Evaluation of *in vivo* Antioxidant and Hepatoprotective Activity of *Portulaca oleracea* L. against Paracetamol-Induced Liver Toxicity in Male Rats

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**Abstract:** Problem statement: Oxidative stress plays a major role in paracetamol induced hepatotoxicity. *Portulaca oleracea* (P.O.) has been shown to exhibit antioxidant properties. The present study aimed to investigate the effect of P.O. on the oxidative stress in Paracetamol-induced hepatic toxicity in male rats. Approach: Forty male rats were divided into four groups. Group I served as control; Group II Received isotonic saline for 20 days and then simultaneously administered with paracetamol 750 mg kg\(^{-1}\) body wt. every 72 h for 10 days; Group III received freshly prepared P.O. for 30 days; Group IV received freshly prepared P.O. for 20 days and then simultaneously administered with paracetamol 750 mg kg\(^{-1}\) body wt. every 72 h for 10 days. All animals were sacrificed cervical decapitation 24 h after the last application and the blood was collected for the determination of serum marker of lipid peroxidation, antioxidant and histology of the liver was performed. Results: Paracetamol treatment resulted in an increase in the hepatic TBARS content and depletion in total antioxidant capacity, reduced glutathione content, catalase and superoxide dismutase activities. Administration of P.O. with paracetamol significantly ameliorated the indices of hepatotoxicity induced by paracetamol. In addition, P.O. alleviated paracetamol induced oxidative changes in liver. Conclusion: The present study demonstrated that P.O. inhibits paracetamol-induced hepatotoxicity and might serve as a protective agent with paracetamol to limit its free radical induced liver injury.

**Key words:** Oxidative stress, *Portulaca oleracea*, hepatoprotection, Superoxide Dismutase (SOD), Reactive Oxygen (ROS), N-Acetyl-P-benzoquinone Imine (NAPQI), Serum Aspartate Transaminase (AST), Alanine Transaminase (ALT)

**INTRODUCTION**

Paracetamol is a commonly used analgesic and antipyretic drug. The drug is safe at therapeutic levels, but an acute paracetamol overdose can lead to potentially fatal hepatic necrosis in humans and experimental animals (Proudfoot and Wright, 1970; Thomas, 1993). It is becoming clear that Reactive Oxygen (ROS) and Nitrogen (RNS) species take an important part in the development of hepatotoxicity caused by paracetamol (Nakae *et al*., 1990; Michael *et al*., 1999; Knight *et al*., 2001). The initial step of its toxicity is cytochrome P450 metabolism of paracetamol to the reactive intermediate N-Acetyl-P-benzoquinone Imine (NAPQI) (Dahlin *et al*., 1984). At therapeutic doses this metabolite is removed by conjugation with Glutathione (GSH). However at large doses of paracetamol, conjugation with GSH leads to its depletion (Mitchell *et al*., 1973a). This paracetamol-induced hepatic toxicity was prevented by antioxidants and also cytochrome P-450 inhibitors (Sener *et al*., 2003; Abraham, 2005). It is logical to consider antioxidants as primary candidates to counteract such toxic effect. An accumulating evidence supported the protective effects of antioxidants from medicinal plants against oxidative stress–mediated disorders. Studies are going on throughout the world for the search of protective molecules that would provide maximum protection of the liver, kidney as well as other organs and practically very little or no side effects would be exerted during their function in the body (Montilla *et al*., 2005; Mansour *et al*., 2006).

*Portulaca oleracea* L. (Purslane) (Portulacaceae) (P.O.) is a grassy plant with small yellow flowers and stems sometimes flushed red or purple, which grows widely in different areas of the world including Libya (Jin *et al*., 2007). The plant contains many biologically active compounds, including free oxalic acids, β-Carotene, omega-3 fatty acids, coumarins, flavonoids, monoterpenes, glycoside and...
anthraquinone glycosides (Hai-Liang et al., 2008; Boroushaki et al., 2004). P.O. has a long history of use for human food, animal feed and medicinal purposes. The whole plant is edible, either raw or cooked. It is used in liver and kidney disorders, as an emollient, astringent and as a diuretic in Arab traditional medicine (Ghazanfar, 1994). P.O. also used for alleviating pain and swelling (Okwuasaba et al., 1987). The entire plant is usually cut into small pieces and eaten with salt; applied topically to soothe skin (Ghazanfar, 1994). It also exhibits a wide range of pharmacological effects, including antibacterial (Zhang et al., 2002), analgesic, anti-inflammatory and skeletal muscle-relaxant activities (Parry et al., 1987; Parry et al., 1993). A bronchodilatory effect in asthmatic patients, skeletal muscle relaxant and antifertility effect were also reported for P.O. (Elkhayat et al., 2008). It has been described as a “power food” of future because of its high nutritive and antioxidant properties (Simopoulos et al., 1995). The hepatoprotective activities of hydroalcoholic extract of stems and leaves of P.O. in rats treated with CCl₄ (Elkhayat et al., 2008) or rifampicin (Kulkarni et al., 2007) were previously reported. The present study was designed to evaluate the protective effects of Portulaca oleracea against Paracetamol-induced hepatic toxicity in male rats. Liver toxicity was induced by administrating Paracetamol in the presence or absence of P.O.

This study includes biomarkers of hepatic toxicity such as histopathological study and serum activity of AST, ALT, ALP and γ-GT. Oxidative stress and antioxidants of liver will study by determination of reduced glutathione (GSH), Superoxide Dismutase (SOD) and catalase (CAT) enzyme activities and lipid peroxidation (Thiobarbituric acid reactive substances, TBARS).

MATERIAL AND METHODS

Chemicals: Paracetamol was supplied by Control Center for Food and Medicines, Benghazi, Libya. Commercial kits to estimate serum hepatic markers were from Randox laboratories Ltd. (Admore, Crumlin, Co-Antrim, UK). All other chemicals and biochemicals were of analytical grade obtained from local firms.

Plant material: The aerial parts of freshly obtained P.O. from local vegetable market of Benghazi were subjected to obtain juice using an electrical blender. The fresh juice was then used in a dose of 300 mg kg⁻¹ body weight in all experiments.

Animals: Forty healthy adult male Wistar albino rats (The central animal house of Garyounis University, Benghazi, Libya) weighting between 200 and 250 g were used. We used only male rats because of their constant metabolism compared to the variation in the female physiology. The animals were housed under standard laboratory conditions (12 h light and 12 h dark) in a room with controlled temperature (24 ± 3°C) and humidity (55%) during the experimental period. All experimental procedures involving animals were conducted in accordance with the guidelines of National Institutes of Health (NIH guidelines). The study protocol were approved by Ethical committee of Garyounis University. The rats were provided ad libitum with tap water and fed with standard commercial rat chow (pellet form, in the sack, Benghazi Animal Feed Company, Benghazi, Libya). The rats were acclimatized to laboratory condition for 7 days before commencement of experiment. The animals were randomly divided into four groups containing teen rats each one. Paracetamol was orally administrated to animals with dose 750 mg kg⁻¹ (Araya et al., 1987) at every 72 h for 10 days. P.O. was freshly prepared and administered to animals by oral gavages with a dose of 300 mg kg⁻¹ day⁻¹. The dose of P.O. used in this study was selected on the basis of the previous study.

Experimental design:

Group 1 (Control) received an orally isotonic saline for 30 days;
Group 2 Received isotonic saline for 20 days and then simultaneously administered with paracetamol 750 mg kg⁻¹ body wt. every 72 h for 10 days;
Group 3 Received freshly prepared P.O. for 30 days;
Group 4 Received freshly prepared P.O. for 20 days and then simultaneously administered with paracetamol 750 mg kg⁻¹ body wt. every 72 h for 10 days.

Sample collection and biochemical assays: The animals in all groups were sacrificed by cervical decapitation 24 h after the last application. Blood samples were collected into the tubes without adding anticoagulant. The samples were centrifuged at 200×g for 5min at +4°C to separate their serum. The serum was stored at -80°C after separation until it was assayed as described below.
Assessment of serum marker enzymes: The activities of Serum Aspartate Transaminase (AST) and Alanine Transaminase (ALT) were determined using the method of Reitman and Frankel. Serum alkaline phosphatase (ALP) was determined according to the method of Klein et al. (1960), Lactate Dehydrogenase (LDH) was assayed spectrophotometrically according to the method of Bergmeyer et al. (1974). γ-Glutamyl transferase (GGT) activity was determined by the method of using γ-glutamyl-p-nitroanilide as substrate.

Protein determination: Serum protein was determined by the method of Lowry et al. (1951) using bovine serum albumin as a standard.

Assessment of antioxidant enzymes: The liver was dissected out, weighed and washed using cooled saline solution. The homogenization of tissues was carried out in Teflon-glass homogenizer with a 5-10 mL buffer containing 50 mM potassium phosphate, pH 7.5 and 1mM EDTA per gram tissue. Homogenates were centrifuged at 10,000×g (+4°C) for 15 min. The resulting clear supernatant was used for various enzymatic assays as described below.

Catalase (CAT) activity was assayed colorimetrically as described by Sinha (1972) using dichromate-acetic acid reagent and was expressed as U (µmol of H₂O₂ utilized/min) /mg protein. Superoxide dismutase assay (SOD) activity was assayed according to Beyer and Fridovich (1987). The assay relies on the ability of the enzyme to inhibit the phenazine methosulphate-mediated reduction of nitroblue tetrazolium dye. SOD activity was expressed in Unit enzyme/mg protein. One unit of SOD is defined as 1µg of SOD needed for half-maximum inhibition of NBT in the assay.

Glutathione S-transferase (GST) activity was determined spectrophotometrically by using dichloro-2,4-dinitrobenzene as the substrate (Habig et al., 1974) and was expressed as U (µmol of CDNB-GSH conjugate formed/min)/mg protein. Glutathione Peroxidase (GPx) activity was determined by the procedure described by Paglia and Valentine (1967). The procedure of analysis performed was based on the oxidation of reduced GSH by GPx coupled to the disappearance of NADPH by GSH-reductase measured at 37°C and 340 nm and was expressed as U (nmol of NADPH oxidized min⁻¹) mg⁻¹ protein. Tissue GSH concentration was measured by a kinetic assay using a dithionitrobenzoic acid recycling method described by Ellman (1959) and was expressed as µmol g⁻¹ tissue. The concentrations of TBARS were determined according to a modified method of Ohkawa et al. (1979) based on the reaction with thiobarbituric acid and were expressed as nmol g⁻¹ tissue.

Histological assessment: Livers from rats of different groups were fixed in 10% neutral formalin solution, dehydrated in graded alcohol and embedded in paraffin. Fine sections obtained were mounted on glass slides and counter-stained with Hematoxylin Eosin (H&E) for light microscopic analyses. The slides were coded and were examined by a histopathologist who was ignorant about the treatment groups after which photographs were taken.

Statistical analysis: The results are presented as mean ± S.E. Analyses were performed using students t-test and Duncan’s multiple range tests for the difference between the control and treatment groups. P<0.05 was considered statistically significant.

RESULTS

Serum hepatic marker enzymes status: The effects of paracetamol on the Serum enzymes AST, ALT, ALP, LDH and γ-GT are shown in Table 1. Oral administration of paracetamol significantly increased the activities of the serum enzymes by 123.03%, 225.70, 96.77, 176.07 and 334.70%, respectively, when compared with the control (p<0.05). Pre and simultaneous treatment of the rats with P.O. (300 mg kg⁻¹) ameliorated these increases significantly by 49.46, 63.94, 44.73, 62.35 and 57.84% in AST, ALT, ALP, LDH and γ-GT respectively, when compared with the paracetamol-treated group. Restoration of hepatic marker enzymes was at maximum in the higher dose level (300 mg kg⁻¹) of P.O. than the lower dose level (150 mg kg⁻¹) when compared with paracetamol-treated rats. Based on these findings 300 mg kg⁻¹ of P.O. was fixed as a dose for further tissue biochemical investigations.
Table 1: The influence of oral administration of *Portulaca oleracea* (P.O.) (300 mg kg\(^{-1}\) day\(^{-1}\)) on serum AST, ALT, ALP, LDH and γGT in paracetamol-treated rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>ALP (U/L)</th>
<th>LDH (U/L)</th>
<th>γGT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>63.87±3.23</td>
<td>47.05±2.61</td>
<td>175.08±6.30</td>
<td>45.84±2.83</td>
<td>2.45±0.46</td>
</tr>
<tr>
<td>P.O. (300 mg kg(^{-1}))</td>
<td>67.89±3.61</td>
<td>46.56±3.09</td>
<td>180.76±5.34</td>
<td>46.89±2.81</td>
<td>3.00±0.88</td>
</tr>
<tr>
<td>Paracetamol (750 mg kg(^{-1}))</td>
<td>142.45±4.35(^{*})</td>
<td>155.24±4.21(^{*})</td>
<td>344.50±13.44(^{*})</td>
<td>126.55±5.13(^{*})</td>
<td>10.65±1.91(^{*})</td>
</tr>
<tr>
<td>P.O. (300 mg kg(^{-1}))+ (750 mg kg(^{-1})) Paracetamol</td>
<td>72.00±2.91(^{**})</td>
<td>55.26±2.89(^{**})</td>
<td>190.39±5.90(^{**})</td>
<td>47.65±2.43(^{**})</td>
<td>4.49±0.92(^{**})</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.E.; *: Significance difference from control group at p<0.05; **: Significance difference from paracetamol-intoxicated group at p<0.05; Number of rats per group n = 10

Table 2: The influence of oral administration of *Portulaca oleracea* (P.O.) (300 mg kg\(^{-1}\) day\(^{-1}\)) to paracetamol-induced lipid peroxidation and reduced glutathione (GSH) content in the liver of rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TBARS</th>
<th>GSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>44.00±1.38</td>
<td>3.95±0.22</td>
</tr>
<tr>
<td>P.O. (300 mg kg(^{-1}))</td>
<td>43.00±1.61</td>
<td>3.90±0.12</td>
</tr>
<tr>
<td>Paracetamol (750 mg kg(^{-1}))</td>
<td>82.00±3.60(^{*})</td>
<td>1.20±0.24(^{*})</td>
</tr>
<tr>
<td>P.O. (300 mg kg(^{-1}))+ (750 mg kg(^{-1})) Paracetamol</td>
<td>49.00±1.09(^{**})</td>
<td>3.59±0.17(^{**})</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.E.; *: Significance difference from control group at p<0.05; **: Significance difference from paracetamol-intoxicated group at p<0.05; Number of rats per group n = 10; TBARS = Thiobarbituric Acid Reactive Substance

Lipid peroxidation and hepatic Glutathione content status: The changes in the levels of hepatic lipid peroxidation and reduced glutathione (GSH) content in control and experimental rats are shown in Table 2. The levels of Thiobarbituric Acid Reactive Substances (TBARS) were significantly increased (p<0.05) in paracetamol-treated rats when compared with normal control rats. Pre and simultaneous oral administration of P.O. (300 mg kg\(^{-1}\)) along with paracetamol significantly lowered the levels of TBARS in the liver of rats when compared to paracetamol-treated rats. A significant depletion (p<0.05) in the level of GSH was noticed in rats treated with paracetamol when compared to normal control rats. Treatments with P.O. (300 mg kg\(^{-1}\)) significantly (p<0.05) restored the level of GSH to near normalcy when compared with paracetamol-treated rats.

Hepatic antioxidant enzymes status: Table 3 illustrates the levels of enzymatic antioxidants namely Superoxide Dismutase (SOD), Catalase (CAT), glutathione peroxidase (GPx), Glutathione-S-Transferase (GST) and the glutathione metabolizing enzyme (Glutathione Reductase) (GR) in the liver of control and experimental rats. A significant decrease (p<0.05) in the activities of hepatic–enzymatic antioxidants in paracetamol-treated rats was seen. Treatment with P.O. (300 mg kg\(^{-1}\)) along with paracetamol significantly increased the activities of enzymatic antioxidants in liver when compared with paracetamol-treated rats.

Histopathology of the liver: Histopathological examination of the liver sections from normal rats showed normal parenchymal architecture; no significant lesions were observed (Fig. 1A). In the rats treated with paracetamol alone, cloudy swelling, fatty degeneration, hepatocellular necrosis, heavy haemorrhage and irregular appearance due to cell death were seen (Fig. 1B). The above changes were reduced in the liver of rats treated with P.O. and paracetamol together (Fig. 1C). The histological pattern were almost normal in rats treated with P.O. alone (Fig. 1D).
DISCUSSION

Hepatotoxicity is the potential complication of paracetamol, which is widely used in general medicine and an assessment of its relative toxicity is important. The primary toxicity of paracetamol is the result of drug metabolism in liver (Gu et al., 2005). At therapeutic doses, paracetamol is metabolized via glucuronidation and sulfation reactions result in the water-soluble metabolites that are excreted via the kidney. The result of the metabolic conversion of paracetamol by the microsomal P-450 enzyme system is that, a highly reactive intermediate, namely, N-Acetyl-P-Benzoquinone Imine (NAPQI) is produced. This metabolite is then reduced by Glutathione (GSH) (Bessems and Vermeulen, 2001). When large doses of paracetamol are ingested, there is more severe GSH depletion as well as massive production of metabolites, which compounds the toxicity, leaving large amounts of reactive metabolite unbound. These intermediates then form covalent bindings with macromolecules on cellular protein (Bessems and Vermeulen, 2001). This process disrupts homeostasis and initiates apoptosis, or programmed cell death, leading to tissue necrosis and ultimately to organ dysfunction. Depletion of hepatic GSH is one of the primary factors which permit lipid peroxidation, suggested to be closely related to paracetamol liver damage. Therefore protection against the paracetamol toxicity can be achieved through the supplementation of antioxidants (Sener et al., 2003). In this context the present study also confirmed that the administration of P.O. (300 mg kg\(^{-1}\) day\(^{-1}\)) significantly preserved the hepatic function against the hepatotoxic effect exerted by paracetamol over dose. Liver injury followed by paracetamol administration is well established by the elevated levels of serum hepatic marker enzymes indicating the cellular leakage and loss of functional integrity of hepatic membrane architecture. High levels of AST and ALT are the crucial parameters to detect liver damage (Benjamin, 1978; Benjamin, 1984). It correlates with the present study which revealed that the increased activities of
AST and ALT in the serum of paracetamol treated rats. Serum ALP levels are also related to the status and function of hepatic cells. Increase in serum alkaline phosphatase is due to increased synthesis in the presence of increasing biliary pressure (Moss and Butterworth, 1974). Changes in the activities of these enzymes are liver specific and have been considered as a tool to study varying cell viability and cell membrane permeability (Yemitan and Izegbu, 2006). Serum LDH, a cytoplasmic marker enzyme and γGT, a membrane bound enzyme are the well-known indicators of cell and tissue damage by toxic substances and their levels are also substantially increased in paracetamol- intoxicated rats. LDH is an intracellular enzyme, the increase of which in serum is an indicator of cell damage (Navarro and Senior, 2006). In the present study increased levels of serum hepatic markers suggested that an extensive liver injury was occasioned by paracetamol due to increased lipid peroxidation which have the ability to cause membrane damage. Paracetamol causes structural and functional damage to the cell membrane and increased the membrane permeability leading to the leakage of hepatic enzymes into the blood. It is well established that paracetamol toxicity significantly elevated the serum hepatic marker enzymes (Maryann and Jeanmarie, 2008; Girish et al., 2009). Administration of P.O. (300 mg kg⁻¹) attenuated paracetamol-induced hepatotoxicity as shown by the decreased levels of AST, ALT, ALP, LDH and γGT thus offering protection against paracetamol hepatotoxicity in rats. The above effects clearly indicate that P.O. may offer protection by stabilizing the cell membrane in hepatic damage induced by paracetamol. Furthermore it has been reported that P. O. decreases the liver marker enzymes during carbon tetrachloride-induced hepatotoxicity.

Paracetamol is known to produce oxidative damage in the liver by enhancing peroxidation of membrane lipids, a deleterious process solely carried out by free radicals (James et al., 2003). The free radicals attack the cell membrane, thus leading to destabilization and disintegration of the cell membrane as a result of lipid peroxidation (Shakun and Vysotski, 1982). In the present study, we observed a marked elevation of hepatic TBARS content following paracetamol administration was in consonance with the other reports in paracetamol- intoxicated rats (James et al., 2003; Botta et al., 2006; Sener et al., 2006). Constituents of P.O. such as flavonoids (quercetin), polyphenolic alkaloids (Oleracin A, B and E), omega-3, ascorbic acid, β-carotene and glutathione scavenge a wide range of free radicals including the most active hydroxyl radical, which may initiate lipid peroxidation. It prevents the loss of lipophilic antioxidant α-tocopherol, by repairing tocopheryl radicals and protection of the hydrophilic antioxidant ascorbate (Yang et al., 2009) and increasing intracellular concentration of glutathione. Therefore, it may decrease the concentration of lipid free radicals and terminate initiation and propagation of lipid peroxidation (Zeng, 1999).

Hepatic peroxides are reported to be increased during oxidative stress (James et al., 2003). Seven et al. (2004) also, reported that, due to liver damage, there was an observed decrease in antioxidant defenses in the liver. The impaired regeneration of protective and antioxidants such as reduced glutathione also contribute to oxidative stress (James et al., 2003). GSH is a sulphhydryl peptide enormously present in all biological systems. It forms the first line of defense against oxidative insult by acting as a non-enzymatic antioxidant by direct inter- action of its sulphhydryl group with ROS or it can be involved in the enzymatic detoxification reaction of ROS as a cofactor or as a coenzyme. Metabolic conversion of paracetamol to NAPQI which reduced by glutathione leading to its inactivation (James et al., 2003). In the present study, the depressed levels of GSH in paracetamol toxicity might increase the susceptibility of the liver to free radical damage. Our findings are in consonance with the other published reports which quoted that GSH concentration is decreased during paracetamol intoxication (Mitchell et al., 1973b; Muriel et al., 1992).

The antioxidant enzymes, CAT is a major antioxidant enzyme with hematin as the prosthetic group and it is ubiquitously present in all aerobic cells containing a cytochrome system. It is most abundant in the liver and is responsible for the catalytic decomposition of H₂O₂ to oxygen and water. SOD is an extremely effective antioxidant enzyme and is responsible for catalytic dismutation of highly reactive and potentially toxic superoxide radicals to H₂O₂ (Sarsilmaz et al., 2003). GPx is a selenoenzyme, which plays a major role in the reduction of H₂O₂ and hydroperoxide to non-toxic products (Freeman and Crapo, 1982).

Paracetamol administration decreased the activities of these enzymes and GSH concentration in the tissues (Cekmen et al., 2009). Administration of P. O. increased the activities of SOD, CAT and GPx in the liver of paracetamol-treated rats, which might be due to the ability of P. O. to reduce the accumulation of free radicals generated during paracetamol-induced lipid peroxidation. Zeng (1999) demonstrated that P. O. protects cells from reactive oxygen species-mediated
cell death via its antioxidant activity. The antioxidant activity or the inhibition in the generation of free radical is important in providing protection against hepatic damage (Shahjahan et al., 2004).

Glutathione Reductase (GR) is the enzyme responsible for the reduction of oxidized glutathione (GSSG) to GSH. Glutathione S-Transferase (GSTs) are a group of multifunctional isoenzymes located both in the cytosol and the endoplasmic reticulum of the liver and plays an important role in the detoxification of toxic electrophiles by catalyzing the conjugation of these electrophiles with glutathione to form more water soluble compounds (Boyer et al., 1984). GST is considered as first line of defense against oxidative injury along with other antioxidant enzymes, decomposing \( \text{O}_2 \) and \( \text{H}_2\text{O}_2 \) before interacting to form the more reactive hydroxyl radicals (Chasseaud, 1979).

In the present investigation the level of reduced glutathione and the activities of glutathione-dependent enzymes (GR and GST) were reduced significantly in rats administered with paracetamol. The depression in GSH contents along with GST activity makes the cells more susceptible to by toxic electrophilic compounds. The overproduction of ROS as indicated by the elevated level of TBRAS by paracetamol in the present study may be associated with the depletion of GSH level and GST activity. Administration of P.O. along with paracetamol significantly elevated the levels of glutathione and glutathione-metabolizing enzymes, P.O. contributed significantly to the intracellular antioxidant defense system by acting as a powerful consumer of singlet oxygen and hydroxyl radicals.

In the present study, the hepatic histoarchitecture of the paracetamol-treated rats resulted severe necrotic changes, inflammatory cell infiltration, fatty degeneration and vacuolization. It might be due to the formation of highly reactive radicals and subsequent lipid peroxidation induced by paracetamol. The accumulated hydroperoxides can cause cytotoxicity, which is associated with the peroxidation of membrane phospholipids by lipid hydroperoxides, the basis for hepatocellular damage. The necrotic conditions coincide with our biochemical observations, which showed the increased level of lipid peroxidation. Administration of P.O. reduced the histological alterations provoked by paracetamol quite appreciable. It can be attributed to the antiradical/ antioxidant efficacy of P.O. which significantly reduced the oxidative stress leading to the reduction of histopathological alterations and restoration of normal physiological state of the liver.

CONCLUSION

In conclusion, the results of this study demonstrated that P.O. protect against the paracetamol-induced liver damage in rats. These results show that the protective effect of the P.O. may be to its antioxidant activities and due to their ability to decrease the metabolic activation of paracetamol. The present results could lead to a possible development of a therapeutic remedy to limit or at least alleviate some of the reported paracetamol-induced side effects in human.

ACKNOWLEDGEMENT

Thanks to Miss A. Alya for her involvement in histopathological examination and Mr A. Abusree for animal care assistance.

REFERENCES


