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Evaluation of anti lithiatic effect of Siruneer Kalluku Kudineer Chooranam (SKKC) on 1% ethylene glycol induced lithiasis in albino rats.

Dr. S. Tamilarasi[1*] , Dr.A.Kingsly, Dr. G. Essakky Pandian, Dr.R.Antony Duraichi.

[1]PG scholar, Department of Gunapadam, Gsmc, Palayamkottai.
[2]HOD,Department of Gunapadam,Palayamkottai.
[3,4]Lecturer, Department of Gunapadam, Gsmc, Palayamkottai.
*Corresponding Author : **Dr. S. Tamilarasi,** PG Scholar.

E-mail: smtamil86@gmail.com

Abstract

Urinary stone disease has afflicted humankind since antiquity and can persist, with serious medical consequences, throughout a patient's lifetime. In our Siddha system Urolithiasis may be compared to *Kalladaippu*. *Kalladaippu*is a common disease of urinary tract which has the following symptoms, *Neererichal* (burning micturition), urinary obstruction (*Neeradaippu*), low back ache, referred pain in genital organs and tip of penis, abnormal deposits in the urine. In modern science, these symptoms can be correlated with 'urolithiasis'.

'Urolithiasis is a common disorder estimated to occur in approximately 12% of population with a recurrence rate of 70% - 80% in male and 47% - 60% in female. In India, 5% of people are seeing affected by kidney stones and 8-10% people who have life time risk of passing the kidney stone. The recurrence rate for urinary calculi is very high, approximately 50% among the Indian population.The efficacy of invasive therapies such as extra corporal shock-wave lithotripsy and ureteroscopy has been proven by several studies. However these techniques are not risk free and they are problematic and quite expensive and complication.

According to *Agasthiyar 2000, volume-Ш, page no-32*,there was a preparation of the *Siruneerkalluku Kudineer Chooranam(SKKC)* is reported to be useful in the treatment of urinary stones. In the present study, an effort has been made to establish thescientific validity for the antilithiatic property of *SKKC* using ethylene glycol induced lithiasis model in albino rats.

Keywords: *SKKC*, urinary stones, antilithiatic, eswl.

Introduction

Siddha system is one of the oldest systems of medicine in India. Siddha system is based on truth and philosophy. This Medicine system has unique features like removal the root cause of the disease and perfect remedy for body, mind and soul. The Siddha system based on three vital humors namely *vatham, pitham and kabam.* Siddha is the first system to emphasize on food habits. If human beings have any alteration in food habits, it will affect the vital elements of their body.

The incidence of Urolithiasis is very common in the world. In our Siddha system Urolithiasis may be compared to *Kalladaippu.Kalladaippu* is the most common diseases of present society due to modern life style and abnormal diethabits. The efficacy of invasive therapies such as extracorporal shock wave lithotripsy and ureteroscopy has been proven by several studies. However these techniques are not risk free and they are problematic and quite expensive and complication. In the Siddha text,

Siruneer Kalluku Kudineer Chooranam is indicated for *Kalladaippu*. It is less expensive and it has no complications. In this Study, Antilithiatic property of *SKKC* is analysed.

Materials and Methods

" Siruneerkalluku Kudineer Chooranam" is a herbo mineral formulation which indicated as a drug in siddha text book of *Agasthiyar 2000, volume-Ш, page no-32* , Dr. S.Venkadarajen LIM, Sarasvathimahal Tanjur for the treatment of urinary stone, burningmicturition, dysuria etc. The ingredients of *Siruneerkalluku kudineer chooranam* are

Borax - *Venkaram*,
Cuscutareflexa - *Muthiyarkoonthal,*
Santalum album - *Santhanam,*
Zingiberofficinale - *Chukku,*
Plectranthusvettiveroides - *Vilamichuver*.
The drug was prepared as per the text.

Animal selection

For acute toxicity studies, Wistar albino mice of either sex weighing between 25 and 30g were selected and healthy adult male Wistar albino rats weighing between 150 and 200g were selected for the antiurolithiatic activity. The animals were acclimatized to standard laboratory conditions (temperature: 25±2°C) and maintained on 12-h light: 12-h dark cycle. They were provided with regular rat chow (Lipton India Ltd., Mumbai, India) and ad libitum. The animal care and experimental protocols were in accordance with Institutional Animal Ethical Committee (IAEC) proposal no 328 constituted under CPCSEA done at K.M.COLLEGE OF PHARMACY.

Acute toxicity studies

The acute oral toxicity study (5) was carried out as per the guidelines set by Organization for Economic Cooperation and Development (OECD) received from Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). One-tenth of the median lethal dose (LD50) was taken as an effective dose.

Ethylene glycol induced urolithiasis model

Ethylene glycol induced hyperoxaluria model was used to assess the antilithiatic activity in albino rats. Animals were divided into six groups containing six animals in each.

Treatment Protocol

The grouped animal's received the treatment as follows

Group I

Received normal diet and served as controls.

Group II

Lithiatic control: The animals were given normal diet and 1% Ethylene glycol in drinking water for 28 days.

Prophylactic Study:

Group III

Received 1% ethylene glycol in drinking water and then treated with *Siruneer Kalluku Kudineer*at a dose of 200 mg/kg orally for 28 days.

Group IV

Received 1% Ethylene glycol in drinking water and then treated with *Siruneer Kalluku Kudineer*at a dose of 400mg/kg orally for 28 days.

Group V

Received 1% Ethylene glycol in drinking water and thentreated with *Siruneer Kalluku Kudineer*at a dose of 600mg/kg orally for 28 days.

Group VI

Received 1% Ethylene glycol in drinking water and thentreated with cystoneat a dose of 100mg/kg orally for 28days.

Collection and analysis of urine

All animals were kept in individual metabolic cages and 24 h urine samples were collected on 14th, and 28th day of calculi induction treatment. The volume and calcium content of urine were measured. Calcium in urine was estimated using kit by "COBAS MIRA PLUS" auto analyzer. Urine was analyzed for oxalate (8), magnesium (9,10), phosphate (11), uric acid (12), citrate(13) and total protein(14).

Serum analysis

The blood was collected from the retro-orbital sinus under anesthetic condition and serum was separated by centrifugation at 10,000g for 10 min and analyzed for creatinine and uric acid. The creatinine kit (Reckon Diagnostics Pvt. Ltd., India) and uric acid diagnostic kit (Span Diagnostics Ltd., India) were used to estimate serum creatinine and uric acid levels respectively.

Statistical analysis

The results were expressed as mean ± standard error mean (SEM). The statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Newmannkeul's multiple range tests and $p < 0.05$ was considered significant.

Results

Antilithiatic activity

In the present study, chronic administration of 1% (v/v) ethylene glycol aqueous solution to wistar rats resulted in hyperoxaluria. Urinary concentration of the various ions investigated varied drastically, following ethylene glycol treatment.

Table -1 Effect on urinary output in urolithiasis induced rats

Days	GP1	GP2	GP3	GP4	GP5	GP6
0	6.18± 0.40	6.25± 0.40	6.45± 0.74	6.65± 0.74	7.56± 0.92	7.35± 0.72
14	6.83± 0.65	5.90± 0.44**a	7.45± 0.93**b	8.20± 1.36**b	9.36± 1.55**b	10.36± 1.63**b
28	7.38± 0.64	5.38± 0.24**a	7.65± 1.24-**b	9.30± 1.35**b	10.46± 1.54**b	10.92± 1.75**b

GP_1- Normal; **GP_2**- Lithiatic Control; **GP_3**- SKK (200mg/kg);
GP_4-SKK (400mg/kg); **GP_5**-SKK (600mg/kg);
GP6-Cystone herbal tablets (100mg/kg)

- Values are expressed as mean ± SEM
- Values were found out by using ONE WAY ANOVA Followed by Newman keul's multiple range tests.
- **(a) Values were significantly different from normal control (GP_1) at P< 0.01
- **(b) Values were significantly different from Lithiatic control (GP_2) at P<0.01

Effect of *siruneer kalluku kudineer* on urinary parameters on day 14 & 28

The oxalate excretion was 24hr on day 14^{th}& 28^{th} respectively for GP_1. It increased significantly ($P < 0.001$) on day 14^{th}& 28^{th} day in GP_2 following ethylene glycol treatment. Treatment at a dose of *Siruneer Kalluku Kudineer (SKK)* 200mg/kg, 400mg/kg and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg (GP_3 to GP_6) reduced the oxalate excretion significantly to ($P<0.01$) on 14^{th} day treatment. Likewise on 28^{th} day, treatment with this SKK reduced the oxalate excretion significantly to ($P<0.01$) in (GP_3 toGP^6) rats respectively. The results are shown in the table no: 2 & 3.

The urinary calcium excretion was increased significantly on day 14^{th} and 28^{th} day in GP_2 following ethylene glycol treatment. The calcium excretion was significantly reduced to treatment with SKK at a dose of 200, 400 and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg (GP_3 to GP_6) reduce the calcium excretion significantly to on 14^{th} day treatment likewise on 28^{th} day calcium excretion was significantly reduced to 24hr ($P<0.01$) in (Gp_3 to Gp_6) rats respectively. The results are shown in the table no: 2 & 3.

Likewise phosphate and creatinine excretion values gradually increased in GP_2 on the 14^{th}& 28th day. However in (GP_3 to GP_6) grouped treated animals these elevated values were significantly reduced on 14^{th} and 28^{th} day respectively. However, regarding creatinine in (GP_3 to GP_6) these elevated values were significantly reduced on 14^{th} day and on 28^{th} day respectively. The results are given in table no: 2 & 3.

Likewise urinary protein and uric acid concentration increased following ethylene glycol treatment in GP_2 and it reached maximum respectively on the 14^{th}& 28^{th} day. On treatment with SKK at a dose of 200,400 and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg (GP_3 to GP_6) the protein and uric acid excretion was restored to near normal limits in (GP_3 to GP_6) for protein on 14^{th}day and on 28^{th} day ($p<0.001$) and for uric acid on 14^{th} day and on 28^{th} day ($P<0.01$). The results are tabulated in table no: (2 and 3).

Table.no:2 Effect on urinary biochemical parameters on the day 14

GP	Protein (mg/dl)	Magnesium (mg/dl)	Calcium (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)	Oxalate (mg/dl)	Phosphate (mg/dl)
GP_1	74.96± 1.73	3.95± 0.54	5.49± 0.76	8.76± 0.88	0.82± 0.13	17.85± 1.54	37.70± 2.78
GP_2	153.31 ± 4.53**(a)	1.34 ± 0.24**(a)	25.25± 1.90**(a)	16.65 ± 1.54**(a)	1.64 ± 0.18**(a)	31.70 ± 3.25**(a)	78.65 ± 4.30**(a)
GP_3	88.38 ± 3.95 **(b)	2.60 ± 0.32**(b)	19.30 ± 2.15**(b)	10.65 ± 0.93**(b)	0.96 ± 0.12**(b)	25.32 ± 2.68**(b)	46.60 ± 3.75**(b)
GP_4	86.52 ± 3.74**(b)	2.35 ± 0.55**(b)	12.42 ± 0.83**(b)	12.34 ± 0.63**(b)	0.94 ± 0.14**(b)	23.80 ± 2.54**(b)	42.40 ± 3.26**(b)
GP_5	84.16± 3.55**(b)	3.36 ± 0.42**(b)	16.60 ± 0.63**(b)	9.74 ± 0.80**(b)	0.86 ± 0.08**(b)	24.24 ± 1.82**(b)	36.25 ± 2.65**(b)
GP_6	80.34± 2.85**(b)	3.34 ± 0.60**(b)	16.63 ± 0.45**(b)	8.92 ± 0.83**(b)	0.82 ± 0.14**(b)	21.15 ± 1.76**(b)	35.25 ± 2.55**(b)

- **GP_1**- Normal; **GP_2**- Lithiatic Control; **GP_3**- SKK(200mg/kg);
- **GP_4**-SKK(400mg/kg);**GP_5**-SKK (600mg/kg);
- **GP6**-Cystone herbal tablets (100mg/kg)
- Values are expressed as mean ± SEM
- Values were found out by using ONE WAY ANOVA Followed by Newman keul's multiple range tests.
- **(a) Values were significantly different from normal control (GP_1) at P< 0.01
- **(b) Values were significantly different from Lithiatic control (GP_2) at P<0.01

Table.no:3 Effect on urinary biochemical parameters on the 28th day

GP	Protein (mg/dl)	Magnesium (mg/dl)	Calcium (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)	Oxalate (mg/dl)	Phosphate (mg/dl)
GP_1	76.85 ±3.74	4.36 ±0.40	7.25 ±0.64	3.42 ±0.73	0.90 ±0.32	18.64 ±1.41	32.25 ±3.48
GP_2	165.30 ±7.26**(a)	1.78 ±0.57**(a)	22.82 ±1.58**(a)	12.52 ±1.40**(a)	1.67 ±0.55**(a)	51.42 ±4.46**(a)	81.51 ±4.78**(a)
GP_3	91.20 ±5.61**(b)	2.46 ±0.40**(b)	13.70 ±1.07**(b)	8.63 ±0.41**(b)	1.28 ±0.75**(b)	26.84 ±2.65**(b)	45.68 ±3.42**(b)
GP_4	88.76 ±5.72**(b)	3.91 ±0.54**(b)	11.65 ±0.94**(b)	8.31 ±0.43**(b)	1.26 ±0.45**(b)	23.45 ±2.54**(b)	44.56 ±3.18**(b)
GP_5	84.68 ±4.72**(b)	3.62 ±0.52**(b)	10.86 ±0.44**(b)	7.92± 0.41**(b)	1.46 ±0.28**(b)	21.30 ±2.18**(b)	43.50 ±2.40**(b)
GP_6	84.65 ±4.84**(b)	3.55 ±0.46*(b)	10.80 ±0.49**(b)	7.22± 0.39**(b)	1.24 ±0.51**(b)	20.70 ±2.19**(b)	41.61 ±2.30**(b)

- **GP_1**- Normal; **GP_2**- Lithiatic Control; **GP_3**- SKK (200mg/kg);**GP_4**-SKK (400mg/kg); **GP_5**-SKK (600mg/kg);
- **GP6**-Cystone herbal tablets (100mg/kg)
- Values are expressed as mean ± SEM
- Values were found out by using ONE WAY ANOVA Followed by Newman keul's multiple range tests.
- **(a) Values were significantly different from normal control (GP_1) at P< 0.01
- **(b) Values were significantly different from Lithiatic control (GP_2) at P<0.01

In GP_2lithiatic control rats, the magnesium level in urine gradually decreased following ethylene glycol treatment on the 14th& 28th day . Subsequent administration of the SKK and cystone herbal tablets enhanced the magnesium excretion significantly on 14th day & 28th day.

Effect of *siruneer kalluku kudineer* on serum parameters on day 28

In prophylactic study the serum parameters such as calcium, uric acid, creatinine, oxalate, phosphate levels were increased significantly in GP_2 (Lithiatic control) following ethylene glycol treatment, Treatment with SKK at a dose of 200,400 and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg (GP_3 to GP_6) reduce the all above mentioned parameters significantly. On the contrary the magnesium levels were decreased significantly in GP_2 (Lithiatic control) following ethylene glycol treatment**.** After treatment with SKK at a dose of 200mg/kg, 400mg/kg and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg (GP_3 to GP_6) the magnesium level was restored near to normal levels.

Table.no:4 Effect on serum parameters on the 28th day

GP	Magnesium (mg/dl)	Calcium (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)	Oxalate (mg/dl)	Phosphate (mg/dl)
GP_1	4.88 ±0.55	10.60 ±1.55	3.30 ±0.26	0.48 ±0.26	6.32 ±0.68	13.80 ±1.44
GP_2	1.64 ±0.40**(a)	17.45 ±2.46**(a)	9.70 ±1.28**(a)	1.20 ±0.56**(a)	13.54 ±1.66**(a)	29.30 ±3.64**(a)
GP_3	3.76 ±0.54**(b)	12.75 ±1.64**(b)	4.30 ±0.78**(b)	0.78 ±0.48**(b)	9.54 ±0.95**(b)	24.30 ±2.80**(b)
GP_4	3.84 ±0.24**(b)	12.75 ±1.51*(b)	4.20 ±0.51**(b)	0.75 ±0.48**(b)	8.80 ±0.84**(b)	22.75 ±2.64**(b)
GP_5	3.80 ±0.55**(b)	11.10 ±1.45**(b)	3.70 ±0.60**(b)	0.65 ±0.58**(b)	8.55 ±0.63**(b)	18.30 ±1.54**(b)
GP_6	4.12 ±0.33**(b)	10.20 ±1.40**(b)	3.15 ±0.45**(b)	0.54 ±0.36**(b)	7.15 ±0.32**(b)	17.28 ±1.53**(b)

- **GP_1**- Normal; **GP_2**- Lithiatic Control; **GP_3**- SKK (200mg/kg);
- **GP_4**-SKK (400mg/kg); **GP_5**-SKK (600mg/kg);
- **GP6**-Cystone herbal tablets (100mg/kg)
- Values are expressed as mean ± SEM
- Values were found out by using ONE WAY ANOVA Followed by Newman keul's multiple range tests.
- **(a) Values were significantly different from normal control (GP_1) at P< 0.01
- **(b) Values were significantly different from Lithiatic control (GP_2) at P<0.01

Discussion

As traditional medicines are usually taken by the oral route, same route of administration was used for evaluation of antilithiatic effect of the SKK at a dose of 200, 400 and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg against ethylene glycol induced urolithiasis in rats.

In the present study, male rats were selected to induce urolithiasis because the urinary system of male rats resembles that of humans and also earlier studies have shown that the amount of stone deposition in female rats was significantly less.

Urinary supersaturation with respect to stone-forming constituents is generally considered to be one of the causative factors in calculogenesis. Evidence in previous studies indicated that in response to 14 day period of ethylene glycol (1% v/v) administration, young male albino rats form renal calculi composed mainly of calcium oxalate.

The biochemical mechanisms for this process are related to an increase in the urinary concentration of oxalate. Stone formation in ethylene glycol fed animals is caused by hyperoxaluria, which causes increased renal retention and excretion of oxalate. Similar results have been obtained when rats were treated with ethylene glycol and ammonium oxalate.

Therefore, this model was used to evaluate the antilithiatic effect of SKK at a dose of 200,400 and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg against urolithiasis.

Lowered the levels of oxalate as well as calcium excretion. Restored phosphate level, thus reducing the risk of stone formation. Lowered the excretion of uric acid and reduces the risk of stone formation.Elevated the urinary magnesium level, and thus, reduced the propensity to crystallize, thereby creating an ambience unfavourable for precipitation, Reduced the urinary protein excretion in the treated group rats, and hence minimizes the conditions favourable for crystal growth. Diuresis and hastens the process of dissolving the preformed stones and prevention of new stone formation in the urinary system.

Suppresses this increase in intracellular calcium. Several studies reported that Flavonoids, polyphones and triterpenes have anti-inflammatory and antioxidant effects. It can be expected that antilithiatic activity might be through an antioxidant activity and free radical scavenging principle.

Saponins derivatives appear as components of a great number of medical herbs with antilithiatic properties Likewise, SKK at a dose of 200,400 and 600mg/kg and cystone herbal tablet at a dose of 100mg/kg studied contains such components. So these components are responsible for antilithiatic activity.

Conclusion

The result shows that the SKKC at a dose of 200, 400, 600 mg/kg and cystone herbal tablet at a dose of 100 mg/kg increased elimination of oxalate, calcium, phosphate, magnesium, uric acid, creatinine which decreased circulating level of those minerals and as prevent calculi formation of kidneys. The test drug siruneerkalluku kudineer prevent calculi formation of kidney. So the test drug are responsible for antilithiatic activity.

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