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Protective Roles of *Grewia asiatica, Basella alba, Solanum nigrum*, and *Ficus carica* Fruit Extracts in Carbon Tetrachloride-Induced Kidney Toxicity in a Mice Model

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ABSTRACT

Background: Kidney toxicology is becoming an alarming issue on the continuously increasing use of environmental chemicals like carbon tetrachloride.
Objective: In the present study, the renopathological effects of single-dose carbon tetrachloride exposure were investigated in male mice kidney. Likewise, rehabilitative properties of 4 medicinal plant-extract-treated groups were explored.
Methods: There were 6 study groups as vehicle control group, carbon tetrachloride group (0.1 mL corn oil and 0.2 mL/kg carbon tetrachloride solution in corn oil, respectively, on day 1 followed by simple drinking water (*ad libitum*) on days 2-6), carbon tetrachloride + *Basella alba* group, carbon tetrachloride + *Grewia asiatica* group, carbon tetrachloride + *Solanum nigrum* group, and carbon tetrachloride + *Ficus carica* group. Mice in the carbon tetrachloride + *Basella alba*, carbon tetrachloride + *Grewia asiatica*, carbon tetrachloride + *Solanum nigrum*, and carbon tetrachloride + *Ficus carica* groups were given with carbon tetrachloride as in the carbon tetrachloride group on day 1, followed by 0.1 mL/12 h of respective fruit pulp extracts for days 2-6. Kidneys were removed from each animal on day 7 after cervical dislocation.
Results: Carbon tetrachloride exposure led to various histopathological alterations (complete obliteration of glomeruli and proximal convoluted tubules, glomerular hypertrophy, peri-glomerular space, and tubular apoptosis) that were recovered in all fruit pulp extract groups except carbon tetrachloride + *Solanum nigrum* group. Histometric outcomes support the histological findings that the mean number of endothelial cells remained significantly ($P < .05$) lower in carbon tetrachloride and carbon tetrachloride + *Solanum nigrum* groups than all other groups. Likewise, the mean number of podocytes remained significantly lower in carbon tetrachloride and vehicle control groups than the 4 plant-extract-treated groups. The biochemical estimations of serum creatinine level remained significantly higher in carbon tetrachloride than the rest of the plant-extract-treated and vehicle control groups.
Conclusion: This study demonstrated the potential positive effects of active phytochemical ingredients of medicinal fruits against kidney damage caused by a single dose of CCl4 exposure.
Keywords: Regeneration, kidney injury, CCl_4 toxicity, kidney histopathology

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INTRODUCTION

Carbon tetrachloride (CCl_4) is used in fluorocarbon production, fabric spotting, grain fumigants, fire extinguisher, and plastic and paint industries.[1] Inhalation of CCl_4 has been reported as a cause of nephritis and nephrosis,[2] which result in oliguria, edema, uremia, proteinuria, and glucosuria.[3] The mechanism of CCl_4 -exposure-related kidney injuries is not clearly understood; however, it is postulated that back diffusion of glomerular filtrate and reduced kidney blood flow may lead to oliguria. Carbon tetrachloride inflicts damage to the epithelial cells of the proximal convoluted tubules

(PCTs) leading to cellular swelling due to granular fatty cytoplasmic changes and general necrosis.[4] Evidence indicates that the nephrogenic stem cells are present in the nephrons of a human kidney and are required in the glomerular capillary repair.[5] Various aggregates of podocytes have been observed in the kidney during the process of self-repairing after the toxicological damage.[6] Similarly the stem/progenitor endothelial cells are regenerative cells of the kidney that are replaced regularly in the normal replacement process and also in various conditions of repairing and regenerative activities. [7]

The regenerative effects of plant extracts have been suggested and chemical composition of the plant extracts mainly includes proteins, fat, vitamins, riboflavin, niacin, thiamine and minerals, phyto-sterols, and plenty of antioxidants (Table 1).[8-10] The present study will provide a wholesome preview of the toxicity of CCl4 exposure on kidney and its histopathology and will explore, the ameliorative and regenerative potential of fruit pulp extracts (FPEs) against histopathological changes in the kidney caused by a single dose of CCl_4 exposure.

METHODS

Ethical Committee Approval

All procedures of this study were approved by the Ethical Committee of the Department of Zoology, University of Sargodha, Pakistan (Approval No: SU/Zol/2667 Date: 25/08/ 2018).

Experimental Animals and Their Maintenance

In this study, male albino mice (*Mus musculus*) were used as model animals. Sixty animals of about 28-30g in weight were randomly divided into 6 groups. These animals were kept in separate iron cages gauzed with stainless steel in the animal house of Department of Zoology, University of Sargodha The experimental animals were kept under a standard protocol of 12-12 h darkness–light cycle under ambient humidity (45%) and temperature (23 ± 3°C). All animals had free access to standard feed and water. Remaining food particles, excreta, and any other debris were removed from cages on a daily basis.

MAIN POINTS

- Kidney-rehabilitative capabilities of 4 medicinal fruits *Basella alba*, *Grewia asiatica*, *Solanum nigrum*, and *Ficus carica* were measured in the kidney tissues of male mice (*Mus musculus*) against carbon tetrachloride (CCl_4) exposure.
- Comparative protective role of 4 commonly available medicinal plants and their antioxidant potential was observed in the current study.
- Various histopathological changes caused by single-dose exposure of CCl_4 were ameliorated by the use of fruit pulp extracts of the 4 medicinal plants.
- Possible mitigation measures and nephron-rehabilitative mechanism were traced by the use of 4 medicinal plants.

The mice were randomly divided into 6 groups each containing 10 animals on the basis of intra-gastric treatment given:

(a) Vehicle control group (Vc group): 0.1 mL corn oil on day 1 through gavage followed by simple drinking water (*ad libitum)* on days 2-6.
(b) CCl_4 group (CC group): 0.1 mL of 0.2 mL/kg CCl_4 solution in corn oil on day 1 through gavage followed by simple drinking water (*ad libitum)* on days 2-6
(c) CCl_4 + *Basella alba* group (CCB group): CCl_4 as in the CC group on day 1 through gavage followed by 0.1 mL/12 h of *Basella alba* FPE for days 2-6.
(d) CCl_4 + *Grewia asiatica* group (CCG group): CCl_4 as in the CC group on day 1 through gavage followed by 0.1 mL/12 h of *Grewia asiatica* FPE for days 2-6.
(e) CCl_4 + *Solanum nigrum* group (CCS group): CCl_4 as in the CC group on day 1 through gavage followed by 0.1 mL/12 h of *Solanum nigrum* FPE for days 2-6.
(f) CCl_4 + *Ficus carica* (CCF group): CCl_4 as in the CC group on day 1 through gavage followed by 0.1 mL/12 h of *Ficus carica* FPE for days 2-6.

Fruit Extracts Preparation

Fresh and fully ripened fruit of *Solanum nigrum* and *Basella alba* were collected from the suburb of Chakwal district Talagang. *Ficus carica* and *Grewia asiatica* fruits were purchased from the local market. Fruits of all plants were separately washed and dried in a laminar flow cabinet. Finally, 0.1 mL FPEs of all plants were prepared and freshly thawed extract was provided to the animals of the relevant groups. The FPEs of all mentioned plants were prepared by following the lab protocol.[34,35]

Preparation of Carbon Tetrachloride Solutions

Laboratory grade CCl_4 (a product of Riedal-de Haen, Germany, batch number 32215) was diluted in corn oil (15 : 85 v/v respectively) to prepare a stock solution that was further diluted (6 : 94 v/v) to prepare the required strength of 0.006 mL CCl_4/0.1 mL. The single dose volume (0.1 mL) of the final CCl_4 solution remained constant for all animals.

Animal Dissections, Organ's Recovery, and Histological Studies

The weight of each animal was recorded before dissection on day 7. Animals were sacrificed through cervical dislocation and finally dissected through the belly with the help of fine forceps, scalpel, and scissors. The in situ observations included the general appearance and coloration of the kidneys. Both kidneys were recovered intact and processed for final sections that were stained with Hematoxylin & Eosin stains and observed under the light microscope.

Digital Histometry of Kidney

Soft images (100×, 400×, and 1000×) of kidney sections from each group were used by using digital scales in corelDRAW11®. Digital histometry of the selected histological sections of kidney

Table 1. Most Important Phytochemical Ingredients of Fruit Pulp Extracts of *Basella alba*, *Grewia asiatica*, *Solanum nigrum*, and *Ficus carica*

Fruit	Phytochemicals	Particular Antioxidants of the Fruit Involved in Kidney Toxicity Prevention
Malabar Spinach *Basella alba*	Minerals; [11] anthocyanins: betacyanins; [12] flavonoids: kaempferol; acids; phenolic acids; sterols: beta-sitosterol, saponins, glycosides, coumarin, anthracene, glycoside, ß-carotene, luteolin, zeaxanthin[13]	Betacyanin, [11] beta-sitosterols, kaempferol[13]
Phalsa *Grewia asiatica*	Vitamins; fatty acids; minerals: sodium, cobalt, zinc, manganese; anthocyanins: cyanidin, pelargonidin; [14] oils;[15] amino acids; phenolic acids; steroids: kaempferol, β-sitosterol, stigmasterol, campesterol;[16] tocopherols [17]	Anthocyanidins, [14] β-sitosterol, stigmasterol,[16] naringenin [18]
Mako *Solanum nigrum*	Vitamins; minerals; organic acids; [19] lipids; anthocyanins; glycosides; glycoalkaloids: solanine; alkaloids: indole terpenoid and purine; polyphenols: gallic acid, rutin; steroidal saponin, sterols alkaloids, solamargine, solasonine, α- and β-solanigrine [20]; non-saponins[21]	Alkaloids, tannins, gallic acid, solanine and sterols, [22] caffeic acid [1]
Fig Latex *Ficus carica*	Vitamins; terpenoid; anthocyanins; [23] phenols; acids; phenolic acids: ferulic acid; polyphenols; [24] sterols: β-sitosterol, campesterol,[25] psoralen[26]	β-sitosterol, campesterol, stigmasterol, fucosterol,[26] pelargonidin [24]

was conducted in CorelDRAW11® under calibrated scales in microns (μ). The mean cross-sectional area (MCSA) of glomeruli was calculated by the following formula:

$$\text{MCSA} = \left(\text{Length} \times \text{Width}/4\right)\pi$$

Moreover, mean number of endothelial cells/per unit area (722 μm^2) and mean number of podocytes/area (722 μm^2) were also calculated.[33]

Data Analysis

Data obtained through histometry were analyzed through one-way analysis variance along with a post hoc analysis, Tukey's Multiple Range Test (TMRT) by using IBM Statistical Package for Social Sciences (SPSS) Statistics version 23 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Mean Weight Parameters for Animals and Organs (Kidney)

A significant decrease in mean animal weight on day 7 of the study was recorded in all groups as compared to Vc. However, the highest decrease was recorded in CCS, CC, and CCF groups. The mean weight of the kidneys in CC group showed a significant increase than the rest of the groups (Table 2 and Figure 1).

Histological Observations

The histological slides of the kidney in the Vc group showed evenly distributed rounded glomerulus throughout the cortical region. Each glomerulus was surrounded by a closely packed PCT (Figures 2 and 3A). In the CC group, general atrophy and complete obliteration of the glomeruli were observed. Intracellular edema and resultant shrinkage of the intra-tubular spaces were present in PCTs. Moreover, complete obliteration of tubular spaces was also observed in some of the sections. These observations indicate the CC treatment has caused hydronephrotic condition, glomerular atrophy, and apoptosis in the tubular cells (Figures 2 and 3B). In CCB group, bowman's capsules hypertrophy, convoluted tubules shrinkage, and peritubular fluid retentions were observed. Additionally, the signs of complete obliteration of the glomeruli were obvious as scattered empty spaces. However, the regenerative activity presenting as accumulation of podocytes in damaged areas was obvious. De novo glomeruli separation was also observed in the CCB group (Figures 2C and 3C). The CCS group reiterate CCB signs in terms of some scattered empty spaces of the obliterated glomeruli. The remaining functional glomeruli mostly showed peripheral atrophy. The intracellular edema in proximal tubular sections was also clearly seen (Figures 2D and 3D). In the CCF group, the peri-glomerular and tubular intracellular edema was prominent. However, some podocytes have also been seen that indicate the initiation of the regenerative process (Figures 2E

Table 2. Mean Animal and Kidney Weights at Days 0 and 7

Weight Parameter	Mean ± SEM					
	Vc	CC	CCS	CCB	CCF	CCG
Mean animal weight at day 0 (g)***	30.52 ± 0.2^a	30.35 ± 0.1^a	30.15 ± 0.1^a	30.03 ± 0.02^a	30.25 ± 0.1^a	30.20 ± 0.1^a
Mean animal weight at day 07 (g)***	30.16 ± 0.7^a	27.08 ± 0.6^b	26.02 ± 0.6^c	29.05 ± 0.7^d	28.32 ± 0.6^e	29.6 ± 0.6^d
Mean kidney weight (g)***	1.3 ± 0.1^a	1.87 ± 0.1^b	1.24 ± 0.1^a	1.28 ± 0.03^a	1.29 ± 0.01^a	1.27 ± 0.01^a

CC, carbon tetrachloride group; CCB, carbon tetrachloride + *Basella alba* group; CCF, carbon tetrachloride + *Ficus carica* group; CCG, carbon tetrachloride + *Grewia asiatica* group; CCS, carbon tetrachloride + *Solanum nigrum* group; Vc, vehicle control group.‡Mean values with a,b,c,d shows the groups not sharing a common lower case letters differ significantly. ‡Mean values ± SEM, (n = 10), statistical analysis (ANOVA) ***$P \leq .0001$.

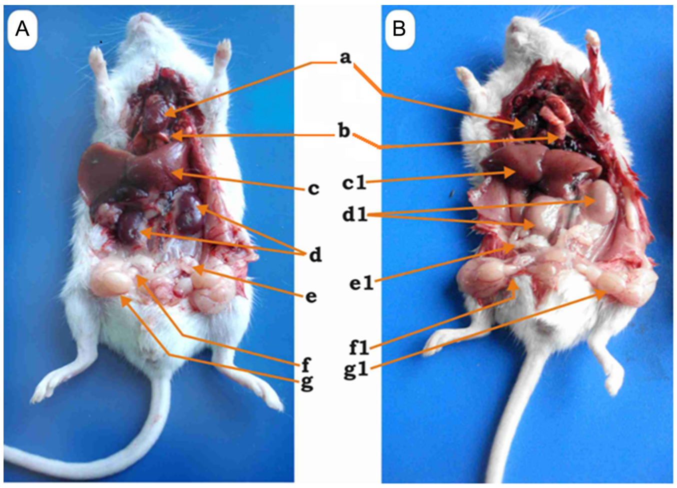

Figure 1. A-B In situ anatomical signs of organ toxicity, (A) vehicle control group animal, (B) CCl_4-treated group animal; a: normal heart, b: normal lungs, c: normal liver lobes with abundant blood supply, c1: ischemic and shrinken liver lobes, d: normal kidney with maximum blood supply, d1: hydronephrotic kidney, e: normal seminal vesicle, e1: swelling in seminal vesicle, f: normal epididymus, f1: shrinken epididymis, g: normal testicles, g1: testicular hypotrophy

and 3E). The CCG group has shown the highest degree of intracellular tubular edema causing obliteration of the central and peri-tubular spaces with a concomitant shrinkage of the glomeruli. Some podocytes have also been seen that indicate initiation of the regenerative activities, and the splitting of glomeruli was very obvious in the CCG group (Figures 2F and 3F).

Histometric Observations of Kidney

The histometric data of the kidney sections also indicated a significantly lower ($P < .001$) MCSA of glomeruli in the CC group, compared with the rest of all groups. The mean number of endothelial cells remained significantly ($P < .05$) lower in group CC and CCS than in all other groups. Likewise, the mean number of podocytes remained significantly lower in CC and Vc than the 4 PETs groups. The biochemical estimations of serum creatinine level remained significantly higher in CC than the rest of the PETs and Vc (Table 3).

DISCUSSION

General autopsy of the CC group's animals revealed ischemic liver lobes, swelling in the seminal vesicle, shrinked epididymis, and testicular hypotrophy. But most adversely, CCl_4 target

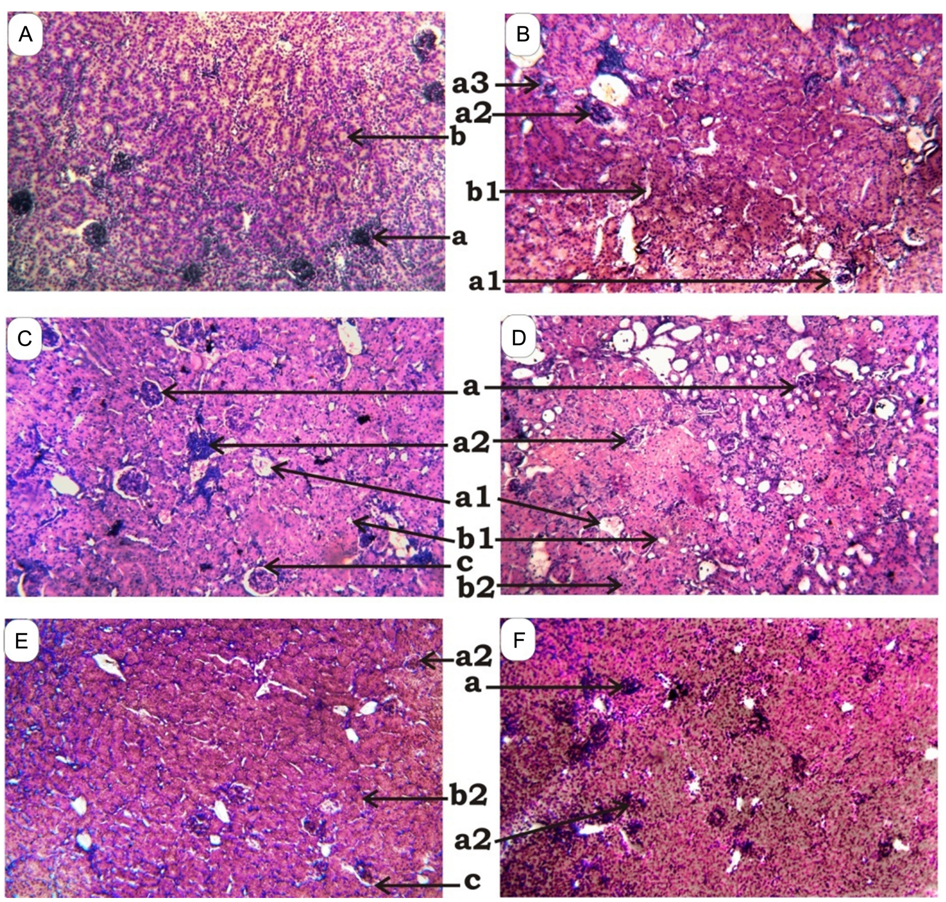

Figure 2. A-F Histological sections of kidney (100×). (A) Vehicle control group (Vc); (B) CCl_4 group (CC); (C) CCl_4 + *Basella alba* group (CCB); (D) CCl_4 + *Solanum nigrum* group (CCS); (E) CCl_4 + *Ficus carica* group (CCF); (F) CCl_4 + *Grewia asciatica* group (CCG) (a: healthy glomeruli, a1: obliterated glomeruli, a2: regenerative glomeruli, a3: shrunken glomeruli, b: normal tubules, b1: damaged tubules, b2: regenerated tubules, c: Bowman's capsule)

Table 3. Micrometric Results and Serum Creatinine Level of the Groups

Micrometric Parameters	Group Mean ± SEM					
	Vc	CC	CCB	CCS	CCF	CCG
Mean CSA of glomeruli (μm^2)***	$^{\ddagger}20.80 \pm 9.61^{a}$	11.57 ± 6.50^{b}	25.51 ± 9.97^{c}	13.85 ± 4.20^{b}	14.18 ± 5.60^{b}	13.99 ± 4.02^{b}
Mean number of endothelial cells unit area (722 μm^2)***	3.62 ± 0.10^{a}	2.82 ± 0.27^{b}	3.92 ± 0.23^{c}	2.90 ± 0.23^{b}	3.42 ± 0.30^{a}	7.76 ± 0.38^{d}
Mean number of podocytes/area (722 μm^2)***	1.38 ± 0.13^{a}	3.54 ± 0.53^{b}	20.88 ± 1.96^{d}	6.92 ± 0.80^{bc}	11.16 ± 0.47^{c}	11.54 ± 0.37^{c}
Serum creatinine level (mg/dL)***	0.34 ± 0.02^{a}	1.14 ± 0.24^{b}	0.64 ± 0.02^{c}	0.80 ± 0.03^{d}	0.60 ± 0.03^{e}	0.70 ± 0.03^{f}

C, carbon tetrachloride group; CCB, carbon tetrachloride + Basella alba group; CCF, carbon tetrachloride + Ficus carica group; CCG, carbon tetrachloride + Grewia asiatica group; CCS, carbon tetrachloride + Solanum nigrum group; Vc, vehicle control group. [a,b,c,d]Groups not sharing a common lower case letters differ significantly. [‡]Mean values ± SEM, (n = 10), statistical analysis (ANOVA) ***$P \leq .0001$.

kidneys and enlarged kidneys with pale whitish coloration were observed in the CC group as compared to dark brown kidneys of Vc group. These observations clearly indicate extreme ischemia and fluid retention in the kidneys (Figure 1). It is well documented that the most pertinent cellular and histopathological effects of CCl_4 exposure are related to an increase in the oxidative stress which damages cell membranes and may lead to cell death. [27] The CCl_4 exposure resulted in extreme shrinkage

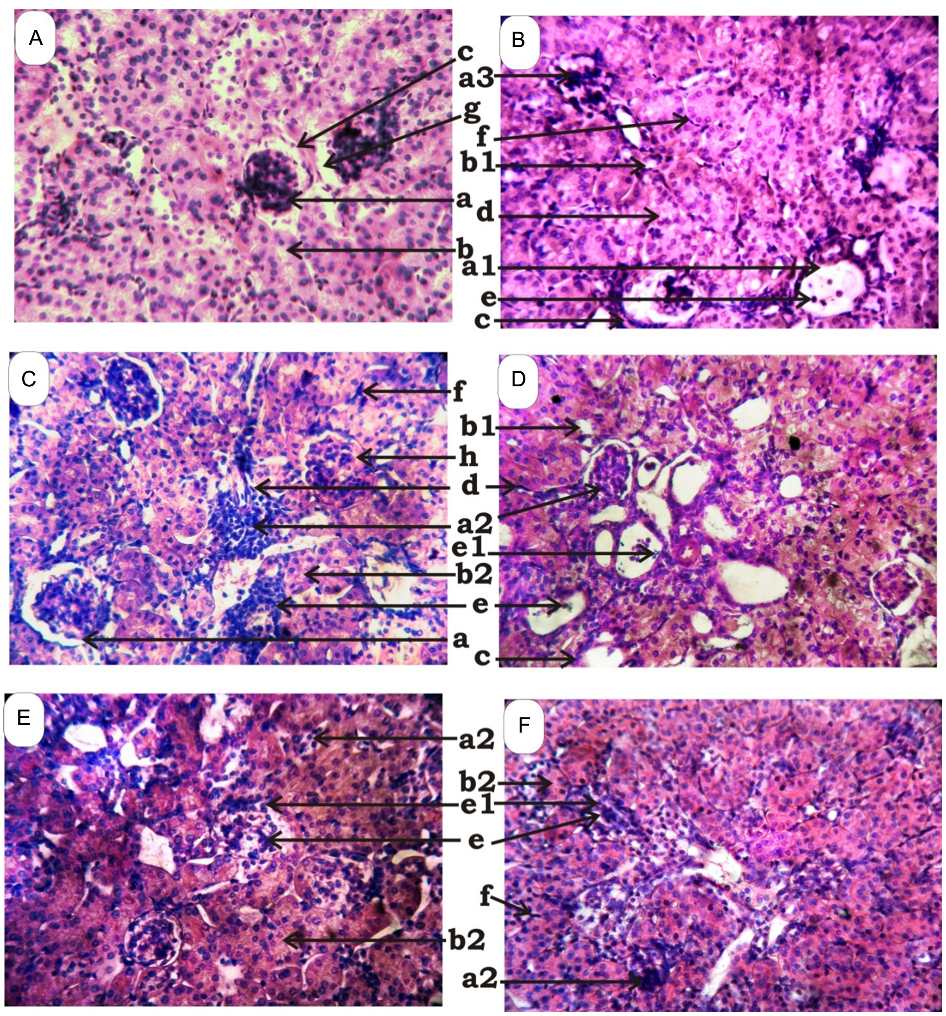

Figure 3. A-F Histological sections of kidney (400×). (A) Vehicle control group (Vc); (B) CCl_4 group (CC); (C) CCl_4+ *Basella alba* group (CCB); (D) CCl_4+ *Solanum nigrum* group (CCS); (E) CCl_4+ *Ficus carica* group (CCF); (F) CCl_4+ *Grewia asciatica* group (CCG); (a: healthy glomerulus, a1: oblitrated glomeruli, a2: regenerative glomeruli, a3: Shrunken glomeruli, b: normal tubules, b1: damaged tubules, b2: repaired tubules, c: Bowman's capsule, d: fibrosis, e: stem cells or podocytes in Bowman's capsule, e1: migration of podocytes into glomeruli, f: endothelial cells, g: Bowman's space, h: capillaries).

and complete obliteration of glomeruli with simultaneous damage to PCTs (Figure 3B). Besides, intracellular vacuolization and water retention were observed in endothelial linings of tubules causing almost complete obliteration of the tubular lumen (Figures 2 and 3).

In general, the regenerative activity in the kidneys involves the endothelial and podocytes cells. The endothelial cells are required for the proliferation of the glomerular capillaries, while the podocytes surround the glomeruli to form special filtration slits and the Bowman's capsule.[30] Large number of endothelial cells and the podocytes were seen in CCG and CCF groups indicating that the phytochemicals present in these fruit extracts mainly sterols like β-sitosterol, campesterol, and stigmasterol inflict anti-inflammatory and proliferative effects upon these regenerative cells. Whereas the unique combination of the antioxidants like anthocyanins, flavonoids, free amino acids, fatty acids, minerals, and vitamins help in suppressing the oxidative stress-related degenerative changes of CCl4 exposure.[31,32]

The most prominent sign of rapid regeneration in terms of hyperplasia of the glomeruli was observed in the CCG group (Figure 3F) followed by CCB, CCF, and CCS groups in decreasing order (Figure 3C, E, and D). This regenerative potential difference must be attributable to the phyto-medicinal ingredients like vitamins, minerals, antioxidants, and phytosterols of these medicinal plant fruit (Table 1). It has already been shown that the elevated creatinine and blood urea nitrogen on CCl_4 exposure indicate impaired kidney function.[28] The significantly higher serum creatinine level seen in the CC group than that of the Vc group likewise indicates severe damage to kidney function in the CC group (Table 3). The common phyto-chemical factor present in *Basella alba*, *Ficus carica*, and *Grewia asciatica* fruit extracts are the phytosterols which are lacking in *Solanum nigrum* extract (Table 1). Beta-sitosterol is the most prominent phytochemical found in CCB that has been attributed to various regenerative and histoprotective activities in the available literature.[29] The hypertrophy observed in CCB and CCF groups is probably a potential rescuing effect of beta-sitosterol (Figure 3C and E).

The CCG and CCB groups showed maximum proliferation of kidney rehabilitative cells (podocytes and endothelial cells). Rapid kidney regeneration in these groups may be attributed to the presence of a unique combination of phytosterols and antioxidants in *Basella alba* and *Grewia asiatica* fruit extracts (Table 1). In the CCS group, minor regenerative indicatives were seen as indicated by a few well-placed functional and healthy glomeruli. However, many empty spaces appeared due to the complete obliteration of the glomeruli mimicking the CC group. The phytochemical compounds present in *Solanum nigrum* include some antioxidants with a unique combination of various alkaloids. The lack of phytosterols, the presence of various alkaloids, and the inclusion of only a limited amount of natural antioxidants in *Solanum nigrum* fruit extract might have restricted the rehabilitative and regenerative capacity in the animals of the CCS groups.

The selection of specific medicinal plants was based on 2 factors. First, their availability in the vicinity of research places and, second, their known phyto-medicinal ingredients like vitamins, minerals, antioxidants, and phytosterols (Table 1).

CONCLUSION

The above findings indicate that among the 4 FPEs, *Basella alba* and *Grewia asiatica* have shown better kidney rehabilitative capacities as compared to the *Solanum nigrum* and *Ficus carica* against CCl_4. This study demonstrated the potential positive effects of active phytochemical ingredients of medicinal fruits against kidney damage caused by a single dose of CCl_4 exposure.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethical Committee of the Department of Zoology, University of Sargodha, Sargodha, Pakistan (Approval no: SU/Zol/2667 Date: 25/08/ 2018).

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