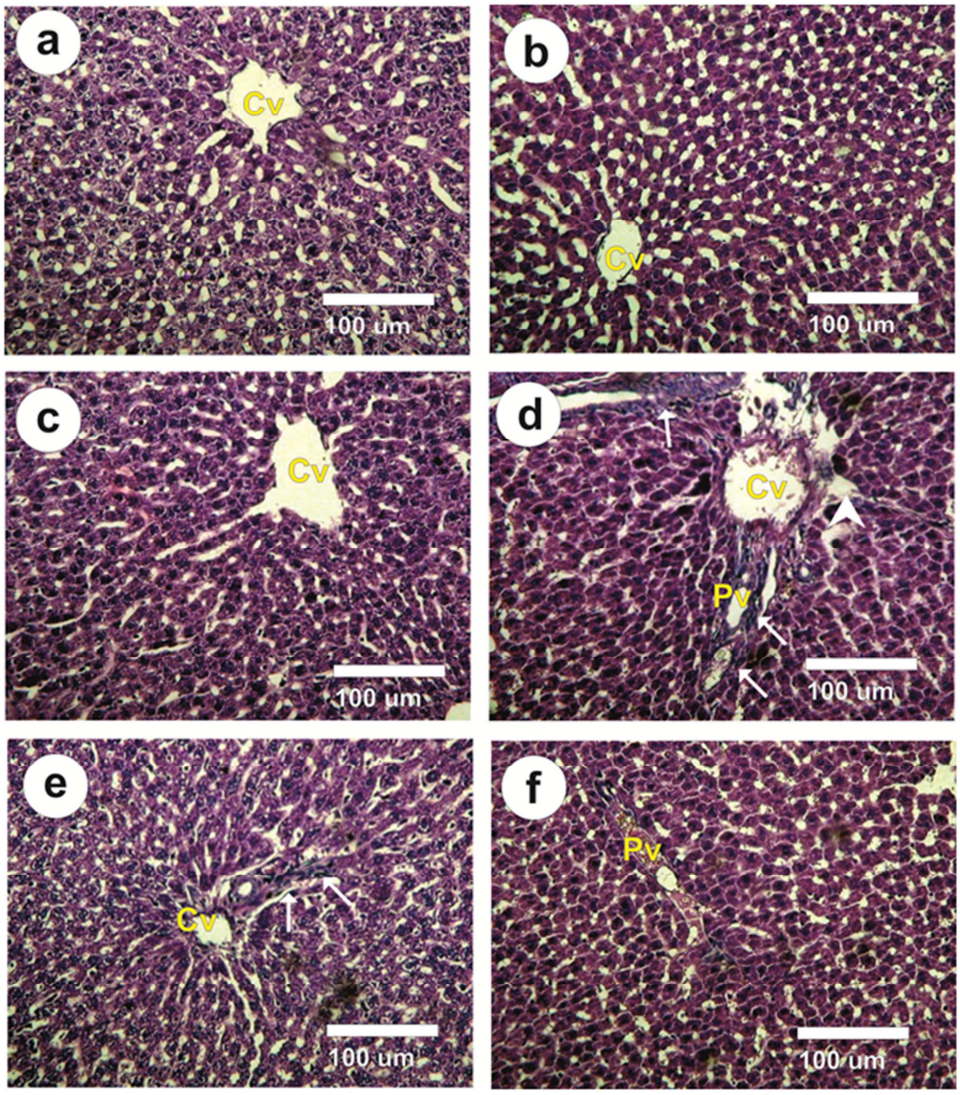

Figure 3. *a-f: Photomicrographs of Liver sections in rat stained with Haematoxylin & Eosin. a-c: Liver sections in C, in treated rats with PuE and with FlE groups respectively revealed normal structure of hepatocytes and normal central veins (CV). d: Liver sections in treated rats with DS showed moderate atrophied, cytoplasmic vacuolization of hepatocytes (arrows heads), mild to moderate inflammatory cells, inflammatory cell infiltrations (arrows) around the portal areas (Pv) and central veins (Cv). e: Liver sections in treated rats with PuE+DS showed mild cellular infiltrations (arrows) and mild focal or multifocal hepatocellular vacuolation. f: Liver sections in treated rats with FlE+DS showed a normal hepatocytes structure except a few vacuolation in hepatocytes with normal blood vessels.*

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