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Formulation and evaluation of Antiurolithiatic herbal tablet

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ABSTRACT

Phytomedicine based on principles of Ayurveda are need of the hour and is more feasible than allopathic drugs which is not only more expensive in terms of "leads" but is also associated with many unwanted effects. Ethnopharmacological usage and the literature review revealed that the *Abutilon indicum, Zea mays, Tribulus terrestris, Phyllanthus niruri* have significant antiurolithiatic activity. After the detailed study of powder of ethanolic extract of seeds of *abutilon indicum*, tassel of *zea mays,fruits of Tribulus terrestris and leaves of Phyllanthus niruri* a formulation using the plant materials was prepared. The formulation was evaluated and standardized as per the Pharmacopoeial standards. The results of preformulation studies revealed that all the values were within acceptable limit. Formulation showed appreciable hardness characteristics (4.35 kg/cm^2), which facilitates its fast disintegration. The friability (0.8%) of formulation indicated that the tablets were mechanically stable. As the average weight of tablets was 505 mg, the acceptable weight variation range is ±7%. Hence the entire formulated tablet passed the weight variation test. The disintegration time of formulations was more than 1 minute. Thus the claims made by the traditional Indian systems of medicine regarding the use of this plant in the treatment of antiurolithiatic activity confirmed. The final conclusion drawn from the above mentioned data is that the possible use of these economical and relatively nontoxic, non-hazardous natural remedies of plant origin may further be explored as they are devoid of major side effects associated with synthetic agents.

Keywords: *Abutilon indicum, Zea mays , Tribulus terrestris, Phyllanthus niruri* , Disintegration, Preformulation

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1. INTRODUCTION:-

Urinary stone disease continues to reside in an important place in daily urological practice. The average life time risk of stone formation has been reported in the range of 5-10 %. A predominance of men over women can be observed with an incidence peak between the fourth and fifth decade of life. **(Yadav R. D., 2011).** *Abutilon indicum* species has been widely used as medicine in Ayurvedic system of medicine. *Abutilon indicum* (Malvaceae), commonly known as "Thuthi" is distributed throughout the hotter parts of India. *Abutilon indicum* commonly known as "Atibala" in Sanskrit gives excessive tonic strength. Phytoconstituents like β-Sitosterol (0.2%), tocopherol oil (0.3%) were isolated. **(Dashputre N. L.,2010)**

The word *zea mays* come from two languages. Zea comes from ancient greek and is a generic name for cereal and grains. In traditional medicine, corn is used for relieving diarrhea, dysentery, urinary tract disorder, prostatitis, lithiasis, angina, hypertension and tumor. **(Parle M., 2013)** ***Tribulus terrestris*** is commonly known as puncture vine, caltrop, yellow vine, goat head and devil's horn. It is is a member of the Zygophyllaceae family and is widely distributed in both tropical and mild temperate regions. *T. terrestris* is native to warm temperate and tropical regions of southern Europe, southern and western Asia, throughout Africa, and Australia. *Phyllanthus niruri* is an important medicinal plant. The plant is widely used for the treatment of hepatic disease, oedema, dropsical condition, and urinary troubles.

2. MATERIALS AND METHODS

2.1 Description of plant

Abutilon indicum:- The botanical name of atibala is *Abutilon indicum* and it belongs to family Malvaceae.The plant grows throughout India and in Sri Lanka, at about an elevation of 1000-1, 500 meters. The perennial shrub grows 1.25-2 meters in height. Plant covered with minute hairs. Leaves are alternate, cordate and acute. The leaves are oblong, opposite, toothed, smooth and covered with fine white hair. The flowers are yellow, 2.5 cm in diameter.

***Zea mays*:-** The word zea mays comes from two languages. Zea comes from ancient greek and is a generic name for cereal and grains. In traditional medicine, corn is used for relieving diarrhea, dysentery, urinary tract disorder, prostatitis, lithiasis, angina, hypertension and tumor.

Tribulus terrestris is commonly known as puncture vine, caltrop, yellow vine, goat head and devil's horn. It is is a member of the Zygophyllaceae family and is widely distributed in both tropical and mild temperate regions *T. terrestris* is native to warm temperate and tropical regions of southern Europe, southern and western Asia, throughout Africa, and Australia.

Phyllanthus niruri originated in India, usually occurring as a winter weed throughout the hotter parts. The *Phyllanthus* genus contains over 600 species of shrubs, trees and annual or biennial herbs distributed throughout the tropical and subtropical areas. *Phyllanthus niruri* is a herb of Euphorbiaceae family that grows upto 60 cm. *Phyllanthus niruri* is an annual herb which grows in the wild after first showers of monsoon in Jharkhand, Bihar, Chhattisgarh, etc. states of India. Extracts of this herb have been proven to have therapeutic effects in many clinical studies. *Phyllanthus niruri* is an important medicinal plant. The plant is widely used for the treatment of hepatic disease, oedema, dropsical condition, and urinary troubles.

Extraction

The dried parts of crude drugs were powdered, weighed (500g) and filled in soxhlet apparatus for solvent extraction. The powdered drug was defatted with petroleum ether. (60-80º C).Defatted drug was then dried and again filled in soxhlet apparatus for solvent extraction with solvent ethanol. Solvents were evaporated to get the dried residue of extract. Percentage yield were calculated for each extract. **(Kokate, C. K. 2000)**

2. 2. Formulation

2.2.1 Powdering of extracts: - Colloidal silicon dioxide (Aerosil 200) was added to the extract in a percentage of 2% of adjuvant to dry residue.

2.2.2 Preformulation Studies

The following Preformulation studies were performed:

- Organoleptic studies
- Solubility testing
- Angle of repose
- Loss on drying:
- Total Ash value determination
- Bulk density
- Tapped density
- % Compressibility
- Hausner ratio
- pH
- Particle size
- Extract Excipient Compatibility studies

2.2.2.1 Organoleptic studies: In these studies the organollepic features like colour, odour and physical appearance were observed and recorded.

2.2.2.2 Solubility testing

The solubility's were checked in water pH (7.0), 0.1 N hydrochloric acid solution, absolute alcohol, ethyl acetate, and hexane.

2.2.2.3 Angle of repose

Angle of repose is an important parameter to study the Flow property analysis of any powdered formulation with respect to their frictional forces. Angle of repose is defined as the maximum angel between the surface of the pile of powdered sample and the horizontal plane. Mathematically angle of repose is calculated by height of the pile (H) divided by radius of the pile(R). **(Lachman, L.et al. 1991,Aulton, et al. 1999, Martin et al. 2005)**

Angle of repose (Tan θ) = height of the pile (H)/ radius of the pile(R)

Table 1 Relationship between Angle of repose and powder Flow property

s.no.	Angle of repose	Flow property
1.	<25	Excellent
2.	20-30	Good
3.	30-40	Passable
4.	>40	Very poor

2.2.2.4 Loss on drying

Weighing bottle was dried a in a oven at 105ºC.and weight (w_1) was taken. 3 g of the drug was placed in it. The drug was dried in oven at 100-105 º C for 3 hrs. Drug was then allowed to cool in desiccators. And weigh it again (w_2).

% Loss on drying (LOD) = {($w_1 - w_2$) / w_1} x 100

2.2.2.5 Total ash

Crucible was heated to redness for 30 min and allowed to cool in a desiccators and weighed (w_1). 3 gram of the powdered drug was carefully weighed in the above crucible. The gross weight of the crucible with the contents was noted (w_2). Sample was evenly distributed and dried at 100-105ºC for 1 hour. Ignited to a constant mass .Allowing the crucible to cool in desiccators after ignition. Than crucible was cooled in desiccators and weighed. (w_3). Total ash was calculated in % w/w by the following formula.

Total ash in % w/w= {(w_3-w_1)/ (w_2-w_1)} X 100

Where, w_1-Weight of the empty crucible in grams

w_2- Weight of the crucible + sample in grams

w_3- Weight of the crucible + ash obtained in grams

2.2.2.6 Bulk density

Bulk density is defined as the mass of powder divided by bulk volume.

Bulk density (D_b) = mass of powder (M) / bulk volume (V_b)

Bulk density was determined by measuring the amount of sample required to fill 3/4th volume of a 10ml. capacity graduated measuring cylinder via a funnel and measuring the volume occupied and weighed. **(Lachman, L.et al. 1987, Aulton et al. 1988, Martin et al. 2005)**

2.2.2.7 Tapped density

Tapped density is defined as the mass of powder divided by tapped volume.

Tapped density (D_t) = mass of powder (M) /tapped volume (V_t)

Tapped density was determined by tapping the graduated 10ml. measuring cylinder 100 times from a height of about 1.5 inch. **(Lachman, L.et al. 1987,Aulton et al. 1999, Martin et al. 2005)**

2.2.2.7 % Compressibility

% Compressibility was determined by the following formula

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

2.2.2.8 Hausner's ratio

Hausner's ratio was determined by the following formula.

Tapped density / Bulk density

2.2.2.9 pH

pH was determined by pH meter.

2.2.2.10 Particle size

These studies were carried out by sieve analysis. Sieve no. 60, 80 and 120 were used. Accurately weighed sample was placed (2 g) on topmost /coarsest sieve. Sieves were arranged in the ascending order from top. Agitated the nest of sieves for 5 minutes. Stopped the sieve shaker. Then carefully removed each sieve from the nest, without any loss of material. Reweighed each sieve and determined the weight of material on each one Determined the mass of material in the collecting pan. Reassembled the nest of sieves and agitated for another 5 min. This was done repeatedly for three times .After three times of agitation the end point criterion was achieved (when the change in mass of any of the test sieve is not more or less than 5% of the previous mass on that sieve).

2.2.2.11 Extract excipients interaction study

Powdered extracts excipients interaction study was performed by determination of total flavonoid in mixture of powder of *Abutilon indicum*, *Zea mays*, *Tribulus terrestris* , *Phyllanthus niruri* and excipients at initial, 15 and after 30 days.

2.2.3 Formulation of Tablets

The dried powder extract and other ingredients were mixed uniformly and granules were prepared by wet granulation technique. The lubricated granules were compressed into tablets in an 8-station machine with 500 mg die cavity.

Table 2 formula of Tablets

Ingredient	Quantity per tablet (mg)
Abutilon indicum extract	150
Zea mays extract	100
Tribulus terrestris extract	50
Phyllanthus niruri extract	50
Lactose	90
Talc	20
Starch paste	3 %
Starch dry	25

2.3. Evaluation of Tablets (Indian pharmacopoeia 2007)

Tablets were evaluated for their physical characteristics

2.3.1. Organoleptic properties

Size (thickness), shape, color, taste were determined.

2.3.3. Weight Variation Test

Weight variation test was done by weighing 20 tablets individually calculating the average weight and comparing the individual tablet to the average .The tablet given below shows the weight variation tolerance for uncoated tablets **(Lachman ,L et al.,1991)**

Table 3 Weight variation tolerance for uncoated tablet

Average weight of Tablet (mg)	Maximum % deviation allowed
130 mg or less	10 %
130 mg to 324 mg	7.5 %
More than 324 mg	5.0 %

2.3.2. Tablet hardness

The strength of tablet was expressed as tensile strength (Kg/cm^2). The tablet crush load, in which the force required to break a tablet into halves by compression. It is measured using a tablet hardness tester (Monsanto hardness tester). The test was performed with five tablets. The mean value and the standard deviation were calculated **(Lachman , L et al.,1991)**

2.3.4 Friability

Friability test is performed to assess the effect of friction and shocks. Which may often cause tablet to chip ,cap or break .Roche friabilator was used for the purpose .This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablet at distance of 6 inches with each revolution. Preweight sample of tablets were placed in the friabilator, which were then operated for 100 revolutions. Tablets were dusted and reweigh. Compressed tablets should not loss more than 1% of their weight **(Lachman, L et al., 1991).**

2.3.5 Disintegration Time

One tablet was placed in each of six tubes of DT apparatus .Disintegration test was performed at 37 $\pm 2^0$C Disintegration time defined as time required to disintegrate and pass all fragments through the sieve (# 10) **. (Lachman ,L et al.,1991).**

2.4 Antiurolithiatic activity of formulation (Mousa al Reza et al 2007, F. Atmani et al 2004, R. Vargas S. 1999)

2.4.1 Experimental design

Animal 4 groups and each group having 5 albino rats weighing 120-180 gm. were selected and housed under standard laboratory condition for a period of 14 days prior to the experiment. Experimental protocols were approved by our Institutional animal ethical committee, which follows guidelines of CPCSEA/ IAEC (Committee for the purpose of Control and Supervision of Experiments on Animals/Institutional Animal Ethics Committee), Reg. 1839/PO/Ere/S/15/CPCSEA

Model Ethylene glycol induced model

Standard drug Cystone tablet 500 mg/kg body weight

Method 0. 75% ethylene glycol induced kidney stone

2.4.2 Experimental group

Four groups contain 5 animals in each group were subjected to 0.75% ethylene glycol into drinking water for four weeks.

GROUP I : Control group received only drinking water.

GROUP II: Model control group received drinking water + 0.75% ethylene glycol

GROUP III: received drinking water +0.75% ethylene glycol + Formulated tablet 500 mg/kg

GROUP V: received drinking water +0.75 % ethylene glycol + Standard drug 500 mg/kg

2.4.3 Statistical analysis

Standard evaluation was done using one-way analysis of variance (ANOVA) Statistical significance was set at *P< 0.0001*. Results are presented as mean ± standard errors (S .E.). **(Mousa al reza Hadizadeh et al 2007)**

2.4.4 Parameters

Total urinary volume

Animal were placed in separate metabolic cages 24 hours before the surgery. And total urinary volume was measured, by using measuring cylinder, and reported in ml **(C.Barbas, A. Garcia 2002)**.

Test for acidity

Uric acid crystals were found to deposit most frequently in the concentrated acid urine. Thus the acidity of the urine was tested using pH meter **(C.Barbas, A.Garcia 2002)**

Biochemical parameter of urine

Urinary concentration of calcium, oxalate and Creatinine were measured **(C.Barbas, A.Garcia 2002, Hodgkinson 1970)**.

3.1.1 Preformulation study of powders of extracts

Preformulation study of powder shows that % compressibility of were found poor so they are unable to process as directly compressible formulation to give sufficient compressibility to the powder they should process through wet granulation.**(Table 13,14)** . Angle of repose concluded that powders having poor flow so sufficient lubricant should be added, to improve flow of powder.

3.1.2 Determination of total flavonoid content

Total flavonoid content of ethanolic extract of Abutilon *indicum* was found to be 0.765 (QE mg/100mg of extract), ethanolic extract of *Zea mays* was found to be 0.733 (QE mg/100mg of extract), ethanolic extract of *Tribulus terrestris* was found to be 0.744 (QE mg/100mg of extract) and ethanolic extract of *Phyllanthus niruri* was found to be 0.757 (QE mg/100mg of extract). (**Table 15)**

3.1.3 Drug - excipient interaction

Drug -excipient interaction was performed by determination of total flavonoid content in mixture of powder extract of *Abutilon indicum,Zea mays, Tribulus terrestris, Phyllanthus niruri* and excipients at initial days and after 15, 30 days. Total flavonoid content were found 0.755 (QE mg/100mg of mixture) at initial day, 0.755 (QE mg/100mg of mixture) after 15 days, 0.755 (QE mg/100mg of mixture) after 30 days. (**Table 16)**

3.1.4 Evaluation of formulation (Tablets)

The prepared tablets were subjected to post compression parameters i.e. thickness, weight variation, hardness, friability, Disintegration time, and total flavonoid content. Prepared tablet obey limit for all the physical parameter. (**Table 17)**

3.1.5 Antiurolithiatic activity of formulation

The changes in the urine parameters in the experiment animals during the study are presented **(in Table 18, 19, 20)**.The urine concentration of oxalate, calcium and Creatinine were increased significantly in animals administered with 0.75 percentage ethylene glycol (group II). Four weeks treatment with formulated tablet significantly decreased urine concentration of oxalate (3.78 ± 0.07), calcium (2.82±0.13) and creatinine (4.51 ± 0.09) as compared to model control (oxalate – 11.29 ± 0.22, calcium – 7.85± 0.19, Creatinine – 7.75 ± 0.17) (**Table 20).**Moreover the group treated with formulated tablets (150 mg *Abutilon indicum* + 100 mg *Zea mays+ 50 mg Tribulus terrestris+ 50 mg Phyllanthus niruri*) was found to be most significant from the entire group. The percentage reduction of all parameters of urine were found more in group III (150 mg *Abutilon indicum* + 100 mg *Zea mays+ 50 mg Tribulus terrestris+ 50 mg Phyllanthus niruri*) and in group IV (standard).

Urinary volume significantly decreased in the animals treated with the 0.75 % of ethylene glycol. Urinary volume were increased by 240 percentage in formulated tablet 246 percentage standard drug with compared to model control group.**(Table 18)** Urinary pH significantly increased in the animals treated with the 0.75 % of ethylene glycol. Urinary pH were decreased by 25.95 percentage in formulated tablet and 26.96 percentage standard drug with compared to model control group.**(Table 19)** From the above results it was noted that the formulated tablets were found significant.

4.1.10 Stability study of formulation

The prepared tablets were subjected to post compression parameters i.e. thickness, weight variation, hardness, friability Disintegration time, and total flavonoid content after 3 month at room temperature and accelerated condition. Prepared tablets obey limit for all the physical parameter. The Prepared tablets were found stable after 3 month. **(Table 21)**

DISCUSSION

Urorolithiasis is caused by several biochemical mechanisms. It is a generalized increase in the calcium content of the kidneys. The major causes include those associated with an increase in the urinary levels of calcium crystals precipitation. Kidney stones usually arise because of an imbalance between the kidney's need to conserve fluid and the need to extrude waste products of low solubility. This imbalance often is precipitated by alternations in diet, fluid intake, climate and extent of physical activity.The majority of patients with calcium containing stones excretes excessive amounts of urinary calcium and often has urine that is supersaturated solution of calcium and oxalate salts**. (Sarkisian M.R 2001)** Animal model of kidney stone provide important tools for testing the pathogenesis of kidney stone and for studying the efficacy of potential therapies and their mechanism of action. In the recent years, important advances have been made in the diagnosis and treatment of kidney stones. Standard screening tests employed for the kidney stone study is the 0.75% ethylene glycol induced kidney stone method. It is an efficient method as kidney stone can be induces in animal in a very short duration of time by simultaneously testing the effect of test drug on the kidney stone in rats.

In the present study of kidney stone, after the administration of ethanolic extract of *Abutilon indicum*,ethanolic extract of *Zea mays,* ethanolic extract of *Tribulus terrestris and* ethanolic extract of *Phyllanthus niruri* and their combination to the group of rats urine analysis shows that the occurrence of stone was decreased when compared to the kidney stone control group and combination (ethanolic extract of *Abutilon indicum*,ethanolic extract of *Zea mays,* ethanolic extract of *Tribulus terrestris and* ethanolic extract of *Phyllanthus niruri)* as effective as the standard group.

Under formulation development the components were examined for incompatibility, with dried extracts being as therapeutically active ingredient. The developed formulation was evaluated for various pharmaceutical parameters including stability studies at different environmental conditions. There was no significant physical change observed out in three month's storage. Formulation showed marked antiurolithiatic activity on albino rats, it was concluded that the developed formulation show significant reduction in urine concentration oxalate, calcium and Creatinine.

Table 4 Preformulation study of powders

S.No.	Parameter	*Abutilon indicum*	*Zea mays*	*Tribulus terrestris*	*Phyllanthus niruri*
1	Description	Light Brown Powder with characteristic odour	Light green Powder with characteristic odour	Light Brown Powder with characteristic odour	Dark green Powder with characteristic odour
2	Solubility				
	Alcohol	Soluble	Soluble	Soluble	Soluble
	Water (pH 7)	Slightly soluble	Slightly soluble	Slightly soluble	Slightly soluble
	0.1 N HCl solution	Soluble	Soluble	Soluble	Soluble
	Ethyl acetate	Insoluble	Insoluble	Soluble	Insoluble
	Hexane	Insoluble	Insoluble	Insoluble	Insoluble

Table 5 Preformulation study of powders

S.No	Parameter	*Abutilon indicum*	*Zea mays*	*Tribulus terrestris*	*Phyllanthus niruri*
1	Angle of repose	32	30	31	31
2	Loss on drying	12.4%	10.9%	9.8%	11.2%
3	Ash value	3.98%	3.85%	4.1%	3.98%
4	Bulk density	0.66 g/ml	0.69 g/ml	0.67g/ml	0.65g/ml
5	Tapped density	0.88g/ml	0.94g/ml	0.91g/ml	0.87g/ml
6	% compressibility	17.92%	18.49%	17.88%	18.22%
7	Hausner ratio	1.19	1.21	1.17	1.23
8	pH	6.3	6.5	6.4	6.5
9	Particle size	50-150 µ	50-150 µ	50-150 µ	50-150 µ

Table 6 Determination of total flavonoid content

S.No.	Extract	Total flavonoid Content (QE mg/100mg of extract)
1	Ethanolic extract of *Abutilon indicum*	0.765
2	Ethanolic extract of *Zea mays*	0.733
3	Ethanolic extract of *Tribulus terrestris*	0.744
4	Ethanolic extract of *Phyllanthus niruri*	0.757

Table 7 Drug - excipient interaction

S.No.	Day	Determination of total flavonoid content (QE mg/100mg)
1	initial	0.755
2	After 15 days	0.755
3	After 30 days	0.755

QE- Quercetin equivalents

Powder of *Abutilon indicum* extract + Powder of *Zea mays* extract+ Powder of *Tribulus terrestris* + Powder of *Phyllanthus niruri* + Excipient

Table 8 Evaluation of Tablet

S.No.	Evaluation parameter	Observation
1	Size (Thickness)	4.7± 0.15 mm
2	Shape	Round
3	Color	Light brown
4	Taste	Characteristic
5	Weight variation	Upper limit 1.3% Lower limit 1.7%
6	Hardness	4.35 kg/cm2
7	% Friability	0.8%
8	Disintegration time	10 min.

Antiurolithiatic activity of Formulation

Table 9 Total urinary volume

S.No.	Groups	Total urinary volume (ml) Mean± SE
1.	Normal control	2.44 ±0.14
2.	Model control	1.57 ± 0.10
3	Formulated tablet	5.35 ± 0.17 ***
4	Standard drug 500 mg/kg	5.44 ± 0.15 ***

P<0.001, the treated groups are compared with groups I and II. Values are expressed in Mean±SEM, Statistics: one way ANOVA followed by Dunnet's test, *** highly significant, ** significant and * less significant

Table 10 Determination of urinary pH

S.No.	Groups	pH of urine
1.	Normal control	7.25 ± 0.17
2.	Model control	9.94 ± 0.23
4	Formulated tablet	7.36 ± 0.15**
5	Standard drug 500 mg/kg	7.26 ± 0.19***

P<0.001, the treated groups are compared with groups I and II. Values are expressed in Mean±SEM, Statistics: one way ANOVA followed by Dunnet's test, *** highly significant, ** significant and * less significant

Table 11 Biochemical parameter of Urine

S. no.	Group	Urine parameter (mg/ dl)		
		Oxalate	Calcium	Creatinine
1	Normal control	3.65 ± 0.08	2.75±0.10	4.35 ± 0.16
2	Model control	11.29 ± 0.22	7.85± 0.19	7.75 ± 0.17
3	Formulation(500 mg/kg)	3.78 ± 0.07***	2.82±0.13**	4.51 ± 0.09**
4	Standard (500mg/kg)	3.81 ± 0.06 ***	2.77±0.09***	4.45 ± 0.12***

Table 12 Stability study

Parameters	Formulation at Different Time Interval		
	0th Day	After 3 month	
		Accelerated Condition	At Room Temperature
Color	Light brown	Light brown	Light brown
Shape	Round	Round	Round
Thickness (mm)	4.7±0.15	4.7±0.15	4.7±0.15
Hardness (Kg/cm2)	4.35	4.11	4.35
Friability (%)	0.80	0.72	0.80
Weight variation (Avg. Weight-502.7 mg)	Within The ±5 Limit	Within The ±5 Limit	Within The ±5 Limit
Disintegration Time (min)	10	10	10
Total flavonoid content	0.755	0.720	0.750

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