DRUG DISCOVERY

16(38), 2022

Effect of the antidepressant drug dapoxetine on acute liver injury caused by carbon tetrachloride in the rat

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To Cite:
Abdel- Salam OME, Youness ER, Morsy FA, Sleem AA. Effect of the antidepressant drug dapoxetine on acute liver injury caused by carbon tetrachloride in the rat. *Drug Discovery*, 2022, 16(38), 76-85

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Peer-Review History
Received: 17 September 2022
Reviewed & Revised: 21/September/2022 to 25/December/2022
Accepted: 29 November 2022
Published: 03 December 2022

Peer-review
External peer-review was done through double-blind method.

ABSTRACT

We examined the effect of dapoxetine, a selective serotonin-reuptake inhibitor used in treatment of premature ejaculation in the carbon tetrachloride (CCl_4) model of acute liver injury. Dapoxetine (5.4, 10.2 or 21.4 mg/kg) was given once daily orally simultaneously with CCl_4 and for 2 consecutive days thereafter. We measured serum aminotransferases activities, liver lipid peroxidation (malondialdehyde: MDA), nitric oxide and reduced glutathione (GSH) concentrations, serum MDA, nitric oxide, serum and liver paraoxonase-1 (PON-1) activities and liver Na^+/K^+-ATPase activity. Hepatic histopathology was also done. *Results:* Rats treated with CCl_4 exhibited significantly raised serum aspartate aminotransferase and alanine aminotransferase activities. There were also increased MDA and nitric oxide concentrations in liver and serum whereas liver GSH concentrations, liver and serum PON-1 activities as well as liver Na^+/K^+-ATPase activity were depressed compared with the vehicle group. The administration of dapoxetine to CCl_4-treated rats attenuated liver injury, as indicated by the decrease in serum liver enzymes and markers of oxidative stress. The histopathological change induced by CCl4 such as centrilobular necrosis, vacuolar and fatty degeneration, distorted architecture was also improved by dapoxetine in a dose-dependent manner. Thus, in acute liver injury caused by CCl_4, the concurrent administration of the antidepressant drug dapoxetine was associated with decreasing oxidative stress and less extent of liver tissue damage.

Keywords: dapoxetine, antidepressants, carbon tetrachloride, liver injury, oxidative stress, paraoxonase, Na^+/K^+-ATPase

1. INTRODUCTION

Premature ejaculation constitutes a common male sexual disorder with psychological consequences which affects the quality of life of men. The estimated prevalence of this disorder is between 20% and 40% (Porst et al., 2007). In the management of premature ejaculation, the selective serotonin reuptake inhibitors (SSRIs) have been used off-label (Waldinger, 2007).

Dapoxetine is an SSRI, a potent inhibitor of serotonin transporter which is approved for the on-demand treatment of premature ejaculation (McMahon, 2012). It differs from other SSRIs such as fluoxetine, sertraline and paroxetine in having a short plasma half-life of 1.31 and 1.42 h for 30 and 60 mg dapoxetine, respectively, in contrast to 21h for paroxetine and 4 days for fluoxetine (Iribarren and Martinez-Salamanca, 2010). The rapid absorption and elimination of dapoxetine in single dosing also applies to multiple dosing leading to minimal accumulation. Dapoxetine undergoes extensive metabolism in the liver and is excreted in the urine, mainly as the metabolized drug (Andersson et al., 2006; Modi et al., 2006). Side effects are usually mild and transient and include nausea, dizziness, headache, diarrhea (Pryor et al., 2006; Iribarren and Martinez-Salamanca, 2010).

The liver is the major side for the metabolism and elimination of drugs and xenobiotics which makes this organ the target of toxic agents or their metabolites eg., electrophilic chemicals or free radicals that might attack cellular proteins, lipids, or nucleic acids, cause damage to the mitochondrial or other organelles or deplete reduced glutathione, thereby increasing the vulnerability of liver tissue to oxidants (Kaplowitz, 2004). In liver disease, because of hepatic cellular dysfunction, drugs that mainly eliminated through hepatic metabolism, are likely to have reduced elimination and thus accumulates in the body (Westphal and Brogard, 1997). Patients with liver disease are therefore susceptible to the toxic effects of drugs (Weersink et al., 2020) with possible further hepatic injury. Hence, the significance of research on the effect of medications in presence of liver injury.

The aim of the present study is therefore to investigate the effect of dapoxetine on the development of acute liver injury evoked in the rat by administering the hepatotoxic agent CCl_4. The CCl_4 model of hepatocellular damage is widely used to investigate potential therapeutics as well as adverse effects of drugs on liver integrity. This industrial solvent causes acute hepatic injury characterized by centrilobular necrosis. On continued exposure to the toxin, however, hepatic fibrosis and cirrhosis ultimately develop (Moleda et al., 2011). The pathogenetic mechanism involves free radical-mediated liver cell injury in which the metabolic activation of CCl_4 by cytocrome P450-dependent monooxygenases leads to the formation of the trichloromethyl radical (CCl_3) within the membrane of the endoplasmic reticulum, causing excessive membrane lipid peroxidation and cellular damage (Boll et al., 2001; Weber et al., 2003).

2. MATERIALS AND METHODS

Animals

Male Sprague-Dawley strain rats (150-160 g) from National Research Centre, Cairo were used in the experiments. Rats were housed under a standard 12-h light/dark cycle and had free access to food and tap water. Animal procedures followed the guidelines of the Institute ethics committee for the use of animals in experimental studies and the Guide for Care and Use of Laboratory Animals by the U.S. National Institutes of Health (Publication No. 85-23, revised 1996).

Drugs and Chemicals

Carbon tetrachloride (Sigma, St Louis, MO, USA) and dapoxetine hydrochloride (International Drug Agency for Pharmaceutical Industry, Egypt) were used in the study. The remaining chemicals and reagents were obtained from Sigma Chemical Co. (St. Louis, MO, U.S.A.). The doses of dapoxetine for rats used in the study were based upon the human dose after conversion to that of rat according to Paget and Barnes conversion tables (1964). The dose of CCl_4 used in the study was based on previous observations (Abdel Salam et al., 2007).

Experimental Groups

Rats were randomly allocated into five equal groups (6 rats each). Group 1 received the vehicle (olive oil) and served as negative control. Groups 2, 3, 4 & 5 were treated by gavage with CCl_4–olive oil (1:1, v/v) at a dose of 2.8 ml/kg through an orogastric tube, for two successive days either alone (group 2: positive control) or together with orally administered dapoxetine at doses of 5.4, 10.2 or 21.4 mg/kg (groups 3, 4 & 5). Rats had free access to food and drinking water during the study. 24h after last treatments, blood samples were obtained from the retro-orbitalvein plexuses under light ether anaesthesia. Rats were then euthanized by cervical decapitation under light ether anaesthesia. The liver of each rat was then quickly removed, washed with ice-cold phosphate-buffered saline (PBS, pH 7.4), weighed and stored at −80°C until the biochemical analyses were carried out. The tissues were homogenized in 0.1 M phosphate-buffered saline at pH 7.4 to give a final concentration of 10 % w/v for the biochemical assays.

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Biochemical Studies

Serum Liver Enzymes

The activities of aspartate aminotransferase and alanine aminotransferase in serum were measured according to Reitman-Frankel colorimetric transaminase procedure (Crowley, 1967) using commercially available kits (Biodiagnostic, Egypt).

Lipid peroxidation

The measurement of malondialdehyde (MDA) was used to determine the extent of lipid peroxidation in the serum and liver tissue. Malondialdehyde was determined by measuring thiobarbituric reactive species using the method of Ruiz-Larrea et al., (1994). In this assay, thiobarbituric acid reactive substances (TBARS) react with thiobarbituric acid to produce TBA-MDA adduct with a red color that can be determined using spectrophotometer at 532 nm.

Reduced Glutathione

In this assay, Ellman's reagent (DTNB; 5, 5′-dithiobis (2-nitrobenzoic acid)) is reduced by the sulfhydryl groups of GSH to produce 2-nitro-s-mercaptobenzoic acid. The nitromercaptobenzoic acid anion has an intense yellow color and the absorption can be measured at 412 nm using a spectrophotometer (Ellman et al., 1959).

Nitric Oxide

Nitric oxide levels were measured using the Griess reaction. In this assay, nitrate is converted to nitrite by nitrate reductase. The Griess reagent then reacts with nitrite forming a deep purple azo compound. The absorbance is read at 540 nm using a spectrophotometer (Archer, 1993).

Paraoxonase 1 Activity

The arylesterase activity of paraoxonase was determined in liver supernatants and serum. Phenyl acetate used as a substrate is cleared by the arylesterase/paraoxonase yielding phenol, the rate of its formation is determined by monitoring the increase in absorbance at 270 nm at a temperature of 25°C. One unit of arylesterase activity is considered equal to 1 μM of phenol formed per minute. The activity of PON-1 is expressed in kU/L (based on the extinction coefficient of phenol of 1,310 M^{-1} cm^{-1} at 270 nm, pH 8.0, and 25°C) (Haagen and Brock, 1982).

Liver Na^+-K^+ ATPase Activity

Na^+-K^+-ATPase activity was determined using an ELISA kit purchased from Sunlong Biotech Co. (Zhejiang, China).

Histopathological Studies

Representative liver samples were fixed in 10% buffered formalin, dehydrated in graded ethanol and embedded in paraffin using standard procedures. Sections of 5 μm thickness were stained with hematoxylin and eosin (H&E) (Drury and Walligton, 1980) for histopathological examination using a light microscope: Olympus Cx 41 with DP12 Olympous digital camera (Olympous optical Co. Ltd, Tokyo. Japan).

Statistical Analysis

Results are expressed as mean ± SE. Statistical analysis of data was performed with the use of one way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test for comparing multiple groups. GraphPad Prism 6 for Windows (GraphPad Prism Software Inc., San Diego, CA, USA) was used. Statistical significance was considered at a probability value of less than 0.05.

3. RESULTS

Biochemistry Results

Effect of dapoxetine on serum transaminases in CCl_4-treated rats

Significant increases in serum ALT and AST activities by 113.8% and 82.3%, respectively, were observed in CCl_4-treated rats as compared with their respective vehicle-treated controls (170.2 ± 5.8 *vs.* 79.6 ± 3.3 and 174.1 ± 8.1 *vs.* 95.2 ± 3.0 U/l). The treatment of rats with dapoxetine significantly decreased serum enzyme activities. Serum ALT activity decreased by 18.6% and 35.0% by dapoxetine 10.8 and 21.6 mg/kg, respectively (from 170.2 ± 5.8 in the CCl_4 control to 138.6 ± 7.7 and 110.7 ± 4.2 U/l, respectively, in

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the CCl_4 + dapoxetine treated groups). Meanwhile, serum AST activity decreased by 19.5%, 27.3% and 32.9% by 5.4, 10.2 and 21.4 mg/kg dapoxetine, respectively (from CCl_4 control value of 174.1 ± 8.1 to 140.1 ± 6.2, 126.6 ± 7.4 and 116.9 ± 4.8 U/l, respectively) (Figure 1).

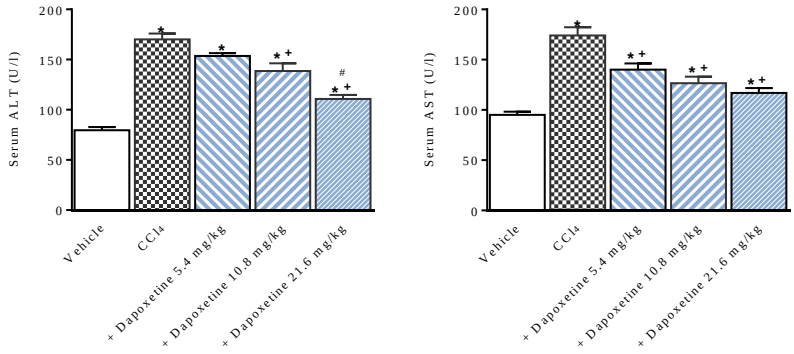

Figure 1 Effect of dapoxetine on serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in CCl_4-treated rats. *: P<0.05 *vs.* vehicle. +: P<0.05 *vs.* CCl_4 control. #: P<0.05 *vs.* dapoxetine 5.4 mg/kg group.

Effect of dapoxetine on oxidative stress in serum of CCl_4-treated rats

Malondialdehyde

Rats treated with CCl_4 showed significantly increased serum MDA by 68.4% compared to the vehicle group (72.9 ± 2.8 *vs.* 43.3 ± 1.3 nmol/ l). In groups treated with dapoxetine, MDA significantly decreased by 26.6%, 32.9% and 41.7%, respectively (from CCl_4 control value of 72.9 ± 2.8 to 53.5 ± 2.1, 48.9 ± 1.6 and 42.5 ± 1.4 nmol/l) (Figure 2).

Nitric Oxide

Following CCl_4 administration, serum nitric oxide level increased by 157.6% compared with the vehicle group (119.0 ± 4.0 *vs.*46.2 ± 2.5 µmol/ l). The treatment with dapoxetine resulted in significant decreases in serum nitric oxide by 46.1%, 55.0% and 62.8% (from 119.0 ± 4.0 in the CCl_4 only group to 64.2 ± 3.4, 53.6 ± 2.1 and 44.3 ± 1.8 µmol/l in the dapoxetine treated groups) (Figure 2).

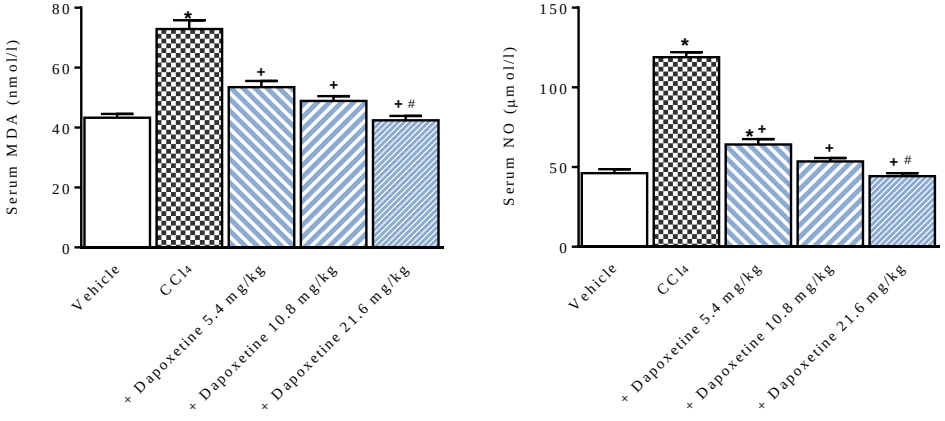

Figure 2 Effect of dapoxetine on serum malondialdehyde (MDA) and nitric oxide (NO) in CCl_4-treated rats. *: P<0.05 *vs.* vehicle. +: P<0.05 *vs.* CCl_4 control. #: P<0.05 *vs.* dapoxetine 5.4 mg/kg group.

Effect of dapoxetine on oxidative stress in liver of CCl_4-treated rats

Malondialdehyde

Rats given CCl_4 alone exhibited significantly increased liver MDA by 93.4% compared to the vehicle group (58.8 ± 2.4 *vs.* 30.4 ± 1.1 nmol/g.tissue). In groups that received CCl_4 and dapoxetine at 10.8 and 21.6 mg/kg, MDA significantly fell by 36.1% and 42.2%, respectively (from CCl_4 control value of 58.8 ± 2.4 to 37.6 ± 1.9 and 34.0 ± 2.1 nmol/g. tissue) (Figure 3).

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Nitric Oxide

Significant increase in liver nitric oxide by 122.8% was observed following CCl_4 administration (81.1 ± 2.5 *vs.* 36.4 ± 0.9 µmol/g. tissue). Dapoxetine given at 5.4, 10.8 and 21.6 mg/kg resulted in significant decrements in liver nitric oxide by 48.3%, 60.0% and 70.3%, respectively, compared with the CCl_4 control group (41.1 ± 2.9, 32.5 ± 2.7, and 24.1 ± 1.2 *vs.* CCl_4 control value of 81.1 ± 2.5 µmol/g. tissue) (Figure 3).

Reduced Glutathione

There was a significant decrease in liver GSH by 64.1% in rats receiving CCl_4 compared with their controls (2.2 ± 0.25 *vs.* 6.12 ± 0.26 µmol/g. tissue). Dapoxetine given at 10.8 and 21.6 mg/kg caused significant increases in GSH levels by 46.8% and 62.7%, respectively, compared with the CCl_4 control group (3.23 ± 0.12 and 3.58 ± 0.10 *vs.* CCl_4 control value of 2.2 ± 0.25 µmol/g. tissue) (Figure 3).

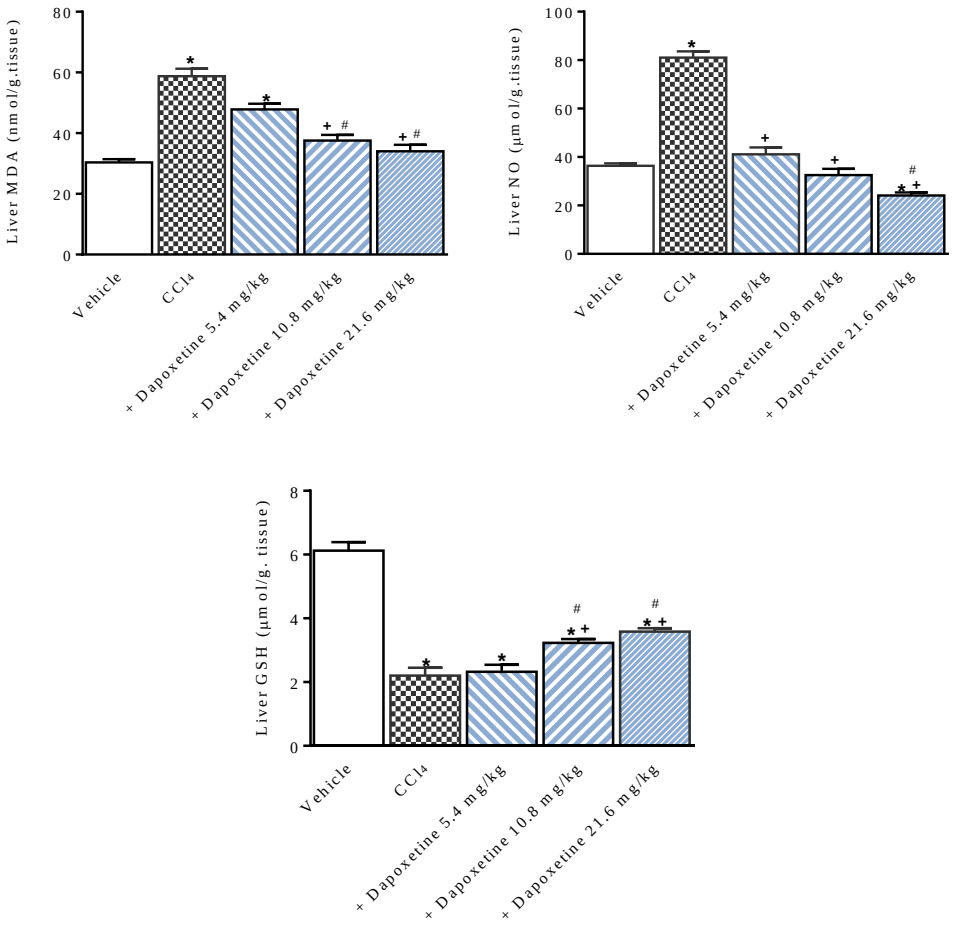

Figure 3 Effect of dapoxetine on liver malondialdehyde (MDA), nitric oxide (NO) and reduced glutathione (GSH) in CCl_4-treated rats. *: P<0.05 *vs.* vehicle. +: P<0.05 *vs.* CCl_4 control. #: P<0.05 *vs.* dapoxetine 5.4 mg/kg group.

Effect of dapoxetine on serum and liver paraoxonase-1 in CCl_4-treated rats

Following CCl_4 administration, serum and liver PON-1 activities showed significant decrease by 48.7% (150.2 ± 10.0 *vs.* 292.8 ± 15.8 kU/l) and 68.4% (7.3 ± 0.48 *vs.* 23.1 ± 1.9 kU/l), respectively, compared to their respective controls. Serum PON-1 activity significantly increased by 41.5% in rats treated with CCl_4 + dapoxetine at 21.6 mg/kg (212.5 ± 11.4 *vs.*150.2 ± 10.0 kU/l). Meanwhile, significant increments in liver PON-1 activity by 93.2% and 184.9% were observed in rats treated with CCl_4 + dapoxetine at 10.8 and 21.6 mg/kg compared to the CCl_4 control group (14.1 ± 0.58 and 20.8 ± 1.5 *vs.* 7.3 ± 0.48 kU/l) (Figure 4).

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Effect of dapoxetine on Na^+-K^+-ATPase activity in liver of CCl_4-treated rats

Compared with the vehicle control group, Na^+-K^+-ATPase activity was significantly lower by 42.7% in liver of CCl_4-treated rats, indicative of liver cell injury (0.192 ± 0.01 *vs.* 0.335 ± 0.018 µg Eq/ml). In groups treated with CCl_4 + dapoxetine at 10.8 and 21.6 mg/kg there were significant increments in Na^+-K^+-ATPase activity by 49.5% and 64.1%, respectively, compared with the CCl_4 control value (0.287 ± 0.015 and 0.315 ± 0.032 *vs.* 0.192 ± 0.01 µg Eq/ml) (Figure 4).

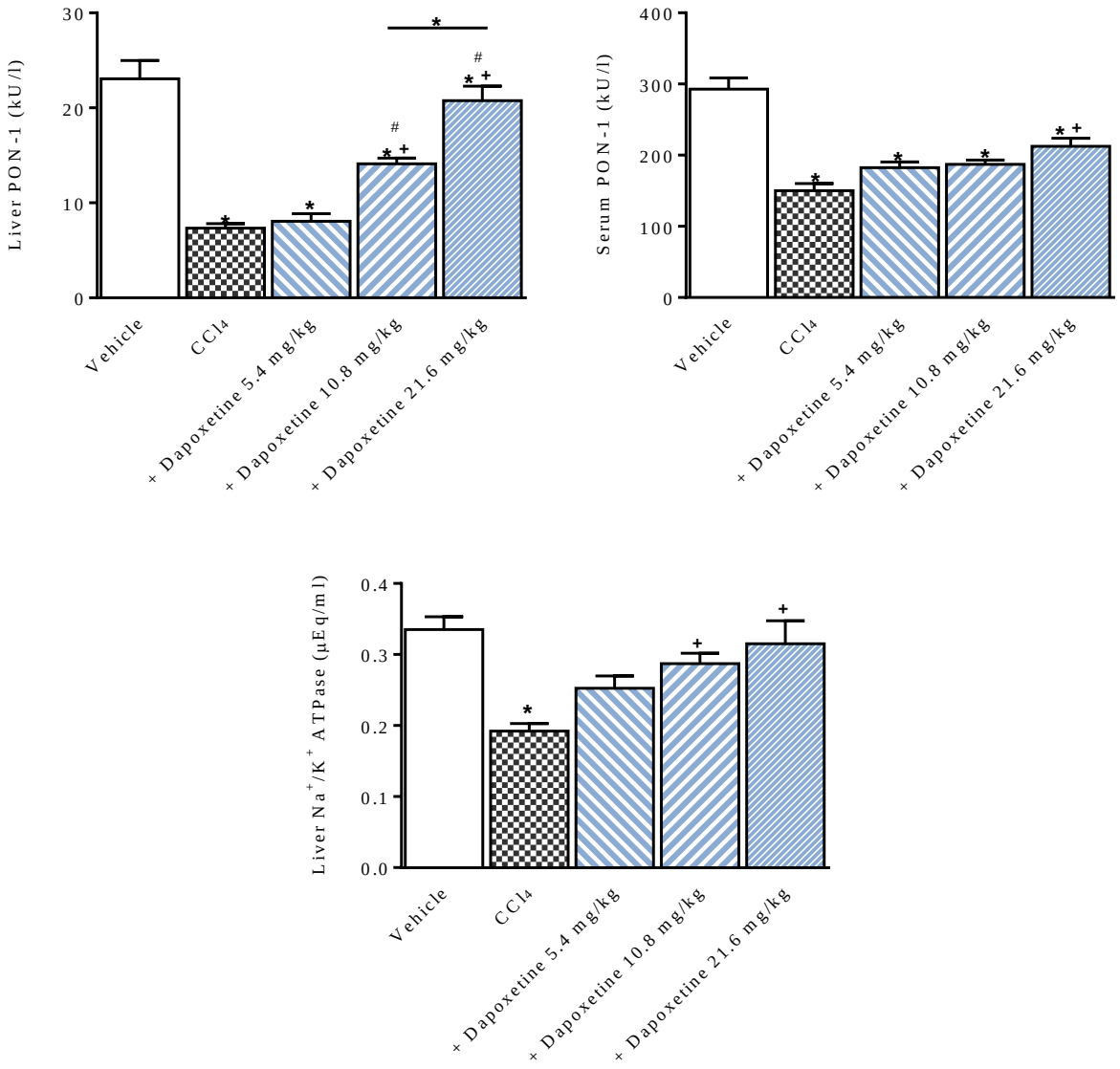

Figure 4 Effect of dapoxetine on PON-1 activity in serum and liver tissue and on liver Na^+/K^+-ATPase activity of CCl_4-treated rats.
*: P<0.05 *vs.* vehicle and between different groups as indicated in the figure. +: P<0.05 *vs.* CCl_4 control.

Histopathological Results

The vehicle-treated group revealed a normal appearance (Figure 5A). On the other hand, liver tissue sections obtained from rats treated with CCl_4 showed severe alterations including distortion of lobular architecture, centrilobular necrosis, some dead and apoptotic cells, vacuolar degeneration, massive fatty degeneration, cloudy swelling and fibrosis. There were also dilatation and congestion of portal vein, central vein and red blood cells in sinusoidal space, hyperplasia of bile duct and thickening of their wall (Figure 5B, C, D). Livers from rats treated with CCl_4 and dapoxetine at dose of 5.4 mg/kg revealed some improvement in pathological changes in the form of some hepatocytes having normal appearance, others showing reduction in hepatic lesions, although few vacuolar and fatty degeneration and area of necrosis were observed. Few inflammatory infiltrate around necrotic

portal vein, dilated central vein, hypertrophy of Kupffer cells and red blood cells in sinusoidal space were also observed (Figure 5 E, F). In rats given CCl_4 along with dapoxetine at 10.4 mg/kg, there were less degenerative changes. Liver sections showed normal hepatocytes but dilated and congested portal vein with thickening of the wall, inflammatory infiltrate, fibrosis, congestion of central vein and hyperplasia of Kupffer cells were still present (Figure 5 G, H). Liver sections from rats treated with CCl_4 and 21.6 mg/kg dapoxetine showed more decrease in hepatic lesions in the form of normal hepatocytes, although micro vacuolar degeneration, dilated and congested portal, central vein and red blood cells in sinusoidal space were still seen (Figure 5 I, J).

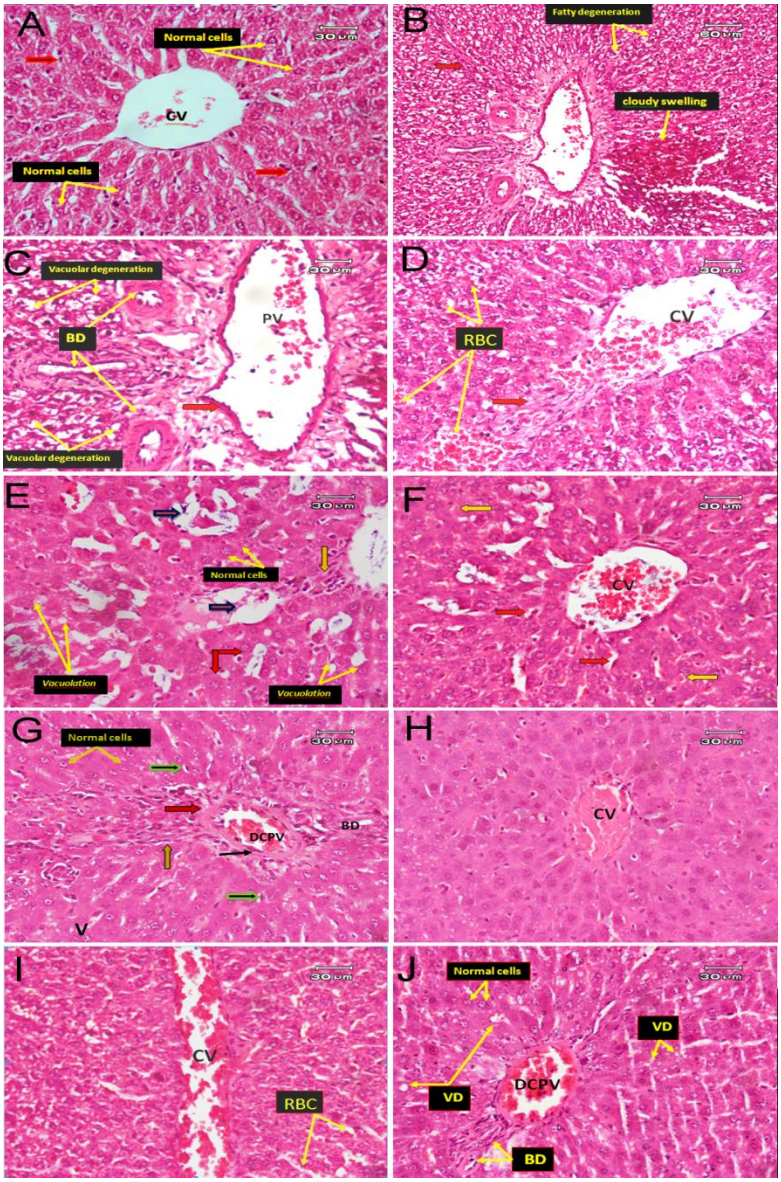

Figure 5 Representative photomicrographs of liver sections after treatment with; (A) Vehicle: Showing normal liver tissue, normal hepatocytes, normal central vein (CV) and Kupffer cell (red arrow); (B) CCl_4 control: Cloudy swelling, massive fatty degeneration, and minimal fibrosis (red arrow); (C) CCl_4 control (higher magnification): Massive vacuolar degeneration, dilated congested portal vein (PV) with thickening of wall (red arrow), hyperplasia of bile duct (BD); (D) CCl_4 control (another filed): Dilatation and congestion of central vein (CV), red blood cells in sinusoidal space (RBC), fibrosis (red arrow); (E) CCl_4 + dapoxetine 5.4 mg/kg: Some improvement in form of normal cells (hepatocytes), some vacuolar degeneration, few fatty changes (red arrow), area of necrosis (black arrow) and few inflammatory cells around portal vein; (F) CCl_4 + dapoxetine 5.4 mg/kg (another filed): Dilated and congested central vein, hypertrophy of Kupffer cells (red arrow) and red blood cells in sinusoidal space (orange arrow); (G) CCl_4 + dapoxetine 10.4 mg/kg: Most hepatocytes appeared normal but dilated and congested portal vein (DCPV) and thickening of wall (black arrow), inflammatory infiltrate (red arrow), fibrosis (orange arrow) and hyperplasia of Kupffer cells (green arrow) were still present; (H) CCl_4 + dapoxetine 10.4 mg/kg (another filed): Dilated and congested central vein; (I) CCl_4 + dapoxetine 21.6 mg/kg: Marked dilation and congestion of central vein, red blood cells in sinusoidal space (RBC); (J) CCl_4 + dapoxetine 21.6 mg/kg: More reduction of degenerative changes, most cells appeared normal although micro vacuolar degeneration (VD), dilated and congested portal vein (DCPV) were still present.

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4. DISCUSSION

The present study investigated the effect of the antidepressant drug dapoxetine in presence of acute liver injury caused by CCl_4 in the rat. We found that the concurrent administration of dapoxetine resulted in decreased biochemical markers of liver l damage. In particular, the release into the circulation of the hepatocellular enzymes alanine aminotransferase and aspartate aminotransferase which is a surrogate marker of liver cell injury (Limdi and Hyde, 2003) is significantly reduced by dapoxetine. The drug also caused a decrease in the lipid peroxidation end product malondialdehyde (Gutteridge, 1995) and nitric oxide in serum and liver tissue together with increased liver reduced glutathione content, indicative of reduced release of free radicals and sparing and/or replenishing of reduced glutathione. The beneficial effect of dapoxetine is further confirmed by histological examination of liver tissue which revealed that the distorted liver architecture, vacuolar degeneration and centrilobular necrosis caused by CCl_4 were markedly decreased by co-administering dapoxetine with the effect being dose-dependent one.

The CCl_4-induced acute liver injury derives mainly from the formation of the reactive intermediate metabolite CCl_3 causing peroxidation of membrane lipids and binding covalently to cellular structures (nucleic acids, proteins, lipids) with potential lethal consequences. The reaction of CCl_3 radical with oxygen results in the formation of the highly reactive trichloromethylperoxy radical CCl_3OO^*, which initiates lipid peroxidation (Boll et al., 2001; Weber et al., 2003). Conversion of CCl_4 to the free radical CCl_3 is increased by low oxygen tension in the centrilobular area and which cannot be prevented by a glutathione-dependent mechanism (Burk et al., 1984). Protection against CCl_4-induced liver toxicity can be achieved by the use of antioxidants like vitamin E (α-tocopherol) (Parola et al., 1992) or antioxidants from natural sources such as silymarin (Flora et al., 1998), hawthorn (*Crataegus* spp.) preparations containing oligomeric procyanidins and flavonoids (Abdel-Salam et al., 2012), the flavonoids diosmin and hesperidin (Abdel-Salam et al., 2013) which prevented the CCl_4-induced lipid peroxidation. The ability of dapoxetine in decreasing oxidative stress in serum and liver tissue may suggest that an antioxidant effect is one mechanism that underlies the beneficial effect of dapoxetine in decreasing the CCl_4-induced liver damage.

In the present study, nitric oxide concentrations in serum and liver tissue were markedly raised after CCl_4, which is in accordance with other studies (Tipoe et al., 2006; Abdel-Salam et al., 2012). Carbon tetrachloride increases the expression of the inducible nitric oxide synthase (iNOS) isoenzyme and the release of nitric oxide (Iwai et al., 2002). Whereas physiological low levels of nitric oxide released by the constitutively expressed endothelial NOS (eNOS) in liver sinusoidal endothelial cells can be protective against liver injury by maintaining adequate microcirculation, the inappropriately high levels of nitric oxide generated by iNOS by Kupffer cells, infiltrating neutrophils and stellate cells for a sustained period of time can lead to cellular toxicity (Clemens, 1999). Several mechanisms contribute to the cytotoxic effect of excessively released nitric oxide such as: (i) oxidative stress; (ii) inactivation of cytochrome c oxidase and consequent mitochondrial dysfunction; (iii) inactivation of cellular enzyme activities by S-nitrosylation of thiol groups or nitration of tyrosine residues of proteins. These effects are largely mediated by nitrogen reactive species eg. peroxynitrite resulting from the reaction of nitric oxide and superoxide (Laskin et al, 2001; Schild et al., 2003; Rockey and Shah, 2004). It has also been shown that CCl_4-induced acute liver injury and upregulation of inflammatory mediators such as tumour necrosos factor-alpha and cyclooxygenase-2 can be ameliorated by iNOS inhibitors (Tipoe et al., 2006). The decrease in nitric oxide by dapoxetine in serum and liver tissue of CCl_4-treated can therefore be involved at least partly in the ability of this drug in reducing the extent of hepatocellular injury.

We have also demonstrated marked inhibition of PON-1 activities in serum and liver of CCl_4 which is in accordance with other studies (Abdel-Salam et al., 2021). Paraoxonase-1 is synthesized by the liver cells and circulates in plasma bound to high density lipoproteins. It has antioxidative effect, in inhibiting the oxidation of low density lipoporoteins (Mackness et al., 2006). Studies have shown that the activity of the enzyme is decreased in several hepatic disorders including non-alcoholic steato hepatitis (Başkol et al., 2005) and chronic liver diseases (Keskin et al., 2009), possibly due to impaired synthesis of the enzyme by the liver. In this context, measuring serum PON-1 enzyme activity has been proposed as an indicator of liver function (Camps et al., 2009). Moreover, mice deficient in PON-1 exhibited marked steatosis and increased oxidative stress upon feeding with high fat/cholesterol diet (Gracia-Heredia et al., 2013).There is evidence suggesting an important role for oxidative stress in several liver disorders (Videla et al., 2009). Paraoxonase-1 is also inactivated by oxidative stress (Aviram et al., 1999) which may at least partly explain the decline in enzyme activity in patients with liver disease. Our results indicated improvement of PON-1 activity in hepatic tissue and also in serum of CCl_4-treated rats after dapoxetine. It is likely that the preservation of liver tissue integrity and lower levels of oxidative stress accounted for this increase in PON-1 activity.

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5. CONCLUSIONS

The findings in the present study provide the first evidence that the administration of the antidepressant drug dapoxetine in the presence of acute liver injury caused by CCl_4 resulted in decreased liver damage. This was indicated by the decrease in serum aminotransferases activities, in biochemical indicators of oxidative stress in serum and liver tissue, the restoration of Na^+/K^+-ATPase activity as well as by histological examination.

Funding

This study has not received any external fundings.

Author contribution

O.M.E.A.S. study concept and design, O.M.E.A.S., A.A.S., and E.R.Y. conducted the research work and biochemical studies, F.A.M. performed the histological study and its interpretation, O.M.E.A.S. prepared the manuscript, O.M.E.A.S., A.A.S., E.R.Y. and F.A.M. approved the final version of the manuscript.

Ethical approval

The Animal ethical guidelines are followed in the study for biochemical & histological studies. Animal procedures followed the guidelines of the Institute ethics committee for the use of animals in experimental studies and the Guide for Care and Use of Laboratory Animals by the U.S. National Institutes of Health (Publication No. 85-23, revised 1996).

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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