

## EVALUATION OF EFFICACY AND SAFETY OF *NIGELLA SATIVA* OIL SUPPLEMENTATION IN PATIENTS OF CHRONIC KIDNEY DISEASE

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### ABSTRACT

**Objective:** To evaluate efficacy and safety of add-on therapy of *Nigella sativa* oil in patients of stage 3 and 4 of chronic kidney disease (CKD).

**Materials and Methods:** The study was conducted in a tertiary care center of north India in stage 3 and 4 patients of CKD. It was a prospective, comparative, and open label study. Patients were randomly divided into two interventional groups. Group I (Control) received conservative management of CKD while Group II (Test) received conservative management along with *N. sativa* oil (2.5 mL, per orally, once daily) for 12 weeks. Hemogram and renal function tests were done, and adverse events were recorded at 0, 6, and 12 weeks of treatment.

**Results:** After 12 weeks of treatment, there was a progressive improvement in clinical features and biochemical parameters in both the groups, but it was more marked in the test group compared to control group. Both groups showed gradual improvement in the biochemical parameters as compared to their pre-treated values which were more marked in *N. sativa* oil supplemented group. There was a reduction in blood glucose, blood urea, serum creatinine, and 24-hr total urine protein. There was an increase in hemoglobin, 24-hr total urine volume, and glomerular filtration rate.

**Conclusion:** *N. sativa* oil supplementation along with conservative management is efficacious and safe in averting the progression of disease in stage 3 and 4 patients of CKD.

**Keywords:** Chronic kidney disease, *Nigella sativa* oil, End-stage renal disease, Glomerular filtration rate.

### INTRODUCTION

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines [1] defined chronic kidney disease (CKD) as: Kidney damage or glomerular filtration rate (GFR) <60 ml/minutes/1.73 m<sup>2</sup> for 3 months or more, regardless of cause. Globally, CKD is a public health problem [2]. According to the Screening and Early Evaluation of Kidney disease (SEEK)-India cohort study, the prevalence of CKD was approximately 17.2% with ~6% have CKD stage 3 or worse [3]. The economic burden of renal replacement therapy (RRT) is augmented with increasing prevalence of CKD, end-stage renal disease (ESRD), and CKD-related cardiovascular disease (CVD), and it is assessed that around 1,00,000 new patients of ESRD require RRT annually in India [4]. Nitrogenous waste products in the body can be reduced with intake of low-protein diet (0.6 g/kg BW/day) and very low-protein diet (0.3 g/kg BW/day) while keeping an adequate nutritional status. So, secondary problems such as bone disease, metabolic acidosis, and insulin resistance as well as proteinuria and deterioration of renal function are reduced [5,6].

Previous studies on *Nigella sativa* have recognized its nephroprotective role as well as anti-hyperglycemic effect in type-2 diabetes mellitus patients [7]. A randomized, clinical trial established that *N. sativa* oil improved renal function, liver function, fasting blood glucose, and HbA1c level. It has also been proved that *N. sativa* has anti-inflammatory properties [8].

*N. sativa* oil contains fixed and essential oils. Fixed oil contains mainly linoleic acid, oleic acid, palmitic acid, and stearic acid. Thymoquinone, cymene, and carvone are main components of essential oil. Thymoquinone is the main active component which has multiple beneficial properties. The use of *N. sativa* oil in association with a low or very low-protein diet permits a decreased ingestion of nitrogen while avoiding the deleterious outcomes of inappropriate intake of dietary protein and malnourishment because it contains a high amount of unsaturated fatty acids [9]. The

antioxidant and anti-inflammatory activities of *N. sativa* are considered the key factors accountable for its renoprotective and hepatoprotective effects [10]. In spite of theoretical association between *N. sativa* and its role as nephroprotectant, there is no clinical study reported in CKD patients. *N. sativa* has been used in diabetic and hypertensive patients previously. Therefore, the aim of this study was to assess the efficacy and safety of *N. sativa* oil supplementation in patients of CKD.

### METHODS

#### Patients

The present study was conducted in patients of CKD attending Renal Clinic or admitted to the hospital ward of a tertiary care center of north India from March 2014 to March 2015. The study was carried out in agreement with the declaration of Helsinki (1964) and its revised form (2008). It was a randomized, prospective, open-label, and parallel group study and was approved by the Institutional Ethics Committee. This study is enlisted with Clinical Trials Registry-India (CTRI) with a registration number CTRI/2015/01/005371. All the patients gave written and informed consent voluntarily before registering for the study. The diagnosis of CKD was made on the basis of detailed medical history, physical examination, and investigations (renal function tests).

#### Inclusion criteria

Patients with CKD (Stage 3-4) and age 20-60 years of either gender were included in the study.

#### Exclusion criteria

Patients that were excluded from the study comprised pregnant females, patients undergoing dialysis, terminally sick, immuno-compromised or having severe renal pathology such as malignancy.

#### Sample size (n)

p=prevalence (prevalence assumed as 17.2% according to the SEEK-India cohort study) [3]; q=1-p. Hence, sample size (n) =

$[(1.96*1.96)/(0.09*0.09)] * [0.172*0.828]=67.54$ . So, a sample size of 68 is the minimum required for each group. Taking into consideration a 12% dropout rate, 77 patients were recruited in each group.

### Study design

Out of 170 evaluated patients, 154 patients were registered in the study. 11 patients (6 of Group I and 5 of Group II) failed to report on successive visits and were omitted from the study. Registered patients were randomized into two groups with the help of table designed by random allocation software in a ratio of 1:1. The randomization table had 20 subjects in each block to lessen the discrepancy between the two groups at any time of study with respect to a number of patients. After final diagnosis, applying inclusion, and exclusion criteria, patients were comprised in the study. Patients of Group I (Control) received conservative management (Telmisartan, Torsemide, Iron, Calcium, Vitamin D3, Erythropoietin, Insulin in case of diabetic patients) of CKD while Group II (Test) patients received conservative management of CKD along with *N. sativa* oil (2.5 mL, per orally, once daily) (Fig. 1). Both groups received treatment for 12 weeks. *N. sativa* oil of 100% purity was used in this study was commercially available and purchased from the local market under brand name "Kalonji oil" from Mohammedia Products, Hyderabad, India (GMP certified company).

All the enrolled patients were regularly followed with hemogram, renal functions test, and serum electrolytes at 0, 6, and 12 weeks of treatment.

### Safety assessments

All adverse events experienced by patient or detected by the investigator were recorded on standard adverse drug reaction (ADR) reporting forms of the Central Drugs Standard Control Organisation at each visit. Naranjo Scale [11] was used for causality assessment while severity assessment was done using Modified Hartwig and Siegel Scale [12]. A physical examination that also included assessment of vital signs was done at the start of the study and on subsequent visits. Additional routine laboratory safety tests such as electrocardiogram, liver function tests, and X-ray of the chest were performed whenever required. All the ADRs were reported to the ADR monitoring center of the institute.

### Statistical analysis

The values were expressed as mean±standard deviation. Statistical significance between pre- and post-treatment values in each group was calculated using Student's Paired T-test, whereas statistical significance between groups was calculated with the help of Unpaired T-test.  $p < 0.05$  was considered significant. Statistical analysis was done using the SPSS-20 software.

### RESULTS

Group I included 71 (42 M, 29 F) patients and mean age was 44 years (range 20-60 years) while Group II included 72 (36 M, 36 F) patients and mean age was 45 years (range 20-60 years). The distribution of patients was almost similar among the groups. There was neither mortality nor anyone required dialysis in either group. According to GFR (mL/minutes/1.73 m<sup>2</sup>), patients belonged to stage 3 (16 and 11 in Group I and II, respectively) and stage 4 (55 and 61 in Group I and II, respectively) CKD in both the groups. The causes of CKD in group I and II were: Hypertensive nephropathy (45.07% and 40.28%), diabetic nephropathy (15.49% and 31.94%), chronic glomerulonephritis (11.26% and 8.33%), tubulointerstitial nephritis (5.63% and 6.94%), autosomal dominant polycystic kidney disease (2.82% and 2.78%), and unknown cause (19.72% and 9.72%), respectively.

The signs and symptoms found in the patients at the start of the treatment were: Anorexia, nausea, vomiting, weakness, weight loss, headache, pruritus, edema over the body, oliguria, anemia, hypertension, and dyspnea. The clinical features were almost similar among the groups at 0 week of the study. The clinical features improved gradually and progressively in both the groups after 12 weeks of treatment but it was more obvious in *N. sativa* oil treated group.

There was progressive and gradual improvement in various biochemical parameters in both the groups but *N. sativa* oil treated group (Group II) showed maximum improvement. Both the groups showed a significant increase in hemoglobin percent ( $p < 0.001$ ) but increment was more in Group II. Both the groups showed a significant decrease in blood urea ( $p < 0.001$ ). Moreover, a significant change ( $p < 0.001$ ) in blood urea level was also observed in Group II as compared to Group I after 12 weeks

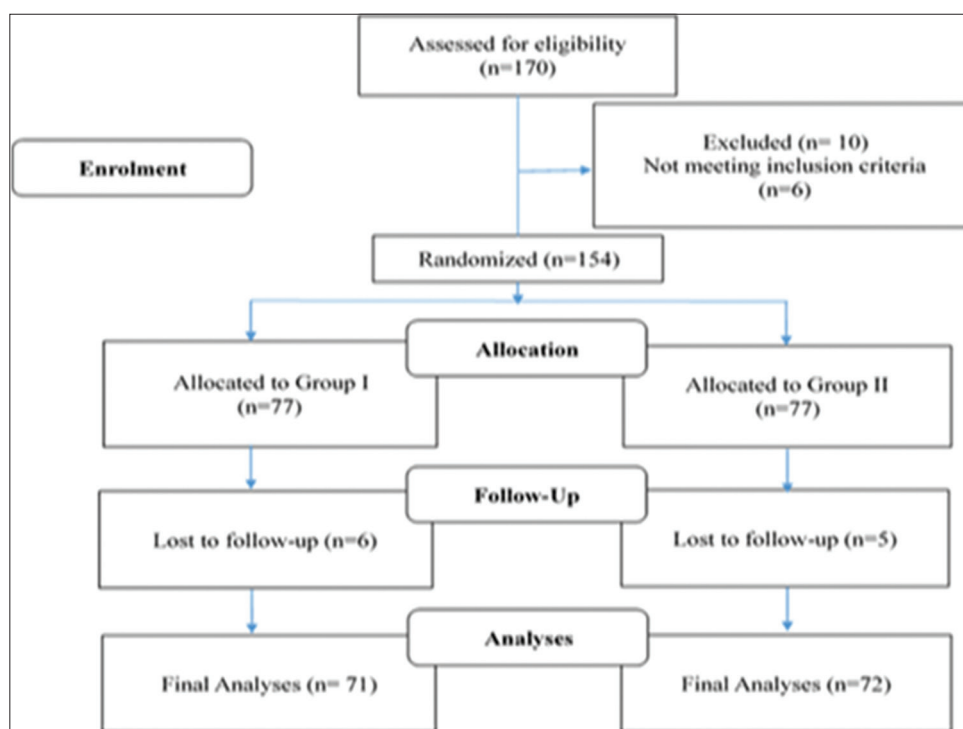


Fig. 1: Recruitment, allocation, and follow-up of participants

**Table 1: Hemoglobin percent, renal function tests, and serum electrolytes in Control and Test groups before and after 12 weeks of treatment**

Parameters	Groups	Mean±SD		% change after 12 weeks
		At 0 week	At 12 weeks	
Hb% (g/dL)	I	8.51±1.33	9.15±1.31 <sup>c</sup>	(+) 7.52
	II	8.46±0.95	9.31±0.93 <sup>c</sup>	(+) 10.05
B. Urea (mg/dL)	I	70.32±21.74	62.87±20.36 <sup>c</sup>	(-) 10.60
	II	71.85±22.20	50.43±26.89 <sup>c3</sup>	(-) 29.81
S. Cr. (mg/dL)	I	2.92±0.82	2.75±0.90 <sup>a</sup>	(-) 5.82
	II	2.93±0.86	2.00±0.59 <sup>c3</sup>	(-) 31.74
TUV (mL/day)	I	1737.32±326.53	1982.40±311.34 <sup>c</sup>	(+) 14.11
	II	1693.75±336.40	2111.11±278.10 <sup>c2</sup>	(+) 24.64
TUP (g/day)	I	1.40±0.99	1.01±0.72 <sup>c</sup>	(-) 27.86
	II	1.20±0.82	0.66±0.51 <sup>c3</sup>	(-) 45.00
GFR (mL/minute)	I	25.07±9.30	28.40±12.35 <sup>b</sup>	(+) 13.30
	II	23.42±7.32	36.64±11.77 <sup>c3</sup>	(+) 56.45
Na <sup>+</sup> (mEq/L)	I	134.92±10.46	135.55±3.22	(+) 0.47
	II	136.53±3.09	139.61±6.24 <sup>c3</sup>	(+) 2.25
Ca <sup>2+</sup> (mg/dL)	I	8.83±0.97	9.19±0.23 <sup>c</sup>	(+) 4.07
	II	8.70±0.37	9.20±0.32 <sup>c</sup>	(+) 5.75
K <sup>+</sup> (mEq/L)	I	4.34±0.42	4.23±0.42 <sup>a</sup>	(-) 2.54
	II	4.38±0.40	4.04±0.23 <sup>c2</sup>	(-) 7.76

Values are mean±SD; p<0.05 was considered significant; <sup>a</sup>p<0.05, <sup>b</sup>p<0.01, <sup>c</sup>p<0.001 compared to 0-week value of respective group; <sup>1</sup>p<0.05, <sup>2</sup>p<0.01, <sup>3</sup>p<0.001 compared to control group. I: Control, II: Test, Hb%: Hemoglobin percent, B. urea: Blood urea, S. Cr: Serum creatinine, TUP: 24 hour total urinary protein, TUV: 24 hour total urinary volume, GFR: Glomerular filtration rate, Na<sup>+</sup>: Serum sodium, Ca<sup>2+</sup>: Serum calcium, K<sup>+</sup>: Serum potassium, -: Decrease, +: Increase, SD: Standard deviation. For Group I (n=71 patients) and Group II (n=72 patients)

of treatment. Serum creatinine was significant decrease in Group I (p<0.05) and Group II (p<0.001) and Group II also showed a significant change (p<0.001) in serum creatinine compare to Group I at 12 weeks. There was significant decrease in total urine protein (p<0.001) in both the groups and Group II also showed statistically significant change (p<0.001) compared to Group I after 12 weeks. There was significant increase in total urine volume (p<0.001) in both the groups and Group II also showed a significant change (p<0.01) compare to Group I at 12 weeks. GFR was significantly increased in Group I (p<0.01) and Group II (p<0.001) while Group II also showed significant change (p<0.001) in comparison to Group I at 12 weeks. Serum calcium was increased significantly in both the groups, but it was more marked in Group II (Table 1).

According to Modified Hartwig and Siegel Scale, the ADRs were mild (no hospitalization, no change of therapy, and no additional treatment) in severity in the test group. No adverse event was of acute onset (within 60 minutes). On Naranjo's Scale, the ADRs were possible (Score=1-4) in 6 cases and probable (Score=5-8) in 2 cases with Group II (Table 2).

## DISCUSSION

Conservative management is imperative to obviate CKD and to avert advancement of CKD to ESRD. It delays the progressive decline of renal functions and offers only symptomatic relief. So, novel modalities of treatment are being explored which can halt injury to nephron, delay the development of ESRD and cost effective. Due to steep rise in the prevalence of diabetes and hypertension globally, CKD has emerged as a leading chronic disease worldwide [13,14]. It leads to premature morbidity and mortality and hampers quality of life. In India, CKD is a major problem for both health sector and economy. RRT is the ideal treatment for CKD-ESRD, which consists of renal transplantation and maintenance dialysis. In India, more than 100,000 new patients enter RRT an annum [15]. Only 10% of Indian ESRD patients receive any RRT due to inadequate resources. The cost of hemodialysis is \$300 a month, whereas continuous abdominal peritoneal dialysis costs \$600. The cost of a transplant is \$8900 in the first year, which decreases later to \$3000 an annum. Among the RRT options, renal transplant is the preferred choice for being economical and offers improved quality of life but still only a fraction of Indians can afford it [15].

**Table 2: ADRs in test group**

Serial number	ADRs recorded	Group II (n=72)
1	Nausea	2
2	Vomiting	1
3	Diarrhea	2
4	Excessive thirst	1
5	Rashes	1
6	Altered taste	1

ADRs: Adverse drug reactions

CKD and CVD are characterized by systemic inflammation and raised inflammatory markers. *N. sativa* and honey mixture reduced the levels of inflammatory markers and improved lipid profile [16]. In another study, it was reported that *N. sativa* seeds supplementation was useful in metabolic syndrome. Blood pressure, blood sugar, total cholesterol, and triglyceride levels were decreased. So, it might be useful in CKD due to prolonged and uncontrolled diabetes and hypertension [17]. Studies have reported the antihypertensive activity of *N. sativa* [18,19]. Thymoquinone is the active constituent of *N. sativa* oil and reduces the serum levels of inflammatory mediators such as tumor necrosis factor- $\alpha$  and interleukin-1 [20]. *N. sativa* has strong antioxidant activity [21]. The antioxidant and anti-inflammatory activities of *N. sativa* are considered the key factors accountable for its renoprotective and hepatoprotective effects [10]. Administration of *N. sativa* extract with an injection of gentamicin led to a statistically significant reduction in serum creatinine, blood urea and malondialdehyde, nitric oxide generation and increased superoxide dismutase, and glutathione peroxidase activities when compared with gentamicin group in rats [22]. Due to its strong antioxidant, antidiabetic, antihypertensive, hypolipidemic, anti-inflammatory, and nephroprotective activity, *N. sativa* oil can be used in CKD of various etiologies.

*N. sativa* oil at a dose of 2.5 mL (p.o., once daily) showed beneficial effects in stage 3 and 4 of CKD. No previous clinical studies have reported the serious and untoward adverse effects of *N. sativa*. Thus, the adverse events might be the indexes of underlying renal pathology or due to some other co-administered medications.

The results of our study are in congruence with those reported previously. Hence, conservative management along with *N. sativa* oil

supplementation produces improvement in biochemical parameters as well as clinical features and safe in patients of CKD. Further studies will help to better understand the role of *N. sativa* in improving renal functions. Thus, we suggest that molecular level studies are needed to confirm its broad spectrum effects not only on CKD but on various diseases in which *N. sativa* is traditionally used as a palliative to cure these diseases.

## CONCLUSION

*N. sativa* oil supplementation improved the therapeutic benefit of conservative management in stage 3 and 4 patients of CKD.

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