Research Article

www.ijrap.net

(ISSN Online:2229–3566, ISSN Print:2277–4343)

NEPHROPROTECTIVE EFFECT OF *BERGENIA LIGULATA* WALL. (PASHANABHEDA) AGAINST CISPLATIN-INDUCED NEPHROTOXICITY: AN *IN VIVO* STUDY

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Received on: 17/11/24 Accepted on: 06/1/25

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DOI: 10.7897/2277-4343.16111

ABSTRACT

The kidneys, which are vital organs inside the human body, are at high risk of getting diseased, as humans have been constantly exposed to a toxic environment. Diseases of kidneys and other organs of excretory system are explained in Ayurveda under the group of diseases e.g. Mutraghata, Mutrashmari, Mutrakruccrah, Mutravaha stroto-vikaras, etc. Pashanabheda i.e. *Bergenia ligulata* wall being one of the drugs explained in treatment of these diseases, is taken for study to investigate its nephroprotective efficacy against cisplatin-induced nephrotoxicity in Swiss albino mice. Mice were divided into 5 groups, each containing six. The first group is normal control (without treatment and without Inj. cisplatin), second group is cisplatin control (Inj. Cisplatin given but no treatment), in third, fourth and fifth groups the drug Pashanabheda was given in three different doses i.e. effective dose, half the effective dose, double the effective dose respectively, along with Inj. Cisplatin. Compared to normal control group, cisplatin control group showed significantly higher levels of Serum Urea, Serum Creatinine, Serum BUN and significantly lower levels of antioxidant enzymes, glutathione, glutathione peroxidase, catalase and superoxide dismutase. Histopathological examination of cisplatin control group showed signs of nephrotoxicity i.e. atrophied glomerulus, widened Bowman's capsule, hyalinization of glomerulus etc. compared to normal control group. On the other hand, groups treated with Pashanabheda ameliorated all biochemical parameters, antioxidant enzymes and histopathological changes. In conclusion, Pashanabheda exerted the nephroprotective effect in mice. The observations were noted, analyzed statistically; results were discussed and concluded.

Keywords: Pashanabheda, *Bergenia ligulata.* Wall, nephrotoxicity, nephroprotective

INTRODUCTION

Ayurveda is defined as the science of life which deals with not only the causative factors, signs, symptoms, and treatment of diseases, but also the measures and methods for preservation of health and longevity. Ayurveda is based on the drugs which are derived mainly from the plant kingdom. Drug therapy based on medicinal plants forms a major aspect of therapeutics nowadays also. And because of the promising effectiveness of these drugs with seldom any side effects; research on these medicinal plants has undergone phenomenal growth during the last few decades. Detailed experimental, clinical and phytochemical investigations of these plants can lead to the development of effective plant drugs for dreadful diseases to which no satisfactory cure exists. Ayurveda offers a challenging area for research in combating these diseases and developing targeted herbal drugs for their cure. So, there is a need of an hour to develop new methods to prove their efficacy with the support of modern scientific methods and statistical evidence.

Pashanabheda is mentioned in the treatment of diseases like mutraghata[1], mutrashmari[2], mutrakruccrah[3], mutravaha srotas-vikaras etc. which have very well relevance with the diseases of the kidneys[4] and other organs of an excretory system which are described in the modern system of medicine. Kidneys[5] are the main organs in the excretory system, which regulates homeostasis inside the human body through the excretion of the waste products formed during metabolism. Kidneys[6] are one of the most complex organs both anatomically and functionally. Any toxic insult to the kidneys can immediately and invariably affect all its functions and so as the whole body. Its damage is frequently observed under toxic conditions caused by different types of compounds and chemicals acting by a variety of biological mechanisms. As the man has been exposed constantly to the polluted atmosphere and toxic environment under circumstances and occupation, the kidneys are at high risk of getting diseased. Also, a wide spectrum of chemicals and drugs are known to have nephrotoxic activity which has been used commonly today. Urban areas have been polluted with poisonous gases like - CO, NH3 etc. and the abuse of pesticides and manure like urea & phosphates in farms of rural areas and chemicals like CCL4, formalin etc. used in labs are also nephrotoxic. Besides these pathological cases like nephritis, nephrotic syndrome etc. have been found increasing in primary health centres and other hospitals. They all ultimately lead to renal failure which is a fatal condition. All the above factors hint at the need to find out a remedy which is effective and safe for the management of nephrotoxicity. Hence this is an attempt to conduct an *in-vivo* study on the Nephroprotective effect of Pashanabheda i.e. *Bergenia ligulata* wall against Cisplatin-induced nephrotoxicity[7].

MATERIALS AND METHODS

Collection of the drug

Pashanbheda i.e. *Bergenia ligulata* Wall. was collected from the northern part of India. It was authenticated by Dr. P. Jayasree, MD, Dravyagunavijnana, Professor, Department of Dravyaguna vijnana, Govt. Ayurveda college, Thiruvananthapuram, Kerala, India. It was also pharmacognostically identified by macroscopic

and microscopic evaluation and purity of the drug was observed by preliminary phytochemical evaluation.

Preparation of churna (i.e. powder)
The rhizomes of Pashanbheda i.e. *Bergenia ligulata* Wall. were properly cleaned with water and dried in the shade. The dried drug was powdered into a fine of 120 mesh size.

Dose of the churna
Considering the 12 gm human adult dose of churna, the effective dose of the test drug for rats was calculated using the formula given below:
Animal dose = Human dose × 0.018 for 200 gm of animal[8]
e.g. for churna: Human dose is 12 gm, then the dose of churna for a 200 gm rat is = 12 × 0.018 = 0.216gm / 200gm of rat
So, the dose of churna for 25 gm of mice is 25 mg.
Drug suspension was prepared in distilled water in the concentration of 25 mg of churna in the 0.2 ml of distilled water and administered according to the body weight of the animals by oral route with the help of an oral feeding cannula attached to a 1 ml syringe.

Selection of animals
Healthy Swiss albino mice of either sex weighing between 20-25 gm were collected from a small animal breeding station, in Mannuthy, Kerala, India. The animals were housed in standard laboratory conditions of light and dark cycle of 7 am to 7 pm, temperature of 25 ºC ± 2 ºC and 30-60 % relative humidity in well-ventilated cages. Animals were provided with normal mouse chow (Sai Durga Food and Feeds, Bangalore, India) and water *ad libitum.* The animals were acclimatized at laboratory hygienic condition for 7 days before starting the experiment. All the animal experiments were done as per the instructions prescribed by the Committee for Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forest, Government of India, and implemented through the Institutional Animal Ethical Committee of the Research Centre. The Nephroprotective study was performed at Amala Cancer Research Institute, Thrissur, Kerala, India.

Method of inducing Nephrotoxicity
The Inj. Cisplatin is widely used to induce the Nephrotoxicity to assess Nephroprotective effect in experimental studies. Hence the same was used for this study. A single dose of Inj. Cisplatin was given intraperitoneally in a dose of 16 mg/kg body wt. to induce Nephrotoxicity[9] in Swiss albino mice.

Procedure
Thirty Swiss albino mice of either sex weighing about 20-25 gm were selected in this study. The animals were kept under observation for one week and grouped into five in such a way that each group consisted of six animals. The first group was considered as a Normal Control group so that Inj. Cisplatin was not injected to them. The second group was considered as a Cisplatin Control group so that Inj. Cisplatin was injected to the animals in a dose of 16 mg/kg body wt. as a single intraperitoneal injection and no drug was given to them. The third, fourth and fifth groups are meant for the drug i.e. *Bergenia ligulata* Wall. To the third group, the drug was given in the effective dose i.e. 25 mg orally for five days and on the sixth day Inj. Cisplatin was injected in a dose of 16 mg/kg body weight intraperitonially as a single dose and the drug treatment was continued for the next 72 hours also. To the fourth group, the drug was given as half the effective dose i.e. 12.5 mg for five days and then on the sixth day Inj. Cisplatin was injected and the drug treatment was continued for the next 72 hours. To the fifth group, the drug was given as double the effective dose i.e. 50 mg for five days and Inj. Cisplatin was injected on the sixth day and the drug treatment was continued for the next 72 hours.

Table 1: Grouping of Animals

No.	Groups
Group 1.	Normal control
Group 2.	Cisplatin control
Group 3.	Inj. Cisplatin + 25 mg churna of *Bergenia ligulata* wall.
Group 4.	Inj. Cisplatin + 12.5. mg churna of *Bergenia ligulata* wall.
Group 5.	Inj. Cisplatin + 50 mg churna of *Bergenia ligulata* wall.

The body weight of all the animals was noted at the first day of study and at the end of the study.
First group: Normal Control group, these animals were sacrificed after 8 days
Second group: Cisplatin Control group, these animals were sacrificed after 72 hours of the Injection of the Inj. Cisplatin single dose.
Third to fifth groups: The drug treatment was given to these groups for five days and then Inj. Cisplatin was injected as a single dose on the sixth day and test drug treatment was continued for the next 72 hours. At the end of 72 hours, all these animals were sacrificed, and blood was collected by heart puncture and was stored carefully in containers. Kidneys were separated and stored in containers containing 10% formaldehyde solution for histopathological examination and in -20 ^{0}C freezer for the antioxidant assay related to kidney tissue antioxidant enzymes. Assessment of the nephrotoxicity and efficacy of the drug was evaluated with the help of three parameters, morphological, biochemical and histopathological.

Morphological parameters include
a) Change in body weight.

Biochemical investigations include
a) Serum Creatinine
b) Serum Urea
c) Serum Blood Urea Nitrogen (BUN)
d) Antioxidant enzymes:
- SOD-Superoxide dismutase enzyme
- Catalase enzyme
- GSH – Glutathione
- Gpx – Glutathione peroxidase enzyme

Histopathological studies include
a) Atrophy of the glomerulus due to necrosis of vessels
b) Widening of the bowman's capsule
c) Hyalinization of the glomerulus
d) Morphology of the renal tubules: proximal convoluted tubules, distal convoluted tubules.

The changes seen in these 3 parameters in the groups from 3rd to 5th were compared with the normal and cisplatin control groups. The efficacy of 3 different doses within the 3rd to 5th groups were also compared and statistically evaluated.

Statistical analysis: The observations and results of pharmacological studies are given below. For the analysis of observed parameters following statistical methods have been used, Descriptive statistics: Mean (± SD) is reported for summarizing the collected data. One-way ANOVA has been carried out to compare different groups to each parameter. Tukey-Kramer Multiple comparison test: If One-Way ANOVA shows significance, then this test was applied for comparing any two groups for each parameter. A p-value less than 0.05 is considered to be statistically significant.

RESULTS AND DISCUSSION

Observation of Physical activities

Normal control group: In this group all the animals were healthy with normal physical activities.

Cisplatin control group: In this group all the animals showed considerable weight loss, less food consumption and fewer activities.

3rd to 5th group: All the animals of these treatment groups showed a gradual increase in consumption of food, body weight and activities as compared to the Cisplatin control group after its injection intraperitoneally.

Morphological parameters

Group 1 which is the Normal control group, shows an average of 0.9 gm of increase in body weight and of Group 2 which is the Cisplatin control group, shows an average of 6.12 gm of decrease in body weight, which is the difference of body weight. on the sixth day before induction of nephrotoxicity by Inj. Cisplatin and body wt. on the ninth day before sacrifice. In case of Group 3, Group 4, Group 5; which were given 25 mg, 12.5 mg, 50 mg churna of the drug i.e. *Bergenia ligulata* Wall*;* showed 0.44, 0.15, 0.5 gm of increase in body weight respectively. The table shows the comparison of the groups by One-Way Analysis of Variance (ANOVA) by Tukey Multiple Comparisons Test. Comparison of Group 1 vs. Group 2 shows p value which is less than 0.001 which is highly significant. And the same is true in case of treatment groups from 3rd to 5th Group vs. Group 2, where p<0.001 which is highly significant.

Table 2: Efficacy of *Bergenia ligulata* Wall. treatment on body weight in cisplatin induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Group 1.	0.9	0.09	P< 0.001
Group 2.	-6.12	1.05	
Group 3.	0.44	0.14	P< 0.001
Group 4.	0.15	0.055	P< 0.001
Group 5.	0.5	0.17	P< 0.001

Biochemical investigations

The mean and standard deviation values of Serum Creatinine, Serum Urea, and Serum BUN are given (mg/dl) in the second and third columns of the table respectively. Compared to the values in Group 1 i.e. Normal group, Group 2 i.e. Cisplatin control group shows much increased values of Serum Creatinine, Serum Urea and Serum BUN. In the treatment groups i.e. from Group 3 to the Group 5, the values reverted back to the normal. In the groups 3, 4 and 5; Serum Creatinine, Serum Urea and Serum BUN values shows gradual decline with respect to the dose of the drug i.e. 25 mg, 12.5 mg and 50 mg churna of the drug received; by which it can be inferred that the efficacy of drug is in dose dependent manner. Comparison of group 1 vs. group 2 shows p value which is less than 0.001 and is highly significant. And the same is true in case of treatment groups from 3rd to 5th group vs. group 2, where p<0.001 which is highly significant.

Table 3: Efficacy of *Bergenia ligulata* Wall. treatment on serum creatinine in cisplatin induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Group 1.	0.95	0.158	P< 0.001
Group 2.	3.15	0.316	
Group 3.	1.42	0.497	P< 0.001
Group 4.	2.198	0.224	P< 0.001
Group 5.	1.198	0.271	P< 0.001

Table 4: Efficacy of *Bergenia ligulata* Wall. treatment on serum urea in cisplatin-induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Group 1.	39.57	5.599	P< 0.001
Group 2.	151.0	6.864	
Group 3.	59.87	6.236	P< 0.001
Group 4.	83.23	8.229	P< 0.001
Group 5.	47.85	4.064	P< 0.001

Table 5: Efficacy of *Bergenia ligulata* Wall. treatment on serum BUN in cisplatin-induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Group 1.	18.477	2.615	P< 0.001
Group 2.	70.517	3.205	
Group 3.	27.957	2.912	P< 0.001
Group 4.	38.87	3.842	P< 0.001
Group 5.	22.431	1.979	P< 0.001

Efficacy of *Bergenia ligulata* Wall. treatment on antioxidant enzymes in cisplatin-induced nephrotoxicity in mice: In the previous investigations, it is seen that in the case of all three parameters – Serum Creatinine, Serum Urea and Serum BUN; the treatment groups 3rd, 4th and 5th receiving 25 mg, 12.5 mg and 50 mg churna of drug i.e. *Bergenia ligulata* wall. have shown dose-dependent effectiveness. It means that the 5th group have shown maximum efficacy. So, to see the role of antioxidant enzymes in relieving the toxicity induced by the Inj. Cisplatin, the 5th group that received 50 mg churna of the drug, was considered.

In the following tables, the second column shows the a] mean values of Superoxide dismutase enzyme in U/mg protein; b] mean values of Catalase enzyme in k/mg protein; c] mean values of Glutathione in nmol/mg protein; d] mean values of Glutathione peroxidase enzyme in nmol/mg protein and the third column shows the standard deviation values.

In the Normal control group, the value of the Superoxide dismutase enzyme was 2.48, which got decreased in the Cisplatin control group up to 1.40. In the 5th group, the values again increased up to normal i.e. 2.52. In the Normal control group, the value of the Catalase enzyme was 11.016, which got decreased in the Cisplatin control group up to 6.238. In the 5th treatment group, the values again increased up to normal i.e. 10.572. In the Normal control group, the value of Glutathione was 15.82, which got decreased in the Cisplatin control group up to 8.70. In the 5th treatment group, the values again increased up to normal i.e. 17.38. In the Normal control group, the value of the Glutathione peroxidase enzyme was 17.775, which got decreased in the Cisplatin control group up to 8.198. In the 5th treatment group, the values again increased up to normal i.e. 19.920.

The tables show the comparison of the groups by One-Way Analysis of Variance (ANOVA) by the Tukey Multiple Comparisons Test. A comparison of Group 1 vs. Group 2 shows a p-value which is less than 0.001 and is highly significant. Also, in the case of the 5th Group vs. Group 2, the p-value is less than 0.001 which is highly significant.

Table 6: Efficacy of *Bergenia ligulata* Wall. treatment on Superoxide dismutase enzyme in cisplatin induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Normal control (1st group)	2.48	0.749	P< 0.001
Cisplatin control (2nd group)	1.40	0.064	
Group 5	2.52	0.125	P< 0.001

Table 7: Efficacy of *Bergenia ligulata* Wall. treatment on Catalase enzyme in cisplatin induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Normal control (1st group)	11.016	1.350	P< 0.001
Cisplatin control (2nd group)	6.238	0.515	
Group 5	10.572	0.557	P< 0.001

Table 8: Efficacy of *Bergenia ligulata* Wall. treatment on Glutathione enzyme in cisplatin induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Normal (1st group)	15.82	2.250	P< 0.001
Cisplatin control (2nd group)	8.70	1.298	
Group 5	17.38	2.495	P< 0.001

Table 9: Efficacy of *Bergenia ligulata* Wall. treatment on Glutathione peroxidase enzyme in cisplatin induced nephrotoxicity in mice

Groups	Mean	S.D.	p value
Normal (1st group)	17.775	1.773	P< 0.001
Cisplatin control (2nd group)	8.198	0.553	
Group 5	19.920	4.180	P< 0.001

Histopathological evaluation

In Normal control group, colour of kidneys were uniform dark reddish which indicates proper vascularization within the kidneys, in Cisplatin control group, the kidneys were very much pale coloured compared to that of Normal group. In Group 3 and Group 5 kidneys showed red colour in increasing order respectively. For histopathological studies five different blocks of tissues were taken from different sites of the kidney. Paraffin sections were prepared and stained with haematoxilin-eosin. Normal control group showed normal glomeruli with normal Bowman's capsule, normal renal tubules and normal interstitial tissue with minimal oedema. Cisplatin control group showed many atrophied glomeruli, some were hyalinized, Bowman's capsules were widened, interstitial tissue was oedematous with scattered inflammatory cells and the lining cells of the renal tubules were larger in size. In Group 3 histopathological examination showed, partial atrophied glomeruli with widening of the Bowmen's capsule, renal tubular cells in some places showed oedema, scattered lymphocytes and plasma cells. In Group 5 histopathological examination showed normal glomeruli with Bowman's capsule, some were partially atrophied; renal tubules were normal, and interstitial tissue showed scattered inflammatory cells. In Cisplatin control group, kidney damage has been produced i.e. nephrotoxicity. From the results of the Group 3, and Group 5, it was seen that there was qualitative improvement in the normalcy of the kidney tissues, so this effect of the drug can be attributed to its Nephroprotective effect against cisplatin-induced nephrotoxicity.

In this study, the Nephroprotective effect of the Pashanabheda was assessed against Cisplatin-induced nephrotoxicity in the Swiss albino mice. The nephroprotective action of Pashanabheda i.e. *Bergenia ligulata* Wall. was assessed by morphological, biochemical and histopathological parameters. Overall observations of all these parameters infer the Nephroprotective effect of the Pashanbheda i.e. *Bergenia ligulata* wall. in the Swiss albino mice.

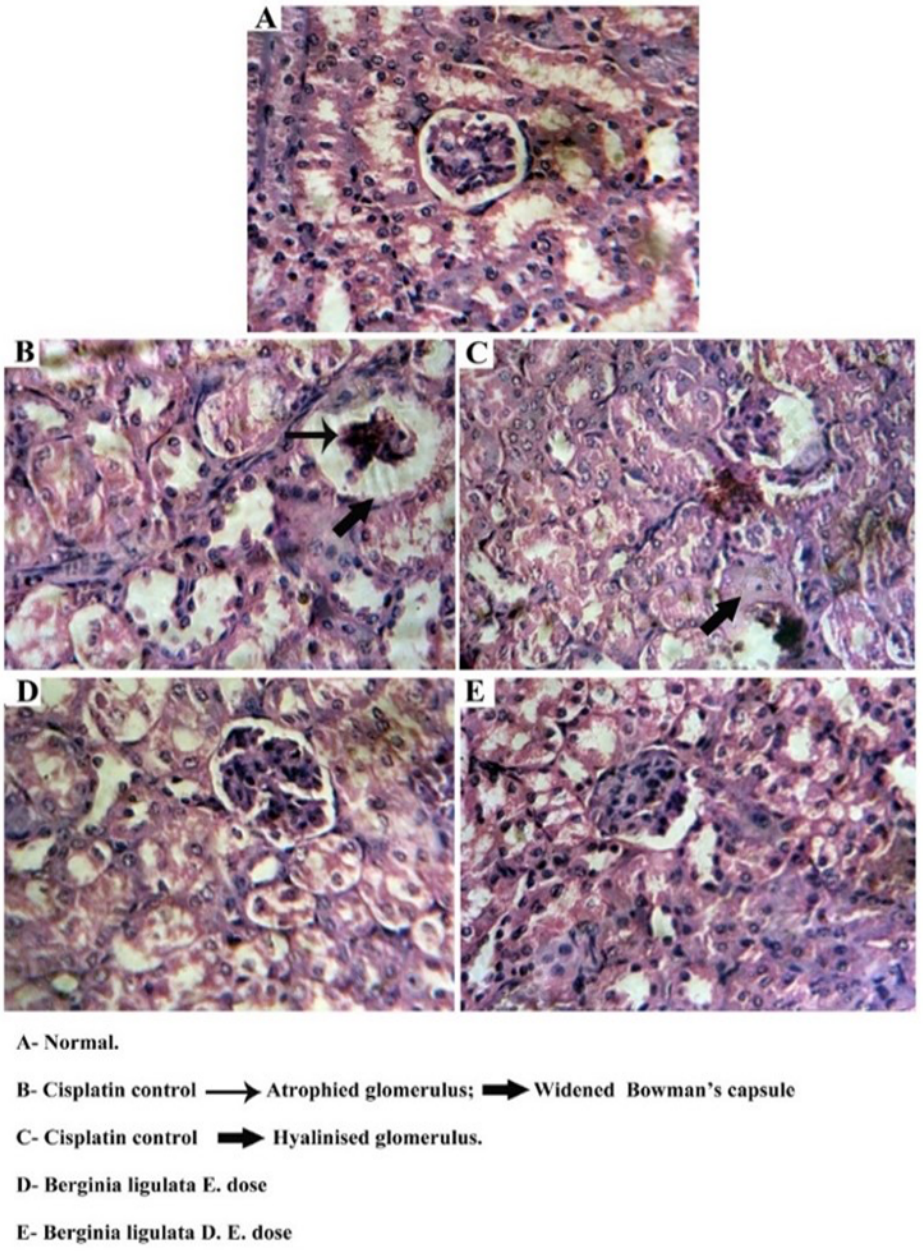

Figure 1: Histopathology of the Kidney - Comparison of the changes in the kidney tissues
A. Group 1- normal control
B. Group 2- cisplatin control -atrophied glomerulus, widened Bowman's capsule
C. Group 2- cisplatin control – hyalinized glomerulus
D. Group 3 - Inj. Cisplatin + 25 mg churna of *Bergenia ligulata* wall.
E. Group 5 - Inj. Cisplatin + 50 mg churna of *Bergenia ligulata* wall.

Mode of action of Pashanabheda: An Ayurvedic view

Hetus (causative factors) involved in the production of diseases like mutrakruccrah (dysuria) and mutraghata (urinary retention) are widespread, out of that the hetu 'tikshnah aushadha sevana'[10] is involved in the vitiation of the pitta causing it to increase abnormally; tikshnah (sharpness) guna is formed predominantly by agni mahabhuta and so it is daha and pakakara[11] (causes burning and inflammation). It destroys the dhatus (major structural components of the body) and results in weakness. As a result of these properties of tikshnah guna, normal functioning gets affected, and it results in the manifestation of mutraghata. So kleda (moistness) in the body gets increased which is to be excreted through the urine, as a result of mutraghata.

The Pashanabheda has kashaya (astringent taste), tikta rasa (bitter taste), sheeta virya, katu vipaka and laghu, snigdha guna. It has mutrajanana (diuretic) action as it is included in mutravirechaneeya mahakashaya[12] and ashmarihara prabhava. It has kashaya[13] and tikta rasa which are the Pittashamaka rasas, and also its virya is sheeta which results in Pittashamana. So, the effects of Pittavridhhi were combated by the use of this drug because of Pittashamana. Again, the sheeta virya (cold potency) of Pashanbheda has mutrajanana[14] action, so the kleda which was got accumulated in the body was its way through the urine with its proper formation. Also, the sheeta virya[15] has its action as daha hara (decreases burning), jeevanam (gives life) and Rakta (blood tissue) - Pitta (dosha responsible for regulating body temperature

and metabolic activities), prasadanam (quality enhancing); so it protects the dhatus from damage also. As a whole it gives protection to the dhatus, maintains normal formation of mutra (urine) and normal functioning of the mutravaha srotasa, keeping body physiology normal.

Mode of action: Modern aspects

Nephrotoxicity means toxic effects exerted on the kidneys in terms of damage to the kidney tissue because of various nephrotoxins. Nephrons, the functional unit of the kidneys are the main site of damage in case of cisplatin induced nephrotoxicity[7]. Cisplatin is mainly responsible for the production of free radicals within the kidney tissue which increases the oxidative stress which further results in the damage to the nephrons – proximal convoluted tubule, glomerulus, Bowman's capsule and distal convoluted tubules. So, the proper functioning of the kidneys got hampered and as a result Serum Creatinine, Serum Urea and Serum BUN got increased. And the levels of antioxidant enzymes were decreased which normally gives protection to the kidney tissue by neutralizing free radicals and so as a result of all this damage done to the kidneys, the urine formation also hampered.

So, in the treatment part, the drug should have an anabolic effect on the antioxidant defense mechanism within the kidney tissue which improves the functioning of antioxidant enzymes against free radicals resulting in the neutralization of free radicals. So, the damage done to kidney tissue can be reversed. The drug which shows diuretic action can help the kidneys for improvement in urine formation.

Pashanbheda i.e. *Bergenia ligulata* Wall. improves the antioxidant defense system within the kidney tissue which further protects the kidneys from damage. Bergenin[16] – one of the phytochemical constituents that shows diuretic action which helps kidneys to eliminate excretory products through the urine. The diuretic action of the drug primarily supported by its anabolic effect on the antioxidant defense system results in the protection of the kidney tissue against the damage induced by Inj. Cisplatin.

In this way, it combats with the free radicals and protects the kidneys from the damage induced by Inj. Cisplatin to the kidney tissue results in the improvement in the normal functioning of the kidneys. In this way the drug Pashanbheda i.e. *Bergenia ligulata* wall. gives protection to the kidneys i.e. the nephroprotective effect.

CONCLUSION

Pashanbheda i.e. *Bergenia ligulata* Wall. is the effective drug in treating mutraghata, mutrashmari, mutrakruccrah, mutravaha srotasa diseases as it is nephroprotective. Further experimental studies on larger samples may be carried out to confirm the results of this study. Clinical trial is required to establish the effects in various kidney diseases.

Ethical Statement

All animal handling procedures in this study were approved by the institutional committee for ethics in animal research [Ref: C2/1441/2010/GAVC], Government Ayurveda College, Thripunithura, Kerala and the Institutional Animal Ethics Committee of Amala Cancer Research Centre [No: 149/1999/CPCSEA], Trissur, Kerala, India.

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Cite this article as:

Sunita Mane and Anil Bhawade. Nephroprotective effect of *Bergenia ligulata* Wall. (Pashanabheda) against Cisplatin-induced nephrotoxicity: An *in vivo* study. Int. J. Res. Ayurveda Pharm. 2025;16(1):58-63 DOI: http://dx.doi.org/10.7897/2277-4343.16111

Source of support: Nil, Conflict of interest: None Declared