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A randomized open label clinical trial of *Khar-E-Khasak* (*Tribulus Terrestris* Linn.) in the management of *Hisat-Ul-Kuliyah* (Nephrolithiasis)

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ABSTRACT

Background: Nephrolithiasis is a complex multi-factorial disorder resulting from the combined influence of epidemiological, biochemical and genetic risk factors. The present study entitled "A Randomized Open-Label Clinical Trial of Khar-e-Khasak (*Tribulus Terrestris* Linn.) In The Management of *Hisat-ul-Kuliyah* (Nephrolithiasis)" demonstrates that *Safoof-e-Khar-e-Khasak* (3 g B.I.D.) has the significant effect on *Hisat-ul-Kuliyah*.

Subject and methods: The data collected through case Report Proforma after completion of the study, were analyzed statistically and subjected to student "t" test.

Results: The study indicates that this Unani medicine has excellent analgesic, diuretic, relieved burning micturition effect with statistical significance. Further, it is observed during the study period (i.e. 90th day of duration), the extremely significant mean reduction size of the stone in U.S.G. The mean reduction of stone size 5.3833 ± 1.7475 , the p-value is <0.001 . It suggests that effect of the drug is highly significant, the significant mean reduction was also observed on no. of stone X-ray K.U.B. 0.900 ± 0.611 , $P = <0.001$. It suggests that effect of the drug is highly significant. The mean reduction of B. Urea 3.600 ± 3.68 , $P = >0.10$. It suggests that effect of the drug is not significant. The mean reduction of S. Creatinine 0.071 ± 0.074 , $P = >0.10$. It suggests that effect of the drug is not significant. The extremely significant mean reduction of urinary pH value 0.2400 ± 0.803 , $P = <0.05$.

Conclusion: It suggests that effect of the drug is significant.

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INTRODUCTION

Hisat-ul-Kuliyah (Nephrolithiasis) is a solid concretion or crystal aggregation formed in the kidney from the dietary minerals in the urine. The disease is also known as renal calculi; it is one of the most common painful disorders of renal disease, which is known by many Unani physicians since ancient times. In 4800 B.C. the complexities of renal pathology has been mentioned by Unani physicians. These kidney stones are mainly four types {Calcium stones, Mixed (Struvite) stones, Uric Acid stones, Cystine stones and other calculi

(xanthenes, indigo)}, sizes vary from the grain of sand to large as golf ball¹. Unani scholars have mentioned the different aspects of disease in their respective works and also may use the different terminologies for renal stones such as Hisat-ul-Kuliyah, Hisat-e-Masana, sang Gurda, Hisat or Ramal-e-Kuliyah-o-Masana etc. A kidney stone typically leaves the body by passage through the urine stream, and many stones are formed and passed without causing symptoms. If stones grow to the large size before passage (usually >5 mm), they

can cause obstruction of the ureter (Drach, 1976). The resulting obstruction causes dilatation or stretching of the upper ureter and renal pelvis, as well as muscle spasm of the ureter, trying to move the stone (McPHEE and Papadakis, 2008). This leads to colicky pain, most commonly felt in the flank, lower abdomen, and groin, it may be associated with nausea, vomiting and blood in the urine, visible with the naked eye or under the microscope (macroscopic or microscopic Haematuria) due to damage to the epithelial lining of the urinary tract (Sainani et al., 2001; Brunicardi, et al. 2010; Hunter, 2002).

The diagnosis of Hisat-ul-Kuliyah is made on the basis of information obtained by the History, symptoms and signs, physical examination, urine analysis and radiographic studies like x-ray (KUB), USG (Abd. & pelvis). Safety parameter can be measured by renal function test like S. Creatinine & B. Urea level (Karamakar and Patki, 2010; Patki, 2010).

Recently, the advanced treatment of urinary stones has been revolutionized by the development of non-invasive methods of stone disruption E.S.W.L (Extracorporeal shock wave lithotripsy) and minimally nephroscopic procedures (removal and fragmentation of stone by ultrasound, laser energy, or Electro hydraulically derived shock wave). When a complete range of extracorporeal and endoscopic techniques are available, only about 10-15 % patients of stone require open surgery for the problem like large, infected and obstructing Staghorn calculi. Although beneficial, this type of major surgical procedure with due risk, besides being expensive & recurrence associated with them has 50-80% (Butterweck and Khan, 2009).

As no effective medicinal therapy is available in the modern system of medicine for the treatment of nephrolithiasis. Unani treatment is commonly recommended in cases, where the tendency of recurrence is high. With Unani Medicine, more than 75-85% of cases escape surgery. Unani therapy is also helpful in cases of Hisat-ul-Kuliyah, where surgery has already taken place, Unani medicine is recommended to prevent the further occurrence of the stone. Alternative treatment for the management of renal stone has great demand in the developed as well as developing countries because of their wide range of biological and medicinal activities, higher safety margin and low cost (Majoosi, 1889).

In the Unani system of medicine there is a large number of single and compound Unani drugs such as Hajrulyahood (Lapis judaicus), Sang-e-Saremahi (Otolith fish), Kulthi (Dalichosbiflorus), Alu Balu (Prunuscercasulinn), Pattherphori, Khar-e-Khasak (*Tribulus terrestris* Linn), Majoos-e- Aqrab, Kushta

Hajrul Yahood, Jawarish Zarooni and Habb-e-Kaknaj etc., for management Hisat-ul-Kuliyah (Nephrolithiasis), these drugs have the properties of litholytic, Lithotriptic, diuretic and litho preventive, therefore being used by ancient and recent Unani physician (Anonymous, 1997; Kabeeruddin, 2010; Syed, 1999). The cure rate with Unani Medicine is high as 75-85%. The stones inside the pelvis dissolve gradually and further deposition is minimized with the help of best selected Unani treatment (Anonymous, 2004; Al-Razi, 1961).

Among those mentioned drugs, Khar-e-Khasak is one of the best drugs for the management of Nephrolithiasis. It has the properties of lithotriptic, litholytic, litho expulsive, diuretic, renal analgesic, healing of the wound, anti-inflammatory, laxative and cardiogenic etc. so keeping the fact in mind, a step was taken with the help of fruit of Khar-e-Khasak (*Tribulus terrestris* linn) to prove the efficacy & safety of this drug. Selection of the drug Safoof-e- Khar-e-Khasak (*Tribulus terrestris* linn.) is supported by the classical Unani literature. The Classical literature claims that it has lithotriptic, litholytic, litho expulsive, diuretic, renal analgesic, the healing action of ulceration (wound) of the urinary tract, aphrodisiac, anti-inflammatory, laxative & cardiogenic etc. But its efficacy and safety have not been studied in clinical trial yet (Rhazes 1509; Jafri, 1995; Ibn Sina, YNM).

The present study was designed as, "A randomized open-label clinical trial of Khar-e-Khasak (*Tribulus terrestris* linn) in the management of Hisat-ul-Kuliyah (Nephrolithiasis)". An official approval of the study was taken from the Institutional Ethical Committee, later on by MUHS, Nasik (M.S.) before starting the trial (MMERC/EC/2009/4). The patients of Hisat-ul-Kuliyah has diagnosed on the basis of clinical history, general physical and systemic examination with specific investigations.

SUBJECTS AND METHODS

The present study was titled as an "A randomized open label clinical trial of Khar-e-Khasak in the management of Hisat-ul-Kuliyah (Nephrolithiasis)" approved by Ethical Committee (MMERC/EC/2009/4). The efficacy of this drug was evaluated on the basis of standard parameters which were based on subjective and objective parameters. The study was conducted on 60 patients. The study duration was 90 days, with total 3 visits; the interval of each visit was 45 days. The observations regarding demography, subjective and objective parameters of the test were recorded on a specially designed Case Report form (CRF), chart and

the interpretation were made by appropriate statistical analysis. They are discussed in the following details.

RESULTS AND DISCUSSION

Age: The highest incidence of Hisat-ul-Kuliyah was observed in the age groups of 20-30 and 31-40 years. The incidence was 70% and 23% respectively. It shows that incidence of stone formation is high in the age group of 20-30 years with the mean of 25 years of age. It is also supported by (Fetter and Zimskind, 1961; Blacklock, 1969)–The peak incidence of urinary calculi is from the 20-40 years.

Sex: 72% cases of Hisat-ul-Kuliyah were males and 28% were females. It means the prevalence ratio of Hisat-ul-Kuliyah in males and female is 2.5:1. This finding also supported by Fetter and Zimskind (1961); Blacklock (1969), the study of Yanagawa et al. (1997) in Thailand.

Religion: It was observed that the Hisat-ul-Kuliyah disease was more common in Muslim 63% than other religion e.g. Hindus (35%) and Christians (02%). Because the maximum number of patients attending OPD's of our Unani Medical College is situated in Muslim populated area.

Diet: 83% of patients of Hisat-ul-Kuliyah were non-vegetarians and 17% patients were Vegetarians. It shows non-veg. is more susceptible to stone diseases. This conclusion is also supported by Al-Razi (1961) in Kitabul Hawi and Hodgkinson, (1976), Thomas (1977)–the study of ingestion of excessive amounts of purines and oxalate, calcium etc.

Mizaj (Temperament): The Highest incidence of Hisat-ul-Kuliyah was noted in the patients of Balghami (phlegmatic) mizaj 65% followed by 17% of Safravi (Bilious) mizaj. It shows that the patients of Balghami Mizaj are more prone to develop the Hisat-ul-Kuliyah disease. This concept is also supported by Almout-ul-saree reported by Al-Razi (1961).

Marital status: Regarding marital status with renal stone, there were 33 (i.e. 55%) married patients. On the other hands, 27(45%) patients were unmarried having renal stones.

Occupational distribution: It was noted that highest incidence of Hisat-ul-Kuliyah was 28% with the students followed by 23% in the Businessman in different fields. These observations show that college going students are more prone to have the Hisat-ul-Kuliyah disease due to decrease water intake and sedentary lifestyle e.g. fast foods etc. This finding was supported by Curhan et al. (1993)– A study of more than 45, 000 men.

Past history of nephrolithiasis: 12% patients of Hisat-ul-Kuliyah reported the past history of Hisat-ul-Kuliyah meaning recurrence of it. This observation is also supported by Menon and Koul (1992).

Family history of nephrolithiasis: 27% of the patients of Hisat-ul-Kuliyah reported having the family history of Hisat-ul-Kuliyah. It shows that genetic factors may also be risk factors in the pathogenesis of Hisat-ul-Kuliyah (which has to be further explored). This observation is also supported by Curhan et al. (1997). According to his, about 25% of patients with kidney stone have a family history of renal stone.

Types of renal stone: While studying the types of renal stone, it was observed that 85% patients were having the stone of Calcium Oxalate and 15% patients were having Uric Acid stone. This observation is also supported by Baggio and Colleagues (1986).

The side of stone in Kidney: The highest incidence of Nephrolithiasis 57% was observed on the right side of the kidney, followed by 33% in the left side kidney in the patients having the unilateral stone. These data show that Rt. Sided unilateral renal stone is the commonest, and kidney is the commonest site of renal stone, which is also supported by Joual et al. (1997) in the Paris.

Evaluation of efficacy: The evaluation of efficacy of Unani medicine (Khar-e-Khasak) on the stones and the associated features of the patients of renal stone was observed and analyzed as under.

Effect on pain (Analgesic effect)

Effects on Pain				
Grade	Visit 1 st	Visit 2 nd	Visit 3 rd	P- Value
G0	00	11	47	<0.001 Significant
G1	13	48	13	
G2	47	01	00	
G3	00	00	00	
Total	60	60	60	

Effect on Burning Micturation

Effect on Burning Micturation				
Grade	Visit 1 st	Visit 2 nd	Visit 3 rd	P- Value
G0	00	31	57	<0.001 Significant
G1	29	29	02	
G2	30	00	01	
G3	01	00	00	
Total	60	60	60	

Effect on haematuria

Effects on Haematuria				
Grade	Visit 1 st	Visit 2 nd	Visit 3 rd	P- Value
G0	37	55	59	<0.001 Significant
G1	21	03	01	
G2	00	02	00	
G3	01	00	00	
G4	01	00	00	
Total	60	60	60	

Effect on nausea: 96.66% effect of Unani Medicine (Khar-e-Khasak) on Nausea was noted in positive cases, which is proved highly significant (p<0.001).

Effect on vomiting: 100% effect of Unani Medicine (Khar-e-Khasak) on Vomiting was noted in positive cases, which is proved highly significant (p<0.001).

Effect on frequency of urine (diuretic effect): 100% patient were having complaints of Frequency of Urine, of which 70% patients were with mild symptoms of Frequency of Urine and 30% patients with still moderate symptoms of Frequency of Urine. On the comparison of visit 1st to visit 3rd with the help of chi-square test the "p" value is <0.001. That is statistically highly significant, which is also support by Chopra et al. (1923); Kirtikar and Basu (1968).

Effects on frequency of urine

Effects on frequency of urine				
Grade	Visit 1 st	Visit 2 nd	Visit 3 rd	P- Value
G0	41	06	00	<0.001 Significant.
G1	19	52	42	
G2	00	02	18	
G3	00	00	00	
Total	60	60	60	

Effect on site of stone

Effect on site of stone				
	Upper Pole	Middle Pole	Lower Pole	Absent
Visit 1 st	35	25	0	0
Visit 2 nd	27	26	2	5
Visit 3 rd	7	9	4	40

Effects on number of stone: After the completion of full 90 days treatment in cases of Hisat-ul-Kuliyah, the following observation and analysis can be made.

Litho-expulsive/Litholytic effect: Litho-expulsive effect was noted in 78.33% of the patients of Hisat-ul-Kuliyah, which has been proved with the help of chi-square test the "p" value is (<0.001). That was

statistically highly significant, which is also support by Chopra et al. (1923); Kirtikar and Basu (1968).

Effect on urinary crystals

Effect on urinary crystals				
Grade	Visit 1 st	Visit 2 nd	Visit 3 rd	P- Value
G0	20	04	39	<0.001 Significant.
G1	35	17	19	
G2	04	35	02	
G3	01	04	00	
Total	60	60	60	

Effect of drug on size of stone in U.S.G (KUB)

Effect of drug on size of stone in U.S.G (K.U.B.)				
Title	Visit 1st	Visit 2nd	Visit 3rd	Visit 1st Vs Visit 3 rd
Mean	7.033	4.733	1.650	5.383
S.D	1.868	2.169	2.455	1.747
"t" paired value	23.86138 with 59 df.			
P value	<0.001 Significant.			

Effect of drug on stones in x-ray (K.U.B.)

Effect on number of stone in X-Ray (K.U.B.)				
Title	Visit 1st	Visit 2nd	Visit 3rd	Visit 1st Vs Visit 3rd
Mean	1.116	0.866	0.216	0.900
S.D	0.323	0.644	0.992	0.611
"t" paired value	11.40458 with 59 df			
P-value	<0.001 Significant.			

Effect on Blood Urea Value: Mean B. Urea at the start of therapy was 25.41 mg/dl with SD 6.697. After the completion of 45 days, the mean gone down to 22.88 mg/dl with SD of 5.763. After the completion of 90 days, the mean of B. Urea further gone down to 21.81 mg/dl with SD of 5.176. After applying paired "t" test on completion of the protocol of 90 days difference of the mean of B. Urea between visit 1st – visit 3rd was 3.60 mg/dl with SD of 3.681 and "t" paired value with 59 df. and P >0.10. It suggests that effect of the drug is not significant.

Effect on serum creatinine value: Mean S. Creatinine before starting of treatment was 0.88 mg/dl with SD 0.885. After the completion of 45 days mean gone down to 0.83 mg/dl with SD of 0.120. After the completion of 90 days, the mean of S. Creatinine further gone down to 0.81 mg/dl with SD of 0.104. After applying paired "t" test on completion of the protocol of 90 days difference of the mean of S. Creatinine between visit 1st – visit 3rd

was 0.07mg/dl with SD of 0.074 and "t" paired value with 59 df and $P > 0.10$. It suggests that effect of the drug is not significant.

Effect on Urinary pH Value: Mean of Urinary pH value at the start of therapy was 6.29 with SD 0.838, after the completion of 45 days the mean went down to 6.13 with SD of 0.281. After the completion of 90 days, the mean of pH value further gone down to 6.05 with SD of 0.161. After applying paired "t" test on completion of the protocol of 90 days difference of the mean of pH value between visit 1st – visit 3rd was 0.240 with SD of 0.080 and "t" paired value 2.31 with 59 df and $P < 0.001$. It suggests that effect of the drug is highly significant.

Effect on urinary specific gravity value: Mean of Urinary Sp. Gravity before starting the treatment was 1.021 with SD 0.0009, after the completion of 45 days, the mean went down to 1.020 with SD of 0.008 After the completion of 90 days the mean of Sp. Gravity further went down to 1.01 with SD of 0.006. After applying paired "t" test on completion of the protocol of 90 days difference of the mean of Sp. Gravity between visit 1st – visit 3rd was 0.016 with SD of 0.011 and "t" paired value 0.00 with 59 df. and $P > 0.10$. It suggests that effect of the drug is not significant.

Renal stone is one of the oldest disease known to human being & has been documented in ancient Greek literature. Urinary stones have been found in Egyptian mummies dating back as far as 7000 years & the symptoms of the condition were described by Hippocrates who suggested that drinking of muddy river water causes the excretion of sand in urine. Roman physician Galen postulated that factors like diet, climate, heredity, gout, race and some abnormalities cause the stone formation (Butt, 1956).

Hisat-ul-Kuliyah (Nephrolithiasis) has been described by ancient Unani physicians like, Razi, Ibn-Sena have discussed the signs, symptoms & complication of the disease. Nephrolithiasis is a common disease with an increasing incidence and prevalence worldwide. Lifestyle and dietary habit implicated in the complex of the metabolic syndrome are important factors contributing to such developments (Rhazes, 1509; Ibn Sina, YNM).

At the completion of this study the highest incidence of age groups involved in between 20 years to 30 years i.e. 70%. It was concluded that the highest incidence of renal stone was common 65% in Balghamimizaj; 72% were male (ratio M: F=2.5:1) with the ratio of Muslim, Hindus and Christian 63:35:02; 83% belonged to Non-veg. and 55% Married having the renal stone. The relation between Hisat-ul-Kuliyah and occupational status the maximum incidence 28% was in student and

relatively common in businessman was 23%. It was observed that 12% were having recurrent & 27% patients were reported to have a positive family history. Calcium oxalate 85% the highest incidence types of renal stone was noted. 57% of the patients with renal stones were having the stone in their right side kidney. After the statistical analysis of observation of the effect of Unani med (Khar-e-Khasak) in the treatment of the stones, it is observed that Litho-expulsive & litholytic effect was 66.66%, p-value is < 0.001 (highly significant), effect on pain (analgesic effect) 78.33% patients were recovered from pain, p-value is < 0.001 (highly significant), effect on burning micturition 95% patients were found free from burning micturition, p-value is < 0.001 (highly significant). The relieving effect of the Unani med. (Khar-e-Khasak) on Haematuria is 98.33% p-value is < 0.001 (highly significant), effect on urinary crystals excretion is 65%, p-value is < 0.001 (highly significant), on Nausea 96.66% p-value is < 0.001 (highly significant), on vomiting 100%, p-value is < 0.001 (highly significant), effect on frequency of urine (diuretic) 70%, p-value is < 0.001 (highly significant). The extremely significant mean reduction of stone in U.S.G. 7.03 + 1.86 to 1.65 + 2.16 m.m. and the difference between 1st vs. 3rd visit mean 5.38 + 1.74, "t" paired value 23.86 with 59 degrees of freedom, the p-value was < 0.001 . It suggested that effect of the drug was highly significant. The extremely significant mean reduction of stone in X-ray K.U.B. 1.11 + 0.32 to 0.21 + 0.99 m.m. and difference between 1st vs. 3rd visit mean 0.90 + 0.61, "t" paired value 11.40 with 59 degree of freedom, p-value was > 0.001 . It suggested that effect of the drug was highly significant. The extremely significant mean reduction of B. Urea 25.41 + 6.69 to 21.81 + 5.17 and difference between 1st vs. 3rd visit mean 3.60 + 3.68, "t" paired value 00.00 with 59 degrees of freedom, the p-value was > 0.10 . It suggested that effect of the drug was not significant. The extremely significant mean reduction of S. Creatinine 0.88 + 0.14 to 0.81 + 0.10 and difference between 1st vs. 3rd visit mean 0.07 + 0.07, "t" paired value 00.00 with 59 degree of freedom, p-value was > 0.10 . It suggested that effect of the drug was not significant. The extremely significant mean reduction of urinary pH value 6.29 + 0.83 to 6.05 + 0.16 and difference between 1st vs. 3rd visit mean 0.24 + 0.80, "t" paired value 2.31 with 59 degree of freedom, p-value was < 0.05 . It suggested that effect of the drug was significant. The extremely significant mean reduction of urinary specific gravity 1.03 + 0.00 to 1.01 + 0.00 and difference between 1st vs. 3rd visit mean 0.016 + 0.011, "t" paired value 00.00 with 59 degree of freedom, p-value was > 0.10 . It suggested that effect of the drug was not significant.

CONCLUSION

This study indicates Khar-e-Khasak (*Tribulus terrestris* linn.) to be an effective and safe treatment in Hisat-ul-Kuliyah (renal calculus) as it expels the stones and brings about the significant reduction of symptoms associated with Nephrolithiasis. The overall result of Safoof-e- Khar-e-Khasak (*Tribulus terrestris* linn.) is good, and no significant adverse reactions were reported or observed during the entire study period. With these observations, it is felt that in the future, this study will provide a better understanding of the renal stone and role of certain Unani medicine. This study indicates Khar-e-Khasak (*Tribulus terrestris* linn.) to be an effective and safe treatment in Hisat-ul-Kuliyah (renal calculus) as it expels the stones and brings about the significant reduction of symptoms associated with Nephrolithiasis.

CONFLICT OF INTEREST

None declared.

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