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Therapeutic Safety and Efficacy of Oral Administration of Joshānda (Decoction) of Parsiaoshan (Adiantum capillus-veneris Linn.) in the Management of Ḥaṣāh al-Kulya (Nephrolithiasis): A single blind Randomized Standard Controlled Study

Dr. Zarfah Fida*[1], Dr. Zaffar Hussain[2], Dr. Fouzia Farooq[3], Dr. Mir Idrees Hanief[3], Dr. Nida Mehraj[4]

[1,3,4]PG Scholar, Department of Moalajat, Regional Research Institute of Unani Medicine, Naseembagh University of Kashmir, Srinagar.

[2]Professor & H.O.D, Department of Moalajat, Regional Research Institute of Unani Medicine, Naseembagh University of Kashmir, Srinagar

***Correspondence** Email id: maheenshahe63@gmail.com

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Abstract

Background: Nephrolithiasis, or kidney stone disease (KSD), is a common condition globally, affecting 3-20% of people in their lifetime. Despite effective treatments, recurrence is frequent. In India, KSD prevalence has risen from 0.9% to 9% over 20 years, impacting about 2 million people annually. This study evaluates the safety and efficacy of *Joshānda* (*Decoction*) of *Parsiaoshan* (*Adiantum capillus-veneris Linn.*) in managing nephrolithiasis.

Methods: A single-blind, randomized controlled trial with 60 patients divided into test and control groups. Data were collected from April to October 2021 and analyzed statistically.

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

Conclusion: *Parsiaoshan* (*Adiantum capillus-veneris Linn.*) shows lithotriptic activity, confirming its safety and efficacy in treating nephrolithiasis and supporting Unani concepts.

Keywords: Nephrolithiasis, *Ḥaṣāh al-Kulya*, *Parsiaoshan*, lithotriptic

Introduction

Kidney stones (also termed urolithiasis, or nephrolithiasis) are hardened deposits of minerals that form in the kidneys and can cause pain as they pass through the urinary tract. Kidney stones do not usually cause permanent damage if recognized early and treated appropriately.

Nephrolithiasis is referred to as "*Ḥaṣāh al-Kulya*" in the Unani medical terminology. Classical literature has a description of etiology, pathophysiology, and treatment. According to Zakariya Razi (Rhazes) [865-925 AD], the deposition of *lesdār mawād* (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 morbid substance settles.[1-2]The body's *Ḥarārat* (heat) dries out the *ratubat* (moisture) from the morbid 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] 97% 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 third most prevalent urological illness related to kidney disease which is widespread throughout the world. Around 3-20% of the population has the predisposition to develop a urinary stone during their lifetime of 70 years, and its incidences are rising globally. 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, and economically owing to the cost of hospitalization and the 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. Kidney stone is now being recognized as systemic disorder associated with chronic kidney disease, nephrolithiasis induced bone disease, hypertension, diabetes mellitus, metabolic syndrome. Recurrence is a rule in nephrolithiasis as naturally passing or removing stone surgically does not eliminate the cause[7]. 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). 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 compound medications with lithotriptic and diuretic qualities are utilized, including; *Ḥajrul yahūd* (*Lapis Judaicus*), *Kharekhask* (*Tribulus terrestris* Linn.), *Māj'ūn Akrab, Habb-i-Kaknaj* etc. Among these drugs *Parsiaoshan* (*Adiantum capillus-veneris* Linn), is one with anti- urolithic, lithotriptic, diuretic, analgesic, anti-obesity, anti-bacterial, anti-inflammatory, anti-spasmodic and wound healing properties. 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* (*Adiantum capillus-veneris* Linn.) in the management of *Ḥaṣāh al-Kulya* (Nephrolithiasis).

Material and Methods

The study was randomized single blind,standard controlled with a sample size of 60 randomly allocated by computer generated method equally in test and control group. Study was 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 the trial, 4 patients dropped out of the study, and rest 60 patients completed the trial. All the patients were kept under strict observation and the assessment was made after every 15 days. The clinical observations were recorded in the case report form specially designed for the study. The efficacy was assessed by different subjective parameters (Flank pain, Dysuria, Hematuria, Nausea and vomiting) and objective parameters (USG Urogenital system, KFT, Urine Examination - Routine and Microscopic). The safety of the drugs was evaluated by parameters like CBC, KFT,LFT, ECG, and Serum Electrocytes: -Potassium, sodium, Chloride which were done before and after the treatment.

The *Mizāj* of each patient was assessed during clinical examination based on ten parameters (*Ajnas'Ashara*) mentioned in *Unani* literature.

Method of Collection of Data:

- History Taking
- Clinical Examination
- Screening

Case selection criteria

Inclusion 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 fulfill the protocol.
- A medical condition that in the investigator's opinion would interfere the treatment, safety, or adherence to the protocol.

Following the screening, patients were assessed in the general OPD/IPD (Moalajat) by medical history, physical/radiological examination, 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.

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* (*Adiantum capillus-veneris* Linn) was made by placing 550 ml of water and 70 g of the medication in a container, mixture was to be boiled and covered until decoction cooled down. Decoction was to be consumed in the morning before breakfast.

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:

- Clinical assessments were performed at each follow-up appointment.
- Before and after therapy, haematological tests including Hb%, TLC, and DLC were performed.
- 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).
- 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.

Data Analysis

On a case record form (CRF) that was specified and developed in accordance with the study's objectives, all the recorded data were subjected to a rigorous statistical analysis. For statistical analysis, recorded data was compiled and entered in a spreadsheet and then exported to the 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. The chi-square test and Fishers exact test were employed for inter-group comparison of categorical variables and for intra-group analysis of categorical variables 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 a continuous scale and satisfies the 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

It was observed mean age of patients in the test group was (35.67±12.46) years and (35.13±12.66) years in the control group.Age distribution of patients in both groups was comparable with a p- value of 0.8699. Out of 60, a 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 age group 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.

Table 1: Showing distribution of patients as per Mizaj among test and control group

Mizaj	Test		Control		Total	
	No.	%age	No.	%age	No	%age
Damwi	19	63.33	17	56.67	36	60
Balghami	10	33.33	12	40	22	36.67
Safrawi	1	3.33	1	3.33	2	3.33
Sawdavi	0	0	0	0	0	0
Total	30	100	30	100	60	100
Chi-Square=0.293, Df=2, P-value (Monte-Carlo significance) =0.894						

Out of 60 participants, 36 (60%) had *Damwī* (sanguine) temperament and 2 2 (36.67%) presented with *Balghami* (phlegmatic) temperament, and 2 (3.33%) presented with *Ṣafrāwī mizāj* (Bilious). As per the modified Kuppuswamy socioeconomic scale (2019), out of 60 participants 2 (3.33%) belonged to the upper class, 57 (95%) belonged to the upper middle class whereas 1 (1.67%) belonged to the 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 were assessed by their presence and absence on an arbitrary 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.

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						

At baseline 20 patients from the test group and 22 patients from the control group had dysuria. After treatment, dysuria was absent in both the test and control groups. A statistically high significant difference was found in both the groups before and after the treatment with a p-value of <0.0001, inferring both treatments are equally effective in resolving the dysuria. Furthermore; 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).

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						

However; in the control group, the overall difference was statistically insignificant with a p-value of 0.08. Since hematuria among the patients of both groups was absent after treatment, there was no scope for comparison between the test and control groups. At baseline, 2 (6.66%) patients in the test group and 2 (6.66%) 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-urogenital system findings in test and control group						
Group	USG	BT		AT		P-value
		No	%age	No	%age	
Test	Normal	0	0	16	53.33	<0.0001*
	Abnormal	30	100	14	46.67	
Control	Normal	0	0	7	23.33	0.05*
	Abnormal	30	100	23	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	93.33	29	96.67	0.905	29	96.67	29.00	96.67	1
Present	2	6.67	1	3.33		1	3.33	1	3.33	
Total	30	100	30	100		30	100	30	100	
Test vs Control (after the treatment), Chi-sq= 0.00, df=1, Fisher's exact test, p-value=1										

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 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	93.33	29	96.67	0.905	29	96.67	29.00	96.67	1
Present	2	6.67	1	3.33		1	3.33	1	3.33	
Total	30	100	30	100		30	100	30	100	
Test vs Control (after the treatment), Chi-sq= 0.00, df=1, Fisher's exact test, p-value=1										

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	27	90	27	90	1	26	86.66	30	100	.05 *
Present	3	10	3	10		4	13.33	0	0	
Total	30	100	30	100		30	100	30	100	
Test vs Control (after the treatment), Chi-sq= 3.157, df=1, p-value=.0756										

Only three patients had red blood cell passage in urine before the treatment in the test group. On the other hand, in the control group, 4 patients had red blood cells in urine passage. Post-treatment 3 patients from the test group still had red blood cells in urine with a p-value of 1 while as in the control group, red blood cells were absent in all the patients with a p-value of 0.05. Even though the standard drug showed a good effect on reducing the number of red blood cells in urine but statistically the difference between the two drugs wasminsignificant with a p-value of 0.0756.

Table 8: Status of calcium oxalates in urine before and after the treatment in test and control group										
Calcium oxalates	Test				P-value	Control				P-value
	BT		AT			BT		AT		
	No.	%age	No.	%age		No.	%age	No.	%age	
Absent	25	83.33	26	86.67	0.91	27	90	28	93.33	0.91
Present	5	16.67	4	13.33		3	10	2	6.67	
Total	30	100	30	100		30	100	30	100	
Test vs Control (after the treatment), Chi-sq= 0.740, df=1, Fisher's exact test, p-value=0.3894										

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 the 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 the test and control group evidently showed statistically no significant improvement with a p-value of 0.38.

Table 9: 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 9. 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). The safety profile was based on the assessment of biochemical investigations such 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 before enrolment in the study and after completion of the treatment. All parameters were normal before and after the treatment in both the test and control groups, which means that both these treatments are not producing any hepatic toxicity and hence 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 groups. The mean age of patients in the test group was (35.67$\pm$12.46) years and (35.13±12.66) years in the 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.[10-12] Overall percentage of males was larger accounting for 56.66% 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 were assessed by their presence and absence on an arbitrary grading scale. Inter-group and intra-group comparisons were made to assess the effectiveness of the test drug. These are discussed as under:

Flank Pain: At the beginning of the treatment in the test group; out of 30 patients, 4 (13.33%) had mild flank pain while 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 highly 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 of 30 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 in5 (16.67%) patients. So, among the control group there also exists a highly 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. In the comparison between the test drug and the control drug in resolving the flank pain wherein it was found that 93.33% of patients had no pain after the treatment in the test group compared to 83.33% in the control group. Evidently, the severity of the pain has been resolved in a bigger proportion of patients with the test drug compared to the control drug. However, statistically, the difference between the groups was insignificant with a p-value of 0.423, which means that both treatments are equally effective. The efficacy of *Parsiaoshan* in relieving pain is due to its potent anti-inflammatory, analgesic, and antinociceptive properties which are constitutive qualities for any

drug to act against pain. Anti-inflammatory activity is mainly by reducing tumor necrosis factor-α and by inhibiting nitric oxide release. Triterpenes are believed to play a 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: in the test group at the baseline visit, out of 30, 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 the control group, 17 (56.67%), 4 (13.33%) and 1 (3.33%) participants reported dysuria of mild, moderate and severe intensity respectively. It was observed that dysuria among patients of both groups was absent after treatment. Evidently, there exists a highly significant difference before and after the treatment among the test group and control group patients with a p-value of (<0.0001). Hence there was no scope for comparison and statistical tests were not applied, which means that both treatments are equally effective. The efficacy of *Parsiaoshan* in the 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 by various studies.[15-18]

***Hematuria*:** in the test group (before the treatment); out of 30 patients 2 (6.67%) patients had mild hematuria while 1 (3.33%) patient had hematuria of moderate severity. After treatment with the 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 the 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 of 0.08. The hematuria among patients of both groups was absent after treatment, which means that both treatments were equally effective. The efficacy of *Parsiaoshan* in the management of hematuria can be attributed to its potential wound healing property.[19]

Nausea and Vomiting: out of 30 patients in the 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 the control group, we observed that two patients (6.66%) had symptoms of mild nausea that were managed successfully with the 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 the constant proportion statistical test was not applied which infers that both drugs are equally effective. Evidently, in the test group at baseline, out of 30 patients, only 04 (13.33%) had complained of mild vomiting which was managed successfully with the test drug and the difference was significant with a p-value of 0.048, while in the control group, no patient had a history of vomiting. Hence the comparison of test and control drugs cannot be performed. The 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 observed in the 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 the trial. Evidently, 4 (13.33%) patients out of 14 remaining patients showed a reduction in their stone size to concretions and 10 patients did not show any significant improvement. In the control group, 30 patients showed renal calculi at baseline, and of them, 7 (23.33%) patients

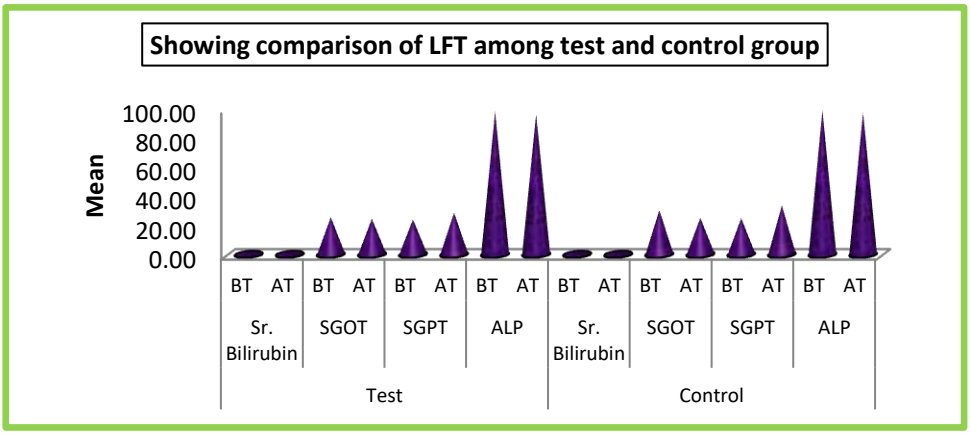
showed no stone in USG after the completion of the trial. And 2 (6.66%) patients out of the remaining 23 patients showed a reduction in their stone size to concretions and the rest 21 patients did not show any significant improvement after the completion of the trial. Clearly, test group patients showed a significant improvement in USG finding after treatment with a 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 the standard drug. This significant result can be attributed to the diuretic, and lithotriptic activity of *Adiantum capillus-veneri*s Linn. as mentioned in classical literature.[20] According to Touhami et al., and Bahugana et al., as concluded from in vitro studies increase in lipid peroxidation and a decrease in antioxidants were found in rats induced with urolithiasis.[21,22] Based on this, oxalate has 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 a causative factor for the development of nephrolithiasis.[21] Pourmorad et al., has reported the antioxidant activity of *Parsiaoshan,* propounding this we can conclude that the antioxidant property of this drug may have antilithogenic effect.[21,23]

Urine: 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 the reduction of pus cells in both the groups. Similarly, only 3 (10%) in the test group and 4 (13.33%) patients from the control group had red blood cells in their urine before treatment. Post-treatment 3 (10%) patients in the test group had red blood cells in urine with a p-value of 1, while as in the control group, all patients were successfully treated with a p-value of 0.05. Even though the 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 the control group had calcium oxalates present in urine before treatment. Post-treatment 4 (13.33%) patients from the test group and 2 (6.66%) patients from the 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).

KFT: the mean of urea and creatinine before treatment in the test group was 24.58 and 0.91 respectively; while 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 the normal range in both the test and control groups 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.

Assessment of safety: the safety profile was based on the assessment of biochemical investigations such 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 before the enrolment in the study and after completion of the treatment. All parameters were

normal before the treatment in both the test and control groups.



Conclusion

The efficacy of the test drug and control drug was assessed using subjective parameters (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 that the test 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 parameters like the USG study of the urogenital system compared to the control drug with a p-value of <0.0001*. *Parsiaoshan's* diuretic and lithotriptic properties are thought to be responsible for this effect.. 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* (*Adiantum capillus-veneris* Linn.) is both safe and effective in the treatment of *Ḥaṣāh al-Kulya* (nephrolithiasis) and has lithotriptic activity. This study also validated unani concept that litholytic drugs work by virtue of *muhalil*(resolvent) and *mufattit i- Ḥaṣāh* (lithotriptic) property. 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.

Limitations of the study: Nephrolithiasis is not a life threatening but an acute, serious disorder which can lead to end stage renal disorder with high recurrence if untreated. Despite the substantial improvement in the development of new therapies in the management of nephrolithiasis, its incidence is increasing globally. The test drug *Parsiaoshan* (*Adiantum capillus-veneris* Linn.) showed significant results. Test drug was given in a dose of 70 g as mentioned in classical literature. So, the clinical trials at different doses and the use of correctives alongside are required to obtain better results. Furthermore, long term study with a large sample size is required for further exploration of the efficacy of the test drug with robust methodology. Furthermore, it would be better if investigations like X-Ray KUB, levels of serum calcium, serum phosphorous, serum PTH, 24-hour urine will be included in objective parameters to evaluate the efficacy of *parsiaoshan* in the above-mentioned parameters.

Future scope: Man has been affected with kidney stones time since immemorial. Individuals of all countries and ethnic groups are commonly involved in renal stones disease. Kidney stones

affects socially, economically owing to the cost of hospitalization and number of days lost from work. The test drug *Parsiaoshan* (*Adiantum capillus-veneris* Linn.) showed highly significant results in improving subjective and objective parameters. Future efforts should be aimed at understanding the molecular and genetic basis of kidney stone. Such an effort is necessary for the development of targeted based therapy on the underlying pathophysiological mechanisms of nephrolithiasis. Moreover, from various experimental studies it was observed that test drug has immense properties like anti-obesity, anti-bacterial, anti-inflammatory, anti-spasmodic, anti-cancer, wound healing property etc. so clinical trials on these above mentioned effects would be an opportunity for future researches and will help in the development of plant based new drugs.

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Conflict of Interest: None

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