

Development and Evaluation of Oral Polyherbal Formulation for Litholytic Activity in Ethylene Glycol-Induced Urolithiasis in Wistar Rats.

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Abstract: A drug administration route is often classified by the location at which the drug is administered, such as oral or intravenous. The choice of routes in which the medication is given depends not only on convenience and compliance but also on the drug's pharmacokinetics and pharmacodynamics profile. For the treatment of urinary stone disorders, numerous treatment plans have been established in recent decades. However, the majority of these treatments require surgery, making them costly and occasionally scarce. Due to this, many individuals prefer or are limited to using traditional herbal remedies to cure urinary stones. Urolithiasis has been regarded as one of the eight most problematic disorders, and urinary stones are typically referred to in Ayurveda as *mutraashmari* (mutra-urine; ashma-stone; ari-enemy) (*mahagad*). Four different forms of urinary calculi, including phosphatic stones (*sleshmaashmari*), urate stones (*pittaashmari*), oxalate stones (*vataashmari*), and spermolite or seminal concretions (*sukraashmari*), have been recorded in Ayurvedic writings.

Keywords: Wistar Rats, Herbal Medicine, Oral route, Litholytic Activity.

Introduction

ROUTE OF DRUG ADMINISTRATION

A drug administration route is often classified by the location at which the drug is administered, such as oral or intravenous. The choice of routes in which the medication is given depends not only on convenience and compliance but also on the drug's pharmacokinetics and pharmacodynamics profile.

Oral Route of Drug Administration

In this route the drug is placed in the mouth and swallowed. It is also called per oral. This is convenient and indicated for patients who can ingest and tolerate oral medication. Some drug with short half-lives is administered orally as timed-release or sustained-release forms that get absorbed over several hours.^[1]

Advantages of Oral Route

1. Ease of administration
2. Widespread acceptance by the patients.
3. Absorption - Takes place along the whole length of the gastrointestinal tract
4. Cheap - Compared to most other parenteral routes.

Disadvantages of Oral Route

1. Variable absorption rates
2. Degradation of some drugs before reaching the site of absorption into the blood stream.
3. The inability of many compounds to effectively traverse the intestinal epithelial membrane cells to reach the blood stream.
4. The insolubility of many drugs at low pH levels is prevalent in the digestive tract.
5. The inactivation of the drug in the liver on its way to the systemic circulation.
6. Irritation of the mucous lining of the gastrointestinal tract. This can be prevented to some extent by coating.

RESEARCH APPROACH TO HERBAL PRODUCTS

Since they form the basis for all life on earth, plants hold a special place in the universe. In every food chain, they are the principal producers. 90% of the calories and 80% of the protein consumed by humans are directly derived from plants. Since the beginning of time, people have exploited plants as possible sources of medicine. The wealth of medicinal herbs

originates from India, where people choose to use conventional medicine techniques. As a result, it is crucial that this vast natural resource be enhanced and used in line with the advancement of technology and human requirements.

The current millennium sets the objective of using nutraceuticals to provide treatment without adverse effects. The success of using various plants to treat ailments has increased interest in traditional medicine worldwide. For ages, the ethnobotanical practices of the people of Asia have included the use of medicinal herbs. Only after extensive chemical and pharmaceutical testing did the contemporary medical system diverge from folk medicine and the old medical system. Modern microbiological and chemical techniques can synthesize aromatic and therapeutic molecules, although the process is frequently expensive.

However, as synthetic medications can have adverse effects, individuals choose to use natural substances derived from plants. 20,000 plant species are thought to be used for therapeutic purposes, according to Penosetal.^[2] According to Farnsworth et al.^[3] (1985), chemical research to identify the active ingredients that were responsible for the traditional uses of 119 plant-derived medications led to the discovery of 74% of them.

The tropical, subtropical, and temperate species found in Asiatic flora serve as systems for herbal-based medicines and are crucial to the region's overall healthcare. According to Farnsworth et al., more than 80% of Asians still rely on traditional and folk treatments for their regular medical requirements. Of India's 1.1 billion people, more than 70% still use traditional herbal medication.^[4] According to Scragg et al.^[5], phytochemical investigation of plants that have historically been used to treat cancer has produced a variety of chemicals having anticancer potential. Alkaloids with anti-HIV action have been found to accumulate in plants from many different families. Hussein disclosed a number of medicines and aromatic substances produced from plants.^[6] These include forskolin from Coleus root, which is used to prevent blood clotting and lower intraocular pressure in glaucoma cases, and anti-malarial drug from Artemisia annua. Forskolin helps the repair of damaged nerves after injury.

For a new to the area, the variety of plant usage in medicine can occasionally be overwhelming. However, the possibilities for research strategy offer strong motivation for the discovery of new pharmacophores for multidisciplinary research and a development network. The development of new drug targets and the possibility of combinatorial chemistry on the novel pharmacophores are two additional ways that new pharmacophores may contribute to the arsenal of herbal medicinal and preventative agents. For instance, a lot of combinatorial compounds have made major efforts to target the chemical curcumin. Through a nationwide network programme, the Council of Scientific and Industrial Research (CSIR) in India has launched sizeable and significant efforts to create herbal-based formulations for diabetes, arthritis, and hepatitis.^[7]

DIAGNOSIS AND MODERN THERAPEUTIC STRATEGIES FOR MANAGEMENT AND CURE OF URINARY STONES:

The medical history of the patient, dietary information, complete blood cell counts, routine urine analyses, and serum creatinine measurements are used to make the diagnosis of urinary stones after a physical examination and taking into account anticipated symptoms of urinary stone illness.^[8] Ultrasound and imaging tests like an X-ray or computerized tomography (CT) scan are the key components of the further diagnostic. Because ultrasonography can detect all kidney stone forms, it is favored in this situation as some kidney stones may not be visible on an X-ray.^[9]

Urinary stones frequently pass on their own. As a result, doctors frequently attempt to control the early stages of stone disease symptoms, which include analgesic pain management. However, the speed of stone transit varies greatly depending on the size and placement of the stone. Medical expulsive therapy is typically preferred if the stone cannot pass naturally. This treatment plan may call for the administration of antibiotics, calcium antagonists, painkillers, and anti-inflammatory medications^[10]. However, when conservative treatment fails owing to the complexity and bigger size of the stones, or when the patient cannot tolerate the level of agony until the stone passes, surgical intervention becomes essential.^[11]

Extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), percutaneous nephrolithotomy (PCNL), and open surgery are the most common surgical procedures.^[12] Despite their many benefits, these surgical methods have certain limitations because stone clearance depends on the patient's age, the size, position, and number of the stones as well as radiological renal characteristics and congenital renal defects^[13]. Another significant risk factor for surgical and drug treatments is the return of stones^[14]. According to research, ESWL may result in acute renal injury because of the traumatic shock wave effect and potential for infection after treatment^[15]

HERBAL MEDICINES FOR THE TREATMENT OF URINARY STONES:

For the treatment of urinary stone disorders, numerous treatment plans have been established in recent decades. However, the majority of these treatments require surgery, making them costly and occasionally scarce. Due to this, many individuals prefer or are limited to using traditional herbal remedies to cure urinary stones. Ayurveda, Traditional Chinese medicine (TCM), Siddha, and Unani are just a few of the traditional medical systems that have described the use of various herbal treatments to treat urinary stone problems.

Urolithiasis has been regarded as one of the eight most problematic disorders, and urinary stones are typically referred to in Ayurveda as *mutraashmari* (mutra-urine; ashma-stone; ari-enemy) (*mahagad*). Four different forms of urinary calculi,

including phosphatic stones (*sleshmaashmari*), urate stones (*pittaashmari*), oxalate stones (*vataashmari*), and spermolith or seminal concretions (*sukraashmari*), have been recorded in Ayurvedic writings. Herbal remedies, alkaline drinks, and surgical techniques are used in Ayurvedic medicine to treat and manage urinary stones.

For the treatment of urinary stone illnesses, Ayurveda prescribes *Shodhana* (external and internal oleation, and induction of sweating), *Shamana* therapy, and *panchakarma* treatments such as medicated emesis, purgation, and enemas. This primarily refers to the oral prescription of herbal medications such as *mutraladavyas* (diuretics), *ashmaribhedana* (lithnotriptic), and *teekshnaushna* (penetrative)^[16]

LITHOLYTIC ACTIVITY:

Urolithiasis is the process of a urine stone developing or showing up anywhere along the renal system. It is a chronic health issue that has been around since the dawn of humanity. Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and Unani are only a few of the ancient literature of traditional medicine that contain information on the symptoms, indicators, and treatment methods of urinary stone illnesses. One of the eight most troublesome disorders according to Ayurveda is urolithiasis. Urinary stone treatment in Ayurveda includes herbal formulae, alkaline drinks, and surgical methods. While, TCM advice using a combination of acupuncture, moxibustion, and multiherbal medications to treat urinary stones. Herbal treatments are still used today to treat and cure urinary stone illnesses among these medicines.

Urinary stones (calculi) are the solid crystalline masses that can occur anywhere in the renal tract and the process of formation of urinary stone or appearance of stone anywhere in the urinary tract is termed as urolithiasis. Urinary stones typically develop when urine loses its normal stone-forming inhibitors or when urine becomes salt-saturated. Numerous environmental and nutritional factors, such as low urine volume and diets high in animal protein, might affect urolithiasis. Additionally, stone formation may be influenced by metabolic changes (such as hypercalciuria and hyperuricosuria) and a lack of stone-inhibiting nutrients (such as citrate, magnesium, and glycosaminoglycans [GAG]).^[19] Urolithiasis can be difficult to prevent since it frequently has no apparent symptoms and can go unrecognized until it is quite advanced if recurrence history is not known. Small urinary stones can be effortlessly removed by urine. For stones with a diameter of 5 mm or less and 10 mm or more, the reported spontaneous transit rates are 68 and 47%, respectively.^[20]

Numerous ancient medical literatures from the "Ayurveda," "Chinese" and "Greek traditional medicine" provide descriptions of the symptoms, warning indications, and treatment of urinary stones. Urinary stone disease symptoms frequently include back or lower abdominal pain, blood in the urine, and pain during urinating.^[21] Along with the discomfort, other symptoms include nausea and vomiting. When a person has a urinary stone, they may experience waves of discomfort that start in the abdomen, frequently spread to the groin, testicles, or vulva, and then go away in 20 to 60 minutes. Renal colic is the name for this distinct pain.

FACTORS RESPONSIBLE FOR FORMATION OF URINARY STONE:

For many years, urolithiasis has been a serious health issue. We still have a limited grasp of the basic processes that lead to the development of urinary stones. It is crucial to have a fundamental understanding of how urinary stones form in order to manage patients effectively, which will lower urolithiasis-related morbidity and medical expenses. It has traditionally been believed that urine super saturation and the consequent production of crystalline minerals cause the development of urinary stones. However, stones may not always form as a result of spontaneous stone salt accumulation in urine. The multidimensional process of urolithiasis comprises crystal nucleation, aggregation, retention of crystals by the urothelium, urine saturation, urine supersaturation, and the continual growth of the stone on the retained crystals.^[22]

DIAGNOSIS

Diagnosis of kidney stones is made on the basis of information obtained from the history, physical examination, urinalysis, and radiographic studies.^[72] Clinical diagnosis is usually made on the basis of the location and severity of the pain, which is typically colicky in nature (comes and goes in spasmodic waves). Pain in the back occurs when calculi produce an obstruction in the kidney.^[73] Physical examination may reveal fever and tenderness at the costovertebral angle on the affected side.^[74]

ROLE OF HERBAL MEDICINES IN MANAGEMENT OF KIDNEY STONE

Urolithiasis has been regarded as one of the eight most problematic disorders, and urinary stones are typically referred to in Ayurveda as *mutraashmari* (mutra-urine; ashma-stone; ari-enemy) (*mahagad*). Four different forms of urinary calculi, including phosphatic stones (*sleshmaashmari*), urate stones (*pittaashmari*), oxalate stones (*vataashmari*), and spermolith or seminal concretions (*sukraashmari*), have been recorded in Ayurvedic writings. Herbal remedies, alkaline drinks, and surgical techniques are used in Ayurvedic medicine to treat and manage urinary stones.

EXPERIMENTAL DETAILS:

List of Materials used

Name of materials	Supplied/ Gifted by
Leaves of <i>Boerhavia diffusa</i>	Collected from Local areas
Pods of <i>Plumeria rubra</i>	Collected from Local areas
Seeds of <i>Celosia argentea</i>	Collected from Local areas
Methanol	Research-Lab Fine Chem, Mumbai
Phloroglucinol	Research-Lab Fine Chem, Mumbai
Hydrochloric acid	Research-Lab Fine Chem, Mumbai
Potassium Mercuric Iodide	Research-Lab Fine Chem, Mumbai
Iodine	Hilab Chemicals, Shirampur
Potassium Iodide	Hilab Chemicals, Shirampur
Picric acid	Research-Lab Fine Chem, Mumbai
Potassium bismuth iodide	Hilab Chemicals, Shirampur
α -naphthol	Reliance Scientific, Pune
Sulphuric acid	Research-Lab Fine Chem, Mumbai
Fehling's solution A	Sahyadri Scientific, Islampur
Fehling's solution B	Sahyadri Scientific, Islampur
Copper acetate	Sahyadri Scientific, Islampur

PHARMACOGNOSTICAL AND PHYTOPHYSICO-CHEMICAL INVESTIGATIONS OF CRUDE DRUGS

Introduction

In recent years more people throughout the world are turning to use medicinal plant products in healthcare systems. Worldwide need of alternative medicine has resulted in growth of natural product market and interest in traditional systems of medicine. Herbal drug technology is used for converting botanical materials into medicines, where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge is important.

Standardization as defined by American herbal product association “Standardization refers to the body of information and control necessary to product material of reasonable consistency”. This is achieved through minimizing the inherent variation of material product composition through quality assurance practices applied to agricultural and manufacturing processes.

Procurement and Authentication of drugs

The plants used in the study consists of whole plant of *Boerhavia diffusa* Linn, were collected from Khandala, Maharashtra, Matured pods of *Plumeria rubra* Linn was collected from Rajuri, Junnar Maharashtra. Seeds of *Celosia argentea* Linn, was purchased from Mankarnika Ayurvedic store, Chinchwad Pune. Plants and seeds were Identified and authenticated by Dr. R.K Chaudhary, Scientist, Agharkar Research Institute, Autonomous Body under DST, GOI, Pune. Herbarium specimen has been preserved in laboratory. The plant material was washed thoroughly in running tap water, rinsed in distilled water and shade dried for seven days then dried plant material was grounded by using laboratory herbal grinding mill. Coarse powder (60#) of dried plants were stored in airtight containers for their Pharmacognostical, physicochemical and phytochemical evaluation.

Preparation of Extracts

Extraction process separating the desired constituents from crude drug with the use of Soxhlet extraction.

Soxhlet extraction: Soxhlet extraction has traditionally been used for a solid sample. A porous thimble loaded with a solid sample is placed inside the main chamber of the Soxhlet extractor. By refluxing the solvent through the thimble using a condenser and a siphon side arm, the extraction cycle is typically repeated many times. Soxhlet extraction is a rugged, well-established technique and permits unattended extraction. However, it requires a long extraction time and the consumption of a large amount of solvent

Steps:

1. Continuous extraction of a component from a solid mixture.
2. Boiling solvent vapors rise up through the larger side arm.
3. Condensed drops of solvent fall into the porous cup, dissolving out the desired component from a solid mixture. When the smaller side arm fills to overflowing, it initiates a siphoning action.
4. Residual solvent then drains out of the porous cup, as fresh solvent drops continue to fall into the porous cup. The solvent, containing the dissolved component, is siphoned into the boiler below.

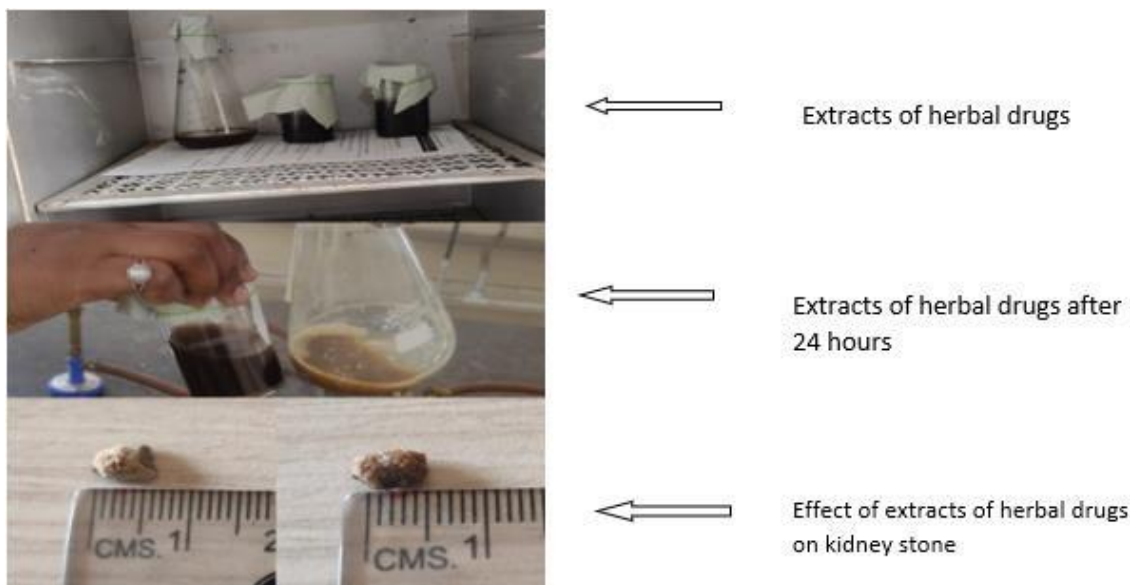


Soxhet Extraction of C.argentea Figure No. 8.8 :SoxhetExtractionofP.rubra

ResultsandDiscussion:

PreliminaryscreeningofIndividualplantfortheirlitholyticactivity:

EachPlantaqueousextractwaspreparedandcheckedprimarilyfortheirdissolutionpotentialofkidneystone.



FigureNo.:10.3Invitrokidneystonedissolutionmethod

After preliminary in-vitro study it is found that Aqueous extract of boerhaviadifussashowed decrease in weight by 10 mg as well as decrease in diameter of stone by 1mm after the treatment of 24 hours. Colour of PHF containing kidney stone was becoming buff as compared to control after 24 hrs and was found effective. Aqueous extract of Celosia argentea showed decrease in weight by 08 mg and diameter of stone was reduced by 1.1mm. Aqueous extract of Plumeriarubra showed dissolution by 12mg while diameter was reduced by 0.9 mm. Therefore it is observed from preliminary screening that, selected herbs showed effectiveness in in vitro dissolution of stone and can be proceeded for further systematic in vitro and in vivo study using ethylene glycol method.

TableNo.10.1:Invitrokidneystonedissolution

Selected Aqueous Herbal Extract	Weight of Stone		Diameter of Stone	
	before treatment	after treatment	before treatment	after treatment
Boerhaviadiffusa	80mg	70mg	6mm	5mm
Celosiaargentea	70mg	62mg	5mm	3.9mm
Plumeriarubra	95mg	83mg	8mm	7.1mm

Optimization of combination ratio of polyherbal extracts for in vitro analysis on cystine calculi, Carbapate calculi and Uric acid calculi:

Although all the treatments (aqueous extracts of individual drugs and polyherbal extracts) showed considerable reduction in size of the stones, antilithiatic treatment with polyherbal extract of combination B (4 parts of B. diffusa + 1 part each of C. argentea and 1 part of P. rubra seed pod) showed better results with better dissolution of stones in 24hrs. as compared to that of combination A (2 parts of B. diffusa + 1 part each of C. argentea and 1 part of P. rubra seed pod). Therefore Combination B is used for further in vivo studies.

TableNo. 10.2:Optimization ofextract combinationstonedissolution

Polyherbalcombination	WeightofStone		DiameterofStone		% Dissolutionafter 24Hrs.
	beforetreatment	aftertreatment	beforetreatment	aftertreatment	
CombinationA	78mg	70mg	6.1mm	5.6mm	10.25
CombinationB	80mg	65mg	6mm	4.9mm	18.75

**Systematic in vitro analysis of plant extracts on cystine calculi, CarapatitecalculiandUricacidcalculi:
Theeffectofplant extractsoncystinecalculiwasinvestigated.**

The three medicinal plant extracts had effects on the dissolution of cystine calculi starting from the second week of the experiment and caused a weight loss of more than 15% for the aqueous extract of all the three plant extracts. As compared to control solution of NaCl this shows weight reduction of 4.8%.

Theeffectofplant extractsoncarapatitecalculiwasinvestigated.

The three medicinal plant extracts had effects on the dissolution of carapatite calculi starting from the second week of the experiment and caused a weight loss of more than 15% for the aqueous extract of all the three plant extracts. As compared to control solution of NaCl this shows weight reduction of 4.8%.

Theeffectofplant extractsonuricacidcalculiwasinvestigated.

The three medicinal plant extracts had effects on the dissolution uric acid calculi starting from the second week of the experiment and caused a weight loss of more than 15% for the aqueous extract of all the three plant extracts. As compared to control solution of NaCl this shows weight reduction of 4.8%.

TableNo. 10.3:Theeffectofplant extractsoncystinecalculi

Sr.No.	Time(week)	%ageof dissolution(A)	%ageof dissolution(B)	%ageof dissolution(C)
1.	0	0	0	0
2.	1	10.25	9.86	9.51
3.	2	18.45	19.76	17.81
4.	3	28.95	27.65	26.98
5.	4	35.78	39.40	38.85
6.	5	58.98	62.86	63.82
7.	6	70.75	78.35	73.45

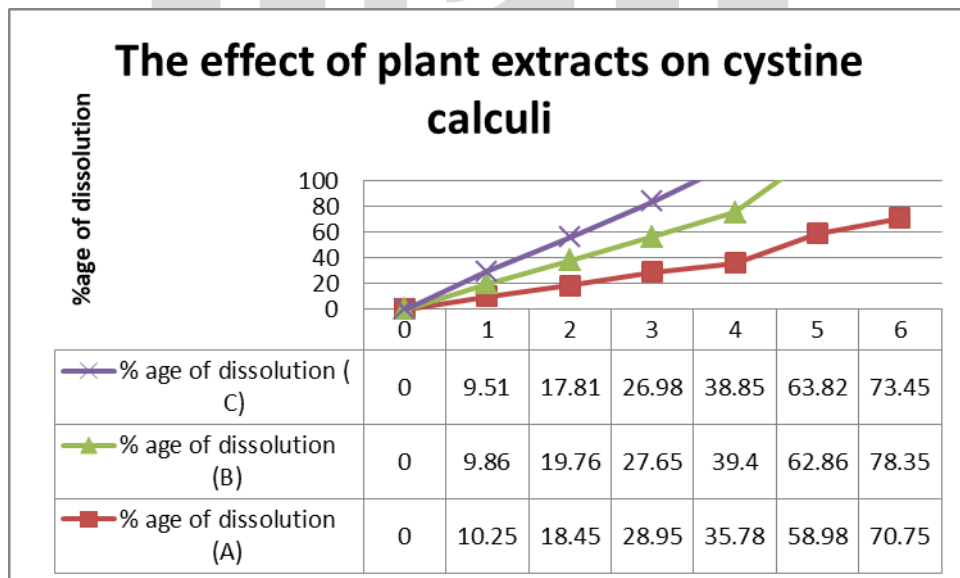
TableNo. 10.4:Theeffectofplant extractsoncarapatitecalculi

Sr.No.	Time(week)	%ageof dissolution(A)	%ageof dissolution(B)	%ageof dissolution(C)

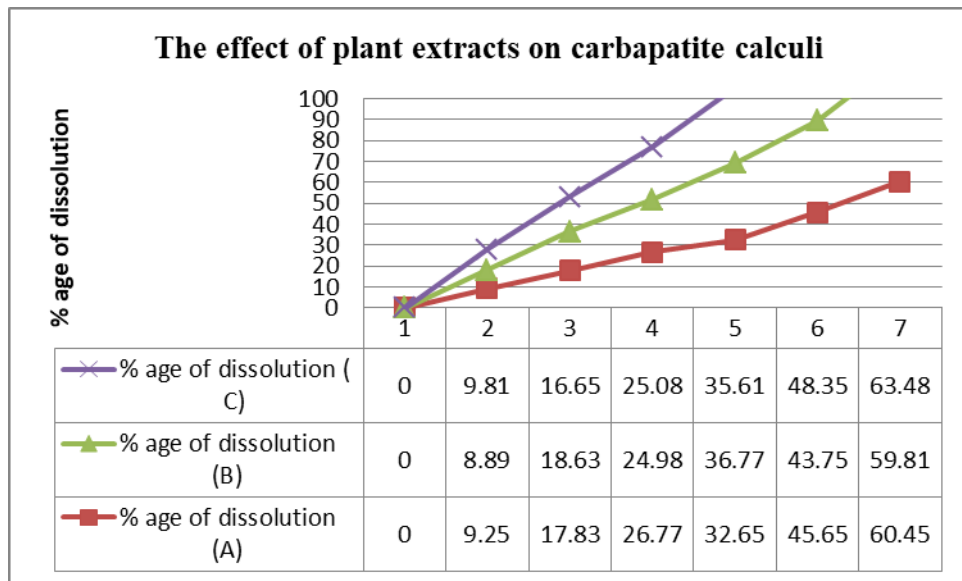
1.	0	0	0	0
2.	1	9.25	8.89	9.81
3.	2	17.83	18.63	16.65
4.	3	26.77	24.98	25.08
5.	4	32.65	36.77	35.61
6.	5	45.65	43.75	48.35
7.	6	60.45	59.81	63.48

TableNo. 10.5: Theeffect ofplant extractsonuricacid calculi

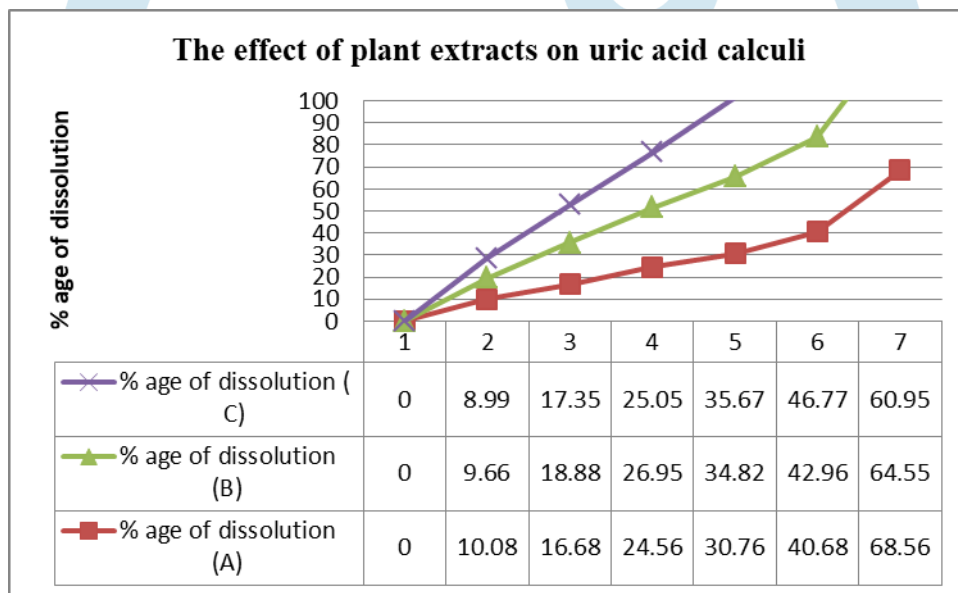
Sr.No.	Time(week)	%ageof dissolution(A)	%ageof dissolution(B)	%ageof dissolution(C)
1.	0	0	0	0
2.	1	10.08	9.66	8.99
3.	2	16.68	18.88	17.35
4.	3	24.56	26.95	25.05
5.	4	30.76	34.82	35.67
6.	5	40.68	42.96	46.77
7.	6	68.56	64.55	60.95



FigureNo. 10.4: Theeffectofplantextractsoncystinecalculi



FigureNo. 10.5: Theeffectofplantextractsoncarbapatitecalculi



FigureNo: 10.6: Theeffectofplantextractsonuricacid calculi

Conclusion

This study presents a set of diagnostic characters of Boerhaviadiffusaleaves, Plumeriarubra pods and Celosia argentea seeds that will help to identify the drug in whole form. Morphology and microscopy are one of the simplest and cheapest methods to start with for establishing the correct identity of the source materials. Physiochemical and qualitative chemical analysis of leaves, seed pod and seeds confirm the quality and purity of plant and its identification. The information collected was useful for further pharmacological and therapeutically evaluation along with the standardization of plant material.

From Preliminary in vitro analysis it is found that each drug has antilithiatic potential. In vitro antilithiatic treatment with polyherbal extract of combination B (4 parts of B. diffusa + 1 part each of C. argentea and 1 part of P. rubra seed pod) showed better results with better dissolution of stones in 24 hrs. as compared to that of combination A (2 parts of B. diffusa + 1 part each of C. argentea and 1 part of P. rubra seed pod). Therefore, Combination B is used for further in vivo studies. Also, on the basis of effect of plant extract on three types of kidney stones viz. cystine calculi, Carbapatite calculi and Uric acid calculi, polyherbal formulation was found effective than and can be studied by in vivo Ethyleneglycol model using wistar rats.

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