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Therapeutic Safety and Efficacy of Oral Administration of Joshānda (Decoction) of Parsiaosh an (Adiantumcapillus-veneris Linn) in the Management of Ḥaṣāh al-Kulya (Nephrolithiasis): A single blind randomized controlled study

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Abstract

Background: Renal calculi, sometimes referred to as kidney stones or nephrolithiasis, are crystal concretions that primarily occur in the kidney. The pathophysiology of stones, as well as their prevention and treatment, are still largely unknown. The present study has been objectively conducted to evaluate the therapeutic safety and efficacy of oral administration of *Joshānda* of Parsiaosh an (*Adiantumcapillus-veneris* Linn.) in the management of *Ḥaṣāh al-Kulya* (Nephrolithiasis).

Methods: The present prospective observational study was conducted at the Department of Moalajat, Regional Research Institute of Unani Medicine, Naseem Bagh, Srinagar J&K with effect from April 2021 to October 2021. A total 60 patients were equally divided into test and control group on the basis of mutual consensus between patient and clinicians.

Results: The present study revealed thattest drug and control drug were equally effective in resolving the subjective parameters. However, the performance of test drug was quite impressive in improving the objective parameters like USG study of urogenital system compared to control drug with a p-value of <0.0001*.

Conclusion: We concluded that the experimental drug Parsiaoshan (*Adiantumcapillus-veneris* Linn.) exhibits lithotriptic activity and is safe and successful in the treatment of *Ḥaṣāh al-Kulya* (nephrolithiasis). This study also provided evidence in favour of the unani theory that the properties of *muḥallil,* and *mufattitsudad* are responsible for the therapeutic effects of litholitic drugs.

Keywords: Nephrolithiasis, *Ḥaṣāhal-Kulya*,Parsiaoshan, lithotriptic.

Introduction

Nephrolithiasis is formed from the Greek words "nephros," which means "kidney," and "lithos," which means "stone." They are solid crystal aggregates generated in the kidney

as a result of dietary minerals in urine. Nephrolithiasis is referred to as "*Ḥaṣāh al-Kulya*" in the Unani medical terminology. Classical literature has the description of etiology, pathophysiology, and treatment. According to ZakariyyRz (Rhazes) [865-925 AD], the deposition of *lesdārmawād* (thick and viscid morbid matter) which the body is unable to throw out is the real cause of stone formation. As a result, secondary deposition occurs and the filthy substance settles.[1-2]The body's *Ḥarārat* dries out the rubat from the filthy substance. Consequently this arid, solid substance becomes a stone. Although nephrolithiasis may not pose a life-threatening hazard, it is a significant, acute condition that can progress to end-stage renal disease.[3] Urinary stones are typically found in the kidney and ureters, with the bladder and urethra hosting the remaining 3% of cases.[4] Nephrolithiasis is the most prevalent urological illness related to kidney disease which is widespread throughout the world. Around 3-20% of the population has a predisposition to develop a urinary stone during their lifetime of 70 years, and its incidences are rising globally.[5] Analysis in India reveals an increased incidence of nephrolithiasis from 0.9% to 9% over a 20-year period.[5]Each year, it affects roughly 2 million people in India. Kidney stone affects socially, economically owing to the cost of hospitalization and number of days lost from work.[6] In the United States, stones account for about $5 billion in economic expenses annually, including hospitalization, surgeries to remove symptomatic stones, and time missed from work.[7] Stones are an avoidable cause of morbidity.Numerous treatment modalities, including diuretics (such as hydrochlorothiazide, furosemide), alkalizers (such as potassium citrate, potassium magnesium citrate, etc.), have been used for renal stones in the modern system of medicine, but they all have side effects, such as GIT disturbances and CNS disturbances.[8]In the event that the stone is too large to pass, open procedures are also performed. Recent advances in the treatment of kidney stones include extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy (PCNL).[9] Although helpful, these operations are pricy and fraught with problems and recurrence.[9] The necessity to confirm the effectiveness of pharmaceuticals stated in the classical Unani literature that are safe, efficacious, and have few adverse effects arises in light of all these negative effects and difficulties.

In the Unani System of Medicine, a variety of single and combined medications with lithotriptic and diuretic qualities are utilised, including; Ḥajrulyahūd (Lapis Judaicus), Kharekhask (Tribulusterrestris Linn.), Māj'ūnAkrab, Habb-i-Kaknaj etc. One of these medications, called parsiaoshan (Adiantumcapillus-veneris Linn), has qualities that help cure wounds and are anti-urolithic, lithotriptic, diuretic, analgesic, anti-obesity, anti-bacterial, anti-inflammatory, and anti-spasmodic. With this in mind, the present study has been objectively conducted to evaluate the therapeutic safety and efficacy of oral administration of *Joshānda*of Parsiaoshan (*Adiantumcapillus-veneris* Linn.) in the management of *Ḥaṣāh al-Kulya* (Nephrolithiasis).

Methods

The present prospective observational study has been conducted at the Regional Research Institute of Unani Medicine, Naseem Bagh, Srinagar J&K with effect from April 2021 to October 2021. An inclusive protocol was framed and approval was obtained from the Institutional Ethics Committee of Regional Research Institute of Unani Medicine (RRIUM), Srinagar on 27-01-2021 with IEC No: RRIUM-SGR/MD-2018/CT/HK/NL/P and registered prospectively in Clinical Trials Registry- India (CTRI) with CTRI No (CTRI/2021/03/032231). After receiving their written informed consent, subjects who met the inclusion criteria were enrolled. For the study, a total of 80 patients were screened. However, during screening 16 patients did not meet the inclusion criteria

and were excluded from the study. During the course of trial, 4 patients were dropped out of study and rest 60 patients completed the trial.

Inclusion criteria

Diagnosed case of Nephrolithiasis fulfilling the following criteria:

- Clinically/Radiologically diagnosed patients of *Ḥaṣāh al-Kulya* (Nephrolithiasis) from size 5 to 8 mm.
- Patients irrespective of gender.
- Patients in the age group of 20 to 60 years.
- Patients who have agreed to sign the informed consent form and follow the protocol.

Exclusion criteria

- Patients below and above the age of 20 and 60 years respectively.
- Pregnant and Lactating Women.
- Diabetes Mellitus.
- Hydronephrosis.
- Poorly controlled Hypertension.
- Significant Liver or Renal dysfunction.
- Cardiovascular disease.
- Unwillingness or inability to fulfil the protocol.
- A medical condition that in the investigator's opinion would interfere the treatment, safety, or adherence to the protocol.

The remaining 60 patients were equally divided into test and control group on the basis of mutual consensus between patient and clinicians. Test group comprised of 30 patients who were given test drug *parsiaoshan* 70 g once a day in the form of decoction. Control group comprised of 30 patients in which standard drug potassium citrate and citric acid 15 ml was given twice a day.Following screening, patients were assessed in the general OPD/IPD (Moalajat) by a medical history, physical exam, and laboratory tests.

Withdrawal criteria

- A lack of follow-up (absence from the study for more than one month).
- Poor protocol adherence, such as not regularly using drugs.
- Any obvious negative impact.

Any mild negative effects were treated with the proper medication

Method of preparation of test drug

With Voucher Specimen No. 4266-KASH Herbarium/2021, the test medication purchased from the open market was identified and authenticated by the Center for Biodiversity &Taxonomy, Department of Botany, University of Kashmir. Joshanda (Decoction) of Parsiaoshan(Adiantumcapillus-veneris Linn) was made by placing 550 ml of water and 70 g of the medication in a container. It was to be consumed in the morning before breakfast and was to be boiled and covered until the decoction had cooled down

Drug dosage and route of administration

For 60 days, a single oral dose of a decoction of 70 g of *Parsiaoshan* (*Adiantumcapillus-veneris*) was administered to patients in the test group. In the control group, 15 ml of a syrup containing 15 ml of potassium citrate and citric acid was given orally twice daily, after meals, for the same period of time.

Efficacy assessment

The efficacy of the test drug and control was assessed using subjective and objective parameters. The data of subjective parameters was recorded on baseline, and at 15th,

30th, 45th and 61st day of the study. The objective parameters were assessed on baseline and 61st day of the study.***Safety evaluation***

The following criteria were used to evaluate the treatment's safety:

a) Clinical assessments were performed at each follow-up appointment.

b) Before and after therapy, haematological tests including Hb%, TLC, and DLC were performed.

c) Biochemical tests were performed before and after treatment, including KFT (Blood urea, Serum creatinine), LFT (Total bilirubin, SGOT, SGPT), and serum electrolytes (potassium, sodium, and chloride).

d) An ECG was taken both before and after the procedure.

Throughout the trial, there were no instances of an unfavourable medication reaction in the test or control groups. Any negative drug reactions would have been reported to RRIUM's pharmacovigilance team.

Statistical Methods

On a case record form (CRF) that was specified and developed in accordance with the study's objectives, all the recorded data was subjected to a rigorous statistical analysis. For statistical analysis, recorded data was compiled and entered in a spread sheet and then exported to data editor of SPSS version 20.0 and Graph pad prism software. The continuous variables were expressed as mean ± standard deviation and categorical variables were expressed in terms of frequency and percentage. Chi-square test, Fishers exact test were employed for inter group comparison of categorical variables and for intra group analysis of categorical variable with more than two levels we applied Mc-Nemar-Bowker's test or wilcoxon rank sum square test. Student's independent t-test was employed for inter-group analysis of data and for intra-group analysis paired t-test was applied subject to the condition that data is measured on continuous scale and satisfies assumption of normality. The graphical representation of data was presented by means of 3D bar graphs. A p-value of less than 0.05 was considered statistically significant.

Results

In this section, we will describe the results of the study:

The meanageofpatients in test group was (35.67$\pm$12.46) years and (35.13±12.66) years in control group. We observed that age distribution of patients in both the groups was comparable with a p-value 0.8699.Out of 60, maximum 28 (46.67%) were found in the age group of 20-30 years followed by 15 (25%) in the 31-41 years age group, 8 (13.33%) patients in the agegroup 42-52 years and 9 (15%) patients in the age group of 53-60 years.Of the 60 individuals that were enrolled in the trial, 34 were men and 26 were women. Males made up a bigger portion of the population overall (56.66%) than did females (43.33%). Even though nephrolithiasis was more prevalent in male patients but with a p-value is 0.118, the difference between the test and control groups with respect to gender was statistically insignificant. In this study, most of the subjects were married. Out of 60 patients, 40 (66.67%) were married whileas 20 (33.33%)wereunmarried. However, no statistical difference was found between the groups (p-value 0.58). Out of 60 studied patients, maximumpatients were found to be businessman 17 (28%)followedby16 (26.67%) housewives,13 (21.67%) government employees, 12 (20%) student and 1 (1.67%) labour and 1% belonged to another category. However, with a p-value of 0.07, the difference between the groups was comparable.

Table 1: Showing distribution of patients as per Mizaj among test and control group						
Mizaj	**Test**		**Control**		**Total**	
	No.	%age	No.	%age	No	%age
Damvi	19	63.33	17.00	56.67	36.00	60.00
Balghami	10	33.33	12.00	40.00	22.00	36.67
Safravi	1	3.33	1.00	3.33	2.00	3.33
Saudavi	0.00	0.00	0.00	0.00	0.00	0.00
Total	30.00	100.00	30.00	100.00	60.00	100.00
Chi-Square=0.293, Df=2, P-value (Monte-Carlo significance)=0.894						

Out of 60 participants, 36 (60%) had *Damwī*(sanguine)temperamentand 2 2 (36.67%)presentedwith*Balghami* (phlegmatic)temperament and 2 (3.33%) presented with *Ṣafrāwīmizāj*(Bilious). As per the modified Kuppuswamy socioeconomic scale (2019), out of 60 participants 2 (3.33%) belonged to upper class, 57 (95%) belonged to upper middle class whereas 1 (1.67%) belonged to lower middle class. We observe that there is an insignificant difference between the groups with respect to SES (p-value 0.235).

Table 2: Showing severity of Flank pain before and after the treatment in test and control group								
Flank pain	Test				Control			
	BT		**AT**		**BT**		**AT**	
	No.	%age	No.	%age	No.	%age	No.	%age
Absent	0.00	0.00	28.00	93.33	0.00	0.00	25.00	83.33
Mild	4.00	13.33	2.00	6.67	2.00	6.67	5.00	16.67
Moderate	23.00	76.67	0.00	0.00	27.00	90.00	0.00	0.00
Severe	3.00	10.00	0.00	0.00	1.00	3.33	0.00	0.00
Total	30.00	100.00	30.00	100.00	30.00	100.00	30.00	100.00
Within groups	Wilcoxon matched pair test, p-value<0.0001*				Wilcoxon matched pair test, p-value<0.0001*			
Test vs Control	BT vs BT		Chi-sq= 1.98, df=2, P-value=0.370					
	AT vs AT		Chi-sq= 1.456, df=1, P-value (Fisher exact)=0.423					

The subjective parameters wereassessed bytheir presence and absence on anarbitrary grading scale. In the current study, we found that both the test group (93.33%) and the control group (83.33%) saw a considerable decrease in the severity of flank pain following treatment. This reduction was statistically significant, with a p-value of <0.0001 in both groups. On the basis of an arbitrary grading system, the flank discomfort was evaluated. With a p-value of 0.423, the difference between the test and control groups is comparable, indicating that both treatments are equally beneficial.At baseline 20 patients from test group and 22 patients from control group had dysuria. After treatment, dysuria was absent in both the test and control group. Statistically high significant difference was found in both the groups before and after the treatment with a

p-value of <0.0001, inferring both the treatments are equally effective in resolving the dysuria.

Table 3: Showing severity of dysuria before and after the treatment in test and control group

Dysuria	Test				Control			
	BT		**AT**		**BT**		**AT**	
	No.	%age	No.	%age	No.	%age	No.	%age
Absent	10.00	33.33	30.00	100.00	8.00	26.67	30.00	100.00
Mild	13.00	43.33	0.00	0.00	17.00	56.67	0.00	0.00
Moderate	7.00	23.33	0.00	0.00	4.00	13.33	0.00	0.00
Severe	0.00	0.00	0.00	0.00	1.00	3.33	0.00	0.00
Total	30.00	100.00	30.00	100.00	30.00	100.00	30.00	100.00
Within groups	Wilcoxon matched pair test, p-value<0.0001*				Wilcoxon matched pair test, p-value<0.0001*			
Test vs Control	BT vs BT	Chi-sq= 1.08, df=2, P-value=0.580						
	AT vs AT	P-value cannot be calculated						

Out of 30 patients in the test group at baseline, 3 (10%) experienced hematuria, compared to 2 (6.66%) in the control group. Hematuria was evidently absent following treatment in both the test and control groups. Patients in the test group showed a significant difference between before and after the treatment, with a p-value of (0.04). However; in the control group, the overall difference was statistically insignificant with a p-value of 0.08.

Table 4: Showing severity of hematuria before and after the treatment in test and control group

Hematuria	Test				Control			
	BT		**AT**		**BT**		**AT**	
	No.	%age	No.	%age	No.	%age	No.	%age
Absent	27.00	90.00	30.00	100.00	28.00	93.33	30.00	100.00
Mild	2.00	6.67	0.00	0.00	2.00	6.67	0.00	0.00
Moderate	1.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00
Severe	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total	30.00	100.00	30.00	100.00	30.00	100.00	30.00	100.00
Within groups	Wilcoxon matched pair test, p-value=0.04				Wilcoxon matched pair test, p-value=0.08			
Test vs Control	BT vs BT	Fishers exact; P-value=0.640						
	AT vs AT	P-value cannot be calculated						

Since hematuria among the patients of both the groups was absent after treatment, there was no scope for comparison between test and control group. At baseline, 2 (6.67%) patients in the test group and 2 (6.67%) in the control group reported experiencing nausea. Both the test and control groups showed 100% improvement after treatment, indicating that both medications are equally effective at relieving nausea. Only 4 (13.33%) of the patients in the test group experienced vomiting at baseline, but they

were successfully treated with the test medicine. This difference was significant, with a p-value of 0.048, demonstrating the efficacy of the test drug.

Table 5: Showing comparison on the basis of USG findings in test and control group

Group	USG	BT		AT		P-value
		No	%age	No	%age	
Test	Normal	0.00	0.00	16.00	53.33	<0.0001*
	Abnormal	30.00	100.00	14.00	46.67	
Control	Normal	0.00	0.00	7.00	23.33	0.05*
	Abnormal	30.00	100.00	23.00	76.67	
Total		Chi-sq=5.71, df=1, p-value= 0.0169*				

USG was the standard radiologic modality used to assess the efficacy of the test medicine. All of the patients in the test and control groups had aberrant USG findings at baseline (renal calculi). Out of 30 patients in the test group, 16 (53.33%) exhibited a substantial improvement and had normal USG findings following the treatment, with a p-value of<0.0001. However, only 7 (23.33%) of the 30 patients in the control group reflected normal USG findings after treatment, with a 0.05 p-value. Individuals in the test group evidently improved their USG findings substantially more than patients in the control group. The two treatments revealed a significant difference (p-value=0.0169), showing that the test medicine has more lithotriptic activity than the control drug.

Table 6: Status of pus cells in urine before and after the treatment in test and control group

Pus cells	**Test**				**P-value**	**Control**				**P-value**
	BT		**AT**			**BT**		**AT**		
	No.	%age	No.	%age		No.	%age	No.	%age	
Absent	28.00	93.33	29.00	96.67	0.905	29.00	96.67	29.00	96.67	1
Present	2.00	6.67	1.00	3.33		1.00	3.33	1.00	3.33	
Total	30.00	100.00	30.00	100.00		30.00	100.00	30.00	100.00	
Test vs Control (after the treatment), Chi-sq= 0.00, df=1, Fisher's exact test, p-value=1										

We observe that pus cells were mostly absent at the beginning of trial in both test and control group; however, only 2 (6.67%) patients had pus cells in urine before the treatment in test group and in control group only one patient (3.33%) reflected pus cells in urine before the treatment. After treatment 1 patient in both test and control group respectively had pus cells present in urine. Statistically after the treatment, no significant

difference (p-value 1) between the groups with respect to the reduction in urine pus cells was found.

Table 7: Status of RBC in urine before and after the treatment in test and control group

RBC	Test				P-value	Control				P-value
	BT		AT			BT		AT		
	No.	%age	No.	%age		No.	%age	No.	%age	
Absent	28.00	93.33	29.00	96.67	0.905	30.00	100.00	30.00	100.00	-
Present	2.00	6.67	1.00	3.33		0.00	0.00	0.00	0.00	
Total	30.00	100.00	30.00	100.00		30.00	100.00	30.00	100.00	
Test vs Control (after the treatment), Chi-sq= 1.016, df=1, Fisher's exact test, p-value=1										

Only three patients had red blood cells passage in urine before the treatment in test group. On the other hand, in control group 4 patients had red blood cells in urine passage. Post treatment 3 patients from test group still had red blood cells in urine with a p-value of 1 while as in control group red blood cells were absent in all the patients with p-value of 0.05. Even though standard drug showed a good effect on reducing the number of red blood cells in urine but statistically the difference between the two drugs was insignificant with a p-value of 0.0756. At baseline, in test group 5 (16.67%) patients had calcium oxalates present in urine. Post treatment 4 (13.33%) had calcium oxalates in urine with a p-value of 0.91 where as in control group before treatment 3(10%) of patients had calcium oxalates and post treatment 2 patients had calcium oxalates in urine with a p-value 0.91. Comparison between test and control group evidently showed statistically no significant improvement with a p-value of 0.38.

Table 8: Showing comparison of KFT among test and control group

KTF			Mean	N	Std. Deviation	Std. Error Mean	
Test	Urea	BT	24.58	30.00	6.52	1.19	0.251
		AT	22.76	30.00	7.82	1.43	
	Creatinine	BT	0.91	30.00	0.21	0.04	0.206
		AT	0.86	30.00	0.24	0.04	
Control	Urea	BT	22.8133	30	8.38145	1.53024	0.959
		AT	22.9033	30	7.77953	1.42034	
	Creatinine	BT	.8390	30	.30342	.05540	0.473
		AT	.8760	30	.20802	.03798	

The comparison of kidney function tests (KFT) among the test and control groups is summarized in Table 8. For the test group, the mean urea levels before treatment (BT) and after treatment (AT) were 24.58 and 22.76, respectively, with standard deviations of 6.52 and 7.82, and standard errors of 1.19 and 1.43 (p-value = 0.251). The mean creatinine levels for the test group BT and AT were 0.91 and 0.86, respectively, with standard deviations of 0.21 and 0.24, and standard errors of 0.04 for both (p-value = 0.206). In the control group, the mean urea levels BT and AT were 22.8133 and 22.9033, respectively, with standard deviations of 8.38145 and 7.77953, and standard errors of 1.53024 and 1.42034 (p-value = 0.959). The mean creatinine levels for the control group BT and AT were 0.8390 and 0.8760, respectively, with standard deviations of 0.30342 and 0.20802, and standard errors of 0.05540 and 0.03798 (p-value = 0.473).

Thesafetyprofilewasbasedontheassessmentofbiochemical investigationssuch as blood urea, serum creatinine, serum bilirubin, SGOT (AST), SGPT (ALT),Alkaline Phosphatase (ALP), serum electrolytes- potassium, sodium, chloride and hematological investigations such as Hb%, TLC, DLC. ECG was also done. These investigations were carried out beforeenrolment in the study and after completion of the treatment. All parameters were normal before the treatment in both test and control group, which means that both these treatments are not producing any hepatic toxicity and are safe.

Discussion

In the present study the demographic parameters like; age, gender, marital status, religion, SES, dietary habits and Mizaj were comparable between the test and control group. The meanageof patients in test group was (35.67±12.46) years and (35.13±12.66) years in control group. The commonest age group of patients with nephrolithiasis was 20-30 years, accounting for 28 (46.67%), which is comparable with the studies of Munjal et al, Rajesh and Joshi et al.[5,10-12]Overall percentage of males was larger accounting for56.66% compared to females (43.33%). Likewise to this study, the predominance of males with nephrolithiasis was reported by Rajesh and Joshi et al.[11,12]The subjective parameters wereassessed bytheir presence and absence on anarbitrary grading scale. Inter group and intra group comparison was made to assess the effectiveness of the test drug. These are discussed as under:

Flank Pain:we observed that at the beginning of the treatment in test group; out of30 patients, 4 (13.33%) had mild flank pain while as 23 (76.67%), 3 (10%) had moderate and severe flank pain respectively. After treatment flank pain of mild severity was found in 2 (6.67%) patients. Evidently there exists a high significant difference before and after the treatment among test group patients with a p-value of (<0.0001,) which means that test group treatment is effective in resolving the severity of flank pain. Evidently, in the control group at baseline it was found that out of30 patients, 2 (6.67%) had mild pain while as 27 (90%)had moderate pain and 1 (3.33%) had severe flank pain respectively. After treatment, the pain decreased significantly as a result pain with mild severity was found in 5 (16.67%) patients. So, among control group there also exists a high significant difference before and after the treatment with a p-value of (<0.0001) which means that the standard treatment is also effective in resolving the severity of pain. We made a comparison between test drug and control drug in resolving he flank pain wherein we found that (93.33%) patients had no pain after the treatment in test group compared to (83.33%) in control group. Evidently, the severity of the pain has been resolved in a biggerproportion of patients with test drug compared to control drug. However, statistically the difference between the groups was insignificant with a p-value of 0.423, which means that both the treatments are equally effective. Efficacy of *Parsiaoshan* in relievingpainisduetopotentanti-inflammatory,analgesic,antinociceptive

propertieswhichareconstitutivequalitiesforanydrugtoactagainstpain. Anti-inflammatory activity is mainly by reducing tumor necrosis factor-α and by inhibiting the nitric oxide release. Triterpenes are believed to play chief role.[13]Also it was found anti-inflammatory activity is due to the suppressing activity on the activation of nuclear factor kappa B and due to the inhibitory effect on the production of cytokines.[14]

Dysuria:we observed that inthe test group at baseline visit, out of30, 20 (33.33%) complained of dysuria, in which 13 (43.33%) had mild dysuria while as 7 (23.33%) had severe dysuria, while as in control group, 17 (56.67%), 4 (13.33%) and 1 (3.33%) participants reported dysuria of mild, moderate and severe intensity respectively. We observed that dysuria among patients of both the groups was absent after treatment. Evidently there exists a high significant difference before and after the treatment among test group and control group patients with a p-value of (<0.0001). Hence there was no scope of comparison and statistical tests were not applied, which means that both the treatments are equally effective. Efficacy of *Parsiaoshan* in management of dysuria can be attributed to the fact that it has anti-microbial activity and diuretic properties as mentioned in classical literature and proven from various studies.[15-18]

***Hematuria*:** we observedthat in test group (before the treatment); out of 30 patients 2 (6.67%) patients had mild hematuria while as 1 (3.33%) patient had hematuria of moderate severity. After treatment with test drug, we found that hematuria was consequently absent in all patients. Evidently,with a p-value of (0.04), there was a significant difference before and after the treatment among test group patients, which means that the test group treatment is effective in resolving the severity of hematuria. In control group, 2 patients before treatment had hematuria with mild severity and post treatment hematuria was consequently absent in all patients. However; statistically the difference was insignificant with a p-value 0.08. The hematuria among patients of both the groups was absent after treatment, which means that both the treatments were equally effective. Efficacy of *Parsiaoshan* in management of hematuria can be attributed to its potential wound healing property.[19]

Nausea and Vomiting: out of 30 patients in test group (before the treatment), only 02 patients (6.66%) had symptoms of nausea, out of 2, one patient had mild nausea and another had nausea of moderate severity who were managed successfully with test drug. However, after the statistical analysis (rank sum square test) the difference (before vs after) was insignificant with of p-value of 0.055. In control group, we observed that two patients (6.66%) had symptoms of mild nausea who were managed successfully with control drug,after the statistical analysis (wilcoxon rank sum square test) difference (before vs after) was insignificant with a p-value of 0.079. Because of constant proportion statistical test were not applied which infers that both the drugs are equally effective. Evidently, in test group at baseline, out of 30 patients, only 04 (13.33%) had complained of mild vomiting who were managed successfully with test drug and the difference was significant with a p-value of 0.048, while in control group, no patient had history of vomiting. Hence the comparison of test and control drug cannot be performed.

Objective parameters of the study were USG-urogenital system, KFT, Urine examination-routine and microscopic. These parameters were assessed before and after the intervention.

***USG-urogenital system*:** We observedin test group 30 patients reflected renal calculi in USG at the baseline. Out of 30 patients,16 (53.33%) patients had no stone in USG after the completion of trial. Evidently, 4 (13.33%) patients out of 14 remaining patients showed reduction in their stone size to concretions and 10 patients did not show any significant improvement. In control group, 30 patients showed renal calculi at baseline,

and of them 7 (23.33%) patients showed no stone in USG after the completion of trial. And 2 (6.66%) patients out of remaining 23 patients showed reduction in their stone size to concretions and rest 21 patients did not show any significant improvement after the completion of trial. Clearly test group patients showed a significant improvement in USG finding after treatment with p-value < 0.0001 as compared to control group patients with a p-value of (0.05). A high statistical difference was observed between the two treatments (p-value 0.0169),indicating test drug has more lithotriptic activity than standard drug. This significant result can be attributed to the diuretic, lithotriptic activity of *Adiantumcapillus-veneri*s Linn. as mentioned in classical literatures.[20] According to Touhami et al., Bahugana et al., as concluded from in vitro studies increase in lipid peroxidation and decrease in antioxidant were found in rats induced with urolithiasis.[21,22] Based on this, oxalate have been reported to induce lipid peroxidation and cause renal tissue damage. It has been seen that conditions which increase lipid peroxidation and decrease thiol content increase oxalate binding activity which in turn is responsible for promoting nucleation and aggregation of stone matrix protein fractions. So, we can infer that peroxidation can be causative factor for development of nephrolithiasis.[21]Pourmorad et al., has reported about the antioxidant activity of *Parsiaoshan*, propounding this we can conclude that the antioxidant property of this drug may have anti lithogenic effect.[21,23] Anti-adherent layer of glycosaminoglycans acts as a protective barrier against stone formation. Damage to this layer as a consequence of bacterial invasion, a stone nucleus may develop resulting in formation of stone. Since, the test drug possesses anti-microbial properties against a number of bacterial strains, so can be considered as one of the possible mechanisms that test drug may have anti lithogenic activity. Ajij et al., from in vitro study reported that test drug has significant lithotriptic activity and reduced crystalluria.[21]It is believed that flavonoids present in *Adiantumcapillus-veneries* Linn may have anti-urolithiasis activity.[21] Thus, various mechanism like anti-inflammatory, antioxidant, antioxaluric, anticalciuric effect of *Parsiaoshan* may contribute to the lithotriptic activity.[21]

Urine:we observedthat only 2 (6.66%) patients in the test group had the presence of pus cells in urine and 1 patient (3.33%) from the control group had pus cells in urine before the treatment. After treatment 1 (3.33%) patient in both the test and control groups had the presence of pus cells,with a p-value of 1 there was no significant difference with respect to reduction of pus cells in both the groups.Similarly, only 3 (10%) in test group and 4 (13.33%) patients from control group had red blood cells in urine before treatment. Post treatment 3 (10%) patients in test group had red blood cells in urine with a p-value of 1, while as in control group all patients were successfully treated with a p-value of 0.05. Even though standard drug revealed a good effect on reducing the number of red blood cells in urine but statistically the difference between the two drugs was insignificant with a p-value of 0. 0756. Around 5 (16.67%) patients in the test group and 3 (10%) patients from control group had calcium oxalates present in urine before treatment. Post treatment 4 (13.33%) patients from test group and 2 (6.66%) patients from control group had calcium oxalates in urine with a p-value of 0.91, which clearly indicates that statistically there was no significant improvement in both the test and control group (p-value 0.38). Present study is first of its kind that has been conducted to evaluate the efficacy of *Parsiaoshan* in single form in the management of nephrolithiasis.So we did not find any related study with our results could be compared.

KFT:we observedthat mean of urea and creatinine before treatment in the test group was 24.58 and 0.91 respectively; while as after treatment it was found to be 22.76 and 0.86 respectively. Similarly mean of urea and creatinine in control before treatment was 22.81

and 0.83 respectively, while as after treatment it was found to be 22.90 and 0.87 respectively. So, we inferred KFT parameters were well within normal range in both test and control group before the onset of treatment and no significant change was found in these parameters after the treatment which means that both the treatments keep these parameters safe during and after treatment protocol.Present study is first of its kind that has been conducted to evaluate the efficacy of *Parsiaoshan* in single form in the management of nephrolithiasis.So we did not find any related study with our results could be compared.

Assessmentofsafety

Thesafetyprofilewasbasedontheassessmentofbiochemical investigationssuch as blood urea, serum creatinine, serum bilirubin, SGOT (AST), SGPT (ALT),Alkaline Phosphatase (ALP), serum electrolytes- potassium, sodium, chloride and hematological investigations such as Hb%, TLC, DLC. ECG was also done. These investigations were carried out beforethe enrolment in the study and after completion of the treatment. All parameters were normal before the treatment in both test and control group. The p-values recorded for all the safety parameters were greater than the level of significance (p-value > 0.5) in test and control group before and after the treatment. However; it is evident that there exists a significant difference in the average levels of SGOT (p-value 0.025) and SGPT (p-value 0.0001) after the treatment in control group (not in test group), pertinently these significant changes with respect to SGOT and SGPT are still under normal range which infers both the test and control group are not producing any hepatic toxicity. So, all these parameters remained under normal range during and after the test and standard treatment, which means that both these treatments are safe.

Conclusion

The efficacy of the test drug and control drug was assessed using subjective parmeters (flank pain, dysuria, hematuria, nausea, vomiting) and objective parameters (USG-urogenital system, KFT, Urine Examination - Routine and Microscopic). Rigorous statistical analysis was applied to assess the performance of test and control in resolving the subjective and objective parameters. The present study revealed thattest drug and control drug were equally effective in resolving the subjective parameters. However, the performance of test drug was quite impressive in improving the objective parameters like USG study of urogenital system compared to control drug with a p-value of <0.0001*. *Parsiaoshan's* diuretic and lithotriptic properties are thought to be responsible for this effect. However, urine analysis of patients in the test and control groups showed that neither treatment was able to reduce the levels of pus cells, RBCs, or calcium oxalate. It's interesting to note that during the experiment, no notable adverse medication reactions were noticed in the test group, and overall treatment compliance was very high. As a result, the test medicine Parsiaoshan (*Adiantumcapillus-veneris* Linn.) is both safe and effective in the treatment of ah al-Kulya (nephrolithiasis) and has lithotriptic activity. This investigation also supported unani theory that the qualities of *muḥallil,* and *mufattitsudad* provide litholitic medicines their therapeutic effects. The majority of patients did not require more than 70g of parsiaoshan to clear their kidney stones. Test medication is cost-effective, accessible, and consistent with higher compliance and is free of any negative side effects. All these characteristics allow the test drug to be confirmed as a secure and useful treatment for *Ḥaṣāh al-Kulya*.

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