ORIGINAL ARTICLE

Clinical assessment of "Neeri KFT" in chronic kidney disease patients

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Abstract

In view of the overall health impact of chronic kidney disease, inventors understand the necessity of improving kidney function in adults with impaired kidney function. Neeri KFT provides an effective treatment option for adults with impaired kidney function who have been inadequately controlled on lifestyle with or without other antihypertensive agents such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, adrenergic receptor antagonists, and vasodilators. Neeri KFT is an appropriate option to consider for addition drug. Treatment with Neeri KFT produced clinically relevant and statistically significant reductions in serum creatinine, blood urea, and serum uric acid when compared with placebo. Neeri KFT showed the promising result with respect to decrease of 17% in serum creatinine, 18% in urea, and 13% in uric acid.

Key words: Chronic kidney disease, impaired kidney function, indian system medicine, Neeri KFT

INTRODUCTION

Among organ failure associated diseases, chronic kidney disease (CKD) is now becoming more common these days and is transformed from a subspecialty issue to global health concern.[1] Based on the WHO report, 13% of the population worldwide is affected by CKD and millions more are hailing from diabetes and hypertension background, as later two contribute nearly 40% and 28.4%, respectively.[2] CKD is characterized by gradual loss of kidney function to end-stage renal disease. Repeated dialysis and kidney transplant are widely used the treatment of CKD.[3] Both dialysis and kidney transplant put an expensive financial weight on patient, their families, and society on the one hand, while still arresting the process of kidney function deterioration, remain a big challenge. In the light of these facts, the use of traditional medicine (TM) for health aids self-healthcare and disease prevention, can actually reduce healthcare costs spent on CKD on the one hand, and plays a significant role in the treatment and prevention of the progression of renal diseases.[4] An extensive list of the single and compound medication specified in TM for treating kidney-related ailments such as Vikradoshas (kidney disorders), Mutrajanan (facilitates urine formation), raktshodhak (blood purifier), mutrakricch (painful urination), mutral (diuretic), and shothahar (relieving edema) is *Boerhaavia diffusa*, *Cichorium intybus*, *Solanum nigrum*, *Tinospora cordifolia*, *Nelumbo nucifera*, *Butea monosperma*, *Tribulus terrestris*, *Albizia lebbeck*, *Pterocarpus santalinus*, *Curcuma longa*, *Moringa oleifera*, *Vetiveria zizanioides*, *Hemidesmus indicus*, *Coriandrum sativum*, and so on.[5-21] Taken together these findings, "Neeri KFT" an herbal formula has been developed by integrating clinical expertise with the best available clinical evidence from systematic research for achieving a synergistic impact in the form of safe and therapeutically effective for patient with disturbed kidney functions. The pre-clinical investigations of "Neeri KFT" on experimental rats revealed significant improvement in impaired kidney functions (such as serum creatinine, serum urea, serum albumin, and serum total protein), urine profile (proteinuria, glycosuria, and urinary creatinine), and also pronounced antioxidant-based protection.[22] The aim of the present study is to evaluate the safety and clinical efficacy of Neeri KFT with following objectives:

i. To prepare the standard drug as per pharmacopoeial procedures.

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ii. To find the safe limits of Neeri KFT dosage through acute toxicity in rats.
iii. To find the effect of Neeri KFT on kidney function parameters in a clinical trial.
iv. To develop information about drug effects (including possible adverse effect if any) associated with Neeri KFT in clinical practice based on Indian Market Survey.

MATERIALS AND METHODS

Identification of Plants

The medicinal plants [Table 1] were procured, from the local herbal market and authenticated in-house by Dr. H.B Singh, former chief scientist, Raw Materials Herbarium and Museum, NISCAIR, New Delhi. Authenticated voucher samples of raw material were preserved in research and development section of Aimil Pharmaceuticals (I) Ltd.

Preparation of Neeri KFT

All ingredients of Table 1 were individually weighed and coarsely powdered/chopped. For ingredients for aqueous extract, decoction was made by heating at 80°C for 8 h. Decoction was allowed to sediment, and supernatant liquid was decanted and filtered. Juices were prepared from juice ingredients. Sugar formulation/formulation sugar free was made, and decoction/juices were incorporated along with excipients.

Standardization of Formulation

The formulation was analyzed for various physicochemical parameters such as pH, weight per ml, total ash, and chloroform soluble extract according to the method given in API.[23]

Phytochemical Analysis

The phytochemical screening was carried out in the formulation using standard procedure.[24]

Quantitative Estimation of Heavy Metals

Analysis of heavy metals in the formulation was quantified as per the WHO guidelines.[25]

Microbial Load Analysis

Microbial load was tested for the polyherbal formulation which includes total bacterial count, total yeast, and molds count and the absence of *Escherichia coli*, *Salmonellae*, *Clostridia*, and *Shigella* as per the WHO guidelines.[25]

Table 1: Composition of Neeri KFT

Plant	Part use
Boerhaavia diffusa	Root
Cichorium intybus	Seed
Solanum nigrum	Whole plant
Tinospora cordifolia	Stem
Nelumbo nucifera	Rhizome
Butea monosperma	Flower
Tribulus terrestris	Fruit
Nelumbo nucifera	Flower
Albizia lebbeck	Stem bark
Pavonia odorata	Whole plant
Curcuma longa	Rhizome
Moringa oleifera	Seed
Vetiveria zizanioides	Root
Hemidesmus indicus	Root
Coriandrum sativum	Fruit
Moringa oleifera	Leaf
Crataeva nurvala	Stem bark
Amaranthus spinosus	Whole plant
Rheum emodi	Root
Cucumis utilissimus	Seed
Carica papaya	Root
Carica papaya	Fruit pericarp
Piper cubeba	Fruit
Ananas comosus	Fruit
Lagenaria siceraria	Fruit
Coriandrum sativum	Whole plant
Emblica officinalis	Fruit pericarp dried

High-performance Thin-layer Chromatography (HPTLC) Fingerprinting of the Polyherbal Formulation

Accurately weighed 10 ml of the formulation was extracted thrice with methanol (50 ml) at room temperature (25°C ± 2°C) in a separating funnel. The methanolic extracts were filtered through Whatman No. 1 filter paper and combined. The combined extracts were concentrated under reduced pressure at a temperature of 45°C and freeze-dried. Accurately weighed 10 mg of the extracts were dissolved in 1 mL methanol and filtered through a 0.45 µm filter membrane; the filtrate was used as a sample solution, and 10 µl of the sample were applied on a pre-coated silica gel F254 on aluminum plates to a bandwidth of 8 mm using Linomat 5 TLC applicator. The plate was developed in toluene:ethyl acetate:formic acid (5.0:4.0:1.0 v/v). The developed plate was visualized under long UV. The plate was visualized and scanned at 366 nm using CAMAG Linomate 5.

Table 2: Evaluation of Neeri KFT

Parameter	Specification
Physical description	
Description	Yellowish-brown-colored viscous liquid, odor characteristic with and sweetish in taste
pH	Between 4.0 and 6.5
Weight per ml.	Between 1.01 and 1.11 g/ml
Average fill volume	Not less than the label claim
Total ash	Not more than 1.0% w/w
Chloroform soluable extract	Not more than 0.05% w/w

Accelerated Stability Testing of Polyherbal Formulation

The accelerated stability study of prepared formulation was carried out for 6 months. The formulation was kept at 40°C ± 2°C/75% RH ± 5% and formulation was stored in ambered-colored bet bottle. The parameters evaluated every month were pH, total solids, specific gravity, and viscosity. The quantitative estimation of phytoconstituents and microbial load was done at the beginning and at end of the 6 months period as per the ICH guidelines.[26]

Toxicity Studies

An acute oral toxicity study was conducted in accordance with the Organization for Economic Cooperation and Development 11–13 Guidelines 425 and 407, respectively.[27] The experimental protocol had been approved by the Institutional Animal Ethics Committee of Shree Dhanvantry Pharmaceutical Analysis and Research Centre Pvt. Ltd. with the Experimental Protocol Approval Number SDPARC/IAEC/2015/046 before the initiation of the study. Experiments were performed as per the instructions prescribed by the Committee for the Purpose of Conduct and Supervisions of Experiments on Rats, Ministry of Environment and Forest, Government of India.

EXPERIMENTAL RATS

Female albino Wistar (Mahaveer Enterprises, Hyderabad) weighing 180–200 g ± 20 were maintained under standard laboratory conditions of temperature (22°C ± 3°C) and humidity 30–70% with 12 h day:12 h night cycle. Rats had free access to water and rodent pellet diet (Hindustan Lever Ltd., Bengaluru, India).

Acute Oral Toxicity Study

Acute oral toxicity study of Neeri KFT carried out in 15 adult female Wistar as per the11 and 12 test guidelines 425. All rats were dosed orally once in a stepwise manner, i.e., next higher dose level was administered to next animal after observation of the previous animal for any mortality for 48 h. Dose levels were progressed in geometric progression with the factor of 2. Dosing was started by oral administration of 250 mg/kg bw of Neeri KFT to first test animal. As no mortality was observed in first animal when observed for 48 h, next animal was treated with 500 mg/kg bw dose and observed in a similar manner and so on up to 2000 mg/kg bw. A total of 5 rats were tested, at test dose 2000 mg/kg bw, and observed for any clinical sign of toxicity for a total of 14 days.

Clinical Study

A clinical trial of the nephroprotective potential of Neeri KFT was conducted as per the Indian Council of Medical Research guidance document, 2006, on conducting trials of ayurvedic substances.[28] The experimental protocol has been approved by the Ethical Committee on human safety trial, and the study was conducted at Aggarwal hospital, New Delhi, India, between 12/3/2015 to 30/2/2016 on OPD basis.

Study Design

Of 96 patients suffering from kidney disorders attending the Aggarwal Hospital, New Delhi, India, 71 were selected based on inclusion and exclusion criteria. They were served with placebo for 1 month duration (the 1 month run-in period with dietary and lifestyle schedule to be followed). The patients were randomizly divided into Neeri KFT as test group and as placebo group [Figure 1]. Group 1 (test drug: 2 teaspoonful thrice a day): 35 patients were kept on a combination of routine management with antihypertensive + NEERI KFT, and Group 2 (PLACEBO: 2 teaspoonful thrice a day): 36 patients were registered in this group and observed without interfering with their routine management, i.e., with antihypertensives, etc., + placebo. Patients underwent clinical examination and biochemical investigations on day 1 and at monthly intervals. Adverse drug reactions/effect (e.g., headache, dizziness, nausea and vomiting) if any were also recorded during the study period. The study protocol was approved by the Hospital's Institute's Ethics Committee with the protocol approval number being AH/IEC/NEERI-KFT 12/1/2015. Informed written consent was obtained from all

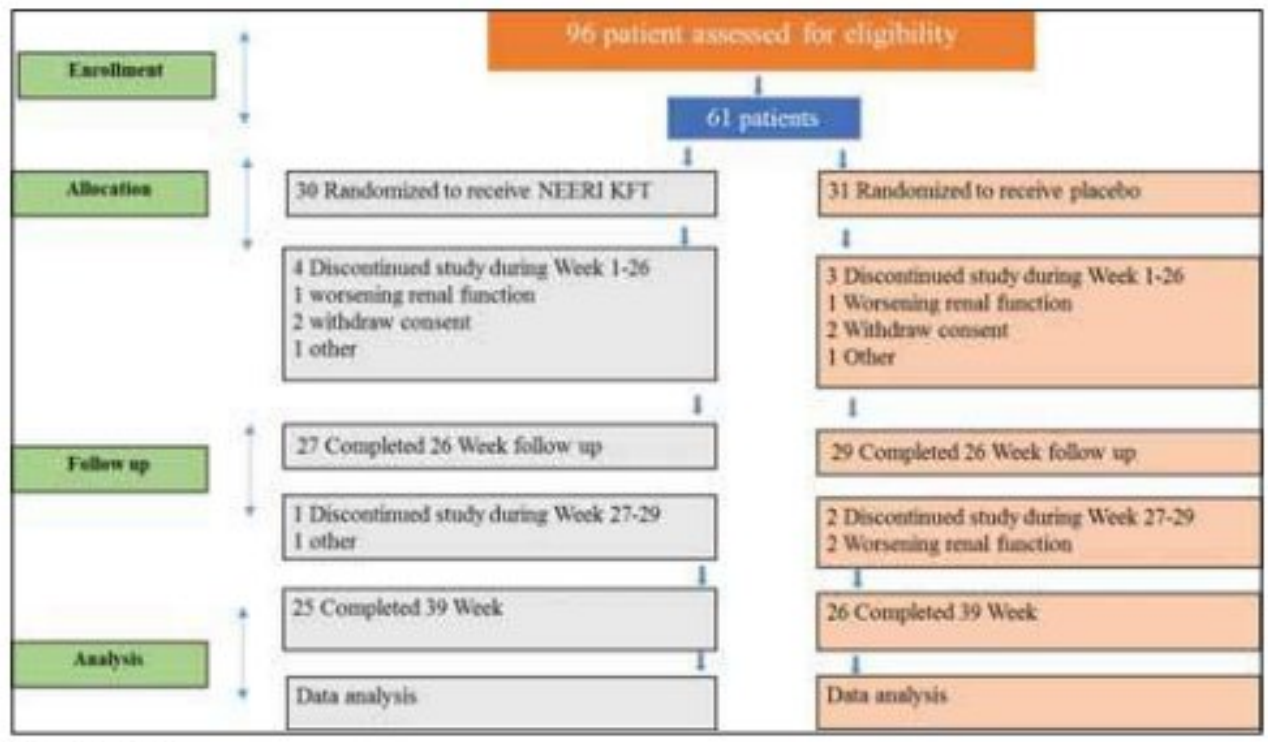

Figure 1: Clinical study design

study participants. If they so desired, patients were free to withdraw from the study.

Inclusion Criteria

The hypertensive patients between the age of 48 and 72 years, either male or female diagnosed with patients suffering from over the past 10 years with hypertension, and characterized by elevated creatinine on 2 occasions, in spite of continued treatment men: ≥1.4 mg/dL (120 µmol/L), women: ≥1.2 mg/dL (106 µmol/L), elevated blood urea (≥20 mg/dL), and elevated blood uric acid (≥20 mg/dL), were selected for the present study.

Exclusion Criteria

Patients with serum creatinine of more than 6 and patients on dialysis and with acute infections or chronic debilitating diseases, tuberculosis, malignancy, HIV infection, etc., were excluded from the clinical study. Pregnant and lactating women and the patients having the history of severe unstable angina, myocardial infarction, and renal failures were excluded from the study.

Follow-up and Assessment

All subjects underwent clinical examination and evaluation of serum creatinine, blood urea, serum uric acid, serum total proteins, globulin, albumin, and serum electrolytes - calcium (Ca), pottasium (K), sodium (Na), and phosphate (P) test were done on entry and at 4 monthly intervals as per assessment method illustrated in Figure 1.

Primary and Secondary Outcome Measure

The primary endpoint was improvement in clinical parameters of chronic kidney disease with reference to improve/control

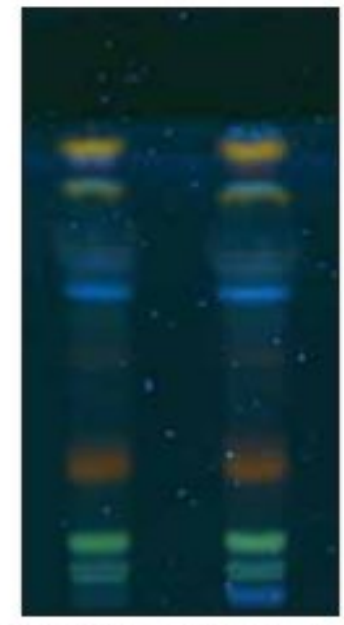

Figure 2: High-performance thin-layer chromatography finger printing of Neeri KFT at 366 nm

of kidney functions tests a 4 months interval and symptoms – swollen feet and ankles, puffiness around eyes, nocturia, muscle cramping, general fatigue and quality of life at: 0, 30, 60, 90, 120, 150, 180, 210, 240 and 270 days.

Post-marketing Study

A total of 1000 doctors from all demographic areas, namely, north, south, east, and west were followed up. The study was based on questionnaire incorporating details pertaining to improvement in patient with any untoward effect obtained if any.

Statistical analysis

Data were arranged in MS Excel. Student's *t*-test was used to compare the difference in mean values between the two groups. Paired *t*-test has been used for within group analysis. For every outcome variable, results are presented as mean ±

standard deviation, and ($P < 0.05$ was considered statistically significant). Statistical analyses were performed using MedCalc for Windows, statistic for biomedical research software.

RESULTS

Standardization of Formulation

The physicochemical evaluation of the formulation was performed and the results are tabulated in Tables 2 and 3. All the tests for safety namely, microbial load, heavy metals, mycotoxin and pesticides [Tables 4-6] revealed to be within permissible limits. The stability test of finished drug as presented in Table 7 showed no change in physical, chemical, and microbial properties over a specified period. Preliminary HPTLC fingerprinting photo documentation as shown in Figure 2 revealed the presence of many phytoconstituents. On photo documentation, 16 spots under 366 nm were observed.

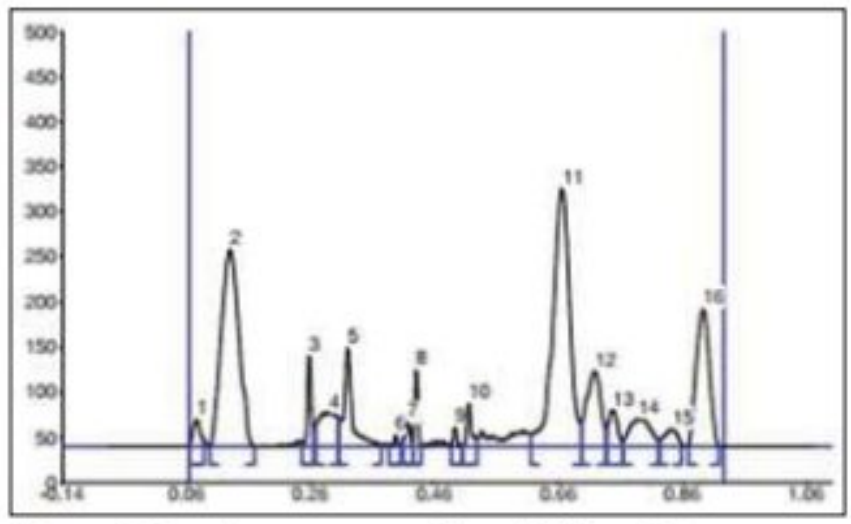

Figure 3: Densitometry scan of Neeri KFT at 366 nm

Table 3: Phytochemical analysis of Neeri KFT

Identification	Observations
Phenols	Present
Tannins	Present
Amino acids	Present
Glycosides	Present
Chloride	Present

Table 4: Microbial load analysis

Microbial load	Result unit	Limit
Total microbial plate count	<1 cfu/ml	10^4/g
Yeast and molds count	<1 cfu/ml	10^3/g
Coliforms	<1 cfu/ml	<1 cfu/ml
Escherichia coli	<10/ml	<10/ml
Staphylococcus aureus	<10/ml	<10/ml
Salmonella	Absent/25 ml	Absent
Pseudomonas aeruginosa	Absent/10 ml	Absent
Shigella	Absent/25 ml	Absent
Listeria monocytogenes	Absent/25 ml	Absent

Table 5: Heavy metal analysis

Heavy metals	Result unit	Limit
Lead	<0.05 mg/kg	1 ppm
Arsenic	<0.05 mg/kg	3 ppm
Cadmium	<0.02 mg/kg	0.3 ppm
Mercury	<0.01 mg/kg	0.1 ppm

Figure 4: Percent change (reduction) in kidney function parameter levels between test ad placebo group

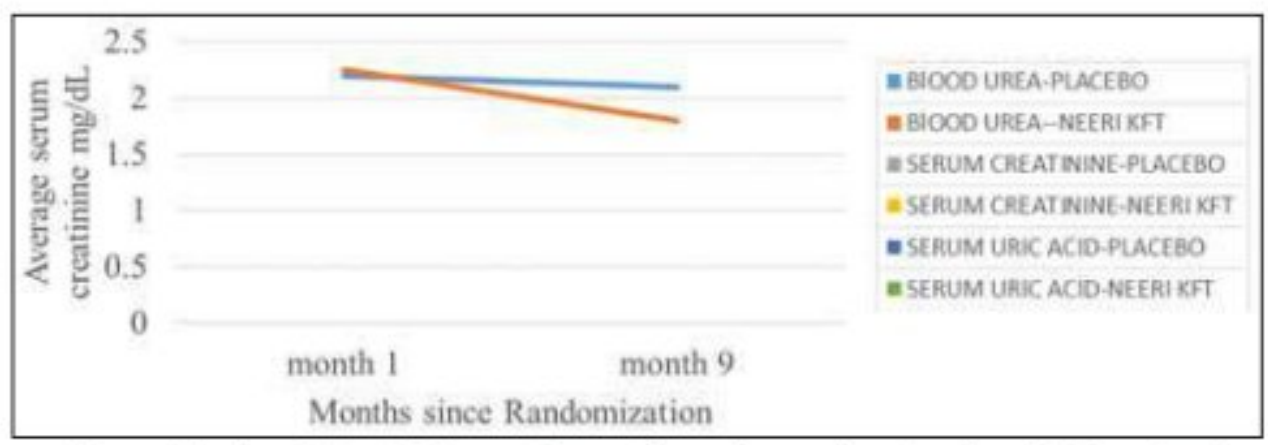

Figure 5: Serum creatinine: A decline 0.4 and 0.1 was observed in patient assigned to Neeri KFT or placebo, respectively

Densitometric scan at 366 nm [Figure 3] showed 16 peaks, peak with Rf - 0.07, 0.13, 0.26, 0.29, 0.32, 0.40, 0.42, 0.13, 0.49, 0.51, 0.67, 0.72, 0.75, 0.79, 0.84, and 0.89.

Clinical Study

Of a total of 96 patients enrolled, 71 patients with impaired kidney functions participated in the study. There were 35 patients in the test drug group and 36 patients in the placebo group. Within 1 to 39 week, a total of 21 patients withdrawn the study during treatment period and 50 completed the study [Figure 1].

Effect on Kidney Function Parameters

The decrease of 17% in serum creatinine, 18% in urea, and 13% in uric acid was observed as against placebo group [Figure 4]. Over the course of study the decline from initial month (0) to the end (9) of treatment, the average achieved serum creatinine was 0.4 in Neeri KFT group ($P = 0.3398$) and 0.1 of serum creatinine of placebo group [Figure 5], the average achieved blood urea was 13.0 in Neeri KFT group ($P = 0.1502$) and 10.5 of blood urea of placebo group [Figure 6]. Moreover, the average decline achieved serum uric acid was 0.9 in Neeri KFT group ($P = 0.1502$) and 0.3 of serum uric acid of placebo group [Figure 7].

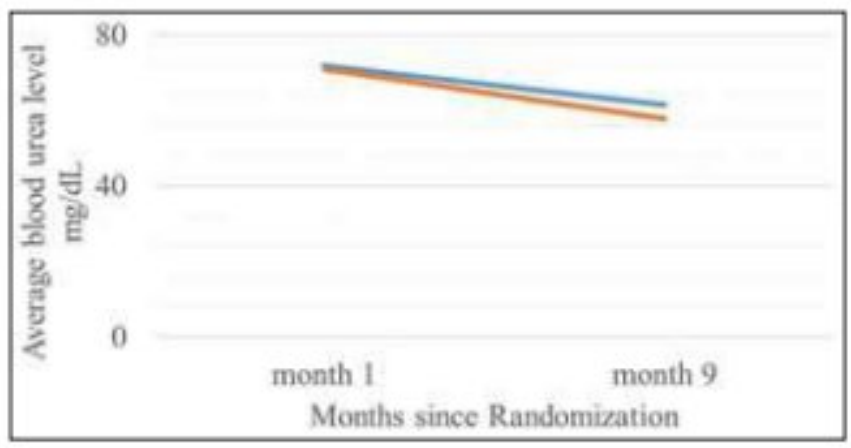

Figure 6: Blood urea: A decline of 13.0 and 10.5 was observed in patient assigned to Neeri KFT or placebo, respectively

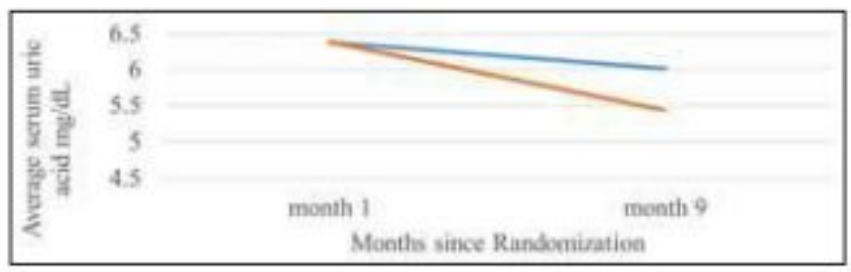

Figure 7: Serum uric acid: A decline of 0.9 and 0.3 was observed in patient assigned to Neeri KFT or placebo, respectively

Table 6: Pesticide analysis

Pesticides	Result unit	Result unit
IR408 IR Screened	EASI-CHE-SOP-21	Not detected
IR409 IR Screened	EASI-CHE-SOP-21	Not detected

Adverse Events

Test drug effect was well tolerated by all patients during the course of the study. Further, no adverse hematological or biochemical abnormalities were experienced by any patient.

Post-marketing Study

The geographic zones of the study were from India namely north, south, east and west. The average treatment period in the patient population was around 140 days month, irrespective of the other medication used. According to the suggested schedule, about 120 doses and no adverse event were recorded. The subjective judgment of the clinical effectiveness in terms of percent average reduction kidney function parameter was for serum creatinine, blood urea, and blood uric acid as 42.4, 31.9, and 39.1, respectively.

DISCUSSION

The quality of herbal medicines has a direct impact on their safety and efficacy. As a part of drug preparation and its standardization, the finished product of Neeri KFT was tested for all the safety and quality parameters which include physical, chemical, microbiological, mycotoxins, heavy metals as well as pesticide residues according to the WHO guidelines. The finished product appeared yellowish-brown viscous fluid and sweet in taste with pH varying between 4 and 6.5. Qualitatively, the presence of phenols, tannins, amino acids, and glycosides was confirmed. The formulation was found to comply with the specification limit for total microbial count. The heavy metal analysis of the formulation indicates that all the heavy metals were in acceptable ppm range, thus showing the purity of the raw drugs and also the finished product. The stability test of finished drug showed no change in physical, chemical, and microbial properties over specified period. Preliminary HPTLC profile of finished product developed can

Table 7: Stability analysis

Stability specification	Observations
Physical properties	No changes observed after 6 months
Chemical properties	No changes observed after 6 months
Microbial properties	No changes observed after 6 months

be considered as the reference standard for validating quality control of formulation in future. The acute oral toxicity study was performed on rats to determine the safe dose limit which came out to be 20 ml/kg body weight, i.e., equivalent to 3.22 ml/kg bw dose for human (for 60 kg adult human dose should be 193.6 ml per day). At safe dose limit, clinical sign of toxicity such as change in general behavior and change in physical activity and mortality was entirely absent. Clinical studies of test drug suggest that it is effective and safe in the management of primary kidney disease. Among 25 patients treated with test drug, a significant improvement in the feeling of well-being was observed due to better control of kidney function parameters. According to several reports achieving near normal, kidney function parameters can prevent or delay the progression of CKD, reduce or prevent the development of complications, and reduce the risk of cardiovascular disease.[29] Other signs and symptoms such as swollen feet and ankles, puffiness around eyes, nocturia and muscle cramping, and general fatigue were also absent. Improvement in appetite and digestion with no gastric discomforts were additionally reported in the test drug group. In addition, nearly all patients have shown the beneficial diagnostic effect on the biochemical parameter and experienced a reasonable improvement after treatment. The therapeutic actions of Neeri KFT may be attributed to antioxidant mechanism.[30] Pre-clinical studies show that antioxidants alleviate renal injury and improve kidney function through reducing oxidative damage and/or inflammation.[31] Based on a clinical study of Neeri KFT, it is further suggested that test drug should be further used as a mono therapy/adjunctive therapy with antihypertensive for the management of hypertension. The synergistic approach of test drug with antihypertensive drugs shall help in reducing the dosage dependence the risk from their long-term usage. It is noteworthy that life-threatening side effect was not reported in post-launch market survey, it is a testimonial of 5000-year-old Ayurveda system of medicine. Advance studies are running on a large number of patients with additional clinical biochemical parameters for the test drug Neeri KFT.

CONCLUSION

Neeri KFT is found to be highly effective against renal disorders. The drug administered patients showed improvement in health by improvement in key indicators of renal features. The serum electrolyte level of serum calcium, potassium, chloride, and sodium of drug administered patients remained normal.

CKD: Early identification and management of CKD in adults in primary and secondary care; NICE Clinical Guidelines (July 2014).

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