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Pharmacological Study

Evaluation of anti-urolithiatic activity of *Pashanabhedadi Ghrita* against experimentally induced renal calculi in rats

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Abstract

Population in an industrialized world is afflicted by urinary stone disease. Kidney stones are common in all kinds of urolithiasis. One distinguished formulation mentioned by Sushruta for management of *Ashmari* (urolithiasis) is *Pashanabhedadi Ghrita* (PBG), which is in clinical practice since centuries. Validation of drug is the requirement of time through the experimental study. In this study, trial of PBG has been made against ammonium oxalate rich diet and gentamicin injection induced renal calculi in albino rats. The calculi were induced by gentamicin injection and ammonium oxalate rich diet. Test drug was administered concomitantly in the dose of 900 mg/kg for 15 consecutive days. Rats were sacrificed on the 16th day. Parameters like kidney weight, serum biochemical, kidney tissue and histopathology of kidney were studied. Concomitant treatment of PBG attenuates blood biochemical parameters non-significantly, where as it significantly attenuated lipid peroxidation and enhanced glutathione and glutathione peroxidase activities. It also decreased crystal deposition markedly into the renal tubules in number as well as size and prevented damage to the renal tubules. The findings showed that PBG is having significant anti-urolithiatic activities against ammonium oxalate rich diet plus gentamicine injection induced urolithiasis in rats.

Key words: Ammonium oxalate, *Ashmari*, gentamicin, *Pashanabhedadi Ghrita*, urolithiasis

Introduction

Mankind has been afflicted by urinary stones (Urolithiasis) since centuries, and it is proven to be an important cause of renal failure. Even in the 4th century B.C., Hippocrates is noted the presences of the renal stone together with renal abscess and he has mentioned that in his Hippocratic oath "*… I will not cut, even for stone, but leave such procedures to the practitioners of the craft.*" The specialty of urology branch has been recognized since ever. It is estimated that at least 10% of the population in the industrialized part of the world is afflicted by urinary tract stone disease. Among those, kidney stones are common in industrialized nations with an annual incidence of 0.5-1.9%.[1,2] About 12% of the population of India is expected to have urinary stones and out of that about 50% of cases encounter loss of one or both kidneys with or without renal damage upto some extent. Nearly 15% of the population of northern India is also suffering from kidney stones. Upper as well as lower urinary tract stones occur frequently but the incidence shows wide variation on the regional basis in India.[3]

Ayurveda, a traditional system of Indian medicine, recommends several medicinal plants and compound medicinal preparations for the treatment of urolithiasis.[4,5] Herbs and herbal drugs have created interest among the people by its clinically proven effects. The overuse of synthetic drugs, results in higher incidence of adverse drug reactions, has motivated humans to return to nature for safe remedies. One such distinguished formulation mentioned by Sushruta in the management of *Ashmari* (urinary stones) is *Pashanabhedadi Ghrita* (PBG)[6] which is more popular among *Vaidyas* (physicians). The name of the formulation itself suggests anti-urolithiatic action, i.e., *Pashana* means stone and *Bheda* means to crush. However, until date there is no experimental basis is available to prove clinical evidence on this formulation, hence the present study was designed to evaluate anti-urolithiatic activity of PBG in experimental animals.

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Materials and Methods

Animals

Wistar strain albino rats of either sex; weighing 160-220 g were used for the study. The animals were obtained from the animal house attached to our institute. Six animals were housed in each cage made up of poly-propylene with stainless steel top grill. The dry wheat (post-hulled) waste was used as bedding material and was changed every morning. The animals were exposed to 12-h light and 12 h dark cycle with the relative humidity of 50-70% and the ambient temperature during the period of experimentation was 22 ± 03°C. Animals were fed with Amrut brand rat pellet feed supplied by Pranav Agro Mills Pvt. Limited. Tap water *ad libitum* was used for their drinking purpose. The experiments were carried out in conformity with the Institutional Animal Ethics Committee (IAEC) after obtaining its permission (IAEC03/08-11/PhD/01).

Test formulation

The raw materials [Table 1] of the test formulation were procured from pharmacy attached to Gujarat Ayurved University, Jamnagar and authenticated by pharmacognosist. From these raw drugs, "PBG" was prepared in the Department of Rasashastra and Bhaishajya Kalpana of I.P.G.T. and R.A. as per the classical reference of *Ghrita Paka Kalpana*.[7] The finished product was stored in air tight glass container and utilized for experimental study.

Dose fixation

The human dose of PBG mentioned in classical texts is 10 g per day. Considering this, the dose of the experimental animals was calculated by extrapolating the human dose to rat dose as 900 mg/kg based on the body surface area ratio by referring to the standard table of Paget and Barnes (1964).[8] The test drug was administered orally with the help of a gastric catheter of suitable size sleeved onto a disposable syringe.

Anti-urolithiatic activity

Hyperoxaluria and calcium oxalate deposition in the kidney was induced by using injection gentamicin (40 mg/kg/ Intra Peritonial) and Calculi Producing Diet (CPD).[9] The diet is made by powdered standard rat pellet feed mixed with ammonium oxalate (5%), then made into pellet and dried up properly. The selected animals were weighed and randomly divided into four groups, consisting of six animals in each group. Group-I received only distilled water orally for 15 days, served as normal control. Group-II received gentamicin (40 mg/kg, Sub-cutaneous., day 1st-8th), CPD and

Table 1: Formulation composition of *Pashanabhedadi Ghrita*

Sanskrit name	Botanical name	Part used
Go Ghrita	Cow ghee	-
Ingredients for *Kwatha* (Decoction)		
Pasanabheda	*Bergenia ligulata* (Wall.) Engl	*Moola* (Root)
Shwetarka	*Calotropis gigantean* (L.) W.T. Aiton	*Panchanga* (Whole plant)
Apamarga	*Achyranthus aspera* Linn.	*Panchanga* (Whole plant)
Changeri	*Oxalis corniculata* Linn.	*Panchanga* (Whole plant)
Shatawari	*Asparagus racemosus* Willd	*Kanda* (Tubers)
Gokshura	*Tribulus terrestris* Linn.	*Phala* (Fruit)
Brihati	*Solanum indicum* Linn.	*Phala* (Fruit)
Kantakari	*Solanum surattense* Burm	*Panchanga* (Whole plant)
Brahmi	*Bacopa monnieri* L. Pennell	*Panchanga* (Whole plant)
Kokilaksha	*Barleria preonitis* Linn.	*Panchanga* (Whole plant)
Usheera	*Vetiveria zizaniodis* (L.) Roberty	*Moola* (Root)
Gunja	*Abrus precatorious* Linn.	*Beeja* (Seed), *Moola* (Root), *Patra* (Leaf)
Vrikshadani	*Dendrophthoe falcate* (L.f) Ettingsh	*Panchanga* (Whole plant)
Shyonaka	*Oroxylum indicum* (L.) Benth. ex Kurz	*Moola Twak* (Root bark)
Varuna	*Crataeva nurvala* Buch. Ham	*Twak* (Bark)
Shakaja Phala	*Tectona grandis* Linn.	*Beeja* (Seed)
Yava	*Hordeum vulgare* Linn.	*Panchanga* (Whole plant)
Kulattha	*Dolichos biflorus* Linn.	*Beeja* (Seed)
Maricha	*Piper nigrum* Linn.	*Phala* (Fruit)
Nirmali	*Strychnos potatorum* Linn.	*Beeja* (Seed)
Drugs for *Kalka* (Paste)		
Ushaka (Ksharmrittika)	-	-
Saindhava	Rock salt	-
Shilajatu	Betumin	-
Kaseesa	$FeSO_4$	-
Hingu	*Ferula foetida* Linn	-
Tuttha	$CuSO_4$	-

water (from day 1st to 15th) and served as negative control (diet control). Group-III received gentamicin (40 mg/kg, SC., day 1st-8th); CPD and plain *Goghrita* (0.9 g/kg, orally, day 1st-15th) and served as Vehicle Control (VC). Group-IV received gentamicin (40 mg/kg, SC., day 1st-8th); CPD and *Pashanabhedadi Ghrita* (0.9 g/kg, orally, day 1st-15th) and coded as PBG. The gentamicin injection was given after 2 h of drug administration, and normal diet was replaced by CPD for 15 days.

Assessment of urinary parameters

On the 15th day after-drug administration, the rats of all the four groups were hydrated with distilled water (2 ml/100 g rat), housed in separate metabolic cages and urine samples were collected for 24 h and the urinary pH and specific gravity were determined by strip method.

Assessment of kidney parameters

On the 16th day the animals were weighed and anaesthetized by diethyl ether. Blood was collected from retro orbital plexus by capillary puncturing for estimation of serum biochemical parameters such as serum urea,[10] serum creatinine,[11] serum uric acid,[12] and serum calcium.[13] Then the animals were sacrificed by over dose of ether anesthesia. The abdomen was opened by midline incision and kidney was dissected out carefully and cleaned off the extraneous tissue. Kidney was weighed and one kidney of each animal was transferred to 10% formalin solution for the purpose of histopathological studies while the other kidney was utilized for estimation of biochemical parameters in tissue homogenate parameters. The parameters such as lipid peroxidation,[14] nitric oxide,[15] total glutathione,[16] and glutathione peroxides[17] activities were estimated as per standard procedures. The histopathological slides were prepared by referring standard procedure.[18] The slides were viewed under binocular research Carl-Zeiss's microscope (Germany) at various magnifications to note down the changes in the microscopic features of the tissues studied.

Table 2: Effect on weight of kidney and urinary parameters

Groups	Relative weight of kidney (g/100 g)	Specific gravity	Urine pH
Control	0.97±0.09	1.007±0.004	7.6±0.35
Diet control	1.26±0.07#	1.019±0.003	6.6±0.18#
VC	1.51±0.20	1.016±0.002	7.0±0.25
PBG	1.53±0.09	1.021±0.002	7.2±0.20

#*P*<0.05 (Compared with normal control),VC: Vehicle control, PBG: *Pashanabhedadi Ghrita*

Statistical analysis

The obtained data have been presented as mean ± SEM, difference between the groups was statistically determined by Student *t*-test for unpaired data with the level of significance set at $P < 0.05$.

Results

An apparent and statistically significant increase in weight of kidney was occurred in the diet control group in comparison to the normal control group. Administration of *Goghrita* and PBG failed to attenuate the weight of kidney to a significant extent in comparison to diet control group [Table 2]. Feeding of ammonium oxalate diet leads to significant decrease in urinary pH in comparison to normal control. Administration of PBG non-significantly attenuated pH of urine.

A statistically significant increase in blood urea and serum creatinine level was occurred by feeding of ammonium oxalate rich diet. Further marked elevation of uric acid level was also noted in comparison to the normal control group. Treatment with PBG failed to attenuate these factors to a significant extent [Table 3].

Feeding of ammonium oxalate rich diet for 15 days along with gentamicin injection leads to significant increase in lipid peroxidation and nitric oxide levels in kidney tissue homogenate in comparison to the normal control group. Treatment with PBG significantly attenuated lipid peroxidation. Further, administration of plain ghee (Vehicle) and PBG significantly enhanced the level of total glutathione and glutathione peroxidase activity [Table 4].

Microscopic examination of kidney sections from the normal control group showed normal cytoarchitecture [Figure 1]. Sections from gentamicin injection plus ammonium oxalate diet control group shows the presence of a large number of crystal material containing tubules, especially in the cortical region; dilatation of tubules (due to stones) along with necrosis of the tubular epithelium [Figure 2]. Sections from VC treated group shows a moderate decrease in the size and number of crystal containing tubules and mild tubular epithelial necrosis [Figure 3], while marked decrease of these features are observed in PBG treated group [Figure 4].

Discussion

The pathogenesis of calcium oxalate (CaOx) stone formation is a multi-step process and in essence includes urinary saturation, urinary super saturation, nucleation, crystal growth, crystal aggregation, and crystal retention. Various substances

Table 3: Effect on serum biochemical parameters

Groups	Serum Blood urea (mg/dL)	Serum creatinine (mg/dL)	Serum uric acid (mg/dL)	Serum calcium (mg/dL)
Control	46.40±3.30	0.52±0.03	1.16±0.13	8.50±0.21
Diet control	81.00±12.57##	0.92±0.12#	1.30±0.14	7.82±0.22
VC	98.83±19.47	1.20±0.28	1.56±0.13	8.37±0.25
PBG	102.80±21.95	0.92±0.36	2.30±0.61	7.76±0.20

#*P* < 0.05,##*P* < 0.05 (Compared with normal control),VC:Vehicle control, PBG: *Pashanabhedadi Ghrita*

Table 4: Effect on tissue biochemical parameters of kidney tissue homogenate

Groups	Lipid peroxidation (μ mole MDA/g)	Nitric oxide (μ mole/g)	Glutathione (*n* mole/g)	Gluthathione peroxidase (μ mole/min/g)
Control	22.23±08.60	1.80±0.14	09.28±0.26	3.58±0.24
Diet control	37.11±05.22#	2.64±0.31#	05.70±1.25#	2.41±0.44#
VC	37.23±22.35	2.08±0.37	12.63±2.59*	14.47±5.47*
PBG	19.71±3.69*	1.82±0.63	13.66±3.05*	14.78±3.46**

#$P<0.05$, (Compared with normal control), *$P<0.05$, **$P<0.05$ (Compared with diet control). MDA: Malondialdehyde, VC: Vehicle control, PBG: *Pashanabhedadi Ghrita*

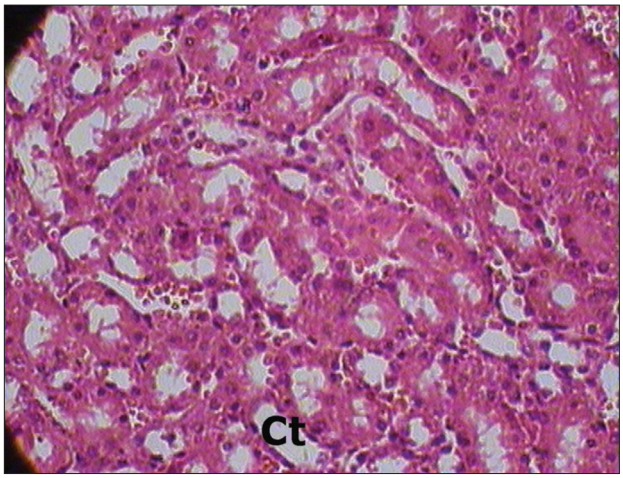

Figure 1: Photomicrograph of representative sections of kidney of albino rats from control group (I × 400 magnification). Ct: Convoluted tubule. Note: Normal cytoarchitecture

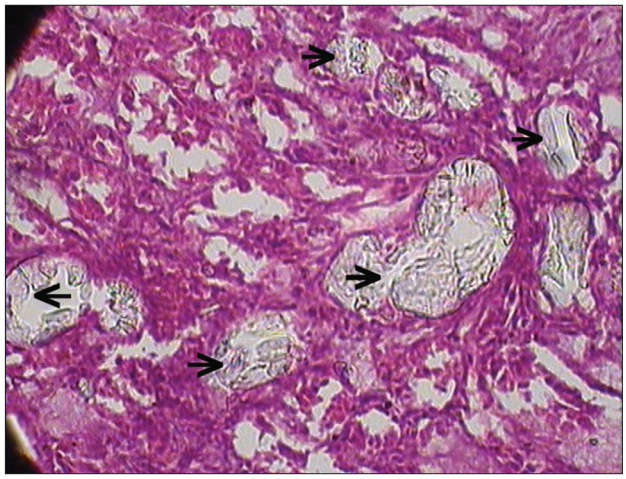

Figure 2: Photomicrograph of representative sections of kidney of albino rats from ammonium oxalate (diet) control group (I × 400 magnification). Note: Presence of large number of crystal material containing tubules especially in the cortical region (Arrow head)

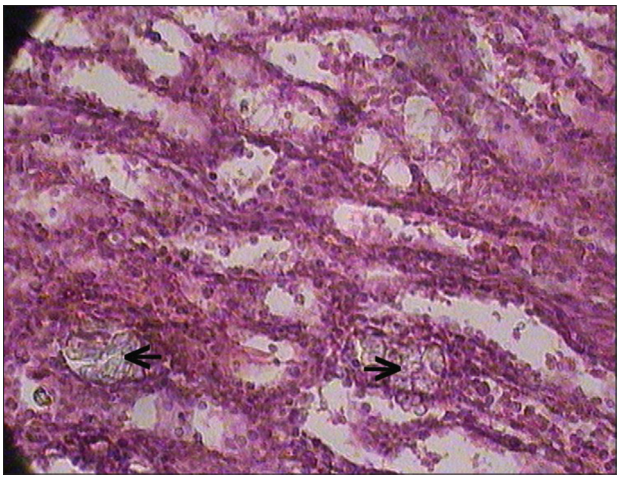

Figure 3: Photomicrograph of representative sections of kidney of albino rats from vehicle (Plain *Ghrita*) control group (I × 400 magnification). Note: Marked decrease in the size and number of crystal containing tubules

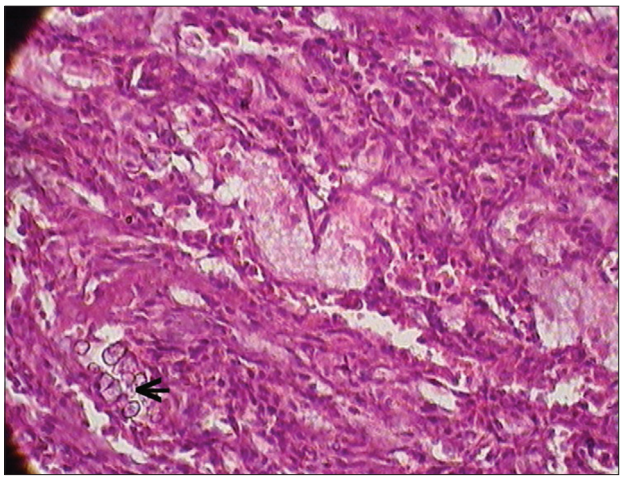

Figure 4: Photomicrograph of representative sections of kidney of albino rats from *Pashanabhedadi Ghrita* treated group (I × 400 magnification). Note: Marked decrease in the size and number of crystal containing tubules

in the body have an effect on one or more of the above stone forming processes and thereby influencing a person's ability of the body to promote or prevent stone formation. Promoters of stone formation facilitate stone formation whilst inhibitors prevent it. Low urine volume, low urine pH, calcium, sodium, oxalate, and urate are known to promote stone formation. Many inorganic (e.g., citrate, magnesium) and organic (e.g., urinary prothrombin fragment 1, glycosaminoglycans, osteopontin) substances are known to inhibit stone formation. Organic inhibitory compounds adsorb to the surface of the crystals, thereby inhibiting crystal growth and nucleation.[19]

The incidence and nature of spontaneous urolithiasis are imperfectly known in the rats.[20] In the present study, 5% ammonium oxalate is used instead of 3% ammonium oxalate

as reported by Sanjay Kumar *et al.*, because the preliminary studies have shown less incidence of calculi deposition with 3% ammonium oxalate. This treatment schedule of gentamicin and ammonium oxalate rich diet increases calcium and oxalate super saturation, renal tubular injury and produce conditions conducive to the formation and growth of CaOx stones.[9] The main causes of CaOx stone formation appear to be chronic hyperoxaluria.[21] In the present study, gentamicin and ammonium oxalate rich diet-induced hyperoxaluria not only increased CaOx deposition in the kidney but also causes papillary damage and incrustations as reported earlier.[22] This treatment schedule of gentamicin and ammonium oxalate increase calcium and oxalate super saturation, renal tubular injury and produce favourable condition to the formation and growth of CaOx stones.[23]

In pondral changes, it is observed that significant increase in kidney weight of the negative control group. This increase supported the results of stone deposition in kidney; it was also supported by histopathological study in which plenty of stones were present in sections of kidney of this group [Figure 2]. Further, extensive degenerative changes are also observed in kidneys of this group, but administration of PBG and VC in animals was failed to attenuate increased kidney weight in comparison to the negative control group.

The type of stones formed can be predicted from the pH of the fasting urine. Crystalluria is pH dependant. Dissolution of calculi can be achieved by alteration in urinary pH form If the pH is acidic 5.5 or below, the stones are likely to be of acidic type (uric acid),[24] if 5.0-6.5 CaOx[25] type and if alkaline (7.2 or above) indicates magnesium ammonium phosphate type. In the present study a decrease in pH was observed on induction of ammonium oxalate type of stones in negative control. Treatment with PBG reversed acidic pH to slightly alkaline pH (7.2 ± 0.20), where as in VC group pH of urine was observed neutral (7.0 ± 0.25). This increase in urinary pH might be responsible for dissolving the complexes of ammonium and oxalate. Thus, some of the anti-urolithiatic effects of PBG and VC are possibly due to its effect on urinary pH.

Due to the presence of stones, there is obstruction to the out flow of urine and because of this, the Glomerular Filtration Rate (GFR) also decreases. Reduction in the GFR leads to accumulation of the waste products, particularly nitrogenous substances such as urea, creatinine, and uric acid in blood.[26] Blood urea nitrogen level is considered as a good indicator of balance in the nitrogen metabolism. It tends to enhance with increase tissue catabolism. In the present study significant increase in blood urea level was observed in the negative control group where as in the treated group with PBG and VC failed to attenuate it. Enhanced serum creatinine indicates renal impairment due to hyperoxaluria. Treatment with PBG and VC failed to attenuate elevated serum creatinine level reflected impaired renal function. Other serum biochemical parameters (serum uric acid and calcium) were not affected to a significant extent by ammonium oxalate rich diet plus gentamicin administration in any group.

Studies show that oxalate, a major stone-forming constituent, has been reported to induce lipid peroxidation and causes tissue damage by reacting with polyunsaturated fatty acids in cell membranes.[27] The polyunsaturated fatty acid content of kidney makes it prone to Reactive Oxygen Species (ROS) attack.[28] Imbalance between oxidants and anti-oxidants level result in Oxidative Stress (OS). Low levels of renal cellular glutathione are reported to favor lipid peroxidation and retain calcium and oxalate in the kidney.[29] In the present study, it is observed that ammonium oxalate rich diet, which was fed to rats with injection gentamicin leads to significant increase in lipid peroxidation level in kidney tissue of the negative control group in comparison to normal control. But in PBG group, it is observed that treatment with PBG significantly attenuated lipid peroxidation. Hence PBG may be considered to prevent the lipid peroxidation-induced renal damage caused by CaOx crystal deposition in the kidney tissue. Therefore, PBG can be attributed to check CaOx crystal attachment and stones formation.

The impaired anti-oxidant protection might be responsible for the accumulation and retention of oxalate and subsequent deposition of CaOx in the kidney. Treatment with anti-oxidants was reported to reduce hyperoxaluria and the resultant OS in rats.[30] In present study ammonium oxalate rich diet with gentamicin administration significantly decreased glutathione and glutathione peroxidation activity and non-significantly increased nitric oxide level in negative control group. Treatment with PBG and VC decreased nitric oxide level non-significantly and enhanced anti-oxidant system like glutathione peroxidase and total glutathione content significantly. This shows anti-urolithiatic effects of PBG and VC, which might be due to quenching oxidant constituents in the kidney. It was reported that the protective effect of *Berginia ligulata* in hyperoxaluric OS and CaOx crystal deposition is due to their potential anti-oxidant activity. *Achyranthus aspera*, *Quercus salieina*, *Amni visnaga*, and *Mimusops elengi*, which are also ingredients of test formulation are also reported to be having the protective effect against oxalate-induced renal tubular epithelial cell injury in cell culture due to their anti-oxidant activity.[31] Further one more ingredient of this formulation, *Varuna* (*Crataeva nurvala*) prevents stone formation due to the anti-lithogenic activity and the anti-crystallization property.[32] It was also reported that *Crateva nurvala*, *Tribulus terrestris*, and *Dolichos biflorus* were found to be effective in preventing the deposition of the stones in experimental rats.[33] The ethanolic extract of *Asparagus racemosus* Wild had an inhibitory potential on lithiasis induced by oral administration significantly reduced the elevated level of calculogenic ions in urine and it elevated the urinary concentration of magnesium, which is considered as one of the inhibitors of crystallization.[30] Thus, the observed anti-urolithiatic activity of test formulation in the present study may be attributed to collective effect of these drugs. The mechanism involved in observed activity profile may be,

- Improving the renal tissue anti-oxidant status and cell membrane integrity
- Inhibition of crystal nucleation, aggregation and growth,
- By increasing urine volume, pH and anti-calcifying activity,
- Regulation of oxalate metabolism.

Conclusion

PBG is having significant anti-urolithiatic activity besides it is having marked anti-oxidant activity. However, further detailed study is required to explore the active principle responsible for this and also to know the exact mechanism involved in observed activity profile.

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हिन्दी सारांश

पाषाणभेदादि घृत का चूहों की वृक्काश्मरी पर एक प्रायोगिक मूल्यांकन

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औद्योगिक जगत में मूत्राश्मरी रोग विशेषकर वृक्काश्मरी का प्रचलन कुछ अधिक ही देखने को मिलता है। सुश्रुत के द्वारा बताये गये एक विशिष्ट योग, 'पाषाणभेदादि घृत' का वर्षों से चिकित्सा में प्रयोग किया जा रहा है, इसकी उपयोगिता निश्चित करना वर्तमान समय की आवश्यकता है । चूहों पर किये गए इस प्रयोग में अमोनियम आक्जलेट प्रचुर आहार एवं जेन्टामाइसिन इन्जेक्शन के प्रयोग से उत्पन्न वृक्काश्मरी पर पाषणभेदादि घृत का मूल्यांकन किया गया है । अध्ययनार्थ औषध का उपयोग इस प्रयोग के आरम्भ से ही किया गया (९०० मि.ली./कि.ग्रा.,१५ दिनों के लिए)। समस्त चूहों को सोलहवें दिन विच्छेदन कर उनके रक्त एवं वृक्कों का उपयुक्त प्रायोगिक अध्ययन किया गया । रक्तगत मानकों में कोई विशेष परिवर्तन देखने को नहीं मिला । जबकि लिपिड पेरॉक्सीडेशन में विशेष गिरावट देखने को मिली। वहीं ग्लूटाथियोन एवं ग्लूटाथियोन पर–आक्सीडेज क्रियायों में बढ़ोत्तरी देखने को मिली । वृक्क व नलिकाओं में क्रिस्टल का जमाव कम होने से वृक्क उत्तकों में हानिकारक प्रभाव कम पड़ा । अंततः यह सिद्व हुआ कि 'पाषाणभेदादि घृत' में, प्रायोगिक चूहों में आमोनियम आक्जलेट युक्त आहार एवं इन्जेक्शन जेन्टामाईसिन द्वारा उत्पन्न वृक्काश्मरी के प्रति अश्मरी प्रतिरोधक क्षमता विद्यमान है ।