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Original Article

Efficacy of *Kabab Chini* (*Piper cubeba* Linn) in Chronic Kidney Disease: A Randomized Controlled Clinical Trial

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Abstract

Background: Chronic Kidney Disease (CKD) is a major public health problem with a global prevalence of approximately 13% with the majority stage 3 and is a global threat to health in general and for developing countries in particular, because therapy is expensive and life-long. In India 90% patients cannot afford the cost of treatment for CKD, over 1 million people worldwide alive on dialysis or with a functioning graft. It is the need of the time to find alternate treatment to control CKD. Hence this study aims to evaluate clinically the efficacy of Kabab Chini (Piper cubeba) in CKD stage 1-3 and also to compare the effectiveness of the marketed drug NEERI KFT® scientifically.

Objectives: To evaluate the efficacy of *Kabab Chini* (*Piper cubeba*) in chronic kidney disease (CKD) stage 1-3 patients.

Methods: In this open-labeled randomized controlled clinical trial, 30 participants, randomly allocated to two groups, received 4 g of either *sufoof* (powder) of *Kabab Chini* in a divided dose thrice a day (Test group, n=15) or 10 mL of Syrup NEERI-KFT three times a day (Control group, n=15) for 42 days. The objective parameters were serum creatinine, blood urea (BU), estimated glomerular filtration rate (eGFR), and urine routine and microscopy, whereas subjective parameters were anorexia, easy fatigability, and edema. Objective and subjective parameters were assessed at weekly follow-ups, and safety parameters were assessed at baseline and after 42 days.

Results: Intragroup data suggest significant improvements in anorexia, easy fatigability, and eGFR in both groups ($P=0.001$), whereas the intragroup serum creatinine value was significantly reduced in the test ($P=0.028$) and control ($P=0.256$) groups. No significant improvement in edema and albumin was observed in both groups ($P>0.05$). The test drug was found to be tolerable with no adverse effects.

Conclusion: The results of the present study revealed that *Kabab Chini* is effective in reducing serum creatinine, eGFR, anorexia, and easy fatigability moderately superior to Syrup NEERI-KFT® with respect to efficacy without any adverse effect and accepted alternate hypothesis.

Keywords: CKD, *Dauf-al-kulya*, *Kabab Chini*, Serum creatinine, eGFR, *Sue Mizaj Barid Kulya*, Unani

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Background

Chronic kidney disease (CKD) is a complex pathological state of the kidney, as per the doctrine of the Unani System of medicine (USM); pathologically, it is a disease of *Sue mizaj*, *Sue tarkeeb*, and *Tafarruque Ittesal*, and literally, it can be termed as *Ḍu'f al-Kulya*.

Various organs of the human body, including kidneys, lungs, liver, heart, and intestines, maintain the body's physiological function, and simultaneously, they gradually decrease with the progression of age. One of such organs is the kidney, a major excretory organ of the body that also performs several functions such as filtration, reabsorption, secretion, water, and electrolyte balance and eliminates toxic substances from the body (1).

The healthy individual kidney contains around 1-3 million nephrons (2). The kidney is the target organ of many diseases; it also aggravates or starts systemic pathophysiological processes, which affect body homeostasis (1).

CKD ranks 19th as a cause of death and a considerable social and economic burden worldwide (3) that affects more than 10% of the world's population (4).

The prevalence of CKD is higher in developing countries. According to WHO's Global Burden of Disease 2015 report, 1.2 and 19 million people died of renal failure and disability-adjusted life-years, and 18 million years of life were lost due to cardiovascular diseases (5). High-income countries typically spend more than 2-3% of their annual

healthcare budget on the treatment of end-stage kidney disease, even though those receiving such treatment represent under 0.03% of the total population (5).

CKD is defined as the atrophy of the kidney or progressive decline of renal function that can result from various etiologically distinct causes (1). Presently, diabetes and hypertension (HTN) are the two leading causes, although infectious glomerulonephritis, renal vasculitis, ureteral obstruction, genetic alterations, autoimmune diseases, and others are also common (6). There are certain risk factors such as race (African-American decent), gender (male), age (older), low birth weight, exposure to heavy metals, habits (excessive alcohol consumption and smoking), use of analgesic medications, and family history, and the like which are highly important for kidney injury (7).

CKD patients remain asymptomatic during the early stages, as kidney function worsens, the symptoms of uremic syndrome develop, including lethargy, anorexia, mucosal ulcers, vomiting, diarrhea, weight loss, edema, anemia, and altered urine output (8).

In CKD, there is no single medication that can enhance kidney function. The normalization of blood pressure and blood glucose levels is the only way to slow the advancement of this condition (1). Patients will eventually need renal replacement therapy, including hemodialysis, peritoneal dialysis, or transplantation, and a host of medicines to alleviate symptoms and improve kidney functions (8).

In the USM, *Ḍu'f al-Kulya* (a CKD-like condition) was managed with drugs possessing actions such as *Mudirr-e-Bawl* (Diuretics) (9-14), *Dafa-e-Taaffun* (Antiseptic) (9-13), *Muhallil-e-Waram* (Anti-inflammatory) (12,14), *Mulattif* (Demulcent) (9-14), *Mufatteh Suddah Kulya* (Deobstruent) (9-14), *Muharrik* (Stimulant)(10,13), *Musakkin* (Analgesics) (13), *Kasir-e-riyah* (Carminative) (10,12,13) and *Munaqq-e-Kulya wa Majari Bawl* (Cathartic to kidney and urinary tract) (9-12), and the like. However, the scientific validation of such drugs was not documented. This is because USM is claimed to be an effective means for CKD-like conditions and presents treatments such as dialysis or transplantation which are expensive and limited access (2) instigates to validate the scientific rational claims.

Therefore, *Kabab Chini* (*Piper cubeba,* Linn) is selected based on augmented pharmacological studies as antioxidant (15-21), diuretic (22), antidiabetic (21), anti-inflammatory (23,24), antibacterial (25-27) activities. Its chemical constituents and active principles are carbohydrates/starch, phenols, proteins, steroids, tannin, iron, zinc, calcium, magnesium, potassium, and volatile oils such as sesquiterpene hydrocarbons, terpenes, alpha and beta cubebenes, copaene, cubebol, delta-cadinene, humulenes.

Lignans include cubebine, cubebinin, dihydrocubebin, kinokinin, cubebic acid, fatty matter, wax, fatty oil, gum, and ash (malates of magnesium and calcium). The data of its pre-clinical study are suggestive of the nephroprotective activity of *Kabab Chini* in drug-induced nephrotoxic kidneys (28).

This study was conducted hypothesizing that *Kabab Chini* may be effective in modifying the impaired renal functions due to CKD because *Kabab Chini* has been prescribed in kidney diseases in the Unani literature; the same is validated in a pre-clinical study. It also possesses nephroprotective activity in drug-induced nephrotoxic kidneys (15). It also displayed *in vitro* antidiabetic and antioxidant activities (16), and its study in an animal model proved its antinociceptive, antipyretic, and antimicrobial activities (17). This study aimed to evaluate the efficacy of *Kabab Chini* (*Piper cubeba*) in CKD stages 1-3 compared with the market compound formulation of Ayurveda NEERI-KFT®.

Materials and Methods

Study Design and Study Duration

An open-labeled randomized, controlled, clinical trial was performed in the Hospital of National Institute of Unani Medicine, Bengaluru, India. The trial was conducted from April 2019 to February 2020.

Sample Size Calculation and Randomization

The sample size was estimated considering the mean (1.445) (29) and standard deviation (0.514) (29) of a previous study with α error of 0.05 and β error of 0.20. The following formula (30) was used to calculate the sample size:

$$N=2\ [\ (Z\alpha-Z\beta) \times \sigma\ /\ (\mu 1-\mu 2)]^2$$

When calculated for the required improvement in serum creatinine, the calculated sample size was 15 for each group (Test and control groups). The subjects were allocated to test and control groups by a simple randomization technique using a computer-generated random allocation table.

Participants and Study Setting

The patients were recruited from the OPD/IPD of NIUM Hospital, Bengaluru, India. The inclusion criteria for patient selection were known cases/newly diagnosed cases of CKD stage 1-3, associated with diabetes mellitus and HTN with treatment, a serum creatinine level ≤ 6 mg/dL (Jaffe method), GFR ≥ 30 mL/min/1.73 m^2 (Cockcroft-Gault equation), blood urea (BU) level ≤ 135 mg/dL, and patients of either gender in the age range of 20-65 years. On the other hand, the exclusion criteria were CKD stage > 3, serum creatinine level > 6 mg/dL (Jaffe method), GFR < 30 mL/min/1.73 m^2 (Cockcroft-Gault equation), BU > 135 mg/dL, a history of metabolic disorders (except for diabetes mellitus), systemic illness, AIDS, TB, cancer, and mental disorder. Patients aged below 20 and above 65 years, as well as pregnant and lactating women, were excluded as well.

Interventions

Collection and Identification of Test Drugs

The test drug (*Kabab Chini*) was purchased from a local market. It was authenticated and certified by the Foundation for Revitalisation of Local Health Traditions, Bengaluru, vide authentication certificate No. 5506, and the control drug (Syrup NEERI-KFT®) was sponsored by the AIMIL pharmaceuticals.

Method of Preparation of Kabab Chini

Dried fruits of *Kabab Chini* (*Piper cubeba* Linn) were cleaned by weeding out unwanted materials and impurities; then, they were powdered and filled in capsules and packed in transparent airtight plastic lock bags (10,12-14).

Drug Dose and Dosage Form

The test drug (*Kabab Chini*) was given in the form of *Sufoof* filled in capsules, in a divided dose of 2 capsules three times a day (04 grams/day) after taking a meal (1.33 gm thrice a day), whereas the control drug (Syrup NEERI-KFT®) 2 teaspoonfuls (10 mL) three times a day after taking a meal, both for 42 days (10, 12-14).

Dietary Advice

Patients were advised to restrict a salt and low protein diet (0.8 g/kg/d), foods such as red meat, egg yolk, and green leafy vegetables, along with a daily intake of 1-1.5 L of water (in addition to usually consumed beverages).

Measurements and Safety Assessment

The efficacy assessment was performed based on improvements in subjective and objective parameters of both groups on every follow-up. Objective parameters were assessed by serum creatinine, BU, urine routine and microscopy, and estimated glomerular filtration rate (eGFR), whereas subjective parameters included anorexia, edema, and easy fatigability. Anorexia was assessed with the Functional Assessment of Anorexia/Cachexia Therapy Questionnaire (31). The 12 items of the FAACT scale were scored on a five-point Likert-type scale (0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, and 4 = Very much). The sum score ranges between 0 and 48, whereby a lower score indicates less appetite. Scores ≤ 30 represent anorexia. Edema is assessed with Dent depth and duration, a grading method for edema (32), and 2 mm or less, 2-4 mm, 4-6 mm, and 6-8 mm pitting indicate grade 1 +, grade 2 +, = grade 3 +, and = grade 4 + edema, respectively. Easy fatigability was assessed by the Fatigue Assessment Scale (33), which is a 10-point scale evaluating the symptoms of chronic fatigue. Each point is a five-point Likert-type scale type ranging from "never" to "always", where 1, 2, 3, 4, and 5 stand for never, sometimes, regularly, often, and always, respectively. Likewise, a sum of the score 10 represents a low level of fatigue, while that of the score of 50 denotes the highest (< 10, > 11-20, > 21-30, > 31-40, and > 41-50 demonstrate mild, mildly moderate, moderate, moderately severe, and severe, respectively).

Safety assessment was performed by investigating Hb%, total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate, serum glutamic oxaloacetic transaminase (aspartate aminotransferase, AST), serum glutamic pyruvic transaminase (alanine transaminase, ALT), and alkaline phosphatase (ALP) before and after the completion of the trial.

Primary and Secondary Outcomes

The primary and secondary outcomes were improvements in objective and subjective parameters, respectively.

Statistical Analysis

The obtained data were analyzed using SPSS 22.0 and R environment 3.2.2 software. Microsoft Word and Excel were used to create graphs, tables, and the like. Changes in various parameters were assessed for statistical evaluation by using Fisher's exact and chi-square test (on a categorical scale and a non-parametric setting for qualitative data analysis) whereas, Student's *t* test (two-tailed, independent, and dependent) was employed to find the significance of study parameters (on a continuous scale) for both intergroup and intragroup analyses, respectively, at each follow-up (0^{th}, 7^{th}, 14^{th}, 21^{st}, 28^{th}, 35^{th}, and 42^{nd} day). Leven's test was performed to evaluate the homogeneity of variance. The results on continuous and categorical measurements are presented as means ± SD (Min-Max) and numbers (%), respectively, and *P* values of less than 0.05 were considered statistically significant.

Results

Study Flow

A total of 180 patients were screened, out of whom 108 patients did not fulfill the inclusion criteria, and 42 patients declined to participate in the study. Finally, 30 patients enrolled after obtaining written informed consent and were randomly allotted to test (n = 15) and control (n = 15) groups. Eight and nine patients in test and control groups were lost to follow up, respectively, and were evaluated using the principle and method of last observation carried forward according to intention-to-treat for analysis (Figure 1).

Socio-demographic Data

The clinical characteristics of participants at baseline are reported in Table 1. The average age of the patients was 56.20 ± 12.27 years, with the predominance of male gender 25 (83.3%), mixed dietary habits 26 (86.7%), and lower middle socioeconomic status 15 (50%), along with the highest number of participants 11(36.7%) were found in two groups with a BMI of 26-30 and >30. Among all patients, family history of both diabetes and HTN patients were leading (n = 11, 36.7%), and HTN (n = 15, 30.0%) was

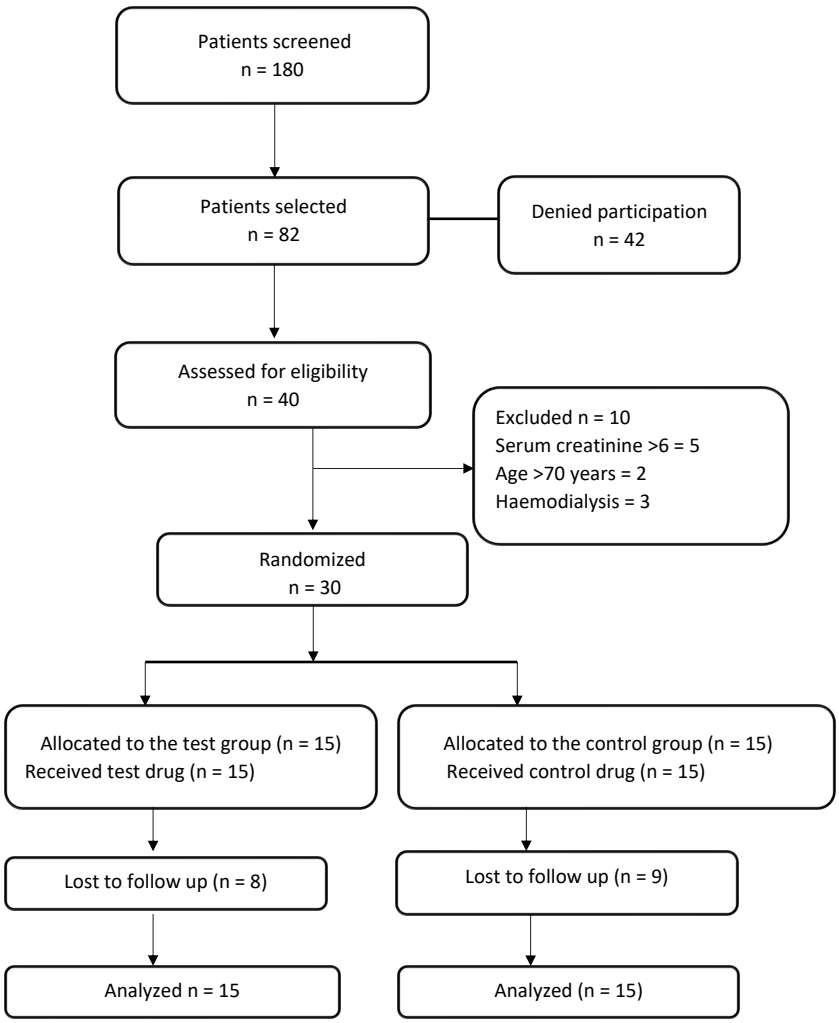

Figure 1. CONSORT Flowchart of the Study

the leading cause of CKD, followed by diabetes mellitus (n = 4, 13.3%), and the chronicity of the disease was observed in a maximum of 14 (46.7%) patients, suffering from less than 12 months of duration of illness, possibly because of the unawareness of patients with CKD and the late referral.

Clinical Outcomes

Primary Outcomes

Serum creatinine demonstrated a decrease from 2.09 ± 0.78 to 1.75 ± 0.62 with a difference of 0.340 ($P = 0.028$) and from 2.68 ± 1.51 to 2.55 ± 1.63 with a difference of 0.135 ($P = 0.256$) in the test and control groups, respectively. BU remained almost the same from 48.33 ± 30.30 to 49.73 ± 27.26 with a difference of -1.400 ($P = 0.865$) and from 69.00 ± 51.78 to 60.27 ± 36.12 with a difference of 8.733 ($P = 0.126$) in the test and control groups, respectively. In the test group, eGFR increased from 42.84 ± 10.62 to 51.59 ± 15.02 with a difference of -8.757 ($P = 0.015$), and in the control group, it was from 43.38 ± 23.04 to 48.87 ± 29.16 with a mean difference of -5.491 ($P = 0.012$). The improvement in urine albumin was 6.7% ($P = 0.354$) and 13.3% ($P = 0.242$) in the test and control groups, respectively, both were not significant. The details of which are depicted in Table 2 and in Figures 2 and 3.

Secondary Outcomes

Anorexia represented significant improvements from 13.13 ± 6.22 to 19.00 ± 6.31 with a difference of -5.867 ($P = 0.013$) and from 11.53 ± 2.39 to 19.60 ± 5.72 with a mean difference of -8.067 ($P = 0.001$) in the test and control groups, respectively. Easy fatigability decreased from 27.87 ± 6.84 to 21.40 ± 6.32 with a difference of 6.467 ($P < 0.001$) in the test group and from 24.67 ± 8.64 to 18.80 ± 8.65 with a difference of 5.867 in the control group ($P < 0.001$). An improvement in edema was 13.3% and 13.4% in the test and control groups, respectively ($P = 0.242$, Table 3 and Figures 4 and 5).

Safety and Tolerability

Both test and control drugs were well tolerated with no adverse effects, and safety parameters were within normal limits.

Discussion

To our knowledge, this is the first clinical trial that has investigated the efficacy of *Kabab Chini* (*Piper cubeba*,

Table 1. Socio-demographic Data

Characteristic	Kabab Chini (n=15)	NEERI-KFT (n=15)	Mean±SD	*P* value
Age				
<40	1(6.7%)	2(13.3%)	56.20±12.27	*P*=0.140
41–50	3(20%)	6(40%)		
51–60	2(13.3%)	2(13.3%)		
61–70	9(60%)	5(33.3%)		
Gender				
Female	1(6.7%)	4(26.7%)		*P*=0.330
Male	14(93.3%)	11(73.3%)		
Diet				
Mixed	13(86.7%)	13(86.7%)		*P*=1.000
Veg	2(13.3%)	2(13.3%)		
Socioeconomic status				
Lower Middle	7(46.7%)	8(53.3%)		*P*=0.791
Upper Lower	4(26.7%)	2(13.3%)		
Upper Middle	4(26.7%)	5(33.3%)		
BMI (kg/m^2)				
<18.5	0(0%)	0(0%)		*P*=0.433
18.5–25	4(26.7%)	4(26.7%)		
26–30	7(46.7%)	4(26.7%)		
>30	4(26.7%)	7(46.7%)		
Family history				
DM	5(33.3%)	4(26.7%)		*P*=1.000
HTN	0(0%)	2(13.3%)		*P*=0.483
Both	5(33.3%)	6(40.0%)		*P*=1.000
None	5(33.3%)	3 (20%)		*P*=0.682
Duration of illness (months)				
<12	8(53.3%)	6(40%)		*P*=0.726
12–24	4(26.7%)	5(33.3%)		
>24	3(20%)	4(26.7%)		
Comorbidity				
DM	1(6.7%)	3(20.0%)		*P*=0.598
HTN	8(53.3%)	7(46.7%)		*P*=0.715
Both	6(40.0%)	5(33.3%)		*P*=0.705

Note. SD: Standard deviation; BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension. Student's t-test, Fisher's exact test, and Chi-square test were used.

Linn) on CKD stages 1-3.

Anorexia is mainly related to the accumulation of unidentified anorexigenic compounds, inflammatory cytokines, and alterations in appetite regulation, including amino acid imbalance, which increases the transport of free tryptophan across the blood-brain barrier. This creates a hyper serotoninergic state that is prone to low appetite (34). An improvement in anorexia is due to *Kasire Riyah* (Carminative) (10,12,35-37), *Muharriq-wa-Muqawwi meda* (digestive and appetizing) (10,12,35), and *Mulattif* was *Mufattih-e-Suddah Jigar* (Deobstruent) (10-12,35) properties of *Kabab Chini*. In an animal study, the ethanolic extract of *Kabab Chini* fruits possesses significant antioxidant and hepatoprotective activities (20). Alsaid et al demonstrated the oxidative and hepatoprotective effect with the *Piper cubeba* ethanolic extract, and it was ascribed to the downregulation of proinflammatory cytokines (TNF-α and IL-6 mRNA expression, as well as iNOS and HO-1 gene) and upregulation of the IL-10 in an in-vivo study (38).

Several factors may perpetuate clinically significant fatigue among individuals with CKD, including sleep disorders, depression, sedentary lifestyle, anemia, and chronic inflammation, whereas anemia and inflammation are the most common factors (39). An improvement in easy fatigability is due to the *Muharrik* (Stimulant) (10,13,35,37) and *Muqawwi* (10,35) properties of *Kabab Chini*. Fatigue is the most common parameter and is associated with oxidative stress due to free radicals; therefore, antioxidant therapy is essential (40). Several in vitro and in vivo studies showed the antioxidant activity of *piper cubeba* (15-21).

Urinary Protein loss decreases plasma albumin concentration and plasma oncotic pressure, resulting in the imbalance of the starling forces. Due to these occurrences, Adaptive neurohumoral responses, stimulation of the renin-angiotensin-aldosterone system, an increase in antidiuretic hormone release, renal sodium retention, and fluid redistribution from the intravascular space towards the interstitial space are all brought on by fluid redistribution, which results in fluid moving from the intravascular space to the interstitial space. The decrease in atrial natriuretic peptide secretion facilitates salt retention and subsequent edema formation (41). The number of outcomes we discovered as a result of *Muhallil* (12,14) *Mufattih-e-Suddah Kulya wa Jigar* (Deobstruent) (9-12,14), and *Mudirr-e-Bawl* (Diuretic) (9-14,35,36) properties of *Kabab Chini*. In an experimental animal study, Ahmad et al reported that *piper cubeba* increased the urine volume significantly and excreted the Na + in urine output (22).

The result of this study is in accordance with a preclinical study, demonstrating the significant effect of *Piper cubeba* in reducing the serum creatinine level in gentamycin-induced nephrotoxicity on rats conducted by Ahmad et al (28). According to reports, antioxidants are used as a therapy vastly for reducing oxidative stress and serum creatinine levels significantly, as well as the risk of end-stage of renal disease development (42). Oxidative stress contributes to the pathogenesis of CKD, either unswervingly by generating glomerular and tubular damage or ramblingly through inflammation, HTN, and/or endothelial dysfunction. Antioxidants are vital in the process of tissue regeneration after inflammation and in the self-preservation system against microbes and other antigens (2). An improvement in serum creatinine is due to *Mufattih-e-Suddah Kulya* (Deobstruent) (9-14), *Mulattif* (Demulcent) (9-14), and *Muhallil-e-Waram* (12,14) properties of *Kabab Chini*.

Previous studies have reported that antioxidant therapy

Table 2. Primary Outcomes

	Test Group					Control Group					Intergroup	
	Baseline	Week 3	Week 6	*P* Value	Difference	Baseline	Week 3	Week 6	*P* Value	Difference	Treatment Difference	*P* Value
Serum creatinine	2.09±0.78	1.76±0.55	1.75±0.62	0.028	0.340	2.68±1.51	2.63±1.75	2.55±1.63	0.256	0.135	0.237	0.013
Blood urea	48.33±30.30	51.00±27.38	49.73±27.26	0.865	-1.400	69.00±51.78	63.73±46.36	60.27±36.12	0.126	8.733	3.667	0.457
eGFR	42.84±10.62	50.72±14.00	51.59±15.02	0.015	-8.757	43.38±23.04	48.73±29.57	48.87±29.16	0.012	-5.491	-7.124	0.001
Albumin												
Nil	3 (20%)	4 (26.7%)	4 (26.7%)		6.7%	2 (13.3%)	3 (20%)	3 (20%)		6.7%		-
Trace	3 (20%)	3 (20%)	3 (20%)		0.0%	1 (6.7%)	2 (13.3%)	2 (13.3%)		6.6%		-
1+	2 (13.3%)	1 (6.7%)	3 (20%)		6.7%	5 (33.3%)	5 (33.3%)	3 (20%)		-13.3%		-
2+	7 (46.7%)	6 (40%)	2 (13.3%)		-33.4%	3 (20%)	2 (13.3%)	3 (20%)		0.0%		-
3+	0 (0%)	1 (6.7%)	3 (20%)		20.0%	3 (20%)	1 (6.7%)	2 (13.3%)		-6.7%		-
4+	0 (0%)	0 (0%)	0 (0%)		0.0%	1 (6.7%)	2 (13.3%)	2 (13.3%)		6.6%		-

Note. eGFR: Estimated glomerular filtration rate.

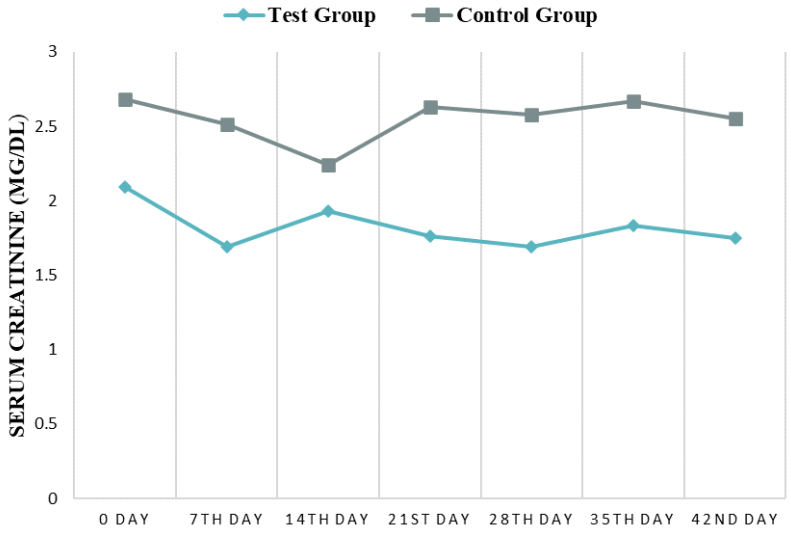

Figure 2. Effects of Drugs on Serum Creatinine

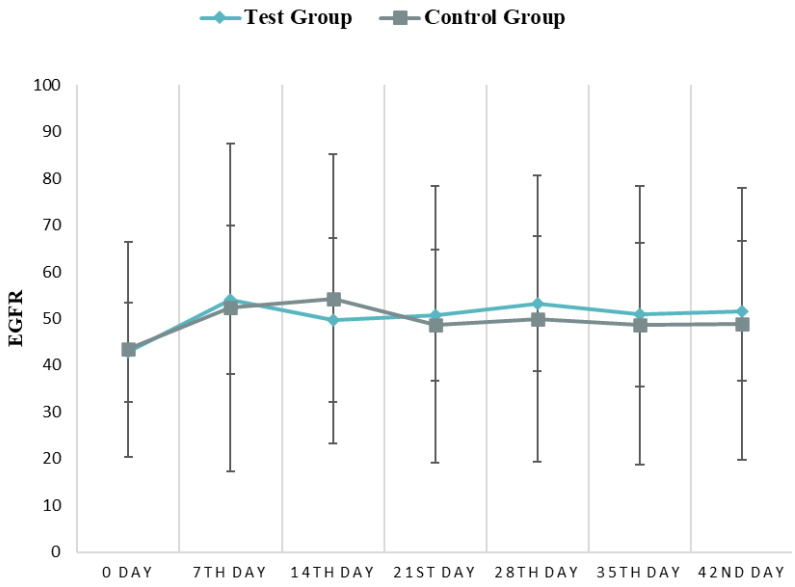

Figure 3. Effects of Drugs on eGFR. *Note*. The applied tests were Student's t-test (Independent) and Student's t-test (Dependent) for between and within groups, respectively. eGFR: Estimated glomerular filtration rate

Table 3. Secondary Outcomes

	Test Group					Control Group					Intergroup	
	Baseline	Week 3	Week 6	*P* Value	Difference	Baseline	Week 3	Week 6	*P* Value	Difference	Treatment Difference	*P* Value
Anorexia	13.13±6.22	15.60±4.31	19.00±6.31	0.013	-5.867	11.53±2.39	15.93±2.74	19.6`0±5.72	0.001	-8.067	-6.97	<0.001
Easy fatigability	27.87±6.84	23.60±6.05	21.40±6.32	<0.001	6.467	24.67±8.64	20.40±9.19	18.80±8.65	<0.001	5.867	6.167	<0.001
Edema												
Nil	10 (66.7%)	12 (80%)	12 (80%)	-	13.3%	0 (0%)	12 (80%)	13 (86.7%)		13.4%	-	
Trace	0 (0%)	0 (0%)	0 (0%)	-	0.0%	3 (20%)	0 (0%)	0 (0%)		0.0%	-	-
1+	3 (20%)	2 (13.3%)	2 (13.3%)	-	-6.7%	1 (6.7%)	2 (13.3%)	1 (6.7%)		-13.3%	-	-
2+	2 (13.3%)	1 (6.7%)	1 (6.7%)	-	-6.6%	0 (0%)	1 (6.7%)	1 (6.7%)		0.0%	-	-
3+	0 (0%)	0 (0%)	0 (0%)	-	0.0%	0 (0%)	0 (0%)	0 (0%)		0.0%	-	-
4+	0 (0%)	0 (0%)	0 (0%)	-	0.0%	0 (0%)	0 (0%)	0 (0%)		0.0%	-	-

Note. The used test included Student's t-test (Independent) between groups; Student's t-test (Dependent) within groups.

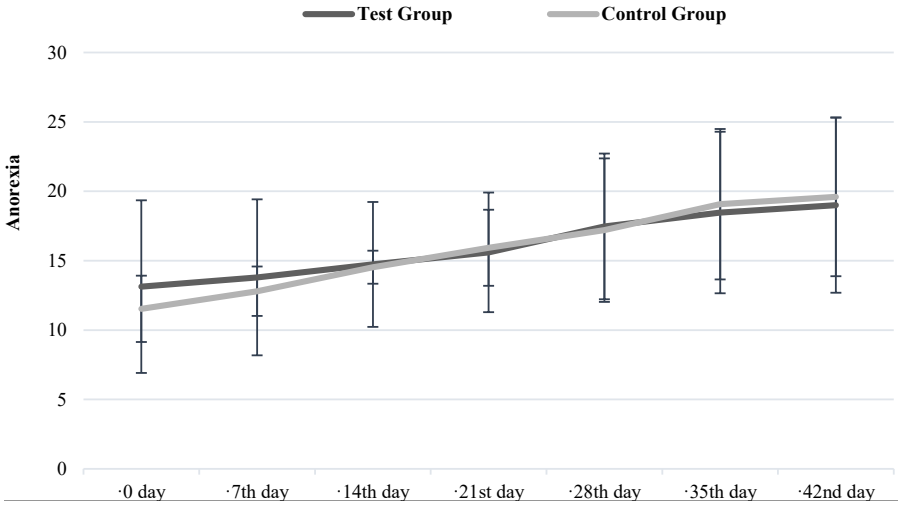

Figure 4. Effects of Drugs on Anorexia

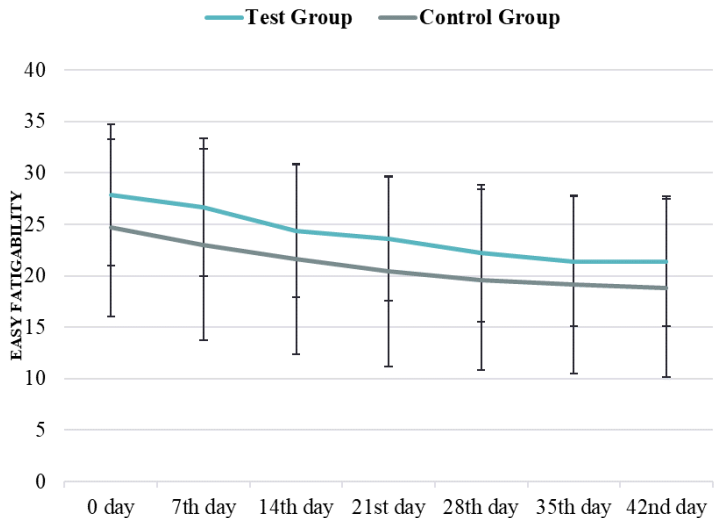

Figure 5. Effects of Drugs on Easy Fatigability

significantly improves kidney function by improving creatinine clearance (41). *Kabab Chini* also has antioxidant properties; thus it increases GFR by decreasing the creatinine level and increasing creatinine clearance, as serum creatinine is inversely proportional to GFR; if creatinine decreases GFR represents an increase (15-21).

An improvement in eGFR is due to *Mufattih-e-Suddah Kulya* (Deobstruent) (9-12,14), *Mulattif* (Demulcent) (9-12,14), and *Muhallil-e-Waram* (12,14) properties of *Kabab Chini*. Loss of albumin in the urine is a result of the abnormal transglomerular passage of proteins due to the increased permeability of the glomerular capillary wall and their subsequent impaired reabsorption by the epithelial cells of the proximal tubule in CKD (43). It is evident that patients with proteinuria in CKD usually suffer from fluid overload or edema (44). Therefore, the slight improvement in albumin is because of *Muhallil-e-Waram* (12,14) *Mufattih-e-Suddah Kulya wa Jigar* (Deobstruent) (9-12,14), and *Mudirr-e-Bawl* (Diuretic) (9-14,35,36) properties of *Kabab Chini*. The diuretic activity of *Piper cubeba* is documented by Ahmad et al in an experimental animal study (22).

Moreover, one case study was also performed on HTN-induced CKD with the same drug, in which *Sufoof-e-Kabab Chini* was found effective in terms of improvements in serum creatinine and eGFR from CKD stage 3b to CKD stage 2 (45).

Study Limitation

The main study limitations were the smaller sample size and short duration, along with frequent follow-ups.

Future Recommendations

The findings of this study included preliminary data; thus, more comprehensive study designs must further authenticate the efficacy of *Kabab Chini* in non-dialysis-dependent CKD on large scales.

Conclusion

Sufoof-e-Kabab Chini was well tolerated with no reported adverse effects, and all safety parameters were within normal limits. Based on the aforementioned results, it can be concluded that *Kabab Chini* (*Piper cubeba* Linn) may be used for improvements in eGFR and serum creatinine in non-dialysis-dependent patients of CKD stage 1-3.

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Authors' Contribution

Data curation: Khan Ishrat Jahan, Mansoor Ahmed Siddiqui, Mohammed Aleemuddin Quamri.
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Investigation: Khan Ishrat Jahan.
Methodology: Mansoor Ahmed Siddiqui, Mohammed Aleemuddin Quamri, Hamiduddin.
Project administration: Khan Ishrat Jahan.
Supervision: Mansoor Ahmed Siddiqui, Hamiduddin.
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Competing Interests

None declared.

Ethical Approval

Before commencing the trial, the study protocol was approved by the Institutional Ethical Committee (IEC) for Biomedical Research (with IEC No. NIUM/IEC/2017-2018/001/Moal/01) on 19.07.2018. The trial was registered with the Clinical Trial Registry of India (CTRI) under clinical trial registration number CTRI/2019/03/018200 on 20.03.2019. All the participants gave written informed consent and duly signed with the date and place.

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