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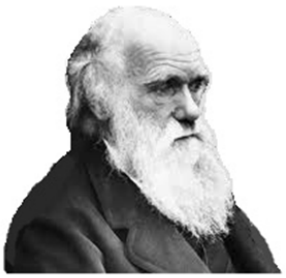

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Nephroprotective role of *Potentilla reptans* L. aqueous extract on paracetamol - induced kidney nephrotoxicity in male mice

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ABSTRACT

Nephroprotective effects (NPE) of simple *Potentilla reptans* - aqueous leaf extract (Pr-ALE) leaves on Paracetamol induced kidney poisonousness in wistar rats. Adult male wistar rats (weight range (WR): 200-220g) were divided into 6 groups (n=6). Paracetamol (PA) and Silymarin (SY) stayed managed intraperitoneally arranged the 5th day to rats in all groups but the normal control. Furthermore, a significant nephroprotective (NP) of the aqueous leaf extract (ALE) and oral dose of PA and SY. *Pr*-ALE did not mortality or significant changes in the body weight. Progression of nephrotoxicity (NT) induced by PA in rats was interfered by *Pr*-ALE managed, and these effects were correspond to those managed with SY. This is the first record on NPE of *Pr* against PA-induced NT.

***Keywords*:** Nephroprotective, Nephrotoxicity, Paracetamol, Silymarin, *Potentilla reptans*

1. INTRODUCTION

Kidney is most affect to impaired caused by reactive oxygen species (ROS), and likewise due to oxidative stress by polyunsaturated fatty acids in the blend of renal lipids, and impaired can also be caused by a high capacity of blood flowing through it, further separating large amounts in toxins, which can accumulate in kidney lobules (Dubey *et al.*, 2011; Begum *et al.*, 2011). Then, it's provides toxicants varies by different morphological methods starting or interstitial something preferred different to nephropathy (Silva, 2004). Continuously, it has

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been extreme strongly interacted that (NADPH) oxidase, as an advantages capability of ROSs provides in the kidney could have a process in developing of renal oxidative damage (Etoh *et al.,* 2003). Furthermore, acute kidney injury (AKI) is a generally clinical difficult situation which is interacted with increased morbidity and mortality, and infecting about 1-7% of hospitalized patients and 1-25% of patients in the intensive care unit (ICU) (Rosita *et al.*, 2018). Numerous epidemiologic explorations have noticed a wide range of potential of the incidence of AKI in critically patients, and the it varied between 15% and 50% (Case *et al.*, 2013).

Drugs are a common cause of AKI responsible for approximately 20% of community and hospital acquired episodes of AKI which may reach as high as 66% in the elderly (Kohli *et al.*, 2000).

Paracetamol (PA) is one of the most famous, very important and broadly utilized drugs for the treatment of fever and pain, placed a unique position among analgesic drugs. In spite of, unlike NSAIDs it is about unanimously suggested to have no anti-inflammatory process and does not produce gastrointestinal damage (Bertolini *et al.,* 2006). It's seened in more productions, available in the first important place of hospitals, and second as suggestion only medicines. Further, because of its broad paired with comparison high toxicity, (compared to ibuprofen and aspirin) there is a much higher capability for very overdose (Sheen *et al.*, 2002).

Commonly, PC is particularly hazardous on the liver if taken most time periods in test animals (Marsha *et al.*, 2000; Ajayi, *et al.*, 2017; Hansat *et al.*, 2020).

Moreover, if toxic levels of PA consist in the liver, the natural anti-oxidant protects of the body are over malignancy and whelmed, and the liver is impaired by the construction of hazardous free radicals. Although NT is less common than in PA over dosage, renal tubular impair and acute renal failure can consist even in the not presence of liver injury (Jones and Vale, 1993). It could even lead to death in humans and research animals (Sarumathy, 2011), even at common NSAID dosages, with adjust kidney process can develop NSAID toxicity (Whelton and Hamilton, 1991).

Studies are going on throughout the worldwide for the research of defenses molecules that would give highest defense to the liver. Kidney as well as other organs, practically very tiny or no problems would be exerted during their process in the body (Palani *et al.,* 2009; Montilla *et al.,* 2005; Mansour *et al.,* 2006). Many herbs are medications used in various countries for mitigation of medicines or toxin induced hepatic and renal disorders (El-Beshbishy, 2005).

Potentilla reptans L. belongs to the Rosaceae family, and is a stoloniferous, creeping perennial and medical plant. It is distributed mainly in coastal regions, especially in dry lands-rocky, sandy and sunny places, but grows also in mown grasslands, lake and river shores. The plant also inhibits places that are influenced by the human activity, which possesses a thick vertical rhizome, prostrate and elongated stem with a rosette of leaves. Petals are golden yellow, usually twice as long as sepals, and the flowers have five petals, rarely four, which has been the least studied among the members of the genus (Vermeulen *et al.,* 2008; Tomovic *et al.*, 2015).

The therapeutic effects, such as anti-ulcerorgenic, antioxidant, anti-inflammotory, hypoglycemic, astringent, and anti-tumor of can be explained by the high amount of biologically active compounds present in all plant parts, and many chemical compounds have been found in the aerial parts, roots of *Pr* such as, triterpenoids, flavonoids, organic acids (Watkins *et al.,* 2012). The aim of present study was to investigate the NP activity of ALE obtained from leaves of a widely distributed in medicinal plant, *Pr* on PC-induced liver poisonousness in wistar rats.

2. MATERIALS AND METHODS

2. 1. Plant material and extract preparation

Pr-mature leave were collected from Vallampadgai village (11°34'N to 11°36'N latitude, and 79°70'E to 79°73'E longitude), Cuddalore District, Tamil Nadu, India, and washed methodically, blotted and shade dried. It was authenticated by plant taxonomist from the Department of Botany, Annamalai University. Coarsely powdered dried leaves, 500 g each of Pr separately extract to exhaustion with aqueous using a Soxhlet apparatus successively. The aqueous extract thus obtained was dried under reduced pressure yielding 20.4 g of extract.

2. 2. Animals

A mature male, *Wistar albino* rats weight between 190-230 gm were acquired from the Animal House Unit (AHU), Annamalai University, Chidambaram, in India. They were maintained in moisture (wire-cages at 27±4 °C), recycle (55-65%, and a 12 h light & dark) for partially a week before the experimental, and were kept under stable animal housing situations with free access to a stable food and water add libium during the experimental.

The standard method was allowed in laboratory experimental by the Institution Animal House (IAH) and use Animal Ethic Committee (AEC), Annamalai University, Approval letter Register Number: 160/1999/CPCSEA, Proposal No:1096/Dt.9/10/14. Throughout the experimental, all criteria given for taking care of animals made and maintained by the "CPCSEA guidelines", Annamalai University.

2. 3. Preparation of Silymarin (SY)

SY with 80% purity, (Pondicherry Scientific Chemicals, Pondicherry, India) as a stable medicine, was dissolved in Tween 20 (10% w/v) and orally inflict to rats at a dose of 50 mg/kg body weight (Alshawsh *et al.*, 2011).

2. 4. Dose administration and induction of nephrotoxicity

The animals of all the groups were lost by low anesthesia on 6th day. Each animal blood sample was gathered separately by carotid artery into sterilized dry centrifuge tubes and administrated to coagulate for 30 mm.

2. 5. Histopathological of the kidney weight

After all the animals were lost, postmortem noticed was accomplished on all the recognized and dissected rat kidneys using an overdose of either on day 10. The kidneys were rinsed in normal saline, cleaned of any fats and dissected out were taken from them. Since kidney is organ of metabolism and excretion, potentially toxic agents are likely to affect them.

The renal tissue (RT) parts inflict were kept in 10% NBF, dehydrated with 100% ethanol solution and embedded in paraffin. Tissue portions of 5 μm in thickness were made, stained with haemotoxylin (HT) and eosin and contained under a photomicroscope (Model N- 400ME, CEL-TECH Diagnostics, Hamburg, Germany).

2. 6. Statistical analysis

The larval killing activity (%) data of invasion mosquito, *Ae. albopictus* larvae were subjected to different statistical baggage, LC_{50}/LC_{90}, LCL, UCL, regression, chi-square, slope, etc. The two-way ANOVA test with post hoc test using Duncan multiple (DM) comparisons in the Window 7 was utilized to analyze the report, with $P< 0.05$ being noticed as the limit of significance.

3. RESULTS

3. 1. Microscopic examination

NPE of Pr-ALE was supported by microscopic examination (ME), and the histopathological changes (HPC) were showed after induced by PA (Figure 1) toxic dose. It is sections of kidneys of normal control rats presented with normal morphological and tubular structures after 21 days. *Pr*-ALE prevented the damages of kidney.

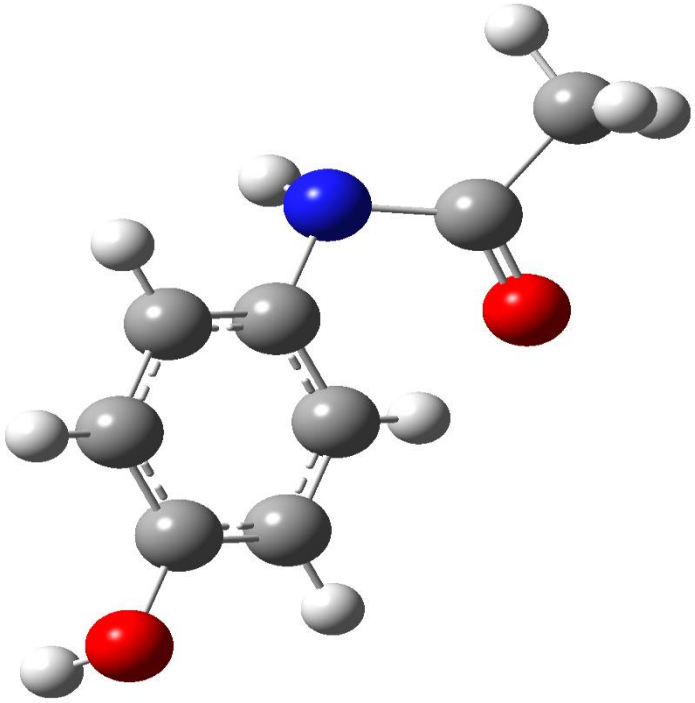

Figure 1. *3D* structure of PC

The control group rat's kidney is showed that the glomerulus rounded by Bowman's capsule. Numerous tubules (proximal and distance) lie in the area adjoining to glomerulus (Figure 2a). Kidney section of PA-treated rat's showed marked microscopic changes like vacuolization, tubular necrosis and degenerative changes were observed (Figure 2b). Oral administration of *Pr*-ALE of 250 mg/kg, and 500 mg/kg, PA-treated rat's brought back the above mentioned changes to near normally (Figure 2c,d). Kidney sections of mature and full healthy rat's managed with extract alone contained no HPC and were comparison to those of

control rat's (Figure 2e,f). The complete protection on kidney was observed after treatment with *Pr* at dose of 500 mg/kg bw as compared to control (Table 1).

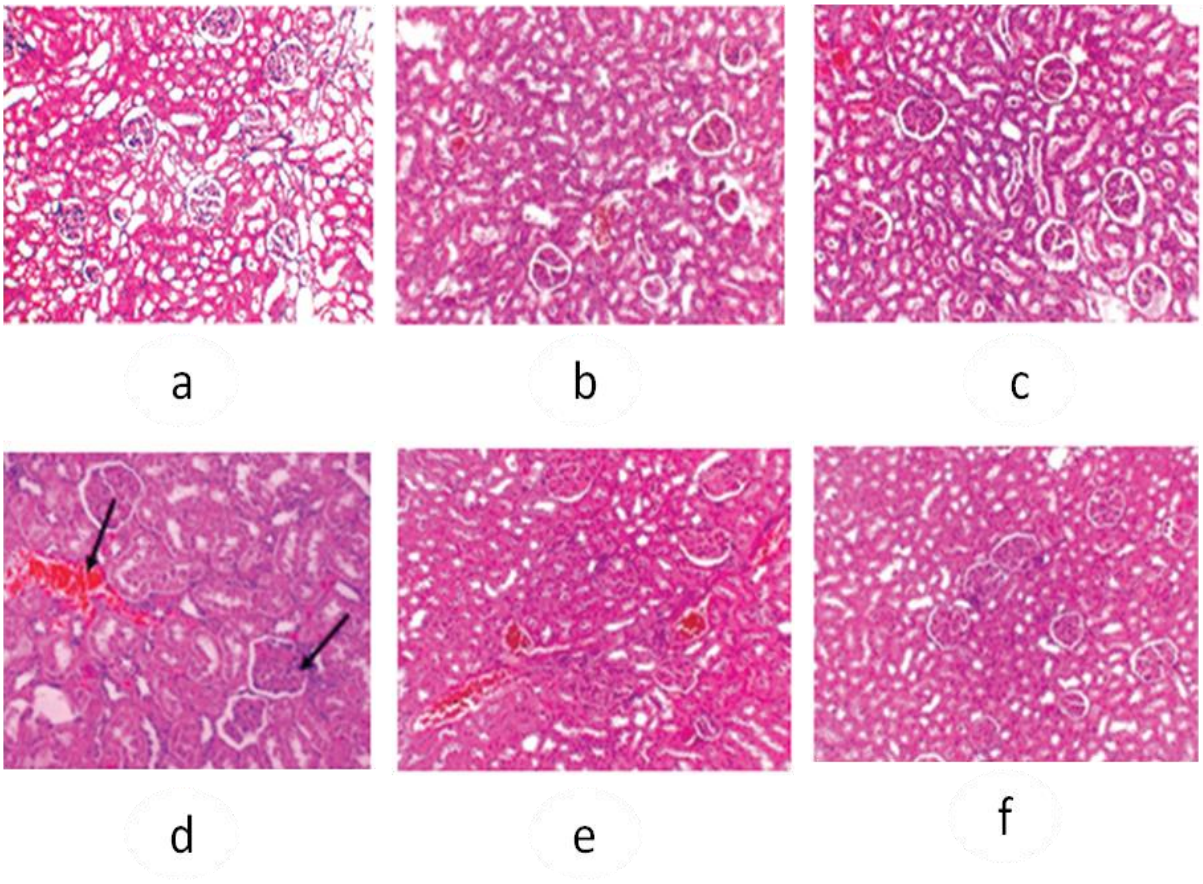

Figure 2. Photomicrographs showing the histopathological images of kidney from differentexperimental groups **(a)** control group- showing normal histoarchitectural pattern, **(b)** PC treated rats, **(c)** PC + *Pr*–aqueous extract (250 mg/kg) treated- showing the normal histoarchitecture, **(d)** PC + *Pr*–aqueous extract (500 mg/kg) treated- showing the normal histoarchitecture, **(e)** PC + SY (25 mg/kg) treated- showing the normal histoarchitecture, **(f)** Pr (500 mg/kg) alone- showing normal histoarchitectural pattern.

Table 1. Organ weights of control rats and PC with *Pr*-aqueous extract measured during acute toxicity study.

Groups	Body weight (g)		Kidney weight (g)
	Initial	Final	
Control	185 ± 4.62	215 ± 6.36	0.95 ± 0.04
PC (600 mg/kg)	180 ± 9.72	158 ± 4.22[b]	1.18 ± 0.12[b]

PC + *Pr* (250 mg/kg)	192 ± 5.46	209 ± 7.42[e]	1.10 ± 0.08[b]
PC + *Pr* (500 mg/kg)	183 ± 3.94	215 ± 5.84[c]	0.98 ± 0.06[c]
PC + SY (25 mg/kg)	190 ± 9.12	212 ± 5.28[d]	0.99 ± 0.04[d]
Pr (500 mg/kg) alone	187 ± 8.55	222 ± 9.45[a]	0.94 ± 0.03[a]

Values are expressed as mean ± standard error, n = 6.
Values were significantly different $p < 0.05$.

4. DISCUSSION AND CONCLUSION

NT is a kidney particular characteristic in which excretion does not go evenly owing to toxic chemicals or medicines (Finn and Porter, 2003; Galley, 2000). Renal proximal tubular cells (RPTC), on account of exposure to toxic levels of drugs in the acts of concentration and re-absorption of glomerular filtrate, are very susceptible to NT (Perazella, 2005). Present studies are comparable with earlier reports that the supported histopathology examination (HPE) which did not show any cell damage. NPE of *Curcuma mangga* was in a dose-dependent manner (DDM). It's extract at dose of 400 mg/kg depicted the strongest NPE (Rosita *et al.,* 2018). Many studies have focused that the toxic doses of PA cause significant tissue damage associated with glutathione depletion and lipid peroxidation resulting in intracellular accumulation and high reactive metabolite binding N-acetyl-p-benzoquinone imine (NABI), liver cell damage (LCD), and often end with death. Similar effects also occur in kidney tissue (Adeneye *et al.,* 2008). This results in the accumulation of PA which results in a biochemical chain reaction (BCR) and culminates in acute (CIA) and chronic nephropathy (CNP) (Schnellman, 2001). In addition, PA also triggers apoptosis in the liver and kidney cells (Ray and Jena, 2000).

PA-induced NT may incorporate several molecular pathways of apoptosis including removal of intracellular protective molecules (IPM) and caspase activation (CA). Although PA does not alter the expression of messenger ribonucleic acid in the antiapoptotic Bcl-xL gene, it can lower Bcl-xL protein, which means it can increase apoptotic activity (Lorz *et al.,* 2005). The reactive oxygen species compound, which is the result of PA metabolism, can also cause glomerular damage that begins with leukocyte infiltration (Singh *et al.,* 2006). One of the adverse effects of PA overdose is renal tubular necrosis (RTN) (Goodman and Gilman, 2006). Primary study of *Carica papaya* contained presence of NP phytochemicals. PA administration reported in necessary elevation of renal function markers. CPE improved the effect of PA by reducing the markers as well as shift the PA-induced replace in kidney architecture (Madinah *et al.,* 2015).

The samples become unbalanced and it consist does'nt neccessory attributes, the accuracy of the classified will be reduced. A new special selection and unbalanced dataset handling algorithm is prescript to make something right this issue and to maximize the precision or disease prediction results of the classified. At first, enhanced SMOTE algorithm helps to make something right the unbalanced dataset (Praba, 2019). Different useful drug similarly gentamicin, acetaminophen, some environmental and industrial toxicants, can cause severe renal through activation of these drugs to highly reactive free radicals (Olagunju *et al.,* 2009). *Tinospora conrdifolia* pre-treated groups exhibited significant limitation in rise in levels of

BUN and serum creatinine in a dose dependent manner. Histopathological (HP) observations further corroborated the biochemical finding (Sharma *et al.*, 2019). A relationship between NP and oxidative stress has been confirmed in many experimental models (Devi and Shyamala, 1999; Arunkumar *et al.*, 2012; Neeraj *et al.*, 2011).

Pr-aqueous was able to protect kidney damage due to toxic dose of PA and SY. According, *Pr*-aqueous extract could be used as an effective herbal product for the prevention of chemical-induced kidney damage. However, further studies are required to elaborate the molecular mechanism of *Potentilla reptans* as NP agent.

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