



Original article

Therapeutic effects of *Typha elephantina* leave's extract against paracetamol induced renal injury in rabbitsBashir Ahmad^{a,*}, Ali Muhammad Yousafzai^a, Ayaz Ali Khan^c, Mohammad Attaullah^b, Waqar Ali^c, Saeed Ahmad^b, Ghazala Yasmin Zamani^d, Farhat Naz^e, Sumayya Raziq^a, Amjad Ali^f^a Department of Zoology, Islamia College Peshawar, Khyber Pakhtunkhwa, Pakistan^b Department of Zoology, University of Malakand, Chakdara, Chakdara, Dir (L), Khyber Pakhtunkhwa, Pakistan^c Department of Biotechnology, University of Malakand, Chakdara, Dir (L), Khyber Pakhtunkhwa, Pakistan^d Department of Biotechnology, Bacha Khan University, Charsada, Khyber Pakhtunkhwa, Pakistan^e Department of Zoology, Warai Campus Shaheed Benazir Bhutto University, Dir (L), Khyber Pakhtunkhwa, Pakistan^f Department of Botany, University of Malakand, Chakdara, Dir (L), Khyber Pakhtunkhwa, Pakistan

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ABSTRACT

Present study focuses on ameliorative potential of *Typha elephantina* leave's aqueous (TE.AQ) extract against Paracetamol (PCM) induced toxicity in rabbits. We fed the male rabbits with 300 mg PCM in alone and in combination with TE.AQ at different doses i.e. (100, 200 and 300 mg/kg body weight) or silymarin (100 mg/kg) daily for 21 days. PCM in alone significantly ($P < 0.5$) increased serum urea, uric acid, creatinine, total protein, albumin, globulin and blood urea nitrogen. Serum sodium, potassium and magnesium level were high. The glutathione, radical scavenging activity and Thiobarbituric acid reactive substances were significantly reduced. Treatment with TE.AQ at dose rate 300 mg/kg body weight and Silymarin significantly ameliorated all the parameters when compared with PCM administered group. The 100 and 200 mg of TE.AQ showed no significant effects. The histopathological examination confirmed the therapeutic potential of TE.AQ. These results established the presence of natural antioxidants in *Typha elephantina* leaves.

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1. Introduction

Kidney is a vital and complex organ that excretes the waste elements like creatinine, urea and uric acid and reabsorbs certain important element back into the blood and maintains homeostasis (Rosner, 2011). It is exposed to various toxic agents particularly organic acids and bases, making this vital organ more susceptible to damage (Burcham, 2014). To assess the toxicity, serum biochemical parameters are the key indices (Li et al., 2011). Renal toxicity or nephropathy often related to several metabolic disorders including serum electrolyte, urea, uric acid and creatinine imbal-

ances and are bio-indicators to detect renal function (Gowda et al., 2010). The elevated levels of creatinine, urea and uric acid are always associated with impaired renal function (Sun et al., 2012) causing chronic kidney disease and arthritis (Kochi et al., 2018), renal failure and renal artery stenosis (Ito et al., 2012) lead to altered blood pressure, fluid retention and heart problem (Hamrahian, 2017). Numerous chemicals and drugs cause acute or chronic renal toxicities (Jager and Fraser, 2017) and Paracetamol (acetaminophen; APAP), at high doses is hepato and nephrotoxic in both humans and animals (Yousef et al., 2010). It produces reactive oxygen species, depletes antioxidants and antioxidant enzymes, and up regulates cytokine (Du et al., 2016) causing tissue injury and cell death (Kehrer and Klotz, 2015). Living organisms have developed an antioxidant defense system to scavenge these ROS but when the rate of ROS production exceeds over its scavenging, develops oxidative stress. The antioxidant defense system includes enzymatic and non-enzymatic elements such as superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST) and glutathione (GSH) (Bhagat et al., 2016). GSH is an important antioxidant and detoxifies and scavenges multiple of electrophilic and peroxides compounds (Sciuto, 2017). Reduced GSH causes

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Table 1
Serum creatinine, urea, uric acid and blood urea nitrogen of various groups in different days.

Groups	Serum Creatinine			Serum urea			Serum Uric acid			Blood urea nitrogen		
	W1 = day 7th	W2 = day 14th	W3 = day 21st	W1 = day 7th	W2 = day 14th	W3 = day 21st	W1 = day 7th	W2 = day 14th	W3 = day 21st	W1 = day 7th	W2 = day 14th	W3 = day 21st
N	0.96 ± 0.0a	0.97 ± 0.7a	1.1 ± 0.45a	40 ± 2.3 a	39 ± 0.76a	38 ± 1.2a	1.8 ± 0.1a	1.5 ± 0.41a	1.8 ± 0.32a	14.85 ± 0.8a	14.20 ± 0.4a	14.4 ± 0.5a
T	2.7 ± 0.1b	2.9 ± 0.0b	2.9 ± 0.3b	77 ± 2.9b	81 ± 0.95b	80 ± 1.3b	4.7 ± 0.4b	4.6 ± 0.37b	4.4 ± 0.29b	21.1 ± 0.5b	21.20 ± 1.0b	22.6 ± 1.1b
A	2.4 ± 0.1b	2.7 ± 0.0b	2.3 ± 0.063c	71 ± 2.8c	65 ± 3.2c	69 ± 2.2c	4.3 ± 0.2b	3.5 ± 0.35c	3.5 ± 0.48c	20.3 ± 0.5b	19.20 ± 0.4c	19.2 ± 0.4c
B	2.5 ± 0.4b	2.4 ± 0.0b	1.8 ± 0.083d	68 ± 0.9c	59 ± 1.6d	56 ± 1.1d	3.6 ± 0.3c	3.1 ± 0.19c	2.6 ± 0.23d	19.0 ± 0.4c	19.17 ± 0.3c	18.8 ± 0.9c
C	2.4 ± 0.4b	1.7 ± 0.0 4c	1.2 ± 0.28a	61 ± 2.3d	49 ± 0.55e	39 ± 0.85a	2.9 ± 0.0d	2.4 ± 0.16c	1.9 ± 0.13a	18.9 ± 0.0c	17.38 ± 0.3d	15.9 ± 0.7a
D	1.1 ± 0.3a	0.99 ± 0.1a	0.99 ± 0.01a	42 ± 4.7a	39 ± 2.2a	39 ± 1.5a	1.7 ± 0.07d	1.5 ± 0.5a	1.9 ± 0.1a	15.7 ± 0.8a	15.00 ± 0.7a	15.2 ± 0.8a
E	1.8 ± 0.03c	0.98 ± 0.2	1.2 ± 0.27a	58 ± 1.7d	45 ± 2.7e	41 ± 0.81a	2.5 ± 0.3a	2.4 ± 0.09d	1.9 ± 0.63a	18.92 ± 0.6c	17.79 ± 0.7d	16.4 ± 0.5a

N = Normal control without any treatment, T = PCM only at dose rate 300 BW, A = PCM (300 mg) + ((TE,AQ) extract (100 mg/kg BW), B = PCM (300 mg) + C = PCM (300 mg) + (TE,AQ) extract (300 mg/kg BW), D = only (TE,AQ) extract (200 mg/kg BW), E = PCM (300 mg) + (silymarine (100 mg/kg BW)).

oxidative stress, elevates ROS that interact with cellular membrane lipids, causing lipid peroxidation (Birben et al., 2012).

Kidney diseases have become a global health problem owing to its strong association with the use of synthetic drugs (Ige et al., 2012). As medicinal plants are rich source of antioxidants with no side effects, therefore are extremely admired all over the world (Sen and Samanta, 2014). The plant *Typha elephantina* (Roxb) locally known as Hogla, belongs to family Typhaceae, commonly found in shallow waters, swamps, ditches and canals. The genus *Typha* includes more than 20 species (Index Kewensis (1895–1958) (Zhou et al., 2018). This plant possesses many medicinal properties (Rahman et al., 2014) therefore, we investigated aqueous extracts of *Typha elephantina* Roxb leaves for its ameliorative effects in PCM toxicity in rabbits.

2. Materials and methods

2.1. Sample collection and extraction

The fresh leaves of *Thypha elepentenia* (T.E) was collected from District swat and was identified in the department of Botany University of Malakand, Khyber Pakhtunkhwa, Pakistan. The fresh leaves of T.E were chopped, grinded and extracted three times with deionized water to prepare the aqueous extract. The filtrate was stored at 4 °C in the refrigerator to avoid the fungal attack (Vaghasiya, Dave, & Chanda, 2011). The whole experiment was carried in the Department of Biotechnology, University of Malakand, Khyber Pakhtunkhwa, Pakistan.

2.2. Treatment regime

The male rabbits were purchased from the local market of Min-gora, Swat, and were acclimatized. Rabbits were divided into different groups at the start of experiment. Different groups were fed orally with various doses of TE,AQ, PCM and Silymarin for regular 21 days.

2.3. Blood collection

The blood samples were collected from all the rabbits by carotid bleeding on day 7th (W1), day 14th (W2) and on day 21st (W3) of the experiment. Serum was isolated and was used for the biochemical parameters' assessment and kidney function tests ((Gautam & Goel, 2014).

2.4. Biochemical analysis

Serum was used for the assessment of urea (URE), uric acid (UA), creatinine (CR) values using protocol of (Al-Daghri et al., 2017). Total protein (TP), albumin (ALB), globulin (GB) and blood urea nitrogen (BUN) were analyzed. The serum sodium (Na), potassium (K) and magnesium (Mg) levels were measured following the procedure described by Abuoghaba.

2.5. Analysis of kidney antioxidants

Total reduced thiol contents (GSH), RSA and thiobarbituric acid reactive substances (TBARS) of kidney tissues were determined according to the method mentioned by (R. A. Khan, Khan, Sahreen, & Bokhari, 2010)

2.6. Histopathological analysis

Histopathology of kidney was done according to the method of (Neuschwander-Tetri et al., 2015). The prepared slides were exam-

Table 2
Serum total protein, albumin and globulin levels of various groups in different days.

Groups	Serum total protein mg/dL			Albumen mg/dL			Globulin mg/dL		
	W1 = day 7th	W2 = day 14th	W3 = day 21st	W1 = day 7th	W2 = day 14th	W3 = day 21st	W1 = day 7th	W2 = day 14th	W3 = day 21st
N	5.9 ± 0.141a	6.14 ± 0.181a	6.32 ± 0.044a	3.3 ± 0.020a	3.2 ± 0.005a	3.2 ± 0.01a	2.4 ± 0.04a	2.4 ± 0.040a	2.4 ± 0.01a
T	3.9 ± 0.095b	4.06 ± 0.054b	3.92 ± 0.109b	2.2 ± 0.015b	2.2 ± 0.015b	2.1 ± 0.00b	1.9 ± 0.01b	2.5 ± 0.036a	1.9 ± 0.06b
A	4.2 ± 0.095c	4.42 ± 0.083c	4.62 ± 0.083c	2.3 ± 0.020c	2.4 ± 0.02c	2.7 ± 0.02c	2.0 ± 0.01b	1.9 ± 0.051b	2.1 ± 0.00c
B	4.5 ± 0.057d	4.72 ± 0.044d	5.02 ± 0.044d	2.4 ± 0.010d	2.7 ± 0.005d	2.9 ± 0.01 d	2.1 ± 0.00c	2.0 ± 0.005c	2.2 ± 0.010d
C	4.9 ± 0.095e	5.06 ± 0.089e	6.14 ± 0.151a	2.43 ± 0.05e	2.9 ± 0.005e	3.1 ± 0.01a	2.2 ± 0.00d	2.1 ± 0.015c	2.47 ± 0.02a
D	5.7 ± 150a	6.08 ± 0.164a	6.22 ± 0.148a	3.2 ± 0.06a	3.2 ± 0.005a	3.2 ± 0.01a	2.4 ± 0.05a	2.2 ± 0.020d	2.4 ± 0.03a
E	4.8 ± 0.05e	5.02 ± 0.130e	6.00 ± 0.158a	2.4 ± 0.05e	2.9 ± 0.010e	3.2 ± 0.01a	2.1 ± 0.01d	2.4 ± 0.045a	2.47 ± 0.02a

N = Normal control without any treatment, T = PCM only at dose rate 300 BW, A = PCM (300 mg) + (TE.AQ) extract (100 mg/kg BW), B = PCM (300 mg) + C = PCM (300 mg) + (TE.AQ) extract (300 mg/kg BW), D = only (TE.AQ) extract (200 mg/kg BW), E = PCM (300 mg) + (silymarine (100 mg/kg BW)

Table 3
Serum electrolytes such as Sodium, Potassium and Magnesium values of various groups in different days.

Groups	Serum sodium Na (mmol/L)			Serum potassium K (mmol/L)			Serum magnesium Mg (mmol/L)		
	W1 = day 7th	W2 = day 14th	W3 = day 21st	W1 = day 7th	W2 = day 14th	W3 = day 21st	W1 = day 7th	W2 = day 14th	W3 = day 21st
N	138.6 ± 0.54a	140.0 ± 0.70 a	138.2 ± 0.83a	5.9 ± 0.004a	5.9 ± 0.004a	6.19 ± 0.32a	1.01 ± 0.06	1.03 ± 0.07a	1.01 ± 0.06a
T	129.9 ± 0.74b	127.0 ± 1.25b	120.0 ± 1.00b	5.1 ± 0.008b	5.1 ± 0.008b	4.62 ± 0.05b	0.65 ± 0.01	0.62 ± 0.01b	0.61 ± 0.01b
A	128.6 ± 1.80b	128.0 ± 0.70b	122.2 ± 0.44b	5.2 ± 0.027b	5.2 ± 0.027b	4.94 ± 0.05c	0.67 ± 0.01	0.70 ± 0.01c	0.76 ± 0.00c
B	130.8 ± 1.64b	130.2 ± 0.44b	125.8 ± 0.83b	5.2 ± 0.06b	5.2 ± 0.06b	5.55 ± 0.06d	0.71 ± 0.01	0.77 ± 0.00d	0.79 ± 0.03d
C	132.8 ± 0.83b	132.4 ± 1.14b	136.0 ± 0.70a	5.3 ± 0.021b	5.5 ± 0.021c	6.000 ± 0.0 a	0.78 ± 0.00	0.85 ± 0.00e	0.96 ± 0.03a
D	138.4 ± 1.14a	139.0 ± 1.00a	136.4 ± 1.14a	5.9 ± 0.14 a	5.9 ± 0.14a	6.07 ± 0.08 a	0.96 ± 0.04	0.99 ± 0.01a	1.06 ± 0.16a
E	129.8 ± 0.83b	130.4 ± 1.14b	134.2 ± 1.30a	5.3 ± 0.032b	5.4 ± 0.032c	6.02 ± 0.05a	0.79 ± 0.00	0.76 ± 0.00d	0.93 ± 0.04a

N = Normal control without any treatment, T = PCM only at dose rate 300 BW, A = PCM (300 mg) + (TE.AQ) extract (100 mg/kg BW), B = PCM (300 mg) + C = PCM (300 mg) + (TE.AQ) extract (300 mg/kg BW), D = only (TE.AQ) extract (200 mg/kg BW), E = PCM (300 mg) + (silymarine (100 mg/kg BW).

Table 4
The GSH, RSA and TBRAS levels of various groups in different days.

Groups	GSH kidney	RSA kidney	TBRAS kidney
N	28.32 ± 0.8765a	30 ± 0.7071a	12 ± 0.77a
T	13.11 ± 2.737b	17.4 ± 1.817b	23 ± 0.53b
A	14.28 ± 0.745b	19.8 ± 1.44b	21 ± 1.2b
B	18.34 ± 1.085c	21.66 ± 0.9025b	19 ± 0.83c
C	27.86 ± 0.3895a	29.9 ± 1.597a	13 ± 1.2a
D	25.35 ± 1.072a	29.5 ± 2.828a	13 ± 0.77a
E	26.59 ± 1.074a	24.86 ± 0.941b	15 ± 0.68a

N = Normal control without any treatment, T = PCM only at dose rate 300 BW, A = PCM (300 mg) + (TE.AQ) extract (100 mg/kg BW), B = PCM (300 mg) + C = PCM (300 mg) + (TE.AQ) extract (300 mg/kg BW), D = only (TE.AQ) extract (200 mg/kg BW), E = PCM (300 mg) + (silymarine (100 mg/kg BW).

ined under microscope and photographs were taken using digital camera.

2.7. Statistical analysis

Results obtained were analyzed statistically, mean, standard deviation, one-way ANOVA and Tukey test were conducted using the Graphpad Prism, Demo Version 05 (www.graphpad.com).

3. Results

3.1. Biochemical analysis

The PCM administration in alone significantly (P < 0.05) elevated serum URE, UA and CR levels. The feeding of animals with TE.AQ at dose rates of 100 mg, 200 mg and 300 mg/kg body weights showed no significant (P < 0.05) effects in the first two weeks of experiment. However, TE.AQ at dose rate of 300 mg/kg body weight and Silymarin at the dose rate of 100 mg/kg body weight significantly (P < 0.05) reduced the serum parameters toward normal in third week of experiment. The administration

of TE.AQ in alone at the dose rate of 200 mg kg body weight kept all the serum biochemical parameters in normal reference range (Table 1).

The TP, ALB, GB and BUN were significantly (P < 0.05) reduced in PCM treated animals. A significant (P < 0.05) ameliorative effect was observed in week three after the administration of TE.AQ at the dose rate of 300 mg kg body weight. The Silymarin had almost same results and normalized the altered parameters. at dose 100 mg/kg body weight significantly (P < 0.05) increase the mention values (Table 2).

The low values of Na, K and Mg were found in PCM fed rabbits and TE.AQ at the dose rates of 100 mg and 200 mg/kg body weight did not show significant (P < 0.05) effect to normalize the electrolytes alteration. The TE.AQ at high dose showed significant effect on the serum electrolytes values in third week of experiment (Table 3).

3.2. Antioxidant potential

The reduced GSH and RSA and elevated TBRAS values were found in animals treated with PCM in alone, and TE.AQ and Silymarin significantly affected the toxic effects of PCM (Table 4).

3.3. Histopathology

A = PCM(300 mg) + (TE.AQ)extract(100 mg/kg BW), B = PCM(300 mg) + C = PCM(300 mg) + (TE.AQ)extract(300 mg/kg BW), D = only (TE.AQ) extract(200 mg/kg BW), E = PCM(300 mg) + (silymarine(100 mg/kg BW).

Histopathology of normal rabbit kidney (Fig. 1N) showed normal glomeruli and flat epithelium lining glomerular capsule with distinct capsular space, normal proximal and distal convoluted

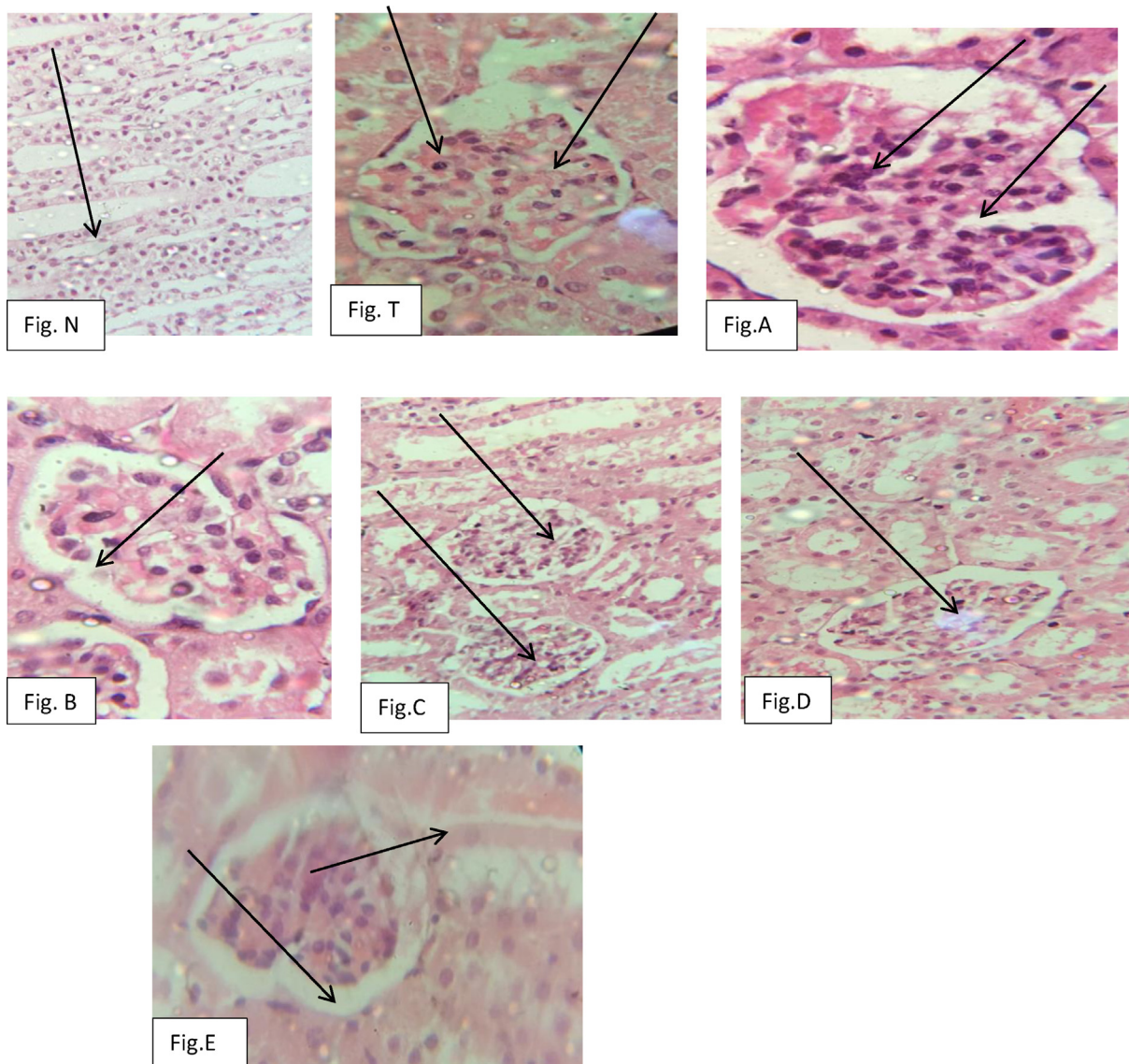


Fig. 1. Renal histopathology (glomeruli) of various experimental groups. N = Normal control, T = PCM in alone at dose rate of 300 mg/kg b.wt., A = PCM and TE.AQ at the dose rates of 300 mg and 100 mg/kg kg b.wt.), B = PCM and TE.AQ at the dose rates of 300 mg and 200 mg/kg kg b.wt. C = PCM and TE.AQ at the dose rates of 300 mg and 300 mg/kg kg b.wt. D = TE.AQ in alone at the dose rate of 200 mg/kg b.wt. E = PCM and Silymarin at the dose rates of 300 mg and 100 mg/kg kg b.wt.

tubules. The kidneys of PCM medicated rabbits, and PCM and TE.AQ at the dose rate of 100 and 200 mg/kg body weight, the kidneys (Fig. 1T, 1A and 1B) showed severe deterioration of vascular glomeruli shape, spreading of the glomerular capsular space with degenerated epithelial lining the Bowman’s capsule, edema and degeneration of some tubular epithelium cells. In the rabbits that were with PCM and TE.AQ at the dose rate of 300 mg/kg body weight, the kidneys (Fig. 1C) were necrotic having low number of inflammatory cells and improved tubule and glomeruli architecture. In the rabbits fed with TE.AQ in alone (Fig. 1D), kidneys had normal tubular brush-borders and intact glomeruli with no signs of congestion or infection in the sinusoids. Same results were also present in the group fed with Silymarin along with PCM (Fig. 1E).

4. Discussion

The high dose of PCM causes tissue damage by promoting lipid peroxidation causing hepatitis and nephritis by decreasing the antioxidant enzymes (Canayakin et al., 2016). PCM is oxidized by

P450 (microsomal cytochrome enzyme) to form toxic electrophile N-acetyl-p-benzoquinone imine (NAPQI) which is detoxified by GSH to form acetaminophen-glutathione conjugate (APAP-SG). Subsequently, higher level of APAP-SG formation take place together with GSH depletion that leads to cell death (Athersuch et al., 2018). In PCM fed rabbits, an increase in BUN, CR, URE and UA with decreased TP, ALB and GB were recorded. The serum Na, K and Mg levels were altered, and the kidney damage was confirmed through histopathology. These results have also been justified by (Besenhofer et al., 2011 and Khan and Siddique, 2012) that documented the effects of drugs and metabolites on the kidneys; the kidneys remove various drugs and metabolites, hence are exposed to damage.

When TE.AQ was administered with PCM in high dose, all the serum biochemical parameters and electrolytes values were normalized in the third week of experiment and results showed the dose and time dependent curative effects. Kadhem, 2019 documented positive effects of ethanolic extract of *Saussurea lappa* against paracetamol-induced hepatic and renal damage in males. Igbinovia et al., 2015 observed the same results of *Carica papaya*

seed extracts on CR, URE and UA in Wistar rats. The curative effects of TE.AQ suggests that T.E leaves may contain active compounds that help in removing metabolic products that hinder the reabsorption machinery of nephrons (Sasidharan et al., 2011).

The TP, ALB and GB, Na, K and Mg values were significantly ($P < 0.05$) decreased PCM fed rabbits. The decrease in serum proteins and electrolytes may be as a result of kidney damage disrupting its normal physiology and leading to leakage of albumin in urine (Levitt and Levitt, 2016). No significant effect was found in elevating the serum proteins and electrolytes levels when low and medium dose of TE.AQ was fed for three weeks along with PCM. A significant positive increase in serum proteins and electrolytes levels was observed at high doses of TE.AQ and Silymarin. It has been reported that electrolytes have an important role in muscle contraction and relaxation (Shrimanker and Bhattarai, 2020). The similar study has been carried out by Enemor and Okaka, 2013, in which they found the beneficial effects of ethanolic extract of *Sarcocephalus latifolius* root on Na and K in rats.

The GSH is a significant non-enzymatic antioxidant that has a vital role in the removal of ROS (Kushwaha et al., 2020). The PCM significantly ($P < 0.05$) elevated TBRAS levels with decrease in GSH and RSA causing kidney function impairment and oxidative stress. The GSH and RSA were significantly improved with decrease in TBRAS values in rabbits that received high dose of TE.AQ. Ganie et al., 2011 have also reported the same results. It has been concluded that TE.AQ efficiently downregulated the toxic effects of paracetamol. The TE.AQ may acts as free radical scavenger and inhibiting oxidative damages to the cell. All these findings were further confirmed by histopathology of the kidneys of all the rabbits.

5. Conclusion

It has been concluded that *Typha elephantina* leave's aqueous extract (TE.AQ) is very potent against kidney damage. The TE.AQ improves serum proteins levels, renal function, normalizes various serum electrolytes and has potent antioxidant capacity. The TE.AQ may be a good source for new medicines and needs exploration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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