Research Article

Prospective Role of Unani Pharmacopeial Formulation *Safoof Hijrul Yahood* in Preventing Recurrence of Nephrolithiasis: An Open Labeled Clinical Study

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ABSTRACT

Background: The recurrence of nephrolithiasis has high incidence in northern region of India posing major health problems. **Aim and Objectives:** To study the efficacy of Unani pharmacopeial formulation *Safoof Hajrul Yahood* (SHY) in preventing recurrence of nephrolithiasis. **Study Design:** Open labeled, single arm, clinical trial. **Materials and Methods:** The study was conducted on 75 cases of uncomplicated nephrolithiasis (*Hisat al Kuliya*). The post-trial assessment was done on 49 cases after five years. Subsequent to written and informed consent, patients of All genders between 18-60 years with 6-8mm calculi were given SHY (5g twice daily orally for 8 weeks). Patients were followed up fortnightly, investigated at day 0, 15 and 60 and enquired about their diet and fluid intake. The data was analyzed on Tukey-Kramer multiple comparison test and paired *t* test. **Results:** Mean age of patients was 33.45±10.99 years CI (30.92-35.99). SHY reduced 24 hr calcium excretion highly significantly ($p<0.0001$). Calculus clearance rate was 64% and recurrence after five years was 29.16%. The drug was well tolerated. **Conclusion:** SHY probably corrects crystalloid colloidal imbalance or the oxalate metabolism and/or renal functions; thus, preventing recurrence. However, the exact mechanism of the drug needs to be studied.

Keywords: Nephrolithiasis, Recurrence Unani, Crystalloid colloidal imbalance, Oxalate metabolism.

INTRODUCTION

Nephrolithiasis (*Hisat e Kulliyah*) has common occurrence worldwide with global incidence of 15%,[1] however, approximately 2 million Indians suffer from urolithiasis annually, with the majority coming from northern states of Jammu and Kashmir, Haryana, Punjab, Delhi, Madhya Pradesh, Rajasthan and Gujarat hence it is termed as the stone belt of India as is seen in Figure 1.[2]

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Principle factors that predispose to nephrolithiasis are high consumption of animal protein and sodium, sedentary lifestyle, high temperature and decreased water intake.[3,4]

Stone formation is a result of a combination of factors that influence the thermodynamic driving force (supersaturation)[5] or condensation of thick humour (*Khilt Ghaliẓ*) due to extreme heat *(Harārat Nāriyya)*[6] and crystallization of stone-forming minerals found in the body.[5] The factors that predispose to stone formation are all present in Kashmir which justifies its position in the stone belt of India. The temperature though not very high due its high altitude (220-861 Km above sea level)[7] however, there has been a surge in the average temperature due to global warming. Kashmiris are mostly non-alcoholic, with distinct dietary and culinary taste. Long winters lead to sedentary lifestyle which

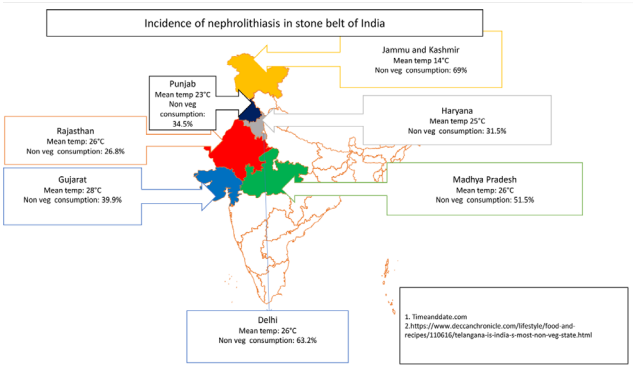

Figure 1: Depicts stone belt of India and the predisposing factors therein viz the mean temperature and non veg consumption.

in turn predisposes them to obesity, hypertension, metabolic syndrome, reduced bone mineral density and coronary artery disease.[8] Hypercalciuria is the main cause of renal calculi globally however; it is coupled with hypocitraturia, hypomagnesuria and hyper phosphaturia in the Kashmiri scenario.[4]

Nephrolithiasis increases the risk of developing chronic kidney diseases by 60% and end stage renal diseases or severe form of chronic kidney diseases by 40%.[9] Apart from this nephrolithiasis has a high recurrence rate of 14% in 1st year, 50% in 5th year and 72% in 10th year.[10] Therefore, prevention of stone recurrence is imperative for a good quality of life devoid of episodes of pain and Urinary Tract Infection (UTI), focusing on improving overall health hence this study was undertaken with *Safoof Hajrul Yahood* which is a classical lithotriptic drug.

MATERIALS AND METHODS

The study was conducted in Srinagar, Jammu and Kashmir, India between 2014 to 2022. Subsequent to the institutional ethical committee approval, uncomplicated cases of nephrolithiasis (*Hisat al Kuliya*) of all genders between 18-60 years with a maximum calculi diameter of 6-8mm confirmed through X-ray/ ultrasonography with or without any symptoms of heaviness or flank pain, dysuria, burning micturation, haematuria, history of recurrent UTI were enrolled after obtaining written and informed consent. Patients having acute condition of nephrolithiasis, acute symptoms of UTI, hydronephrosis, or any other renal diseases, elevated serum creatinine (>2mg%), long-term medications for cardiac, pulmonary or hepatic diseases, pregnancy and lactation, alcoholics or drug abusers were excluded.

This open labeled single-arm clinical trial had a sample size of 75 patients. The study period was 60 days; however post-trial assessment was done after five years of completion of study (2020-2022). In the post-trial assessment period patients were observed for any episodes of recurrence (Confirmed through USG), dysuria, flank pain and hematuria. During the study period 5g of powdered Unani pharmacopoeial formulation *Safoof Hajral Yahood* (SHY) was advised orally in two divided doses for 8 weeks.

Patients were followed up every two weeks. Investigations were done at baseline after first 2 weeks and at the end of the study. The drug efficacy was assessed on decrease in pain (through Visual Analogue Scale (VAS)), change in size of calculus, change in number of daytime and nocturnal micturition, decrease in nausea and vomiting (through Halpin Nausea and Vomiting Scale); change in 24-hr urine calcium and urine sodium whereas; safety parameters were haemogram, Liver Function Test (LFT) and Kidney Function Test (KFT). The patients' consumption of salt, fruit, fluid, vegetable and protein were documented. Data about fluid intake and frequency of tea consumption to evaluate sodium, calcium, oxalate and protein intake were also gathered.

The constituents of which are Hajar al-Yahud (*Lapis Judaicus*), Sang-e-Sar-e-mahi (*otolith of a freshwater fish* also known as the sheephead fish *(Aplodinotus grunniens),* Habb-ul-Qilt (*Dolichosbiflorus*) 10 grams each and Namak-e-Turb (*Raphanus indicus*) 20 g.

Table 1: Physico-chemical standards of SHY.

Appearance	Powder
Colour	Whitish with black particles
Smell	Metallic with aliphatic characters
Taste	Mild Bitter
Loss of water on drying at 105^0	0.89-0.98%
Alcohol soluble matter	6.7-7.98%
Water soluble matter	44.17 – 44.70%
Successive extractions:	0.30-0.416%
Petroleum ether	Alcohol Water 5.88-5.99%
Chloroform	30.27-56.29%
Benzene	0.23 – 0.29%
	0.18-0.29%
pH of 1%	6.65
pH of 10%	7.12
Total Ash	80.11-80.12%
Acid insoluble Ash	13.51-13.86%
Bulk density (wt./mi.)	1.54
Crude fibre	7.95-8.25%
Calcium	232.81 mg/g
Iron	0.62 mg/g
Magnesium	1.30 mg/g

Table 2: Thin Layer Chromatography (TLC) results of SHY.

Extracts	Solvent System	Spray/Treatment	No. of spots	R_f Values
Petroleum ether	Pet. Ether, Diethyl ether, Acetic acid (90:10:1)	10% H_2SO_4/ Iodine vapour and UV light	2	0.91 0.14
	Chloroform 100%	Ceric ammonium Suplhate solution	3	0.33 0.24 0.10
	Chloroform, Ethanol (3:1)	Ceric ammonium Suplhate solution	4	0.96 0.79 0.66 0.12
Benzene	Benzene, Methanol, Acetic acid (95:5:1)	10% H_2SO_4/ Iodine vapour and UV light	2	0.97 0.54
	Chloroform, Methanol (95:5)	10% H_2SO_4/ Iodine vapour and UV light	1	0.96
Chloroform	Chloroform 100%	Ceric ammonium Suplhate solution	3	0.13 0.10 0.07
	Chloroform, Ethyl acetate (3:1)	Ceric ammonium Suplhate solution	1	0.10

RESULTS

Table 3: Symptomatic improvement with SHY.

		Mean ± SD		Mean Diff	95% Confidence Interval		*P* value
	Parameters	BT	AT		BT	AT	
1	Burning Micturation	6.147±2.437	1.347±2.043	4.8	5.585-6.708	0.876-1.817	<0.0001
2	Pain	4.8±2.8	2.63±2.5	2.17	4.1-5.5	2-3.2	<0.001
3	Stone size LK (mm)	3.013±2.436	0.907±2.035	2.106	2.45-3.575	0.438-1.375	<0.0001
4	Stone size RK (mm)	3.107±2.768	1.493±2.637	1.614	2.469-3.745	0.886-2.101	<0.0001
5	24 hr urine Calcium	3.307±1.827	2.277±0.973	1.03	2.886-3.728	2.052-2.501	<0.0001
6	Urine Sodium	61.804±24.716	68.403±29.713	-6.6	56.109-67.499	61.557-75.248	=0.0207

The test drug SHY complies with the physio-chemical standards set by the Ministry of AYUSH and are mentioned in Table 1.

DISCUSSION

115 diagnosed cases of nephrolithiasis (*Hisat al Kuliya*) were registered for the clinical trial. Out of which 75 patients completed the trial and 40 patients dropped out. 15 (20%) patients refused investigation on follow up and another 20% were lost due to floods that hit the state at that time, 10 patients (13.33%) dropped out due to gastric discomfort or bitter taste of the drug.

The mean age of the patients in the study was 33.45 ± 10.99 years CI (30.92-35.99) which was highly significant with $p<0.001$. The study showed a definite female dominance of 28% with male:female ratio being 0.6:1. This is despite the fact that elevated testosterone plays a role in the pathogenesis of nephrolithiasis.[11] Nephrolithiasis classically is a disease common in men but a paradigm shift is observed due to lifestyle changes, coronary artery disease, and reduced bone mineral density; dietary changes and decreased fluid intake.[8,12]

Our study revealed that majority of the patient's diet was heavy on salt and protein (Table 4). Though the consumption of packed food which is a major source of sodium intake was less, however their sodium consumption was high as their tea (*Noon chai* or salt tea) and bread contain salt and sodium bi carbonate. This is highly significant as every 100mmol increase in dietary sodium results in approximately 25mg rise in urinary calcium.[4] Whereas increased dietary calcium reduces urinary excretion of oxalate[13] by increasing oxalate binding capacity of intestines thereby decreasing risk of nephrolithiasis.[4] It is known that initially electrolytes and proteins inhibit crystallization in solution but the same can act as promoters when they are immobilized.[14]

Table 4: Diet wise distribution.

Variables	High		Low	
***n*=75**	**Frequency**	**Reference range**	**Frequency**	**Reference range**
		Salt consumption		
Bread	50 (66.66%)	Kandur (local baker)	25 (33.33%)	Home made
Tea	43(57.33%)	≥2 cups per day	32 (42.66%)	≤ 2 cups per day
Salt in food	57 (76%)	>2 tsp per day	18 (24%)	≤2 tsp per day
Butter	18 (24%)	Yes	57 (76%)	No
Consumption of packed food	18 (24%)	Yes	57 (76%)	No
		Protein Consumption		
Red meat	35 (46.66%)	>3 times a week	27 (33.33%)	≤3 times a week
Chicken	15 (20%)	>4 times a week	8 (10.66%)	≤4 times a week
Fish	5 (6.66%)	>2 times a week	15 (20%)	≤2 times a week
Egg	2 (2.7%)	>2 times a week	73 (97.3%)	0-1 times a week
		Water		
Source	47 (62.67%)	2,3	28 (37.33%)	1,4
Quantity	10 (13.33%)	>4 glasses per day	28 (37.33%)	3 glasses per day
		Supplements		
Vitamin D	50 (66.67%)	Yes	25(33.33%)	No
Milk	17 (22.67%)	1glass per day	58 (77.33%)	0
Fruit	5 (6.67%)	4 per week	13 (17.33%)	3 per week
Nuts	26 (34.67%)	Yes	49 (65.33%)	No
Intake of Calculus causing vegetables	11(14.67%)	>3 per week	17 (22.67%)	<3 per week

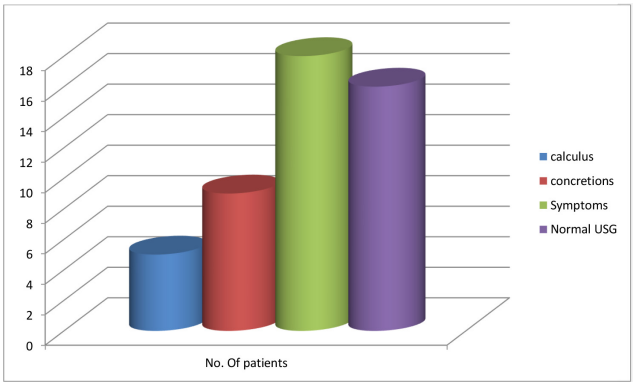

Figure 2: The percentage representation of recurrence of nephrolithiasis five years after using SHY.

The environmental conditions of Kashmir make them in-frequent water drinkers. Most of the water consumed by patients was either boiled or purified; however the high incidence of calcium-oxalate stones in Kashmir is attributed to hard water.[2] Decreased fruit intake causes low potassium and magnesium level, which again predisposes them to stone formation. Maximum patients were enrolled from the Ganderbal district of Kashmir. The water supply of this area is not very good. The patients were counseled regarding intake of diet they were asked to decrease the intake of salt tea (noon chai), abstain from spinach, tomatoes, red meat and pulses for a period of 2 months. They were encouraged to take more fruits and 6-8 glasses of water per day.

Most high protein intake countries around the world like Middle East, China, Japan, USA, Germany, Italy and Scotland have reported high incidence of calcium oxalate stones.[15] Since Kashmir too is a high protein intake state hence, the discussion focuses on calcium oxalate stones alone.

The main problem with nephrolithias is its recurrence which is found to be 50% after 5 years of first episode and 72% after 10 years.[9] A pooled analysis of more than 5,000 stone-free patients was conducted recently by the EAU Guidelines Urolithiasis Panel. The Panel suggested 2 years of imaging for radiopaque stones and upto 3 years for radiolucent stones to achieve an 80% stone-free "safety margin", whereas 5 years of imaging for follow-up to achieve a 90% "safety margin."[16] Hence post-trial assessment was done at 5 years. During post-trial assessment of *Safoof Hajrul Yahood* after five years (2020 to 2022) only 48 patients (64%) could be contacted. the recurrence rate of *Safoof Hajrul Yahood* was calculated as:

No. of patients having calculus or concretions (divided by) total number of patients, which is 29.16% five years

after treatment, with no change in diet or lifestyle or environment as in Figure 2.

Stone formation is an indication of metabolic imbalance, presaging other comorbidities and its recurrence indicates the persistence of these imbalances.[5] Indigenous medicines are rich in phytoconstituents, which exert their beneficial effects through multiple mechanisms like: diuretic activity, crystallization inhibition activity, lithotriptic activity, improving renal function, regulating oxalate metabolism, correcting crystalloid colloid imbalance, antioxidant activity, antimicrobial activity, analgesic and anti-inflammatory activity.[5] SHY demonstrates short term and long-term effects.

Short term effects

Short term effects were observed during the eight weeks of using the intervention as is evident from Table 3. During that period SHY exhibited diuretic, lithotriptic and analgesic properties per say and through its phytoconstituents. These properties help in providing symptomatic relief and in expulsion of the calculus (Table 3). However, there were long term effects too.

Long term effect

These were observed after a period of five years and helped in reducing the recurrence of nephrolithiasis. The three-fold process by which *Safoof Hajrul Yahood* exhibits its long-term effects are probably: 1. correcting crystalloid colloidal imbalance; 2. correcting oxalate metabolism and 3. improving renal functions

1. Correcting crystalloid colloidal imbalance

As observed in the study, the drug decreases 24 hr urinary calcium ($p < 0.001$) highly significantly (Table 3). This reduction provides less calcium to bind with oxalate and thus reduction in calcium oxalate crystals reducing supersaturation.[18] This influences the thermodynamic solubility product (Ksp) of urine, preventing crystallization.[14] Thereby discouraging a homogeneous neucleation, critical for further stone formation. Alternately, persistent damage to anti adherent Glucosaminoglycans (GAG) layer due to bacterial infection forms a nidus for heterogeneous nucleus.[14] The test drug has been reported to have antimicrobial and anti-inflammatory activities preventing formation of heterogeneous nidus too.[19]

2. Correcting oxalate metabolism

Source of oxalates in human is either diet or hepatic production and is cleared by gut microbiome. Since oxalate metabolism is a part of nephrolithiasis and the drug was able to cure and prevent nephrolithiasis hence it can be concluded that it has an effect on oxalate mechanism through management of gut microbiome dysbiosis.[20] Apart from this it has been discussed that indigenous medicine manage oxalate metabolism through their phyto-constituents.[17] The prolonged effect demonstrated by SHY could be due to persistent significant reduction in oxalate excretion even in the absence of dietary oxalate. This could be due to the diverse gut bacteria, including the known oxalate-degrading bacteria from the Oxalobacteraceae family.[20] It was found that quercetin (active phenolic compound of *Dichotomiflorum* an active ingredient of SHY) decreased urinary oxalate may be due to the inhibition of oxalate formation. Alternately, it could also be due to the inhibition of oxalate oxidase enzyme reportedly responsible for the stone formation.[21]

3. Improving Renal Functions

Tonics have the capability to restore and maintain the physiological functions of the organ system.[22] Given that *Safoof Hajrul Yahood* is a renal tonic, it thus has the capability to restore and maintain the physiological renal functions, probably by enhancing renal perfusion and oxygenation. Some of its components are rich in vitamin B whereas its polyphenols regulates calcium intake and helps in transporting oxygen to cells.[23]

All these processes work independently but are interdependent, since the calcium oxalate crystals form the crystalloid either due to real weakness or vice versa. However, the drug works either through all these processes independently or by synergizing them to obtain the long-term effect. These changes occurred during the 8 weeks of drug administration because no changes in diet or socio-environmental conditions have been reported post treatment. Therefore, it can be concluded that the drug *Safoof Hajrul Yahood* corrected the colloidal imbalance and/or oxalate metabolism and/or renal functions.

Clinical studies conducted by Zaheer *et al*[24] and Rajesh *et al*[25] have endorsed our results regarding the safety of *Safoof Hijarul Yahood* on biochemical parameters.

CONCLUSION

The drug *Safoof Hajrul Yahood* brought about significant symptomatic relief and improved the quality of life significantly within 15 days. The patients reported complete ablation of pain, nausea/vomiting and hematuria on the first follow up i.e.,15 days resulting in better patient compliance

The drug demonstrated short term and long-term effects. Among its short-term effects are the astounding effect on the symptoms of pain, haematuria and burning micturation. It also decreased urinary calcium excretion considerably. The rate of stone expulsion was calculated as 64%. The factors that contribute to nephrolithiasis are readily available in the Kashmir which justifies their placement in the stone belt of India. The Kashmiri diet is hypercalciuric, hypomagnesuric and hyperphosphaturic. The long-term effect could be observed after five years of taking *Safoof Hajrul Yahood* for 8 weeks, wherein the recurrence rate is 29.16%; even when the dietary and socioeconomic factors remain the same. This could probably be because SHY was able to prevent urinary supersaturation thereby inhibiting crystallization and nucleation thus correcting the crystalloid colloidal imbalance. Alternately, the drug could be effective because it corrects oxalate metabolism by correcting the gut microbiome dysbiosis. Thus, through these means the drug was able to reduce the recurrence rate. However, the correct mechanism is still a speculation and scope for further study. The drug was well tolerated and only 13.33% reported gastritis apart from this there was no major changes in the safety parameters.

The small sample size lack of a control group and inability to analyze the stone were the limitations to the study.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACE: Angiotensin Converting Enzyme; **AT:** After Treatment; **AYUSH:** Ayurveda, Yoga, Unani, Siddha and Homeopathy; **A2:** Arachidonic acid; **BT:** Before treatment; **CI:** Confidence Interval; **USG:** Ultrasonography.

SUMMARY

An open labeled clinical trial was conducted on 75 patients in Srinagar, Kashmir, India to study the effect of a pharmacopeial lithotriptic drug *Safoof Hijul Yahood* (SHY), in expelling renal calculi and preventing its recurrence. The post-trial assessment was done after five years. Uncomplicated cases of nephrolithiasis (*Hisat al Kuliya*), subsequent to written and informed consent aged between 18-60 years having a calculi diameter of 6-8mm were given 5g of SHY twice daily orally for 8 weeks. Patients were followed up fortnightly. They were asked to fill a questionnaire regarding their diet and fluid intake. The data was analyzed on Tukey-Kramer multiple comparison test and paired t test.

The mean age of patients was 33.45 years CI (30.92-35.99). SHY reduced 24 hr calcium excretion highly significantly and the calculus clearance rate with SHY was calculated as 64%. The recurrence rate after five years of no intervention period was 29.16%. The drug was well tolerated and only 13.33% reported gastric discomfort.

The plausible mechanism of action of SHY is that it decreased calcium excretion correcting supersaturation and thereby positively impacting crystalloid colloidal imbalance or the gut microbiome dysbiosis and/or renal functions; thus, preventing recurrence. This is despite the unchanged environmental factors and sedentary lifestyle. However, the exact mechanism for this effect needs to be studied. The small sample size and lack of control group were limitation to the study.

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