Archives of Nephrology

Volume 1, Issue 1, 2018, PP: 19-27

Pharmacological Potential of Polyherbal Root Extracts Combination for the Management of Nephrotic Disorders in Rats

Harikesh Maurya[1]*, Sunil Kumar[2], Tirath Kumar[1]

[1]Dept. of Pharmaceutical Sciences, Kumaun University, Bhimtal Campus, Nainital, India.

[2]Hygia Institute of Pharmaceutical Education and Research, Prabandh Nagar, Lucknow, India.

mauryaharikesh2@gmail.com

***Corresponding Author:** Harikesh Maurya, Department of Pharmaceutical Sciences, Kumaun University, Bhimtal Campus, Bhimtal, Nainital, India.*

Abstract

***Objective:** The present study was designed to evaluate pharmacological activity of polyherbal combination of root extract 'BCCTFV' for the management of nephrotic disorders in rats.*

***Methods:** Nephrotoxicity was induced by administration of gentamicin i.p. 100mg/kg for 7 days in experimental animal. The effect of simultaneous administration of hydroalcoholic root extract of BCCTFV prepared for combining six medicinal herbs, i.e., B. diffusa, C. nurvala, C. fistula, T. cordifolia, F. hispida and V. negundo for the suppression of nephrotic symptoms. The prepared extract was administered at different dose level, i.e., 12.5mg/kg, 25mg/kg, and 50mg/kg body weight and the marketed drug Cystone 500mg/kg was used as standard control.*

***Result:** The study reveals that in BCCTFV treated rats maintained all the elevated parameters such as serum creatinine (1.40±0.57mg/dl), serum urea (22.72±1.73 mg/dl), serum uric acid (2.98±0.44 mg/dl) and blood urea nitrogen (21.66±1.88 mg/dl) levels and also evident by the histopathological analysis.*

***Conclusion:** Finally it was concluded that the hydroalcoholic extract of BCCTFV 25mg/kg shows better response to protect rats' kidney and maintain all those markers causing nephrotic disorder.*

Keywords: *BCCTFV, Nephroprotective, Gentamicin, Creatinine, Urea, Uric acid, BUN.*

Introduction

Nephrotic disorders (ND) are a group of diseases that causes dysfunction of the kidney, founded in severe condition to prevent damage of organs. Many herbs represent nature's central storehouse of raw materials for the management of various human ailments [1]. The alternate of kidney function leads to kidney failure and the patient undergoing critical dialysis will highly dependent on hemodialysis, in which several patients don't afford the complete treatment cost [2]. The drug complications were seen in earlier stages of kidney failure patients and 10% exceedingly at risk with renal insufficiency with serum creatinine >1.5 mg/dl. The drug-related adverse event experienced with >0.5% of these proceedings considered severe, and 4.5% of the events found life-threatening, which departed for kidney transplantation [3].

A large number of affected patients even though costs concerned and distressing consequences of medication-related problems like prolonging hospitalization, dialysis even organ transplantation, etc. presently identified regarding the impact of renal impairment on drug disposition, including those drugs eliminated primarily by hepatic pathways play the critical role for worsening conditions [4].

The prepared Polyherbal combination BCCTFV consist of six major well-reported herbs for the management of ND, i.e., Boerhaavia diffusa, Crateva nurvala, Cassia fistula, Tinospora cordifolia, Ficus hispida and Vitex negundo. This study was designed to evaluate the protective effect of BCCTFV against Gentamicin-induced ND in rats [5]. The free radical scavenging and antioxidant activity of used herbs reported that

similar action in renal collapses and also well known for the same work in the presence of their chemical constituents such as flavonoids and polyphenolic compounds [6,7]. The extent of the protective effect was analyzed by studying serum and toxic urine markers and confirm with histopathology of kidney tissues [8]. Gentamicin is a broad spectrum antibiotic frequently used due to its high efficacy against gram-negative bacteria [9]. The prime side effect of this class of antibiotics is nephrotoxicity and the use is restricted due to the development of ototoxicity and Nephrotoxicity.

Materials and Method

Plant Collection and Authentication

Freshly dried root parts of all selected herbal plants were collected from Khari baoli New Delhi and were thoroughly made free from foreign matter. The collected plant materials were taxonomically identified, and botanical scientist has done authentication, the specimen letter no. BSI/NRC/Tech. (Ident.)/2017/194 at Botanical Survey of India (BSI), the northern regional center, Dehradun, India.

Preparation of Extract

BCCTFV was prepared by the equal proportion of hydroalcoholic root extract of selected plants (500gm each) by using cold maceration method (table 1). The collected extract was dried by using rotatory evaporator at temperature of 45±5°C until the entire solvent gets evaporated. The obtained dried extract powder was stored in a well tightly closed container [10].

Table 1. *The list of the selected polyherbal plant used in the polyherbal combination*

S. No.	Botanical Name/ Family	Part	Dose	Properties	Reference
1	*Boerhaavia diffusa* (Nyctaginaceae)	Root part of each plant was used	The prepared drug at the dose of 12.5, 25 & 50 mg/kg body weight administered orally	Diuretic, Relieves edema	Rajpoot K, et al. 2011 [11]
2	*Crateva nurvala* (Capparaceae)			Improve Kidney failure, Kidney stone, Dysuria	Khattar V, et al. 2012 [12]
3	*Cassia fistula* (Fabaceae)			Restoring kidney functions	Wankhade TR et al. 2014 [13]
4	*Tinospora cordifolia* (Menispermaceae)			Boosting immune system, Bacterial infection	Soham S, et al. 2013 [14]
5	*Ficus hispida* (Moraceae)			Nephroprotective, blood Purifier	Anasane PD, et al. 2017 [15]
6	*Vitex negundo* (Verbenaceae)			Urinary disorders, Diuretic action	Kadir FA, et al. 2013 [16]

Experimental Animals

Albino Wistar rats (150-200g) were procured and followed the animal ethical clearance from the animal house of Hygia Institute of Pharmaceutical Education & Research, Lucknow IAEC Reg. No. HIPER/IAEC/11/18/01. All experimental animals were kept in polypropylene cages (6 rats per cage) at 25±2°C temperature with relative humidity 45-55% under 12h light and dark cycles. All the animals were acclimatized for laboratory condition as per CPCSEA guideline for a week before starting the experiment. All the animals were fed with standard diet and fresh water ad libitum. The experimental protocol complied with the animal ethics committee and nationally accepted principles for the use and care of the laboratory animals.

Experimental Design

After acclimatization Wistar rats (150-200g) were divided into six groups having six animals each. Group, I treated as normal control. Group II disease control treated with (Gentamicin 100mg/kg i.p. for 7 days) continued with normal saline. Group III treated with test combination-BCCTFV at a dose of 12.5mg/kg p.o.; Group IV treated with test combination-BCCTFV at a dose of 25mg/kg p.o.; Group V treated with test combination-BCCTFV at a dose of 50mg/kg p.o.; Group VI treated with standard drug (Cystone 500mg/kg p.o.) next day after Gentamicin administration, all the experiment was continued for 42 days.

Biochemical Estimations

Body Weight

The animal body weight was recorded on the first day and at the end of the study in each group of animals.

Kft Profile in Blood & Urine

Creatinine, total protein, urea, uric acid levels and total bilirubin in serum and in urine sample along with 24 hours urinary volume were determined by using commercial glucometer kit at the end of this experiment.

Antioxidant Activity

Malondialdehyde (MDA), Glutathione reduced (GSH), Catalase (CAT), Superoxide dismutase (SOD), and Nitric oxide (NO) were estimated in kidney supernatant [17-21] using Biodiagnostic kits manufacture by Avi Chem Industries. Total protein was also determined in kidney supernatant using the Biodiagnostic kit as per method described by Gornal et al. 1949 [22].

Histopathological Analysis

Kidney tissues were obtained at the end of study after scarification of animals and immediately fixed in 10% neutral formalin buffered solution. The tissue section was stained with hematoxylin and eosin (H & E stain) and examined under the light microscope at 40x.

Statistical Analysis

All the data were expressed as Mean±SEM followed by one way ANOVA with Bonferroni's multiple comparison test (n=6). $^{\#}P<0.05$ represents statistical significance against normal control, while $^{**}P<0.05$ represents statistical significance against disease control whereas NS shows a non-significance comparison between the groups.

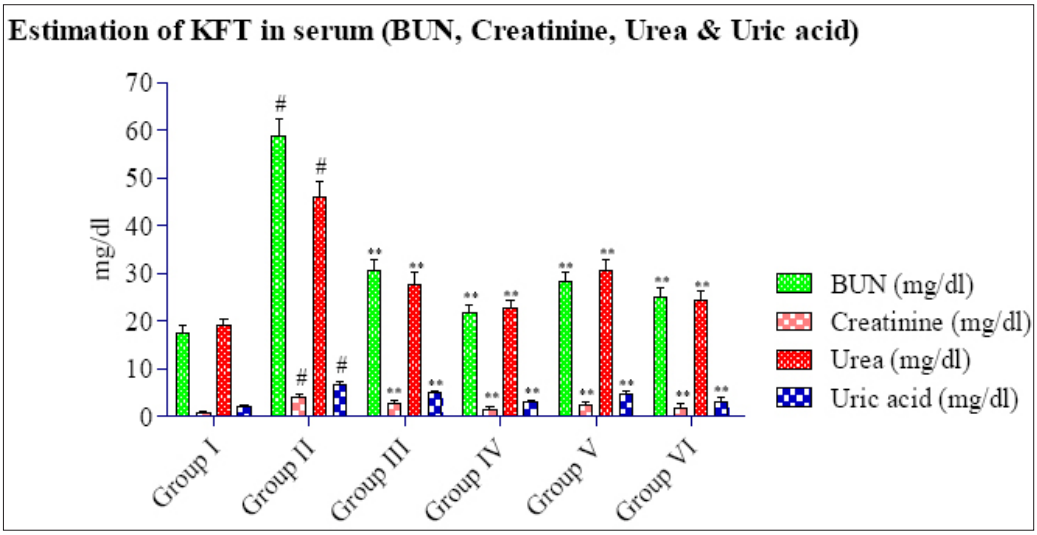
Results and Discussion

Body Weight

The average body weight of the animal in gentamicin treated rat showed a slight decrease in body weight (160g) compared with treatment as well as normal control rat (200g), while the combination BCCTFV and standard drug-treated animals showed a little increase in body weight (185g) as compared to Gentamicin treated group of animal.

Estimations of Blood Profile

Gentamicin treated rats showed significant ($^{\#}P<0.05$) increase in levels of total BUN (58.67±3.66mg/dl), creatinine (4.08±0.72 mg/dl), urea (45.91±3.34 mg/dl), and uric acid (6.70±0.64 mg/dl) in serum sample as compared to normal control. While in standard and BCCTFV treatment group significantly ($^{**}P<0.05$) maintain these elevated levels compared to Gentamicin treated rats (graph 1) and also support up to normal values obtained from the normal control group. The BCCTFV low dose treatment group improve more significant ($^{\#}P<0.05$) in the maintenance of total BUN (21.66±1.88 mg/dl), creatinine (1.40±0.57 mg/dl), urea (22.72±1.73 mg/dl) and uric acid (2.98±0.44 mg/dl).



Graph 1. *Estimation of kidney function test in serum BUN, creatinine, urea and uric acid*

Values are given as Mean±SEM of experimental animals (n=6), $^{\#}P<0.05$ represents statistical significance against normal control, $^{**}P<0.05$ represents statistical significance against disease control.

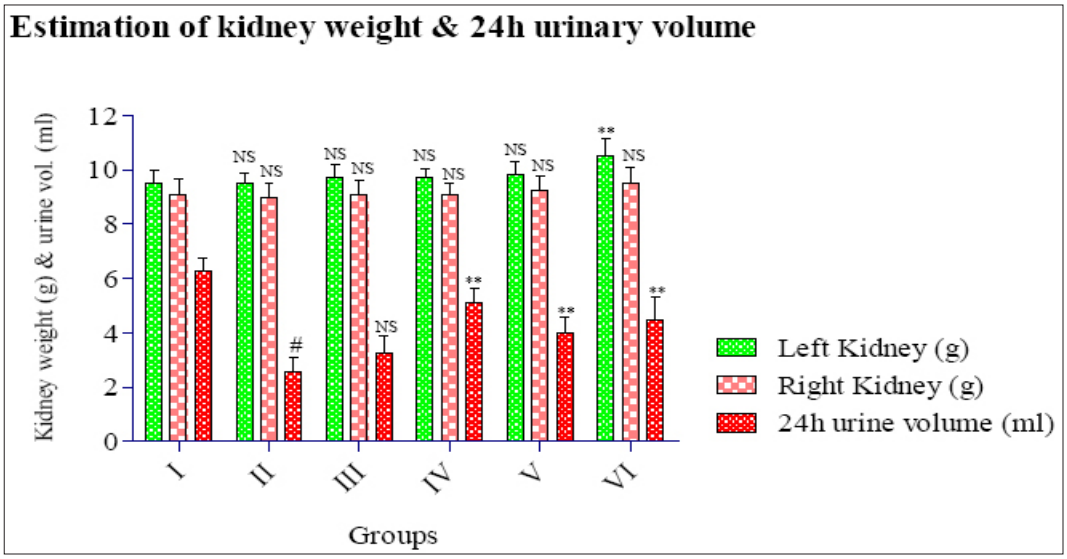
Estimation of Electrolytes Concentration

The estimation of test for electrolytes includes the measurement of sodium, potassium, calcium and Magnesium in serum shows that the concentration of serum Sodium observed as remarkably increased ($^{\#}P<0.05$) in disease control (182.00±13.06 mmol /L). The herbal combination at doses of 12.5mg (163.33 ± 10.49 mmol/L), 25mg (146.83±8.67 mmol/L) and 50mg (157.17 ± 9.56 mmol/L) treatment group shows significantly ($^{**}P<0.05$) maintained the levels of sodium. Standard treatment (cystone 500mg/kg) shows significant ($^{**}P<0.05$) improvement in the level of sodium (155.33±9.34 mmol/L) at the end of the study. The serum potassium (5.52±1.22 mmol/L) and calcium (12.23±2.00 mmol/L) were significantly ($^{\#}P<0.05$) increased in disease control. On the other hand the level of magnesium (1.31±0.88 mmol/L) significantly lowers. The prepared herbal combination at doses of 12.5, 25 and 50 mg/kg/day treatment and standard (cystone) drug significantly ($^{\#}P<0.05$) reduces the elevated levels of serum potassium and calcium while the magnesium level was observed as lowered in disease control. After treatment with herbal combination at doses of 12.5, 25 and 50 mg/kg/day treatment and cystone significantly ($^{**}P<0.05$) maintained the level of magnesium i.e., BCCTFV-12.5 (2.19±0.90 mmol/L), BCCTFV-25 (2.44±0.76 mmol/L) and BCCTFV-50 (2.64±0.83 mmol/L) which was compared as normal control group (2.77±0.53 mmol/L) (table 2).

Table 2. *Estimation of electrolytes in serum potassium, calcium, magnesium and sodium*

Group Description	Sodium (mmol/L)	Potassium (mmol/L)	Calcium (mmol/L)	Magnesium (mmol/L)
Normal control (Saline 0.9%)	142.83±11.40	3.45±0.85	8.59±1.88	2.77±0.53
Disease control (Gentamicin 100mg/kg)	182.00±13.06$^{\#}$	5.52±1.22$^{\#}$	12.23±2.00$^{\#}$	1.31±0.88$^{\#}$
Gentamicin + BCCTFV-12.5mg/kg	163.33±10.49**	3.29±0.88**	9.31±1.05**	2.19±0.90^{NS}
Gentamicin + BCCTFV-25mg/kg	146.83±8.67**	3.74±0.86**	8.61±1.00**	2.44±0.76^{NS}
Gentamicin + BCCTFV-50mg/kg	157.17±9.56**	5.15±1.04^{NS}	9.04±1.75**	2.64±0.83**
Gentamicin + Cystone 500mg/kg	155.33±9.34**	4.12±1.00^{NS}	9.03±1.54**	2.46±0.92^{NS}

Values are given as Mean±SEM of experimental animals (n=6), $^{\#}P<0.05$ represents statistical significance against normal control, $^{**}P<0.05$ represents statistical significance against disease control, and NS=Non significance.



Graph 2. *Estimation of left & right kidney weight and 24h urinary volume*

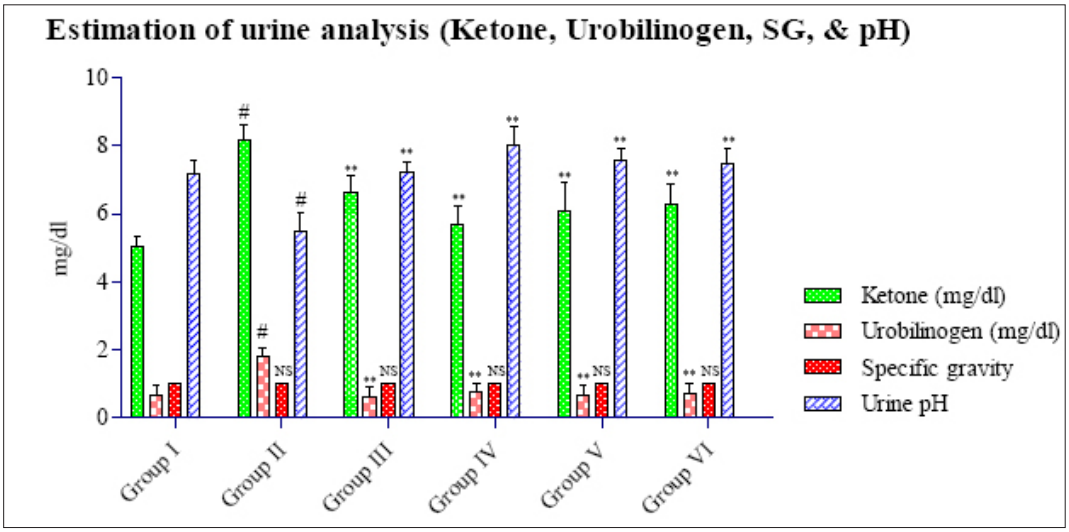
Values are given as Mean±SEM of experimental animals (n=6); $^{\#}P<0.05$ represents statistical significance against normal control, $^{**}P<0.05$ represents statistical significance against disease control and NS=Non significance.

Estimations of Kidney Weight and Urinary Volume

The left and right kidney weights all the groups shows non-significant (NS) variation in comparison within the groups. The average weight of left kidney was observed between (9.49-10.53 gm) and in case of right kidney, i.e. (9.11-9.50 gm). Gentamicin treated the group of rats significantly ($^{\#}P<0.05$) lower the levels of 24-hour urine volume as compared to control group as well as all treatment groups. Meanwhile, the BCCTFV-25 shows significantly ($^{**}P<0.05$) improvement in 24-hour urine volume (5.10±0.54 ml) which were comparable to normal control, i.e.; (6.25±0.48 ml) (graph 2).

Estimation of Urine Analysis

Gentamicin (100 mg/kg) produced significant increase ($^{\#}P<0.05$) in Ketone (8.16±0.44 mg/dl), Urobilinogen (1.81±0.24 mg/dl) and pH (5.50±0.52) of urine decreases. Glucose (99.71±0.4 mg/dl) and specific gravity (1.02±0.00) shows non-significant (NS), as compared to control group. The Polyherbal combination at doses of 12.5, 25 and 50 mg/kg/day was observe as very effective and significantly ($^{**}P<0.05$) maintain the elevated level of Ketone (5.70±0.52 mg/dl), Urobilinogen (0.76±0.28 mg/dl), Glucose (97.75±0.38 mg/dl), specific gravity (1.01±0.00) and pH (8.00±0.55) of urine induced by Gentamicin. The standard treatment group also significantly ($^{**}P<0.05$) improve these elevated level Ketone (6.30±0.59 mg/dl), Urobilinogen (0.70±0.30 mg/dl), Glucose (98.77±0.2 mg/dl), SG (1.02±0.00) and pH (7.50±0.43) as compare to disease control (graph 3).



Graph 3. *Estimation of urine analysis ketone, urobilinogen, glucose, SG, and pH*

Values are given as Mean±SEM of experimental animals (n=6); $^{\#}P<0.05$ represents statistical significance against normal control, $^{**}P<0.05$ represents statistical significance against disease control and NS=Non significance.

Table 3. *Estimation of urine analysis bilirubin, protein, blood, Leucocyte, nitrite*

Group Description	Bilirubin (mg/dl)	Protein (mg/dl)	Blood (Ery/µL)	Leucocyte (Leu/µL)	Nitrite (Nit/µL)
Normal control (Saline 0.9%)	+	+	+	+	+
Disease control (Gentamicin)	+++	++++	++++	++	+
Gentamicin + BCCTFV-12.5mg/kg	+++	++++	+++	++	+
Gentamicin + BCCTFV-25mg/kg	+	++	+	+	–
Gentamicin + BCCTFV-50mg/kg	+	+++	++	++	+
Gentamicin + Cystone 500mg/kg	–	+++	++	++	+

The estimation of urine analysis Bilirubin, Protein, Blood, Leucocyte, and Nitrite were significantly increased ($^{\#}P<0.05$) in disease control. All the treatment groups at different doses remarkably maintain these elevated parameters. But in case of BCCTFV-25 shows significantly ($^{**}P<0.05$) maintained the elevated levels of Bilirubin, Protein, Blood, Leucocyte, and Nitrite as compare to disease control (table 3).

Estimation of Antioxidant Enzymes

The antioxidants biomarkers like malondialdehyde (MDA), glutathione reduced (GSH), catalase (CAT), superoxide dismutase (SOD), and nitric oxide (NO) contents have been estimated in kidney supernatant (table 4) by using Biodiagnostic kits (Biodiagnostic, Dokki, Giza, Egypt). Total protein was also determined in kidney supernatant using the Biodiagnostic kit as per the method described by Gornal et al., 2010.

Table 4. *Estimation of the Antioxidant enzyme in kidney homogenate*

Group No.	MDA (mmol/g. protein)	GSH (mg/g. protein)	CAT (U/g. protein)	SOD (U/g. protein)	NO (Mmol/g. protein)
Group I	6.47±1.69	21.07±3.44	10.87±2.11	964.53±28.89	166.56±10.88
Group II	11.10±2.49$^{\#}$	13.02±2.81$^{\#}$	5.92±1.60$^{\#}$	659.97±18.92$^{\#}$	317.04±18.52$^{\#}$
Group III	8.02±1.72**	16.01±2.04^{NS}	8.21±1.82^{NS}	791.24±23.13**	274.98±20.45**
Group IV	7.01±1.05**	18.08±3.55**	9.09±2.55**	849.45±27.87**	207.04±13.54**
Group V	8.31±2.31^{NS}	16.54±2.0^{NS}	7.82±1.38^{NS}	856.16±25.99**	260.88±16.08**
Group VI	8.08±2.02^{NS}	17.59±2.43**	7.78±1.49^{NS}	840.26±24.01**	252.08±15.74**

Values are given as Mean±SEM of experimental animals (n=6); $^{\#}P<0.05$ represents statistical significance against normal control, $^{**}P<0.05$ represents statistical significance against disease control and NS=Non significance.

In the estimation of antioxidant biomarkers, it was observed that, Gentamicin (100 mg/kg) produced a significant increase ($^{\#}P<0.05$) in MDA (11.10±2.49 mmol/g). Protein contents of renal tissue, as compared to normal control group. On the other hand, Gentamicin diminishes the antioxidant defense system by significantly ($^{\#}P<0.05$) decreasing the GSH (13.02±2.81 mg/g.protein), and CAT (5.92±1.60 U/g.protein) renal contents compared with the subsequent values of the of the normal control group. The treatment with polyherbal combination at doses of 12.5mg/kg MDA (8.02±1.72), GSH (16.01±2.04) and CAT (8.21±1.82), 25mg/kg MDA (7.01±1.05), GSH (18.08±3.55) and CAT (9.09±2.55) and 50 mg/kg MDA (8.31±2.31), GSH (16.54±2.0) and CAT (7.82±1.38) was very useful in the preservation of oxidative damage. The standard treatment group also significantly ($^{**}P<0.05$) improve these elevated level MDA (8.08±2.02), GSH (17.59±2.43), CAT (7.78±1.49) as compared to disease control. In case of SOD and NO, it was observed that the Gentamicin (100 mg/kg) produced a significant decrease ($^{\#}P<0.05$) in SOD (659.97±18.92 U/g. protein) and NO (317.04±18.52 Mmol/g. Protein) significantly increases contents of renal tissue, as compared to normal control group. The treatment with polyherbal combination at doses of 12.5mg/kg SOD (791.24±23.13), NO (274.98±20.45), 25mg/kg SOD (849.45±27.87), NO (207.04±13.54) and 50 mg/kg SOD (856.16±25.99), NO (260.88±16.08) was very effective in the preservation of oxidative damage. The standard treatment group also significantly ($^{**}P<0.05$) improve these elevated level SOD (840.26±24.01), NO (252.08±15.74) as compared to disease control.

Histopathological studies

Kidney tissues were obtained on last day of the experiment after scarification of animals and immediately fixed in 10% buffered neutral formalin solution. The tissue section was stained with hematoxylin and eosin (H & E stain) and examined under light microscope. The histological changes such as cortical glomerular, peritubular blood vessels congestion, and interstitial inflammation, etc. were observed in all group of the rat (figure 1).

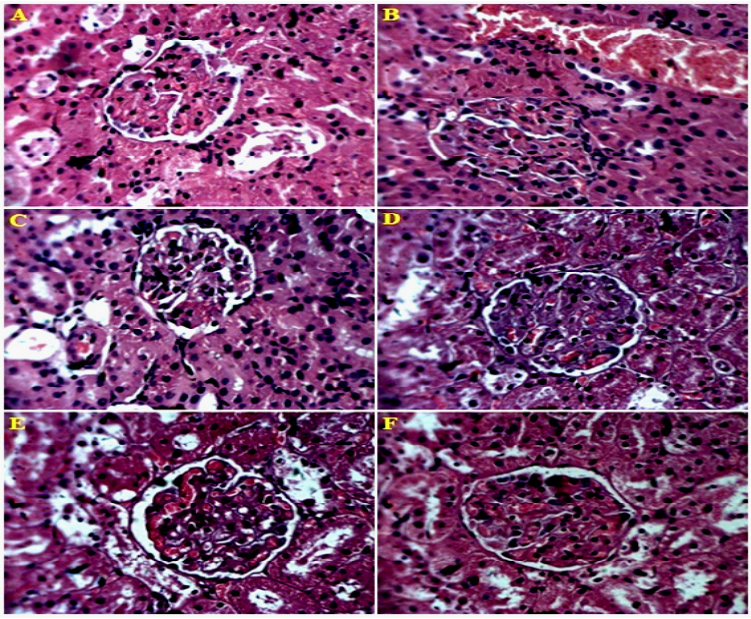


Fig 1. *Histopathology of kidney tissue of entire groups of rat stained by hematoxylin and eosin.* ***(A)*** *Kidney section of control rats showing normal glomeruli , Bowman's space and normal tubules;* ***(B)*** *Gentamicin group showing severe glomerular degeneration , dilatation in Bowman's space, and degeneration in tubular cells in kidney, tubular necrosis invaded by inflammatory cells ;* ***(C), (D)*** *&* ***(E)*** *group of the polyherbal combination at doses of 12.5, 25 and 50 mg/kg/day showing ordinary renal corpuscle and renal tubule more or less like a normal structure with the regeneration of some renal tubules.* ***(F)*** *Standard treatment drug cystone (500 mg/kg body weight) also maintained the elevated level of the normal renal corpuscle and renal tubule more or less like a normal structure with the regeneration of some renal tubules.*

The histological changes observed in the kidneys of control rats exhibited normal renal tissue, where normal corpuscular and tubular histological structure presented. The Gentamicin-exposed rats showed distinctive pathologic alterations such as degenerated glomeruli, glomerular atrophy, and dilatation in Bowman's space, tubular degeneration, luminal dilatation, and tubular necrosis with invading inflammatory cells. Evidence from numerous sections indicates that the changes mentioned above were extensive and nephrons were observed. The polyherbal combination at doses of 12.5, 25 and 50 mg/kg/day dramatically reduced gentamicin nephrotoxicity as evidenced by the fact that renal corpuscles and tubules appeared to be similar to those of the control group. Evidence from the histological study supports the biochemical analyses and ascertains that BCCTFV has antinephrotoxic activity.

Conclusion

The herbal plant has been used from ancient time to manage the human ailments without adversely influencing to the body and living organs [23]. Kidneys are such vital organ, which is profoundly controlled by chemical and other synthetics drugs. Current therapies to remove uremic solutes for the renal disorders patient include peritoneal dialysis, hemodialysis, and kidney transplantation, which is costly and time-consuming regimens, and also linked to high morbidity [24]. These types of treatments are predominantly available in developed countries, and therefore patients in developed countries are more likely to have an extended life expectancy. In underdeveloped countries, uremia is generally untreated, and patients appear to have a lower life expectancy [25].

The polyherbal combination has been developed by using geometrical dilution method and administered in the animal at a dose of 12.5mg/kg, 25mg/kg and 50mg/kg body weight. The pretreatment administration of the drug showed the stunning result to maintain the elevated parameter in nephritic rats within the very short duration of time [26]. Our data also indicate that the serum profile in Gentamicin-induced GN in rats' shows that urea (45.91±3.34mg/dl), uric acid (6.70±0.64mg/dl), creatinine (4.08±0.72mg/dl)

and BUN (58.67±3.66mg/dl) content was observed in treatment group, which was more significant in comparison with disease [27] control group. Simple calculations based on the volume of urine from experimental animals and the difference between uremic and normal rats of 24 h urinary volume estimating that about 2.55±0.31ml of urine per day must be observed with improvements in urine color. Our data suggest that the histopathology of the kidney confirms its remodeling and vigorous glomerular capillaries [28]. Our data also proposed that the herbal combination will remove urea from the uremic animals in an amount that will prove beneficial to rats suffering from any degree of renal insufficiency.

The study suggests that BCCTFV-25 provides adequate protection against Gentamicin-induced ND as evidenced by body weight, biochemical and histological parameters. The protective effect of BCCTFV-25 may be due to its antioxidant potential and free radical scavenging mechanism of these herbs which shows a synergistic effect on restoring kidney function. However, further studies are needed to confirm it's a precise mechanism of action on ND and to characterize the phytoconstituents responsible for its action on the kidney.

Acknowledgment

We are thankful to the Director of Hygia Institute of Pharmaceutical Education & Research, Lucknow, for providing necessary facilities to carry out this research work. All the authors have no conflict of interest for the publication of this manuscript in the journal.

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Citation: **Harikesh Maurya, Sunil Kumar, Tirath Kumar.** *Pharmacological Potential of Polyherbal Root Extracts Combination for the Management of Nephrotic Disorders in Rats. Archives of Nephrology. 2018; 1(1): 19-27.*