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Tremendous effect of *Salsola tetrandra* and *Salsola baryosma* on a liver toxicity using paracetamol overdose

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ABSTRACT

The study was conducted to compare the defensive role of Salsola tetrandra and Salsola baryosma plant extracts against paracetamol-instigated intense hepatorenal toxicity in rats. Toxicity was stimulated by administration of a single oral dose of paracetamol (3 g/kg body weight). The extract of the aerial parts of plants (100 mg/kg) was utilized on a pre-and post-treatment basis. Both extracts significantly ameliorate liver and kidney functions with the prophylactic (pre) or therapeutic (post) treatments. Other biochemical markers as malondialdehyde (MDA) content, serum paraoxonase-1(POX-1) enzyme activity interleukin-1(IL-1β) and tumor necrosis factor alpha (TNF-α) level were also reduced. Histopathological and histochemical studies showed parallel effects with the biochemical measured. Both extracts seem to have a plethora of antioxidative compounds with marked effect against paracetamol-induced hepatorenal toxicity in rats. Salsola tetrandra was more potent than S. baryosma on the basis of all measured parameters.

Keywords: *Salsola* extract- Paracetamol- liver function- IL-1β - TNF-α.

INTRODUCTION

Human beings are daily exposed to various toxic compounds that may cause serious diseases either *per se* or through their metabolic activation to highly reactive substances such as reactive oxygen species (ROS). Free radical-induced lipid peroxidation is considered one of the main causes of cell membrane damage leading to various pathological conditions [1]. Detoxification of chemicals and other harmful agents is the main role of liver. Accordingly, any disorder in the liver may induce several health problems [2]. Certain drugs, when taken in overdoses or presented inside remedial reaches, can also be a typical wellspring of intense hepatorenal harm [3]. The dose of any drug must be applied in a way to avoid hepatorenal dysfunction.

The overdose of paracetamol (acetaminophen, N-acetyl-p-aminophenol, 4-hydroxyacetanilide, APAP), an analgesic and antipyretic agent, induces severe liver injury, liver failure and even death [4]. Paracetamol induces protein adduct in mitochondria which initiate the activation of various mutagen-activated protein kinases [5]. Protection against paracetamol side effects using different plant extracts has been studied by several investigators [6-9]. They found that medicinal plants are a rich source of new effective drugs which can help in ameliorating liver toxicity.

The genus *Salsola*, family Chenopodiaceae (Goosefoot family) consists of over 100 species found in the dried regions of Asia, Europe, and Africa [10]. Some *Salsola* plants are widely used as folk medicine for the treatment of

different diseases [11-14]. *Salsola tetrandra* is rich in chemical constituents and previously showed promising biological activities which could be attributed to the presence of triterpenes and/or sterols, saponins, alkaloids and coumarins (phenol compounds) and glycosides as well as unsaturated long chain fatty acids [14]. Up to our knowledge, there is no publication mentioned for either *S. tetrandra* or *S. baryosma* as protecting agent to liver and kidney as new herbal remedies. As liver diseases cause serious hazards on health, therefore, the work has prompted us to explore the effect of both extracts on hepatotoxicity and compare between their protective or therapeutic effect in rats intoxicated with the high dose of paracetamol.

MATERIALS AND METHODS

Drugs and Chemicals

Paracetamol was purchased from Alexandria Company for Pharmaceuticals and Chemical Industries. Kits for determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin and urea were obtained from Biomed Diagnostics, Egypt. The interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) were carried out using an ELISA reagent kits obtained from Biosource, USA.

Animals

Male rats weighing 100-120 g were obtained from the Animal Breeding Lab of National Research Centre, Cairo, Egypt. The animals were kept under constant temperature conditions (22 ± 2 ºC), relative humidity (50–60%), and lighting (12 h light/dark cycle). Food and water were accessible *ad libitum* [15]. The study was carried out according to the guidelines of the Ethics Committee of the National Research Centre.

Plant material: The plants were collected in 2014-2015 from Saudi Arabia and taxonomically identified in March 2014 by Dr. Sherifa Arafa, Assistant Professor of Taxonomy and Flora in Prince Sattam Bin Abdul-Aziz University, Saudi Arabia**.**

Extraction of Plant Materials

Air-dried and powdered aerial parts of *Salsola tetrandra* and *Salsola baryosma* (500g) were defatted with petroleum ether (40-60^{o}C) in continuous extraction apparatus. The defatted powder was re-extracted three times at room temperature with 70% ethanol-water. The solvent was evaporated under reduced pressure and gave (8 and 8.5 g respectively).

Experimental design

Doses: Paracetamol was used as a single dose (3 g/kg body weight) 24 h before sacrification (Group 2). Group 3 and 4 (prophylactic groups): paracetamol was orally applied after 7 days of plant extract administration. Group 5 and 6 (therapeutic groups): paracetamol was conducted once before plant extracts administration (100 mg/kg b.w). The plant extracts were administrated daily for 7 days with nutritional dose.

Groups:

Six groups each of six male albino rats were selected. Group1: served as negative control. Group 2: rats received a single dose of paracetamol (positive control). Group 3 & 4: rats received *S. tetrandra* and *S. baryosma* extracts before paracetamol induction. Group 5 & 6: rats received the *S. tetrandra* and *S. baryosma* extract after paracetamol induction.

Twenty–four hour after treatments, the rats of all groups were anesthetized and blood samples were collected directly from retro-orbital plexus. The blood samples were allowed to clot for 20-30 min. Serum was separated by centrifugation at 37 ^{o}C and used for estimation of various biochemical parameters. Animals were sacrificed by decapitation. Livers were rapidly isolated; a part of each was homogenized using cold saline to prepare a 10% homogenate that was used for estimation of malondialdehyde (MDA). The second part of the liver was preserved in 10% formalin for histopathological and histochemical examinations.

Biochemical analyses

The activities of AST and ALT were determined according to the method of Reitman and Frankel [16]. Alkaline phosphatase was determined using the method described by Demetriou *et al*. [17]. Bilirubin was carried out by the method described by Young [18]. Creatinine was measured by the method of Bartels and Bohmer [19]. Urea was calculated by the method of Tabacco *et al*. [20]. Arylesterase activity of paraoxonase 1 (POX-1) was measured spectrophotometrically using phenylacetate as a substrate [21,22]. IL-1β was carried out using an ELISA reagent kit and expressed as pg/ml. TNF-α was determined by ELISA using TNF-α kit (Biosource International, USA) and microtiter plate reader (Fisher Biotech, Germany). Lipid peroxidation was assayed by measuring the level of malondialdehyde (MDA) in the tissue homogenates using the method of Ruiz-Larrea *et al*. [23].

Histopathological and Histochemical Studies:

After the experimental period, animals were sacrificed, liver removed immediately, sliced and washed in saline. Liver pieces were preserved in 10% formalin for histopathological studies. Sections were taken and stained with hematoxylin and eosin (H&E) [24] and then they were examined for histopathological changes and photographed. The histochemical study was performed by periodic acid-Schiff method [25] for visualization of the polysaccharide in the liver. These materials were demonstrated in sections with 5 µm thickness.

Statistical analysis:

The protection percent is calculated by 1-(T-V/C-V) x100. Data were expressed as mean ± SD. The data were analyzed by one-way ANOVA followed by Duncan's multiple tests, using SPSS software (SAS Institute Inc., Cary, NC, USA). A probability value of less than 0.05 was considered statistically significant.

RESULTS

Biochemical Results

A significant increase in liver function parameters including ALT, AST, ALP levels and total bilirubin concentration in rats administered paracetamol (3 g/kg b.w) was measured when compared to the normal control (table 1). Prophylactic treatment with *S. tetrandra* and *S. baryosoma* modulated paracetamol-induced elevations in ALT, AST, ALP and bilirubin levels by a percentage of 42.12, 29.82, 23.19 and 13.44 for *S. tetrandra* and 37.15, 17.1, 25.9 and 11.51 for *S. baryosoma*, respectively, when compared to the paracetamol group. Therapeutic treatment with *S. tetrandra* and *S. baryosoma* corrected paracetamol-induced elevations in ALT, AST, ALP and bilirubin levels by a percentage of 52.65, 51.74, 37.29 and 18.79 for *S tetrandra* and 54.13, 48.91, 37.03 and 17.58 for *S. baryosoma*, respectively, compared to the paracetamol group.

Table 1: Effect of *Salsola tetrandra* and *Salsola baryosma* extract on rat liver function treated with paracetamol overdose

Parameter / Groups	ALT (U/L)	AST (U/L)	ALP (U/L)	bilirubin (mg/dL)
1- Control LSD	12.13± 1.17 (2, 3,4,5,6)	12.15 ± 1.71 (2, 3,4,5,6)	92.61 ± 2.93 (2, 3,4,5,6)	0.92 ± 0.15 (2, 3,4,5,6)
2- Paracetamol LSD	60.11± 2.41 (1,3,4,5,6)	53.85 ± 2.23 (1,3,4,5,6)	261.98 ± 4.07 (1, 3,4,5,6)	1.65 ± 0.18 (1,3,5,6)
3- *S. tetrandra* pretreated LSD	34.79 ± 3.09 (1,2,5,6)	37.79 ± 2.07 (1,2,4,5,6)	201.23 ± 3.96 (1,2,4,5,6)	1.42 ± 0.035 (1,2)
4- *S. baryosma* pretreated LSD	37.78 ± 3.84 (1,2,3,5,6)	44.64 ± 2.43 (1,2,3,5,6)	194.12 ± 2.18 (1,2,3,5,6)	1.46 ± 0.34 (1,2)
5- *S. tetrandra* post treated LSD	28.46 ± 1.93 (1,2,3,4)	25.99 ± 1.99 (1,2,3,4)	164.3 ± 2.32 (1,2,3,4)	1.34 ± 0.04 (1,2)
6- *S. baryosma* post treated LSD	27.57 ± 1.84 (1,2,3,4)	27.51 ± 1.58 (1,2,3,4)	164.96 ± 3.32 (1,2,3,4)	1.36 ± 0.03 (1,2)

Values represent mean of six animals ±SE.
Significant change at P < 0.05
LSD: Least significance difference

Table 2: Effect of *Salsola tetrandra* and *Salsola baryosma* extracts on antioxidant marker in rat treated with paracetamol overdose

Parameter / Groups	MDA (µM/L)	POX-1 (U/mL)
1- Control LSD	19.91 ± 1.65 (2,3,4,5,6)	26.61 ± 1.70 (2,3,4,5,6)
2- Paracetamol LSD	59.59 ± 2.43 (1,3,4,5,6)	13.18 ± 1.14 (1,3,4,5,6)
3- *S. tetrandra* pretreated LSD	44.54 ± 1.84 (1,2,5,6)	16.96 ± 1.23 (1,2,5,6)
4- *S. baryosma* pretreated LSD	44. 68 ± 2.42 (1,2,5,6)	17.02 ± 1.39 (1,2,5,6)
5- *S. tetrandra* post treated LSD	36.61 ± 2.12 (1,2,3,4)	20.24 ± 1.68 (1,2,3,4)
6- *S. baryosma* post treated LSD	36.68 ± 1.78 (1,2,3,4)	20.24 ± 1.68 (1,2,3,4)

Values represent mean of six animals ±SE.
Significant change at P < 0.05
LSD: Least significance difference

Paracetamol group resulted in an almost three-fold significant increase in liver MDA content and a two-fold significant decrease in serum POX-1 enzyme activity compared to the normal group (table 2). Pretreatment with the two *Salsola* extracts modulate these effects by 37.9%, 28.15% and 37.57%, 29.59 % for *S. tetrandra* and *S.*

baryosoma, respectively. These increases were also highly ameliorated by the two *Salsola* extracts after induction with paracetamol by percentages of 42.08, 52.57 and 42.26, 52.57 for *S. tetrandra* and *S. baryosoma*, respectively, compared to the paracetamol control group.

Table 3: Effect of *Salsola tetrandra* and *Salsola baryosma* extracts on rat kidney function treated with paracetamol overdose

Parameter / Groups	Urea (mg/dL)	Creatinine (mg/dL)
1- Control LSD	28.97 ± 1.95 (2,3,4,5,6)	1.15 ± 0.19 (2,3,4,5,6)
2- Paracetamol LSD	66.49 ± 2.57 (1,3,4,5,6)	4.20 ± 0.59 (2,3,4,5,6)
3- *S. tetrandra* pretreated LSD	52.95 ± 1.94 (1,2,5,6)	3.48 ± 0.27 (1,2,5,6)
4- *S. baryosma* pretreated LSD	55.98 ± 1.13 (1,2,5,6)	3.48 ± 0.38 (1,2,5,6)
5- *S. tetrandra* post treated LSD	36.68 ± 1.83 (1,2,3,4)	2.25 ± 0.16 (1,2,3,4)
6- *S. baryosma* post treated LSD	36.79 ± 1.98 (1,2,3,4)	2.24 ± 0.18 (1,2,3,4)

Values represent mean of six animals ± SE
Significant change at P < 0.05.
LSD: Least significance difference

Data in the table (3) showed a significantly increased (P<0.05) in both urea and creatinine of rats administered paracetamol when compared with normal control group. Pre-treatment with *S. tetrandra* and *S. baryosoma* ameliorate paracetamol-induced elevation in urea and creatinine levels by a percentage of 20.36, 17.14 for *S. tetrandra* and 15.81, 17.14 for *S baryosoma*, respectively compared to the paracetamol control group. Post-treatment with *S. tetrandra* and *S. baryosoma* decreased paracetamol-induced elevation in urea and creatinine levels by a highly protective percentage of 44.83, 46.43 for *S. tetrandra* and 44.67, 46.67 for *S. baryosoma*, respectively, compared to the paracetamol group.

Results in Table (4) showed that paracetamol significantly increased both serum IL-1 β and TNF- α levels compared to the control group. The increases in serum IL-1 β and TNF-α level were attenuated by 29.35, 25.89 and 27.15, 25.98 in groups pretreated with *S. tetrandra* and *S. baryosoma* compared to the paracetamol group. While post-treatment with both extracts induced greater improvement than pre-treatment with a percent of 48.96, 39.62 and 48.12, 40.10 for *S. tetrandra* and *S. baryosoma* extracts respectively compared to the paracetamol control group.

Table 4: Effect *Salsola tetrandra* and *Salsola baryosma* extract on inflammatory markers in rat treated with paracetamol overdose

Parameter / Groups	IL-1β (Pg/ml)	TNF (Pg/ml)
1- Control LSD	29.00 ± 1.58 (2,3,4,5,6)	17.79 ± 1.18 (2,3,4,5,6)
2- Paracetamol LSD	93.46 ± 2.78 (1,3,4,5,6)	45.46 ± 1.63 (1,3,4,5,6)
3- *S. tetrandra* pretreated LSD	66.03 ± 2.05 (1,2,5,6)	33.69 ± 1.43 (1,2,5,6)
4- *S. baryosma* pretreated LSD	68.09 ± 2.18 (1,2,5,6)	33.65 ± 1.38 (1,2,5,6)
5- *S. tetrandra* post treated LSD	47.70 ± 2.12 (1,2,3,4)	27.45 ± 1.83 (1,2,3,4)
6- *S. baryosma* post treated LSD	48.49 ± 1.59 (1,2,3,4)	27.23 ± 1.90 (1,2,3,4)

Values represent mean of six animals ± SE.
Significant change at P < 0.05
LSD: Least significance difference

Histopathological Results

The microscopic examination of control liver shows the normal hepatic lobules and portal areas structure. The central vein is surrounded by the hepatocytes with eosinophilic cytoplasm and distinct nuclei. The hepatic sinusoids are shown between the hepatocytes (Fig. 1.A, B). Histopathological investigation of the liver of rats administered paracetamol dose (3 g/kg/b.w) showed widespread swelling, ballooning degeneration and focal necrosis that associated with inflammatory infiltration in the hepatocytes (Fig. 1.C). In some rats dilated and congested portal tracts were noticed (Fig. 1.D).

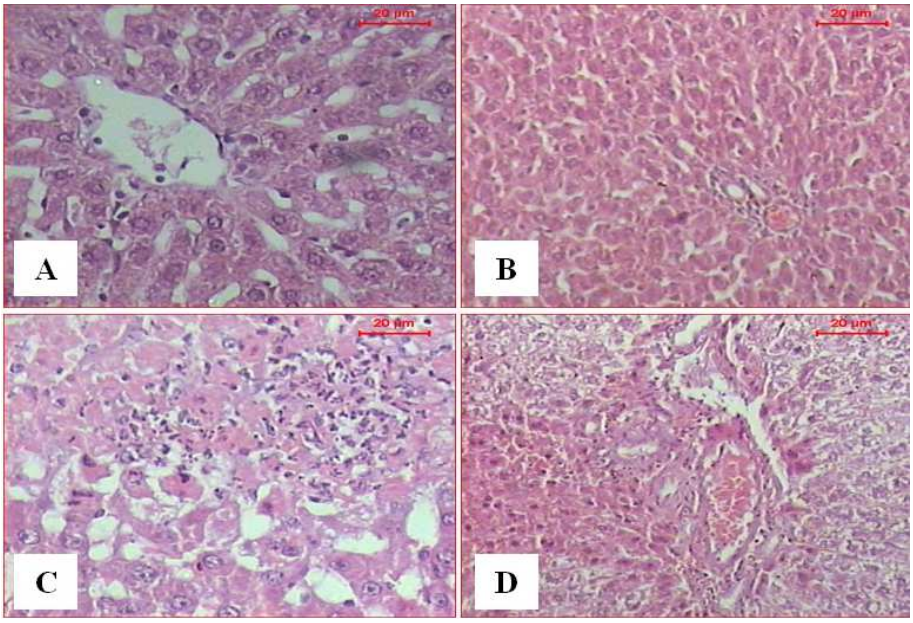

Fig. (1): Liver sections A, B) control rat show hepatic lobule normal structure and portal tract, respectively, C) rat administered paracetamol (3 g/kg/b.w) shows widespread swelling, ballooning degeneration and focal necrosis that associated with inflammatory infiltration in the hepatocytes, D) rat administered a single dose of paracetamol shows the portal and periportal area with dilated and congested veins (H & E stain, Scale bar: 20µm)

Microscopic examination of liver sections of rats given *S. tetrenda* extract and paracetamol showed the hepatic lobules that appeared more or less like control (Fig. 2.A). In some rats, hydropic degeneration was noticed (Fig. 2.B).

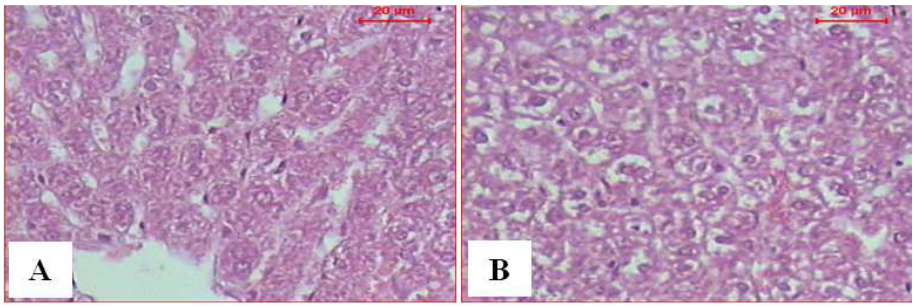

Fig. (2): Sections of the liver of A) rat was given *S. tetrandra* extract and paracetamol shows the hepatic lobule that appears more or less like control, B) rat given *S. tetrandra* extract and paracetamol shows hydropic degeneration (H & E stain, Scale bar: 20 µm)

Sections of the liver of rats given *S. baryosoma* extract and paracetamol showed the hepatic lobules that appeared more or less like control (Fig. 3.A), but in some rats, hydropic degeneration was noticed (Fig. 3.b). Sections of the liver of rats given paracetamol and *S. tetrandra* and *S. baryosoma* extracts showed the hepatic lobules that appeared more or less like control (Fig. 4.A and B, respectively).

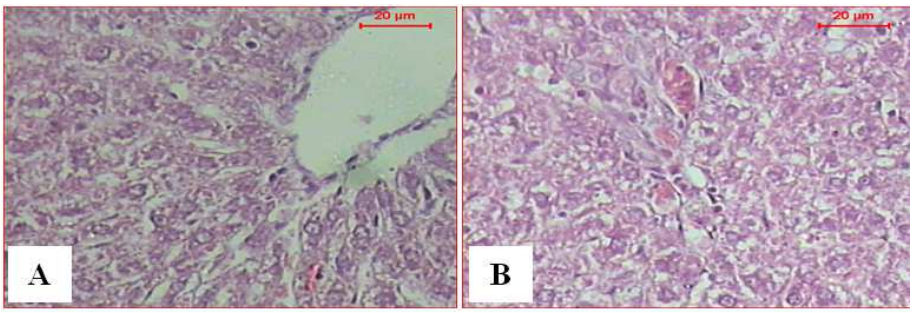

Fig. (3): Sections of the liver of A) rat was given *S.baryosma* extract and paracetamol shows the hepatic lobule that appears more or less like control, B) rat given *S.baryosma* extract and paracetamol shows hydropic degeneration (H & E stain, Scale bar: 20µm)

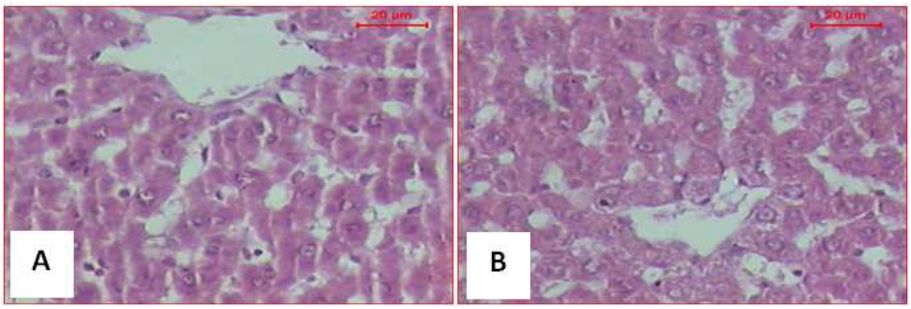

Fig. (4): Liver sections of A) rat was given paracetamol and *Salsola tetrandra* extract shows the hepatic lobule that appears more or less like control, B) rat given paracetamol and *S. baryosma* extract shows the hepatic lobule that appears more or less like control (H & E stain, Scale bar: 20 µm)

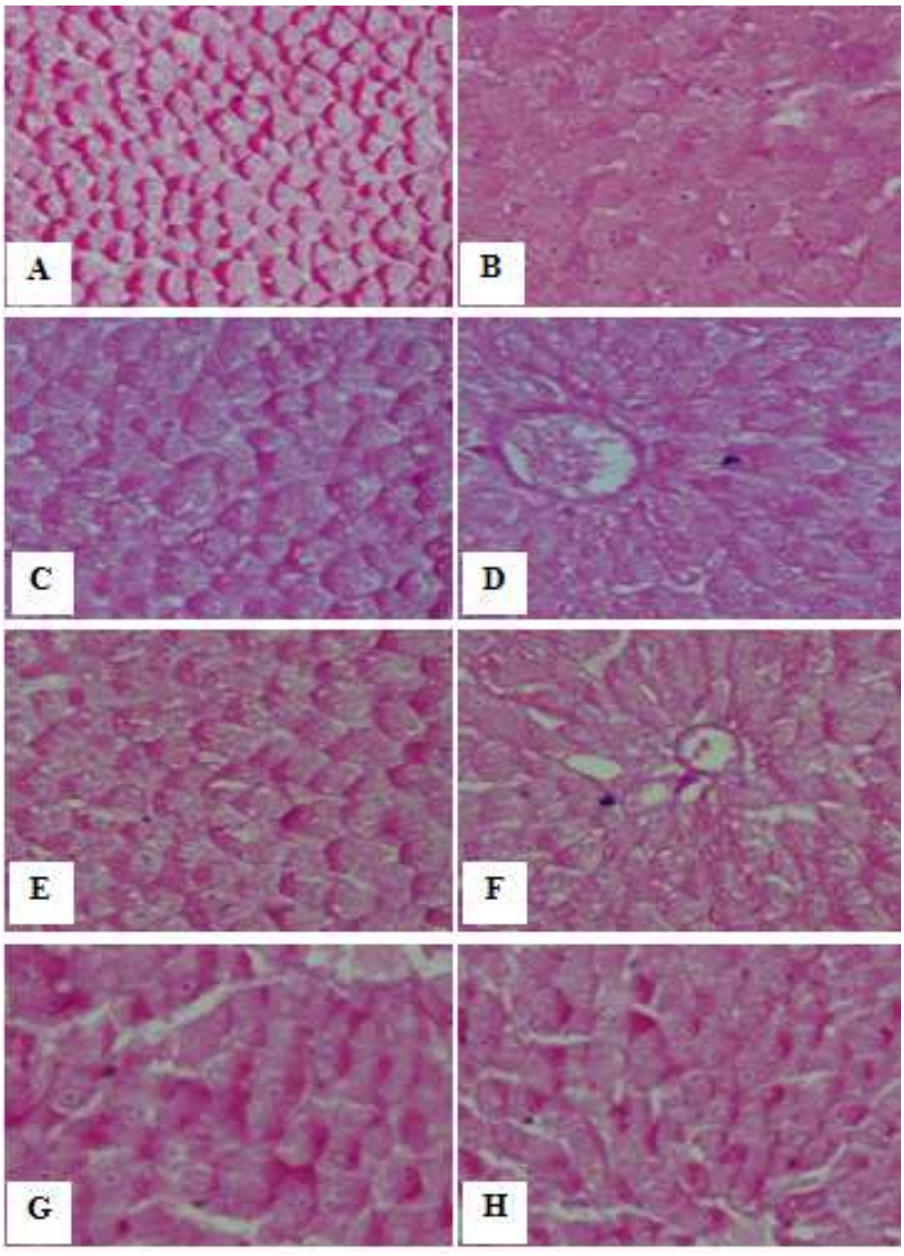

Fig. (5): Liver sections. A) normal rat liver shows ordinary distribution of glycogen in the hepatocytes, B) rat administered one dose of paracetamol (3 g/kg/b.w) shows a marked depletion in the glycogen contents, C) rat was given *S. tetrandra* extract and paracetamol shows glycogen contents in the hepatic lobule that appear more or less like control, D) rat given *S. tetrandra* extract and paracetamol shows depletion in the glycogen contents, E) rat given *S. baryosoma* extract and paracetamol shows glycogen contents in the hepatic lobule that appear more or less like control, F) rat given *S. baryosoma* extract and paracetamol shows depletion in the glycogen contents, G) rat given paracetamol and *S. tetrandra* extract shows normal distribution of glycogen in the hepatocytes, and H) rat was given paracetamol and *S. baryosoma* extract shows normal distribution of glycogen in the hepatocytes (PAS stain, Scale bar: 20 µm)

Examination of control liver sections stained by PAS reaction shows the abundance of glycogen in the cell of hepatic lobule. The glycogen particles appear accumulated at one side of the cytoplasm leaving the other side almost devoid of such materials (Fig. 5.A). Histochemical investigation of the liver of rat administered a single paracetamol dose (3 g/kg/b.w) showed a marked depletion in glycogen distribution in the hepatocytes as compared with control group (Fig. 5.B).

On the other hand, liver of rats given *Salsola tetrandra* or *S. baryosma* extracts for 7 successive days before a single oral dose of paracetamol showed distribution of glycogen that appeared like normal (Fig. 5.C, E respectively), while in some rats, a decrease in glycogen in the hepatocytes was noticed (Fig. 5.D, F, respectively). Liver of rat given a single oral dose of paracetamol and *Salsola tetrandra* or *S. baryosma* extracts for 7 successive days showed the distribution of glycogen that appeared like normal (Fig. 5.G, H, respectively).

DISCUSSION

Paracetamol drug is safe in therapeutic dose (20 mg/kg) [26]. Increased dose paracetamol cause intense hepatic corruption; as a consequence of glutathione exhaustion [27].

In this study, an acute overdose of paracetamol (3 g/kg b.w) led to increasing in ALT, AST, and AlP in serum. ALT is a liver specific enzyme and its elevation confirms hepatocyte damage which results in excess of cytosolic enzymes into the bloodstream [28]. Paracetamol overdose is activated into N-acetyl-p-benzoquinone imines (NAPQI) which limit the ability of animals to metabolize a variety of toxic substances [29]. This elevation returned to normal when the liver cells undergo healing and regeneration [30]. In the present study, the plant extracts used could be considered as hepatoprotective against paracetamol intoxication since ALT level, that is thought to be specific for hepatic injury [31], was significantly improved. This improvement can be due to the presence of triterpenoid saponin. Two triterpenoid saponin glycosides namely, salisomide and salisoflavan [32] are reported to interact with the mucosal cells in the gut and increase permeability. This may reinforce the absorption of various nutrients [33] helping in curing and regeneration of hepatic cells. Saponins also enhance the absorption of phenolic compounds and possess antioxidant activity against liver injury induced by paracetamol [34]. In the current study, supplementation with both extracts*; Salsola tetrandra* and *Salsola baryosma*; decreased the levels of liver enzymes either in prophylactic or therapeutic groups. The extracts supplementation is able to protect the cell membrane integrity against the threatening effect of paracetamol and hence improved liver functions.

The present data are in harmony with the previous results of several authors [28,35]. Prolonged destruction in the hepatic cells resulted in more cytoplasmic releases of alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and bilirubin in serum. An increase in serum bilirubin is a signal for a liver disorder caused by hepatotoxin [36]. A significantly higher level of total bilirubin was measured in the positive control group when compared to the normal negative control as reported by [37,38].

The excess in NAPQI leads to depletion in cytosolic and mitochondrial GSH, which triggers the loss of cellular homeostasis leading to liver injury [39, 40]. Adam *et al*. [41] mentioned that high-dose acetaminophen treatment significantly induced oxidative stress, as indicated by elevated MDA concentrations in liver and kidney of rats and led to liver and kidney injury.

The liver plays a key part in the synthesis of serum POX-1 and hence the measurement of serum POX-1 activity is a biomarker of liver function status. The high production of active metabolite N-acetyl-p-benzoquinone imines (NAPQI), in group 2, triggered lipid peroxidation and hence, increased tissue MDA contents and decreased serum POX1 enzyme activity. Previously patients with liver disease, for example, alcoholic liver infection, hepatitis, cirrhosis showed a decrease in POX1 due to liver injury [42,43]. Bindu et al. [44] found that serum PON-1 level declines in various types of liver diseases as a result of peroxidative changes.

Administration of both *Salsola* extracts ameliorated paracetamol-induced increase in MDA level and decrease in POX-1 activity. However; it is more significantly improved in the therapeutic route than prophylactic treatment. The improvement in the enzyme activity helps to repair hepatocytes as a result of catalyzing the hydrolysis of some xenobiotics [43,45]. The tannins and flavonoids polyphenols, as antioxidants, present in *Salsola tetrandra* and *Salsola baryosma* extracts are responsible for this improvement. Previous results have demonstrated that medicinal plants, with nephro-hepatic-defensive properties, can produce their protection by means of cell reinforcement and/or free radical scavenging activities because of the high centralization of flavonoids and alkaloids they contain [46,47]**.** Paracetamol toxic overdose is often manifested by many metabolic disorders including serum urea and creatinine. Serum urea and creatinine are considered the major nephrotoxicity markers [48], although serum urea concentration is often considered a more reliable renal function predictor than serum creatinine [37]. Blood urea nitrogen is

produced from liver protein that is derived from diet or tissue sources and is normally excreted in the urine. Creatinine, on the other hand, is mostly derived from endogenous sources by tissue creatine breakdown [49]. In the present study, administration of paracetamol overdose to rats resulted in a significant elevation of serum urea and creatinine group within 24 hours of exposure when compared to the normal control group. These results are in agreement with Isik *et al*. [50] who noticed an elevation in serum urea and creatinine in rats after administration of paracetamol at a dose of 1 g/kg body weight. Moreover, the elevation in serum urea and creatinine in patients following a therapeutic dose of paracetamol three days before hospital admission was reported [51]. These elevations in the levels of urea and creatinine were clarified by the nearness of solid connection amongst nephrotoxicity and oxidative anxiety [52]. Anyway, everyday treatment with *Salsola* extracts for 7 days induced nephroprotection in the paracetamol treated rats where post treatment offered the greatest amelioration.

Serum cytokines; particularly TNF-alpha and IL-1β together with oxidative stress were shown to be involved in case of liver necrosis, as a consequence of paracetamol toxicity [53, 54]. In addition to initiating the aggressive inflammatory process and deteriorating the cellular damage by both markers, they also act as a central regulator that stimulate apoptosis and cell proliferation and part of the healing process [55]. Such cytokines cause amid irritation and forced amino acids to combine forming proteins critical to the inflammatory process.

In the current study, TNF-alpha and IL-1β levels were increased 3-fold in paracetamol group relative to the control group. The results are in accordance with several authors [56-58].

Tumor necrosis factor alpha (TNF-α) is released following the injury in order to maintain the liver function and enhance the regeneration capacity of liver tissue [59]. This increase is changed into a significant improvement in our trial by using the two plant extracts which are in parallel with previous studies [60]. Elsharabasy, *et al*. [14] proved the gastroprotective effect of the aerial parts of *Salsola tetrandra* against inflammation in rats with gastric ulcer. Recently, Küçükboyacı *et al.* [61] found that *Salsola grandis* has an anti-inflammatory efficacy and antinociceptive activity. The improvement is not reached to control group.

Histopathological studies revealed a widespread swelling and ballooning degeneration and focal necrosis were observed in paracetamol administrated rats that were associated with hepatic inflammatory infiltration. The dilated and congested portal tracts were also found. These results were in agreement with Jafri *et al*. [62] who expressed that the liver specimens of paracetamol treated rats demonstrated gross corruption of the centrilobular hepatocytes associated with nuclei pyknosis, karyolysis, and lymphocytic invasion. Additionally, the results of Oliveira, *et al.* [63] indicated centrilobular corruption with provocative cell invasion in acetaminophen-treated mice.

Glycogen is the primary wellspring of vitality in the liver and is likewise used to keep up blood glucose levels. The present histochemical results of liver tissues showed that polysaccharides decreased with the paracetamol administration. This is also in agreement with Bhadauria [40] who found that hepatorenal glycogen was reduced markedly after administration of paracetamol. The drug expanded glucose discharge and glycolysis from endogenous glycogen (glycogenolysis) and restrained oxygen uptake. Diminishment in hepatorenal glycogen contents indicated the alterations in their synthesis.

On the basis of foregoing measured parameters, it can be concluded that *Salsola tetrandra* and *Salsola baryosma* have hepatoprotective activity. This can be attributed to the presence of tannins and flavonoids which have the ability to reinforce the injured cells and scavenge the free radical.

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