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Reactions of Renal Calculi with Natural Product (Phyllanthus niruri Leaves Extract) and Heterocyclic Acid (Nicotinic Acid)

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ABSTRACT
Urolithiasis is a complex process results from a succession of several physiochemical events including super saturation, nucleation, growth, aggregation and retention, within the kidneys.
Traces of impurities cause marked modification in the growth and habit of both soluble and insoluble metal salts. It has been reported that strong absorption occurs on certain crystal faces only, and their rate of growth is markedly reduced, this may be due to formation of complexes with the additives. These complexing agents when complexed through polar groups are especially effective. This has further demonstrated that such absorption is much more active in solutions of the highly soluble metal salts than on the sols of less soluble metal salts of complexing cation.
During the early stage of the growth, these additives may completely inhibit the formation of 'embryo' or 'micelle', while at the later stage they may preferentially reduce the growth of some specific crystal face.
Most renal stones contain calcium as dominating part. Therefore studies on calcium metabolism have long been done on recurrent stone formers. There are also considerable evidences indicating that in most of the cases increased urinary calcium is caused by an inappropriately increased interstitial absorption, the cause of which still remains unclear therefore a logical approach for stone prophylaxis should reduce the calcium output by decreasing the amount of calcium absorbed.
Taking into account the above factors discussed, we have attempted to solubilise these insoluble ingredients of renal calculi ('whole renal calculi' and 'powdered renal calculi') with nicotinic acid and natural products viz. Phyllanthus niruri leaves extract (Fresh and hydrolysed).

I. INTRODUCTION

Urinary stones affect 10–12% of the population in industrialized countries. There are only a few geographical areas in which stone disease is rare, e.g., in Greenland and in the coastal areas of Japan. The incidence of urinary stones has been increasing over the last years while the age of onset is decreasing. With a prevalence of > 10% and an expected recurrence rate of ~50%, stone disease has an important effect on the healthcare system. Once recurrent, the subsequent relapse risk is raised and the interval between recurrences is shortened. Features associated with recurrence include a young age of onset, positive family history, infection stones and underlying medical conditions. Epidemiological studies revealed that nephrolithiasis is more common in men (12%) than in women (6%) and is more prevalent between the ages of 20 to 40 in both sexes. The etiology of this disorder is multifactorial and is strongly related to dietary lifestyle habits or practices. Increased rates of hypertension and obesity, which are linked to nephrolithiasis, also contribute to an increase in stone formation.

Management of stone disease depends on the size and location of the stones . Stones larger than 5 mm or stones that fail to pass through should be treated by some interventional procedures such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), or percutaneous nephrolithotomy (PNL). Unfortunately, the propensity for stone recurrence is not altered by removal of stones with ESWL and stone recurrence is still about 50%. In addition, ESWL might show some significant side effects such as renal damage, ESWL induced hypertension or renal impairment.

Although there are a few recent reports of beneficial effects of medical treatments in enhancing clearance of stones in the distal ureters, de facto there is still no satisfactory drug to use in clinical therapy, especially for the prevention or the recurrence of stones. In this regard, many plants have been traditionally used to treat kidney stones and have been shown to be effective.

We have selected nicotinic acid which is a heterocyclic acid and Phyllanthus niruri leaves extract to solubilise the renal calculi. For which Urinary stones with sample nos. 10,20,40,45 have been collected from R.N. institute of Urology, Patna. Chemical analysis of all the above mentioned Urinary stones has shown that they contain calcium oxalate and calcium phosphate as major constituents.

II. EXPERIMENTS

PREPARATION OF PHYLLANTHUS NIRURI LEAVES EXTRACT AND ITS HYDROLYSATE

100 g of Phyllanthus niruri leaves was crushed and the juice was centrifuged for few minutes and again filtered through G4 crucible the clear filtrate obtained was used for assaying its inhibitory effect on renal calculi.

Now to prepare the hydrolysed extract, the filterate was treated with about 10 ml of 2N HCl and refluxed for 2 hrs. After cooling the hydrolysed extract, solid sodium bicarbonate was added with constant stirring to bring the pH back to approximately 7 and again filtered through G4 crucible.

DISSOLUTION OF RENAL STONE, WHOLE STONE AND POWERED STONES, IN SOME NATURAL EXTRACTS (FRESH HYDROLYSED) AND IN NICOTINIC ACID

(A) DISSOLUTION OF WHOLE RENAL STONES:

All the renal stones viz. sample nos. 10,20,40,45 were washed properly with distilled water and then each stone was suspended separately in 20 ml of 0.1N sodium chloride solution for 24 hours. The samples were filtered, washed with distilled water, dried in an air oven at 80°C for overnight, cooled and weighed.

(i) Weighed amount of renal stones (sample nos. 10,20,40,45) were suspended separately in 20 ml of Phyllanthus niruri leaves extract (fresh) prepared above and stirred slowly and constantly over magnetic stirrer for 5 hours and then kept overnight. The next day, the solutions were again stirred for another 5 hours and then filtered. The undissolved stones were taken out washed with distilled water, dried in an air oven at 80°C for overnight cooled and then weighed out. Next, the above weighed renal stones (that is the undissolved stones) were again suspended separately in another 20 ml of Phyllanthus niruri leaves (fresh) and the process of the experiments were repeated as above. These experiments repeated 5 times with every stone Inhibitor condition was kept that same throughout the experiments.

(ii) Weighed amount of renal stones (sample nos. 10, 20, 40, 45) were suspended separately in 100 ml of M/20 Nicotinic and the experiment was continued exactly in the same manner as mentioned in (i).

(iii) The above experiment in (i) was repeated using the hydrolysate extracts of the natural product Phyllanthus niruri leaves.

(B) DISSOLUTION OF POWERED RENAL STONES:

Powder of renal stones viz. sample nos. 10,20,40,45 were suspended separately in 20 ml of 0.1 N sodium chloride solution for 24 hours. The samples were filtered separately, washed with distilled water, dried in an air oven at 80°C for four hours, then cooled and weighed.

(i) Weighed amount of powdered renal stones (samples nos. 10,20,40,45) were suspended separately in 100 ml. of Phyllanthus niruri leaves extract (fresh) and stirred constantly on a magnetic stirrer for 5 hours and then filtered out washed with distilled water, dried in an air oven at 80°C for 4 hours, cooled and weighed.

(ii) The above experiment, that is, (i) was repeated by using hydrolysate extracts instead of fresh extract of the Phyllanthus niruri leaves.

(iii) Weighed amount of powdered renal stones (sample nos. 10,20,40,45) were suspended separately in 100 ml of M/20 nicotinic acid solution and the experiment was continued exactly in the same manner as mentioned in (i).

III. RESULTS

(A) SOLUBILITIES OF WHOLE RENAL STONES:

(i) Solubility of whole renal stones (sample nos. 10,20,40,45) in Phyllanthus niruri leaves extract is shown in table 1.

(ii) Solubility of whole stones (sample nos. 10,20,40,45) in Phyllanthus niruri leaves extract fresh and hydrolysate in given in table 2

(iii) Solubility of whole renal stone (10,02,40,45) in nicotinic acid solution is given in table 3

(B) SOLUBILITIES OF POWDERED RENAL STONE:

(i) Solubility of powdered renal stones (sample nos. 10,20,40,45) in Phyllanthus niruri leaves extract (fresh) is given in table 4

(ii) Solubility of powdered renal stones (sample nos, 10,20,40,45) in Phyllanthus niruri leaves extract (hydrolysed) is given in table 5

(iii) Solubility of powdered renal stones (sample nos. 10,20,40,45) in nicotinic acid solution is given in table 6

Table -1

SOLUBILITY OF WHOLE RENAL STONES IN PHYLLANTHUS NIRURI LEAVES EXTRACT (FRESH)

No. of Obs.	Natural Product	Fresh/hydrolysed fresh	Sample no.	Wt. of whole renal stone (mg)	Wt. remained after extract treatment(mg)	Difference solubility in mg/100 ml	% solubility mg /100 ml of extract
1.	Phyllanthus Niruri leaves extract	Fresh	10	165	129	36	21.82
2.	Phyllanthus Niruri leaves extract	Fresh	20	112	105.5	6.5	05.80
3.	Phyllanthus Niruri leaves extract	Fresh	40	202	154	48	23.76
4.	Phyllanthus Niruri leaves extract	Fresh	45	85	56.5	29.5	34.30

Table -2

SOLUBILITY OF WHOLE RENAL STONES IN PHYLLANTHUS NIRURI LEAVES EXTRACT (HYDROLYSED)

No. of Obs.	Natural Product	Fresh/hydrolysed fresh	Sample no.	Wt. of whole renal stone (mg)	Wt. remained after extract treatment(mg)	Difference solubility in mg/100 ml	% solubility mg /100 ml of extract
1.	Phyllanthus Niruri leaves extract	hydrolysed	10	125	83	42	33.6
2.	Phyllanthus Niruri leaves extract	hydrolysed	20	104	96	8.0	07.7
3.	Phyllanthus Niruri leaves extract	hydrolysed	40	152	147	50	34.0
4.	Phyllanthus Niruri leaves extract	hydrolysed	45	55	24	31	56.36

Table 3

DISSOLUTION OF WHOLE RENAL STONE IN NICOTINIC ACID SOLUTION

No.of Obs.	Inhibitor	Sample No.	Wt of whole renal stone (mg)	Wt. remained after acid treatment (mg)	Difference solubility in mg/100 ml	% solubility in mg/100 ml of extract
1.	0.01M Nicotinic acid	10	80	66	14	17.5
2.	0.01M Nicotinic acid	20	95	80	15	15.78
3.	0.01M Nicotinic acid	40	142	132	10	07.42
4.	0.01M Nicotinic acid	45	20	18	02	10.0

Table -4
SOLUBILITY OF POWDERED RENAL STONES IN PHYLLANTHUS NIRURI LEAVES EXTRACT (FRESH)

No. of Obs.	Natural Product Fresh hydrolysed	Sample no.	Wt. of powdered renal stone (mg)	Wt. remained after extract treatment (mg)	Difference solubility in mg/100 ml	% solubility mg/100 ml of extract
1.	Phyllanthus Niruri leaves extract fresh	10	100	66.6	33.4	33.4
2.	Phyllanthus Niruri leaves extract fresh	20	100	81.3	12.7	12.7
3.	Phyllanthus Niruri leaves extract fresh	40	100	70.0	30.0	30.0
4.	Phyllanthus Niruri leaves extract fresh	45	100	65.4	34.6	34.6

Table -5
SOLUBILITY OF POWDERED RENAL STONES IN PHYLLANTHUS NIRURI LEAVES EXTRACT (HYDROLYSED)

No. of Obs.	Natural Product Fresh hydrolysed	Sample no.	Wt. of powdered renal stone (mg)	Wt. remained after extract treatment (mg)	Difference solubility in mg/100 ml	% solubility mg/100 ml of extract
1.	Phyllanthus Niruri leaves extract hydrolysed	10	50	27.4	22.6	45.2
2.	Phyllanthus Niruri leaves extract hydrolysed	20	50	34.8	15.2	30.4
3.	Phyllanthus Niruri leaves extract hydrolysed	40	50	20.3	29.7	43.4
4.	Phyllanthus Niruri leaves extract hydrolysed	45	50	35.5	15.0	30.3

Table- 6
SOLUBILITY OF POWDERED RENAL STONE IN NICOTINIC ACID SOLUTION

No.of Obs.	Inhibitor	Sample No.	Wt of whole renal stone (mg)	Wt. remained after acid treatment (mg)	Difference solubility in mg/100 ml	% solubility in mg/100 ml of extract
1.	0.01M Nicotinic acid	10	50	38	12.0	24.0
2.	0.01M	20	50	41.4	08.6	17.2

	Nicotinic acid					
3.	0.01M Nicotinic acid	40	50	34.2	15.8	31.6
4.	0.01M Nicotinic acid	45	50	29.8	20.2	40.4

IV. DISCUSSION

Renal calculi are, in general, hard to break, the hardness varies from stone to stone depending on their constituents for example, calcium oxalate monohydrate stones are hard and compact while calcium oxalate dihydrate stones are roughly aggregated brittle. Renal calculi are sometimes hard enough to be broken, particularly when they are big in size, even with the most sophisticated and the latest developed machine, that is, extracorporeal shock wave lithotripsy (ESWL) in a single treatment and necessiate for a second treatment. To some extent the number of shock wave used increases as the size and hardness of the stone increases, but not more than 1,800 shocks could be given to a patient. However, this procedure, that is the treatment of large volume renal calculi with ESWL, always carries a high risk of leaving fragment behind that eventually will obstruct the ureter and necessiate further endomological procedures.

In this chapter, our main aim is to break the hard crust of a renal calculus by dissolving part of it. Once a portion of the hard crust is gone, the calculus becomes susceptible to attack. These reagents (that is natural product extracts rich in phosphates and acids) then further dissolve the calculus and the calculus crumbles once the renal calculus is broken into small pieces, it can be easily flushed out of the system.

Keeping all these in view, we have endeavoured to solubilise the insoluble ingredients of renal calculi (whole renal calculi and powdered renal calculi) with extract of some natural products by carrying out reactions at room temperature in vitro.

The whole calculi were treated with fresh extracts of the natural product viz. Phyllanthus niruri leaves extract followed by treatment with hydrolysate extracts of the same natural products and the difference in weight of whole calculus, before and after the treatment with extracts gave a clear indication of dissolution of some ingredients of the calculus, which remained in the solution. The results of the experiments show that, the percentage solubility of the whole renal calculi in the hydrolysate extracts are more than in their corresponding fresh extract.

When powdered renal calculi were treated with fresh and hydrolysate extracts of the natural product and the weight difference calculated before and after the treatments, it was found that the percentage solubility of powdered renal calculi are more in hydrolysate extracts than in their corresponding fresh extracts. Further, it was found that the dissolution of stone ingredient in powdered renal calculus was more than the whole renal calculus.

Our experimental studies have indicated that by increasing the surface area of the calculus available for dissolution of natural products, the percentage solubility increased markedly. Further, it can be inferred that, the outer surface of the calculus is much stubborn and the extracts are not able to react so easily, to make soluble the ingredients of the whole renal calculus, definitely loosen the hardness of the calculus. This calculus then become very much susceptible to attacks; and the extracts then further dissolve the calculus and the calculus crumble.

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