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NEPHROPROTECTIVE ACTIVITY OF *VACCINIUM MACROCARP* EXTRACT ON WISTAR RATS

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ABSTRACT
Canner is a group of disease, due to which large number of population is affected. Cisplatin is widely used anticancer drug, but it cause nephrotoxicity. The drug induced toxicity is a world-wide major cause of death. Till 2040 nephrotoxicity is expected to become fifth leading cause of death. Several pharmacological studies have reported nephroprotective activity of various Indian Medicinal plants. In this research work we evaluated nephroprotective activity of *Vaccinium Macrocarpon* leaves extract and against nephrotoxicity induced by cisplatin in wistar rats. Nephrotoxicity was induced in Wistar rats by intraperitoneal administration of Cisplatin (0.75%). Activity of extract was evaluated at a dose of 200 and 400 mg/kg by oral route and measure serum creatinine, blood urea level, body weight. Lipoic acid was used as standard drug to compare study results. Significant changes were observed in body weight, serum creatinine and urea levels. It was observed that the extract significantly decrease the cisplatin induced nephrotoxicity.

KEYWORDS: Cisplatin, *Vaccinium Macrocarpon*, Lipoic acid, serum creatinine.

1. INTRODUCTION

Drugs cause approximately 20 percent of community- and hospital-acquired episodes of acute renal failure **(Nash *et al.*, 2002).** Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 percent (**Kohli *et al.*, 2000).** Compared with 30 years ago, patients today are older, have a higher incidence of diabetes and cardiovascular disease, take multiple medications, and are exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function **(Hoste *et al.*, 2006).** Although renal impairment is often reversible if the offending drug is discontinued, the condition can be costly and may require multiple interventions, including hospitalization (**Gandhi *et al.*, 2000).** The kidney is an excretory organ. It is located on the posterior abdominal wall, one on each side of the lumbar part of the vertebral column. They reside against the back muscles in the upper abdominal cavity. They sit opposite each other on either side of the spine. The right kidney sits a little bit lower than the left to accommodate the liver (**Kodner *et al.*, 2003).** The Nephron is the basic structural and functional unit of the kidney (**Pocock *et al.*, 2006).** Its functions are vital to life and are regulated by the endocrine system by hormones such as antidiuretic hormone, aldosterone, thyroid and parathyroid hormone (**Maton *et al.*, 1993).** In humans, a normal kidney contains 800,000 to 1.5 million of Nephrons (**Guyton *et al.*, 2006).** Nephrotoxicity is toxicity in the kidneys. It is a poisonous effect of some substances, both toxic chemicals and medications, on renal function. There are varies forms, and some drugs may affect renal function in more than one way. Nephrotoxins are substances which displaying Nephrotoxicity. Nephrotoxicity should not be confused with the fact that some medications have a predominantly renal excreation and need their dose adjusted for the decreased renal function (example: heparin**) (Jaya *et al.*, 2013).** Many plants have been used for the treatment of kidney failure in traditional system of medicine throughout the world. Indeed along with the dietary measures, plant preparation formed the basis of the treatment of the disease until the introduction of allopathic medicine. Ethnomedicinal plants can be used to help forestall the need of dialysis by treating the causes and effect of renal failure, as well as reducing the many adverse effect of dialysis (**Yarnell E *et al.*, 2007)**. There are few chemical agents to treat acute renal failure. Studies reveal back synthetic Nephroprotective agents have adverse effect besides reduce Nephrotoxicity, various environmental toxical and clinically useful drugs, acetaminophen, gentamycin and Cisplatin, can cause severe organ toxicities through the metabolic activation to highly reactive free radicals (**Adejuwon *et al.*, 2008**). The term acute renal failure (ARF) is currently substituted by acute kidney injury (AKI). Acute kidney injury is a reversible condition in which there is a sudden decline in renal function, manifested by hourly/ daily/ weekly elevation in serum creatinine and blood urea nitrogen (BUN) (**Schrier R *et al.*, 2004)**. Different organisation such as acute dialysis quality initiative (ADQI), acute renal injury network (AKIN) and kidney disease international global outcome (KDIGO) have proved different definition for acute kidney injury. Among the definition of acute kidney injury (AKI) the

most acceptable one is kidney disease international global outcome (KDIGO**) (Cerda J *et al.*, 2008).**

2. MATERIALS AND METHODS

2.1. Chemical reagents

All the chemicals used in this study was purchased from Hi Media Laboratories Pvt. Ltd. (Mumbai, India), SD Fine-Chem Chem. Ltd. (Mumbai, India), Sunchem and SRL Pvt. Ltd. (Mumbai, India). For evaluation we used analytical-grade compounds.

2.2. Plant collection

The leaves of *Vaccinium macrocarpon* were collected locally from Bhopal; M.P. Authentication of *Vaccinium macrocarpon* plant was authenticated by a plant taxonomist in order to confirm its identity and purity.

2.3. Extraction of leaves

Coarsely powered leaves of *Vaccinium macrocarpon* (300 gm) was taken for extraction using different organic solvents, defatted with petroleum ether (40-60^{0}C) and successively extracted with ethanol and distilled water for 36 hrs using soxhlet apparatus **(Alara *et al.*, 2019**).

Formula;

$$\% \ yield = \frac{\text{Actual yield}}{\text{Theoretical yield}} \text{x100}$$

2.4. Phytochemical screening of the extract

Several phytoconstituents, including alkaloids, carbohydrates, glycosides, phytosterols, saponins, tannins, proteins, amino acids, and flavonoids were qualitatively examined in the leaves extracts of *Vaccinium macrocarpon.*

2.4.1. Test for Carbohydrates

- **Molisch'sTest:** The aqueous solution of the *Vaccinium macrocarpon* extract to 1 ml were mixed with few drops of Molish reagent (naphthol) and conc. H_2SO_4 (sulphuric acid) was added dropwise along the wall of the test tube. When two liquid mixes up, formation of purple colour ring at the junction occurs. It indicates the presence of carbohydrates.
- **Fehling's Test:** Equal amount of Fehling A and Fehling B solution were mixed (1ml each) and 2ml of aqueous solution of *Vaccinium macrocarpon* extract was added. Boil it for 5-10 minutes on water bath. Formation of reddish brown coloured precipitate due to cuprous oxide formation shows the presence of reducing sugar.
- **Benedict's test:** In a test tube equal amount of Benedict's reagent and *Vaccinium macrocarpon* extract were mixed and heated for 5-10 minutes in the water bath. Depending on the amount of reducing sugar present in the test solution, appears green, yellow or red which shows the presences of reducing sugar.
- **Barfoed's Test: In** the aqueous solution of *Vaccinium macrocarpon* extract, 1 ml of Benedict solution was added and heated for boiling. In the presence of monosaccharides red colour indication was seen due to formation of cupric oxide.

2.4.2. Tests for Alkaloids

- **Dragendorff's Test:** 1 ml of *Vaccinium macrocarpon* extract was taken. Alcohol was mixed and was shaken well with little drops of acetic acid and Dragendroff's reagent. The presence of alkaloids indicates by the presence of an orange red precipitate.
- **Wagner's Test:** In acetic acid 1ml of *Vaccinium macrocarpon* extract was dissolved. Few drops of Wagner's reagent were added. The presence of alkaloids indicated the reddish-brown precipitate.

2.4.3. Test for Saponins

Froth Test: 1ml of *Vaccinium macrocarpon* extract was added in distilled water and shaken well. The presence of saponin was indicated by stable froth formation.

2.4.4. Test for Triterpenoids and Steroids

- **Libermann-Burchard Test:** The *Vaccinium macrocarpon* extract was dissolved in chloroform. To it 1 mL of acetic acid and 1 mL of acetic anhydride were added, then heated on a water bath and subsequently cooled. Then added few drops of concentrated sulphuric acid along the sides of the test tube. Presence of steroids indicated by the appearance of bluish green colour.
- **Salkowski Test:** The *Vaccinium macrocarpon* extract was dissolved in chloroform and equal volume of concentrated sulphuric acid was added. The presence of steroids was indicated by the formation of bluish red to cherry red colour in chloroform layer and green fluorescence in the acid layer.

2.4.5. Total phenolic content

The total phenolic content of *Vaccinium macrocarpon* extract was determined using the Folin-Ciocalteu Assay. The Folin-ciocalteu reagent is sensitive to reducing compounds including polyphenols. They produce a blue colour upon reaction (**Tangco *et al.*, 2015**).

2.4.6. Total Flavonoid Content

The flavonoid content was determined using Aluminium chloride method. Total flavonoid content was determined from the calibration curve and results were indicated as mg Rutin equivalent per gram dry extract weight (**Parthasarathy S *et al.*, 2009).**

2.5. Quantitative Phytochemical Estimation

2.5.1.Total phenolic content

The total phenolic content of *Vaccinium macrocarpon* extract was determined using the Folin-Ciocalteu Assay. The extracts (0.2 mL from stock solution) were mixed with 2.5 mL of Folin-Ciocalteu Reagent and 2mL of

7.5% sodium carbonate. This mixture was diluted up to 7 mL with distilled water. Then the resulting solutions were allowed to stand at room temperature for 2 hrs before the absorbance was measured spectrophotometrically at 760 nm. Calibration curves were composed using standard solutions of Gallic Acid Equivalent (GAE) mg/gm. Concentration of 20, 40, 60, 80, and 100 µg/mL of Gallic aid was prepared. The Folin-ciocalteu reagent is sensitive to reducing compounds including polyphenols. They produce a blue colour upon reaction. This blue colour was measured spectrophotometrically. (**Tangco *et al.*, 2015**).

2.5.2. Total flavonoid content

The flavonoid content was determined using Aluminium chloride method. 0.5 ml of *Vaccinium macrocarpon* extract solution was mixed with 2 ml of distilled water. Then, 0.15 ml of sodium nitrite (5%) was added and mixed properly. After that, wait for 6 minutes before adding 0.15 ml Aluminium chloride (10 %) and allowed to stand for 6 minutes. Then, 2 ml of 4% sodium hydroxide was added. The mixture was shaken and mixed thoroughly. Absorbance of mixture was estimated at 510 nm using UV spectrophotometer. Calibration curves were composed using standard solutions of Rutin Equivalent (GAE) mg/gm. Concentration of 20, 40, 60, 80, and 100 µg/mL of Rutin was prepared. Total flavonoid content was determined from the calibration curve and results were indicated as mg Rutin equivalent per gram dry extract weight (**Parthasarathy S *et al.*, 2009).**

2.6. Acute Toxicity Study

The acute toxic class method set out in guideline is a stepwise procedure with the use of 3 animals of a single sex per step. The substance is administered orally to a group of experimental animals at one of the defined doses. The substance is tested using a stepwise procedure, each step using three animals of a single sex. Absence or presence of compound-related mortality of the animals dosed at one step will determine the next step, i.e.; no further testing is needed, dosing of three additional animals, with the same dose and, dosing of three additional animals at the next higher or the next lower dose level. Three animals are used for each step. The dose level to be used as the starting dose is selected from one of four fixed levels, 5, 50, 300 and 2000 mg/kg body weight **(Guideline Document on Acute oral Toxicity 1996).**

2.7. Antioxidant activity by DPPH free radical

The antioxidant activity of *Vaccinium macrocarpon* extract was determined by using the DPPH free radical scavenging assay. 1 mg/ml methanol solution of extracts/standard was prepared (**Athavale *et al.*, 2012).**

Percentage antioxidant activity of sample/standard was calculated by using formula:

% Inhibition = [(Ab of control- Ab of sample/ Ab of control x 100]

2.8. *In vivo* study

2.8.1. Animals Protocol

All animal experiments were approved by Institutional Animal Ethics Committee (IAEC). Wistar Albino rats aged 5-6 weeks and weighing 250-300 were taken for the study.

2.8.2. Experimental protocol (Yousef *et al.*, 2009)

The Nephroprotective activity was tested on five groups of albino wistar rats of either sex, each group consisting of six animals. Group-I: Served as normal control received 0.5 % DMSO (Dimethyl sulphoxide); for 15 days. Group-II: Served as Nephrotoxic control, received vehicle (Cisplatin). Group-III: Received the standard Nephroprotective drug, (Lipoic acid (50mg/kg; p.o)). Group-IV: Received methanolic extract of *Vaccinium macrocarpon* (200mg/kg; p.o).Group-V**:** Received methanolic extract of *Vaccinium macrocarpon* (400mg/kg; p.o).

2.8.3. Blood collection techniques used in the present study

At the end of the experimental period, ie on the 15th day animals were sacrificed under mild ether anesthesia. The blood was collected by retro-orbital vein puncture using a fine capillary to an anticoagulant tube and allowed to stand for 30 min at 37°C and then centrifuged to separate the serum to evaluate the biochemical markers (Yousef *et al.*, 2009).

2.8.4. Preparation of kidney homogenate

The kidney was quickly removed and perfused immediately with ice-cold saline (0.9% NaCl). A portion of the kidney was homogenized in chilled Tris-HCl buffer (0.025 M, pH 7.4) using a homogenizer. The homogenate obtained was centrifuged at 5000 rpm for 10 minutes, supernatant was collected and used for various biochemical assays (Yousef *et al.*, 2009).

2.8.5. Analysis of general parameters

1. Estimation of urine volume

The animals are kept in separate metabolic cages for 24 hours. Each rat urine volume are taken after 24 hours. The food wastes and fecel matters are removed from the urine. And the volume of urine is measured by using measuring cylinder.

2. Estimation of Body weight

At the end of the experiment, each group of the animals were kept individually in the cages. Remove the food and water, and each animal are individually weighed and the weight were recorded.

2.7.6. Analysis of serum biochemical parameters

2.7.6.1. Estimation of Serum Creatinine

Five test tubes were labelled as A, B, C, D and E. Where A&B is taken as standard, C &D taken as test and the E where taken as blank. Into E (blank), 2 ml of distilled water, into C&D (test), 0.5 ml serum and 1.5 ml of water, into A& B (standard), 1.5 ml of water and 0.5 ml

of creatinine standard (3mg/dl) were pipette out. 6 ml of picric acid and 0.4 ml of sodium hydroxide (NaOH) (2.5M) were added in all the five test tubes (Slot C *et al.*, 1965).

2.7.6.2. Estimation of Serum Blood urea nitrogen (BUN)

The blood urea was estimated by Berthelot method (Fawcett and Scott, 1960) using the commercially available kit (Kamineni Life Sciences Pvt. Ltd. Hyderabad, India). The intensity of the colour produced is directly proportional to the concentration of urea in the sample and is measured spectrophotometrically at 578 nm. The blood urea was calculated using the following formula (Fawcett, J.K *et al.*, 1960):

$$\text{Blood urea (mg/dl)} = \frac{\text{Absorbance of test} \times 40}{\text{Absorbance of std}}$$

3. RESULTS

3.1. Percentage Yield

In phytochemical extraction the percentage yield is very crucial in order to determine the standard efficiency of extraction for a specific plant, various sections of the same plant or different solvents used. The yield of extracts received from the *Vaccinium macrocarpon* is shown in **Table 1.**

Table 1: Percentage Yield of crude extracts of *Vaccinium macrocarpon* extract.

Plant name	Solvent	Theoretical weight	Yield(gm)	% yield
Vaccinium macrocarpon	Pet ether	300	1.21	0.40%
	Methanol	283.02	5.99	2.11%

3.2. Preliminary Phytochemical study

Phytochemical study of both pet ether and methanolic extract are shown in Table 2. Study revealed that methanolic extract showed the presence of alkaloids, glycoside, carbohydrate, protein, amino acid, flavonoids, tannin, saponin, Triterpenoids and Steroids. But Pet ether extract contains only glycoside, protein, amino acid, saponin, Triterpenoids and Steroids.

Table 2: Phytochemical testing of extract.

S. No.	Experiment	Presence or absence of phytochemical test	
		Pet. Ether extract	Methanolic extract
1.	**Alkaloids**		
1.1	Dragendroff's test	Absent	Present
1.2	Mayer's reagent test	Absent	Present
1.3	Wagner's reagent test	Absent	Present
1.3	Hager's reagent test	Absent	Present
2.	**Glycoside**		
2.1	Borntrager test	Present	Present
2.2	Legal's test	Present	Present
2.3	Killer-Killiani test	Present	Present
3.	**Carbohydrates**		
3.1	Molish's test	Absent	Present
3.2	Fehling's test	Absent	Present
3.3	Benedict's test	Absent	Present
3.4	Barfoed's test	Absent	Present
4.	**Proteins and Amino Acids**		
4.1	Biuret test	Present	Absent
5.	**Flavonoids**		
5.1	Alkaline reagent test	Absent	Present
5.2	Lead Acetate test	Absent	Present
6.	**Tannin and Phenolic Compounds**		
6.1	Ferric Chloride test	Absent	Present
7.	**Saponin**		
7.1	Foam test	Present	Absent
8.	**Test for Triterpenoids and Steroids**		
8.1	Salkowski's test	Present	Present
8.2	Libbermann-Burchard's test	Present	Present

3.3. Quantitative Analysis

Preliminary phytochemical testing of crude extracts confirmed the presence of phenolics and flavonoids in plant material. The estimated amount of total phenolic (TPC) and total flavonoid content (TFC) assays is shown in **Table 3.**

Table 3: Total phenolic and total flavonoid content *Sesbania cannabina* extract.

S. No.	Solvents→ Bioactive compound↓	Methanolicextract
***Vaccinium macrocarpon* extract**		
1.	Total phenol (Gallic acid equivalent (GAE) mg/100mg)	54
2.	Total flavonoid (Rutin equivalent (RE) mg/100mg)	42.33

3.4. *In vitro* Antioxidant Assays

In the present investigation, the *in vitro* anti-oxidant activity of extracts of *Vaccinium macrocarpon was* evaluated by DPPH (1,1-diphenyl-2-picryl hydrazyl Assay) radical scavenging activity. The results of DPPH radical scavenging activity of reference ascorbic acid and plant extract are summarized in **Tables 4. Figure 1, 2** showed DPPH radical scavenging activity of Std. Ascorbic acid and extract of *Vaccinium macrocarbon*.

Table 4: DPPH radical scavenging activity of reference ascorbic acid and methanolic extract.

Concentration	Ascorbic acid (% Inhibition)	Methanolic extract of *Vaccinium macrocarpon* (% Inhibition)
20	52.757	42.919
40	56.919	46.871
60	65.660	49.835
80	71.279	53.238
100	86.368	60.153
Control	0.961	0.911
IC_{50}	19.31	57.10

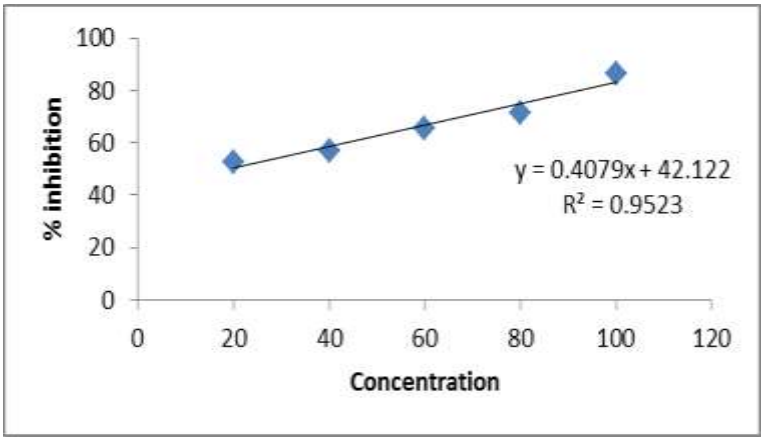

Figure 1: DPPH radical scavenging activity of Std. Ascorbic acid.

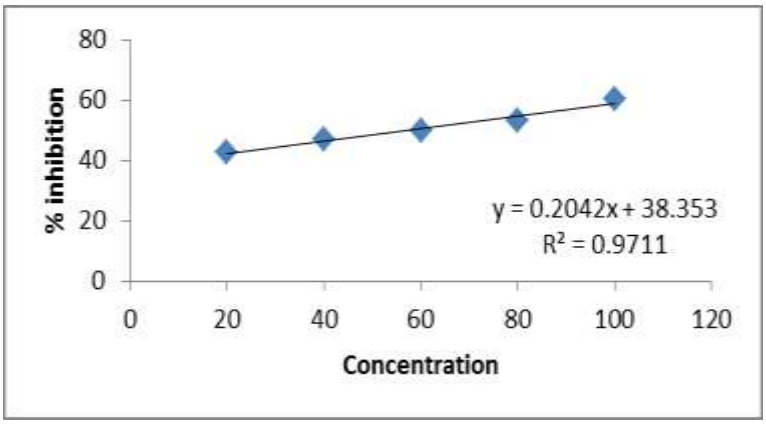

Figure 2: Represents the Percentage Inhibition Vs Concentration of extract of *Vaccinium macrocarbon.*

3.5. Analysis of general parameters

3.5.1. Estimation of urine volume

Urine volume of each rat of all groups was measured and reported in **Table** 5 and graph is shown in **Figure 3**.

Table 5: Urine volume.

Groups	Urine volume
Normal Control(0.5% DMSO)	10.90±0.223
Nephrotoxic Control Cisplatin (0.75%)	6.01±0.762
Standard Lipoic acid (50mg/kg)	10.86±0.24
Vaccinium macrocarpon extract (200mg/kg)	9.45±0.40
Vaccinium macrocarpon extract (400mg/kg)	9.87±0.28

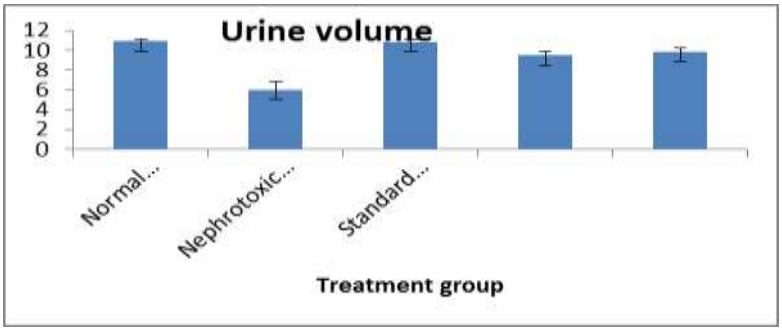

Figure 3: Urine volume.

3.5.2. Estimation of Body weight

Body weight of each rat of all groups was measured and reported in **Table 6** and graph shown in **Figure 4.**

Table 6: Body weight of all group animal.

Groups	Body weight
Normal Control(0.5% DMSO)	250±3.406
Nephrotoxic Control Cisplatin (0.75%)	158.22±2.658
Standard Lipoic acid (50mg/kg)	235.12±4.355
Vaccinium macrocarpon extract (200mg/kg)	206.54±3.43
Vaccinium macrocarpon extract (400mg/kg)	223±3.742

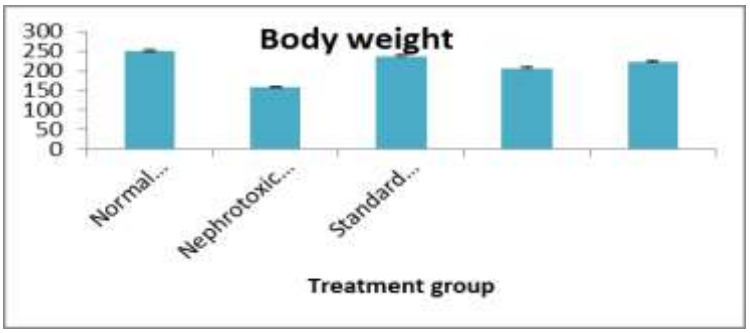

Figure 4: Body weight.

3.6. Analysis of serum biochemical parameters

3.6.1. Estimation of Serum Creatinine

Serum Creatinine level of each rat of all groups was measured and reported in **Table 7** and graph shown in **Figure 5.**

Table 7: Serum Creatinine.

Groups	Serum Creatinine
Normal Control(0.5% DMSO)	0.68±0.055
Nephrotoxic Control Cisplatin (0.75%)	4.78±0.131
Standard Lipoic acid (50mg/kg)	0.76±0.206
Vaccinium macrocarpon extract (200mg/kg)	1.48±0.020
Vaccinium macrocarpon extract (400mg/kg)	0.83±0.062

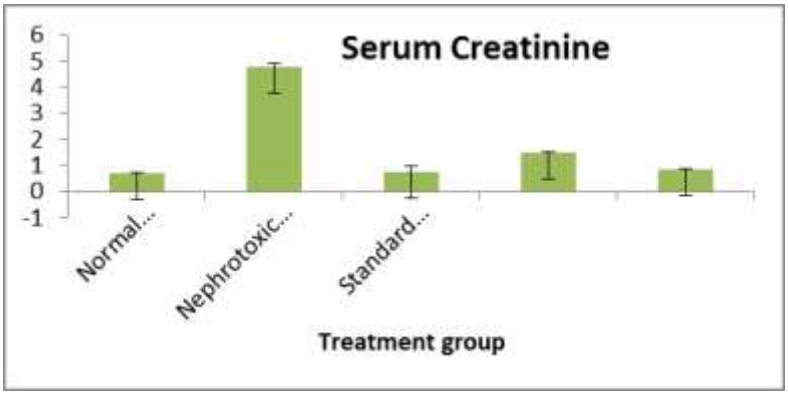

Figure 5: Serum Creatinine.

3.6.2. Estimation of Serum Blood urea nitrogen (BUN)

Serum Blood urea nitrogen level of each rat of all groups was measured and reported in **Table 8** and graph shown in **Figure 6.**

Table 8: Serum Blood urea nitrogen.

Groups	Serum Blood urea nitrogen
Normal Control(0.5% DMSO)	24.66±0.505
Nephrotoxic Control Cisplatin (0.75%)	59.77±0.792
Standard Lipoic acid (50mg/kg)	25.15±0.50
Vaccinium macrocarpon extract (200mg/kg)	31.02±0.94
Vaccinium macrocarpon extract (400mg/kg)	25.55±0.55

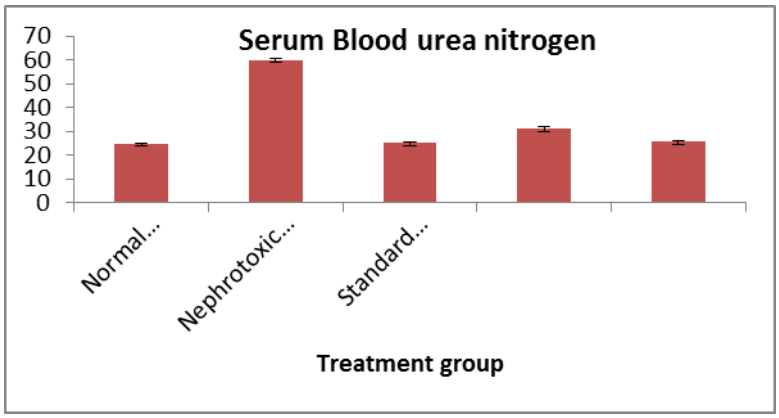

Figure 6: Serum Blood urea nitrogen.

3.7. *In vivo* study

3.7.1. Histology of Group 1 animal: normal control received 0.5 % DMSO (Dimethyl sulphoxide); for 15 days.

Histology of Group 1 animals are shown in Figure 7.

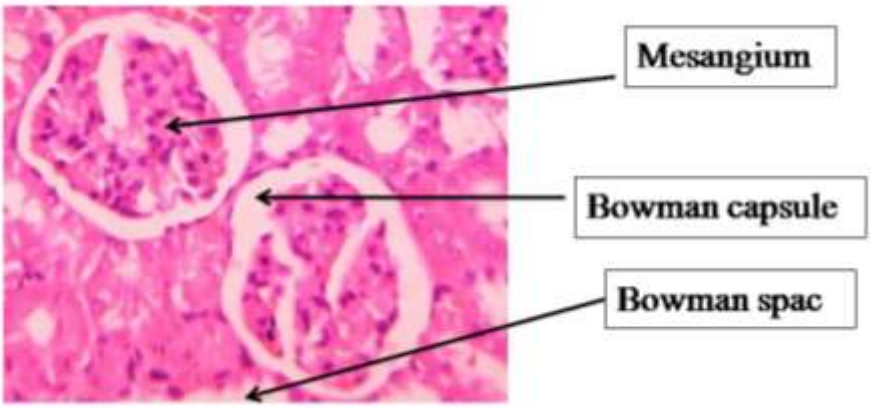

Figure 7*:* Normal Control.

3.7.2. Histology of Group-II: Served as Nephrotoxic control, received vehicle (Cisplatin)
Histology of Group 2 animals are shown in **Figure 8**.

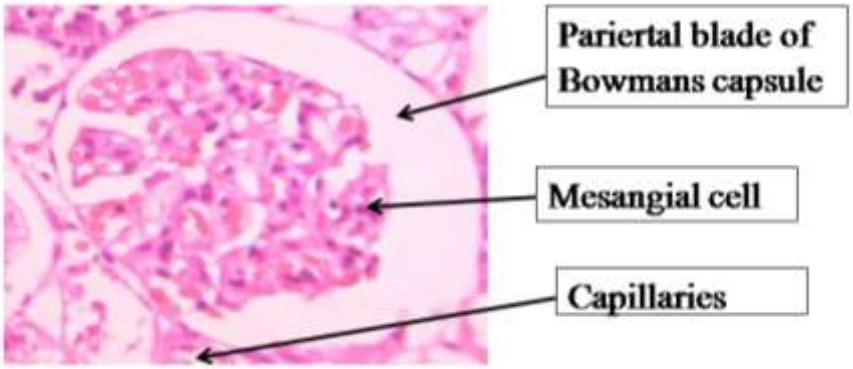

Figure 8*:* Nephrotoxic Control Cisplatin.

Histology of Group-III: Received the standard Nephroprotective drug, (Lipoic acid (50mg/kg; p.o))

Histology of Group 3 animals are shown in **Figure 9**.

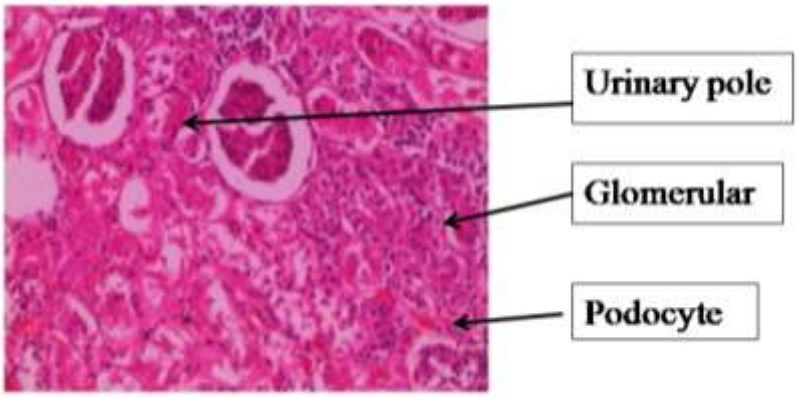

Figure 9*:* Standard Lipoic acid.

Histology of Group-IV: Received methanolic extract of *Vaccinium macrocarpon* (200mg/kg; p.o).

Histology of Group 4 animals are shown in **Figure 10**.

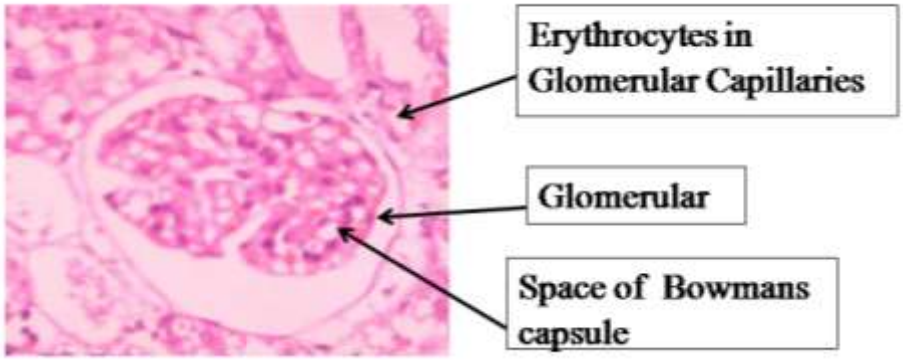

Figure 10*: Vaccinium macrocarpon* extract (200mg/kg).

Histology of Group-V: Received methanolic extract of *Vaccinium macrocarpon* (400mg/kg; p.o) Histology of Group 5 animals are shown in **Figure 11**.

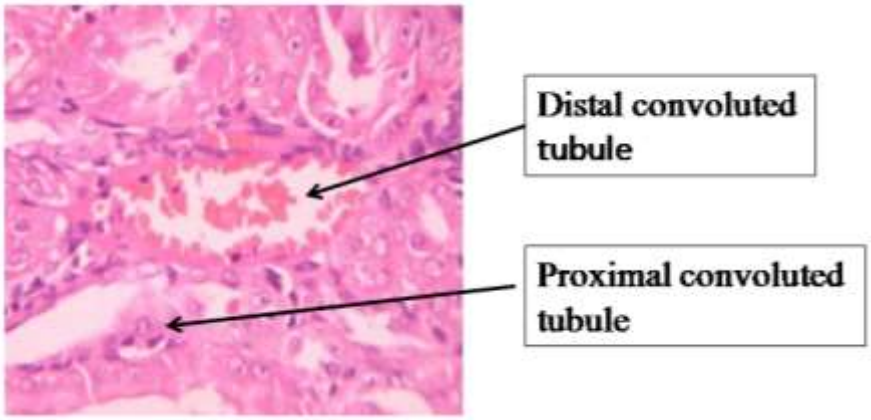

Figure 11*: Vaccinium macrocarpon* extract (400mg/kg).

4. DISCUSSION

Phytochemical analysis of methanolic extract of *Vaccinium macrocarpon* showed the presence of carbohydrate, alkaloids, phenolics, tannin, flavonoids and glycoside. Quantitative phytochemical assay was performed by calculating total phenolic content (TPC) and total flavonoid content (TFC). The TPC was calculated with respect to gallic acid (standard) and TFC was then calculated with respect to rutin taken as standard. Results shown in Table 3. In the oral acute toxicity studies, *Vaccinium macrocarpon* was found to be safe as it did not cause any mortality up to 2000 mg/kg. Hence, 200 and 400 mg/kg doses were selected for the present study. DPPH radical scavenging activity of *Vaccinium macrocarpon* extract exhibited percent inhibition 60.15% and its IC_{50} value was found to be 57.10µg/ml. Ascorbic was used as a reference compound which exhibited percent inhibition 86.36% and showed IC 50 value of 19.36 µg/ml. In present study, the rats treated with single dose of Cisplatin shown marked reduction of body weight as compared to normal group also caused a marked reduction of glomourular filtration rate, which is accompanied by increase in serum creatinine level indicating induction of acute renal failure with *Vaccinium macrocarpon* at the dose level of 200 and 400 mg/kg body weight for 15 days significantly lowered the serum level of creatinine with a significant weight gain and increased urine output when compared with the nephrotoxic control group. Cisplatin administration to control rats produced a typical pattern of nephrotoxicity which was manifested by marked increase in serum blood urea nitrogen (BUN).[65] *Vaccinium macrocarpon* supplementation to Cisplatin treated rats recorded decrement in levels of blood urea nitrogen (BUN) in plasma. Histopathological studies on isolated kidney revealed that the *Vaccinium macrocarpon*, reversed the kidney damage and also restored normal kidney architecture. In summary, the *Vaccinium macrocarpon* an methanolic extract showed statistically significant nephroprotective activity. The plant extract proved to have nephroprotective potentials may because of its known flavonoid contents and antioxidant properties.

5. CONCLUSION

The administration of cisplatin during experimentation is effectively induced apoptosis and necrosis, which was similar to acute renal failure in human. Therefore it is an effective and an ideal model for nephrotoxicity research. The evaluation of renal parameters on nephrotoxic rats with *Vaccinium macrocarpon* showed significantly elevate the attenuated body weight, urine volume and

significant reduce in elevated serum creatinine level, which supports its Nephroprotective activity.

6. REFERENCES

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