Evaluation of Safety and Efficacy Profile of *Nigella sativa* Oil as an Add-On Therapy, in Addition to Alpha-Keto Analogue of Essential Amino Acids in Patients with Chronic Kidney Disease

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ABSTRACT. Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiological processes associated with abnormal kidney function. When it reaches end-stage renal disease (ESRD), the only option is dialysis and renal transplantation. This is unaffordable by most patients. Hence, newer treatment modalities are being looked for, which can slow down the progression of CKD and delay the development of ESRD. This study aimed to evaluate the efficacy and safety of *Nigella sativa* oil as an add-on therapy in addition to alpha-keto analogue of essential amino acids in patients with CKD Stages 3 and 4. The study was conducted at a tertiary care center in North India on patients with CKD Stages 3 and 4. It was a prospective, comparative, and open-labeled study. One hundred and fifty patients were enrolled and were randomly divided into two interventional groups. Fourteen patients were lost to follow-up. Group I (control) which had 66 patients received conservative management of CKD consisting of alpha-keto analogue (600 mg tablet three times a day), whereas Group II (test) which had 70 patients received conservative management along with alpha-keto analogue and *N. sativa* oil (2.5 mL, per orally, once daily) for 12 weeks. Hemogram, renal function, and serum electrolyte tests were done, and adverse events were recorded at baseline and at 4, 8, and 12 weeks of treatment. After 12 weeks of treatment, there was a marked improvement in clinical features and biochemical parameters in both the control and test groups. There were a significant reduction in blood urea, serum creatinine, and 24-h total urine protein and a significant improvement in 24-h total urine volume and glomerular filtration rate. *N. sativa* oil supplementation along with alpha-keto analogue is more efficacious and safe in delaying the progression of disease patients with CKD Stages 3 and 4.

Introduction

The Kidney Disease Improving Global Outcomes guidelines¹ classified chronic kidney
disease (CKD) as a heterogeneous group of disorders characterized by alterations in kidney structure and function. CKD results in estimated glomerular filtration rate (eGFR) $\leq 60$ mL/min/1.73m$^2$, or kidney damage (usually detected as urinary albumin excretion of $\geq 30$ mg/day) for three months, irrespective of the cause. CKD is a global public health problem. Screening and early evaluation of kidney disease (SEEK) which is an India-specific cohort study, estimated the prevalence of CKD to be approximately 17.2%, with $\sim 6\%$ having CKD Stage 3 or worse. More than 100,000 new patients enter renal replacement therapy (RRT) in India annually. In fact, CKD patients have a greater probability of dying from comorbidities rather than dying due to progression of CKD to end-stage renal disease (ESRD). The ideal treatment for CKD-ESRD is RRT which includes renal transplantation and maintenance dialysis. Among the RRT options, renal transplant is the most preferred choice as it offers better quality of life, but still, only a segment of the Indian population can afford to have it being too costly. Conservative management is very essential to prevent CKD and to prevent the advancement of CKD to ESRD. It consists of dealing promptly with any potentially reversible cause and delaying the progressive worsening of renal function.

Alpha-keto analogues of essential amino acids (KAA) are nitrogen-free analogs of essential amino acids. Keto-amino acids are known to delay the progression of renal insufficiency. They are being used in diabetic nephropathy as they have good glycemic control, thereby improving insulin sensitivity and reducing hyperinsulinemia. They tend to improve the nutritional status and metabolic abnormalities associated with renal insufficiency. When alpha-KAA is administered with low protein diet (0.6g/kg/day) or very low protein diet (0.3 g/kg/day), there is improved nitrogen balance and decreased urea accumulation in the body.

Earlier studies on Nigella sativa have established its neproprotective role as well as antihyperglycemic effect in type-2 diabetes mellitus patients. A randomized, clinical trial proved that N. sativa oil improved renal function, liver function, fasting blood glucose, and HbA1c level. It has also been proven that N. sativa has anti-inflammatory properties.

Alpha-KAA is now being given as a standard treatment protocol in patients with CKD; also, N. sativa oil has established itself strongly as having hepatoprotective and nephroprotective effects. Till now, no study has been reported to observe the add-on effect of N. sativa oil on alpha-KAA, which is now being used in the conservative management of CKD. Hence, this study was conducted to evaluate the efficacy of N. sativa oil as an add-on therapy in patients receiving alpha-KAA, in the conservative management of CKD.

**Methodology**

**Patients**

The present study was conducted on patients with CKD attending renal clinic or admitted to the hospital ward of a tertiary care center in North India from February 2016 to August 2017. It was a prospective, randomized, open-label, and parallel-group study which was approved by the institutional ethics committee. This study was enlisted with the Clinical Trials Registry-India (CTRI) with a registration number of CTRI/2018/01/011429. All the patients gave written and informed consent before registering for the study. The diagnosis of CKD was made on the basis of detailed medical history, physical examination, and investigations [renal function test (RFT) and ultrasonography].

**Inclusion criteria**

Patients with CKD (Stages 3–4) and aged 20–60 years of either gender were included in the study.

**Exclusion criteria**

Patients that were excluded from the study comprised of pregnant females, patients undergoing dialysis, psychotic patients, immunocompromised patients, or those having severe renal pathology such as malignancy.
Sample size (n)

The sample size was calculated as follows: \( p = \text{prevalence (prevalence assumed as 17.2\% according to the SEEK-India-specific cohort study)};\)
\[ q = 1 - p. \]
Hence, sample size \( (n) = \frac{(1.96 \times 1.96)/(0.09 \times 0.09)}{(0.172 \times 0.828)} = 67.54. \]
Hence, a sample size of 68 was the minimum requirement for each group. Taking into consideration a 10\% dropout rate, 75 patients were recruited in each group.

Study design

A total of 150 patients were enrolled, out of which 14 patients (9 patients of Group I and 5 patients of Group II) failed to report on subsequent visits, and they were excluded from the study. All patients were put on conservative management for one month. Out of the remaining 136 patients, 66 patients of Group I (control group) received alpha-KAA (600 mg tablet), three times a day, along with conservative management, and 70 patients of Group II (test group) received \( N. \text{ sativa} \) oil (2.5 mL once daily) and alpha-KAA in addition to conservative management (Figure 1). Registered patients were randomized into two groups with the help of a table designed by random allocation software in a ratio of 1:1. After final diagnosis, applying inclusion and exclusion criteria, patients were included in the study. Conservative management included telmisartan, torsemide, iron, calcium, Vitamin D3, erythropoietin, and insulin in case of diabetic patients with CKD, whereas Group II (test) patients received conservative management of CKD along with \( N. \text{ sativa} \) oil (2.5 mL, per orally, once daily). Both groups received treatment for 12 weeks. Alpha-keto analogue tablets (KETOLOG) were of Claris Lifesciences Limited, Ahmedbad, India. The commercially available \( N. \text{ sativa} \) oil of 100\% purity used in this study was procured from the local market under the brand name “Kalonji oil” from Mohammedia Products, Hyderabad, India (good manufacturing practices-certified company). The drugs above were procured from the same pharmaceutical company throughout the study.

All the enrolled patients were regularly followed up at four, eight and 12 weeks of treatment with hemogram, renal function tests, and serum electrolyte test at baseline.

Safety assessments

All adverse events experienced by a patient or observed by the investigator were recorded at each visit. Severity assessment was done by Modified Hartwig and Siegel Scale.\(^{10}\) Physical examination and routine investigations were performed at the start of therapy and at each visit. Additional laboratory tests such as liver function test and lipid profile test were done at the start and end of the study. All the adverse drug reactions (ADRs) were reported to the ADR monitoring center of the institute.

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**Figure 1. Patient recruitment flowchart.**
Statistical Analysis

Statistical analysis was done using IBM SPSS Statistics for Windows version 23.0 software (IBM Corp., Armonk, NY, USA), and charts were prepared using Microsoft Excel 2013. For descriptive statistics, frequency, percentage, mean ± standard deviation, tables, and figures were used to present the study result. Intra- and intergroup analyses of the control and test groups were done using repeated-measures analysis of variance (RMANOVA) test. Post hoc analysis was done by post hoc Dunnett’s test. P<0.05 was considered statistically significant.

Results

The majority of patients were in the age group of 30–60 years in both the groups. Group I included 66 (34 males and 32 females) patients with a mean age of 48.82 years (range 20–60 years), whereas Group II included 70 (41 males and 29 females) patients with a mean age of 49.2 years (range 20–60 years). There were no mortality nor did anyone require dialysis in either group. According to glomerular filtration rate (GFR) (mL/min/1.73 m²), 19 patients belonged to Stage 3 (5 and 14 in Groups I and II, respectively) and 116 patients belonged to Stage 4 CKD (60 and 56 in Groups I and II, respectively). The causes of CKD in Groups I and II were hypertensive nephropathy (24.24% and 25.71%), diabetic nephropathy (30.30% and 37.14%), chronic glomerulonephritis (16.6% and 14.2%), tubulo-interstitial nephritis (6.06% and 8.57%), autosomal dominant polycystic kidney disease (4.54% and 5.71%), and unknown cause (18.1% and 8.57%), respectively.

The signs and symptoms found in the patients at the start of the treatment were nausea, vomiting, weight loss, weakness, pruritus, headache, edema over the body, oliguria, burning during micturition, fever, dyspnea, anorexia, anemia, and hypertension. The clinical features were almost similar among the groups at baseline. The clinical features improved gradually and progressively in both the groups after 12 weeks of treatment, but they were more significant in N. sativa oil-treated group (Table 1).

On within-group comparison, both the groups showed a highly statistically significant increase in hemoglobin percent (Hb%) (P <0.001), but increment was more in Group II, after 12 weeks of treatment, whereas on between-group comparison, the results were not statistically significant with (P>0.05) (Table 1).

Within-group comparison of both the groups showed an extremely statistically significant decrease in blood urea (P <0.001), whereas in between-groups comparison, the results were statistically significant with P <0.05, (Table 1 and Figure 2).

In the case of serum creatinine within the groups, comparison from baseline to 12 weeks revealed highly statistically significant results (P <0.001) in both the test and control groups, whereas on between-group comparison, the results were extremely statistically significant (P <0.01) (Table 1 and Figure 3). On within-group comparison, there was a highly significant decrease in total urine protein (TUP) (P <0.001) in both the groups, whereas on between-groups comparison, the results were statistically significant (P <0.05) (Table 1 and Figure 4). In the case of total urinary volume (TUV) within the groups, comparison from baseline to 12 weeks revealed highly statistically significant results with P <0.001, whereas between-groups comparison revealed statistically significant results with P <0.05 (Table 1 and Figure 5). In eGFR estimation, within-groups comparison from baseline to 12 weeks revealed highly statistically significant results (P <0.001), whereas between-groups comparison revealed statistically significant results with P <0.05 (Table 1 and Figure 6). Serum sodium and serum calcium levels increased significantly in both the groups, and serum potassium level decreased significantly, but it was more marked in Group II (Table 1).

According to the Modified Hartwig and Siegel Scale, the symptoms were mild to moderate (no hospitalization, no change of therapy, and no additional treatment) in severity in the both control and test groups. No
adverse event of acute onset (within 60 min) was seen (Table 2).

Discussion

Conservative management is very vital in preventing the progression of CKD to ESRD. It delays the progressive derangement of renal function and provides only symptomatic relief without treating the underlying cause. Hence, new fangled treatment modalities are being reconnoitered, which can cease nephron damage.

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          | Percentage change after 12 weeks |
|------------------|--------------|------------------|----------------------------------|
|                  |              | At 0 week        | At 12 week                       |
| Hb% (g/dL)       | Control (I)  | 8.71±1.82        | 9.80±1.63                        | 12.5 |
|                  | Test (II)    | 8.84±1.31        | 10.24±1.10                      | 15.83 |
| B. Urea (mg/dL)  | Control (I)  | 85.21±31.79      | 63.17±29.31                     | 25.86 |
|                  | Test (II)    | 84.02±20.15      | 54.38±17.73                     | 35.27 |
| S. Cr. (mg/dL)   | Control (I)  | 3.09±0.84        | 2.22±2.71                       | 28.15 |
|                  | Test (II)    | 2.87±0.84        | 1.79±0.79                       | 37.6  |
| TUV (mL/day)     | Control (I)  | 1320.46±320.48   | 1650.23±180.14                  | 25    |
|                  | Test (II)    | 1250.69±303.74   | 1660.14±258.78                  | 32.7  |
| TUP (g/day)      | Control (I)  | 2.76±1.21        | 1.89±1.14                       | 31.52 |
|                  | Test (II)    | 2.50±0.75        | 1.43±0.75                       | 42.8  |
| GFR (mL/min)     | Control (I)  | 21.68±9.20       | 36.21±21.77                     | 67.02 |
|                  | Test (II)    | 22.71±7.28       | 42.42±17.38                     | 86.78 |
| Na+(mEq/L)       | Control (I)  | 133.54±6.16      | 140.21±4.74                     | 4.99  |
|                  | Test (II)    | 132.37±6.94      | 140.97±4.67                     | 6.49  |
| Ca2+(mg/dL)      | Control (I)  | 7.82±0.93        | 8.59±0.66                       | 9.84  |
|                  | Test (II)    | 7.68±0.66        | 8.67±0.51                       | 12.89 |
| K+(mEq/L)        | Control (I)  | 5.71±1.00        | 5.11±0.65                       | 10.5  |
|                  | Test (II)    | 5.76±0.98        | 5.05±0.66                       | 12.32 |

Hb%: Hemoglobin percent, B. urea: Blood urea, S. Cr: Serum creatinine, TUP: 24-h total urinary protein, TUV: 24-h total urinary volume, GFR: Glomerular filtration rate, Na+: Serum sodium, Ca2+: Serum calcium, K+: Serum potassium. Values are mean ± SD; for control group I (n=66 patients) and test group II (n=70 patients). SD: Standard deviation.

Figure 2. Blood urea levels of chronic kidney disease patients.
Figure 3. Serum creatinine levels of chronic kidney disease patients.

Figure 4. 24-h total urine protein of chronic kidney disease patients.

Figure 5. 24-h total urine volume of chronic kidney disease patients.
can defer the development of ESRD, and is cost-effective. Due to a steep rise in the prevalence of diabetes and hypertension globally, CKD has emerged as a leading chronic disease worldwide.\textsuperscript{1,11,12} CKD tends to cause premature morbidity and mortality and hampers standard of life, both economic and healthwise. The gold standard treatment for CKD-ESRD is RRT which include renal transplantation and maintenance dialysis. There are about 5500 dialysis centers in India, 90\% of above which are in the private sector.\textsuperscript{13} The government sector cannot afford to provide maintenance dialysis, and it runs only pre-transplant dialysis units. In India, more than 100,000 new patients enter RRT an annum.\textsuperscript{4} In India, the monthly cost of the common dialysis prescriptions is approximately Rs. 29,852 (USD 609).\textsuperscript{14} Patients often cut down on dialysis frequency for economic reasons. Frequent and often long-term hospitalizations add to the financial burden.\textsuperscript{15} The cost of transplant is $8900 in the 1\textsuperscript{st}year, which declines later to $3000 annual cost. Renal transplant is the preferred choice as it is cost-effective and offers better quality of life, but still only a

Table 2. Improvement in symptoms due to KAA and KAA + N. sativa oil.

| Serial number | Symptoms recorded | KAA \((n=66)\) | KAA + N. sativa oil \((n=70)\) | 2 Tailed Significance |
|---------------|-------------------|----------------|----------------------------|----------------------|
| 1.            | Nausea            | 25             | 20                         | 4                    | 0.681                |
| 2.            | Vomiting          | 20             | 22                         | 4                    | 0.681                |
| 3.            | Diarrhea          | 26             | 16                         | 3                    | 1.000                |
| 4.            | Constipation      | 20             | 12                         | 0                    | 0.233                |
| 5.            | Anorexia          | 30             | 24                         | 4                    | 1.000                |
| 6.            | Excessive thirst  | 12             | 16                         | 5                    | 0.442                |
| 7.            | Abdominal pain    | 10             | 6                          | 0                    | 0.233                |
| 8.            | Muscle and joint pain | 16         | 12                         | 1                    | 1.000                |
| 9.            | Headache          | 30             | 20                         | 2                    | 1.000                |
| 10.           | Rashes            | 8              | 7                          | 0                    | 0.488                |
| 11.           | Altered taste     | 10             | 8                          | 5                    | 0.209                |
| 12.           | Weakness          | 46             | 32                         | 0                    | 1.000                |
| 13.           | Frequent urination| 16             | 22                         | 2                    | 1.000                |

KAA: Keto analogue of essential amino acids.
fraction of Indians can afford it.\(^4\)

In the present study, the clinical features found in the patients were anorexia, nausea, vomiting, weakness, weight loss, fever, pruritus, headache, dyspnea, hypertension, swelling over the body, oliguria, burning during micturition, and anemia. The clinical features were in conformity with the symptomatology described in literature. There was improvement in clinical features in both groups after 12 weeks of treatment, but there was more improvement in the test group. There was a progressive increase in the Hb% in both groups. Both groups showed highly significant improvement in Hb% when compared with baseline (\(P < 0.001\)). However, \(N.\ sativa\) oil-supplemented group showed more marked improvement as compared to control group at 12 weeks of treatment, but it was not statistically significant. Thus, \(N.\ sativa\) oil supplementation along with KAA produces more or less similar effect on Hb%.\(^1^6\) It has been shown in previous studies\(^1^7\) that daily administration of \(N.\ sativa\) oil at a dose of 1 mL/kg body weight in rats increased Hb% (mg/dL) statistically significantly (\(P < 0.01\)) from 13.12 ± 1.45 to 15.4 ± 0.64 after 12 weeks of treatment. Our results were also in accordance with those of previous studies.

Previous studies showed that blood urea level decreased statistically significantly (\(P < 0.001\)) in patients with type 2 diabetes mellitus treated with \(N.\ sativa\) tea (hot water extract as 5 g/day for 6 months).\(^7\) The fall in blood urea level in this study was comparable to previous studies, which showed that blood urea level decreased statistically significantly (\(P < 0.001\)) with both KAA and \(N.\ sativa\) supplementation, and in this study, it was proved that \(N.\ sativa\) has add-on effect in decreasing serum urea levels in CKD patients. Similar results were shown in the study by Khan et al.,\(^1^8\) where significant reduction was seen in blood glucose, blood urea, serum creatinine, and 24 h TUP along with an increase in Hb, 24-h TUV, and GFR. It was postulated that supplementation of thymoquinone, an active component of \(N.\ sativa\) oil, prevents the development of renal failure by a mechanism related, at least in part, to its capability to decline oxidative stress and to preserve the activity of the antioxidant enzymes, as well as, its ability to prevent the energy decline in kidney tissue and also might be due to its diuretic action.\(^1^9\) 24-h TUP declined steadily in both groups, and the reduction was statistically significant (\(P < 0.001\)) as compared to their baseline values at the end of 12 weeks. It was demonstrated that \(N.\ sativa\) oil supplementation in patients with CKD was associated with a reduction in proteinuria and other RFT parameters.\(^2^0\) There was a progressive increase in 24-h TUV, and this increment was statistically significant (\(P < 0.001\)) in both the groups, and Group II also showed statistically significant (\(P < 0.01\)) change in TUV when compared to Group I at 12 weeks of treatment. This implied that supplementation of \(N.\ sativa\) oil as add-on leads to a more marked increase in TUV than control group treatment. It was also shown that administration of the ethanolic extract of \(N.\ sativa\) (100 mg/kg) in male rats resulted in a significant increase in urine volume, although less than found with the reference drug furosemide.\(^2^1\) Both the groups showed a gradual and progressive increment in estimated glomerular filtration rate (eGFR), and it improved statistically significantly in both the control (\(P < 0.001\)) and test (\(P < 0.001\)) groups, when compared with their baseline values. The test group also showed statistically significant (\(P < 0.05\)) change in eGFR, when compared to Group I after 12 weeks of treatment. This indicated that add-on therapy of \(N.\ sativa\) oil leads to more prominent increase in eGFR than conservative management with KAA alone. Keto-analogue supplementation showed improvement in GFR in CKD patients (Stages III and IV).\(^2^2\) It was observed that administration of \(N.\ sativa\) oil at a dose of 1000 mg/kg body weight/day for eight weeks caused the restoration of renal hemodynamic and functions in streptozotocin-induced diabetic rats in the form of increased GFR and effective renal blood flow.\(^2^3\) There was a steady rise in serum sodium level; it was within normal physiological range in both the groups, and the results in both groups were statistically significant (\(P\)
<0.001) at the end of 12 weeks, but Group II showed more marked improvement. Serum potassium level in both the groups reduced steadily, but this change was statistically significant in Group I (P <0.001) as well as in Group II (P <0.001) after 12 weeks of treatment. Both the groups showed a steady and progressive rise in serum calcium level, which was highly statistically significant (P <0.001) after 12 weeks of treatment as compared to their pretreatment values. These findings are similar to that reported by Ansari et al., who exhibited that N. sativa oil supplementation in CKD patients improved renal functions in CKD patients, including serum sodium, potassium, and calcium.

There are only a few studies with alpha-KAA in patients with CKD, while no comparative study of KAA (control group), with N. sativa oil as an add-on therapy in addition to alpha-KAA (test group), in the conservative management of CKD KAA, has been reported till date.

Some scientists postulated that KAA are transaminated by taking nitrogen from non-essential amino acids, thereby decreasing the formation of urea by re-using the amino group. Thus, the levels of uremic toxins are decreased. Keto-acids tend to reduce protein degradation and urinary protein excretion. It was also shown that keto-acid supplements caused reduction of plasma urea and serum creatinine and improved eGFR in patients with CKD Stages 3 and 4.

It has been also shown that there is a significant reduction in tumor necrosis factor-α, C-reactive protein, and adiponectin on keto-acid supplementation in type 2 diabetic nephropathy. These might be the plausible mechanisms for the beneficial effects of KAA in our study also.

Earlier studies have described the favorable effects of N. sativa regarding renal functions, hepatic functions, blood glucose level, blood pressure level, and lipid profile. It was suggested that thymoquinone, an active ingredient of N. sativa oil, has strong anti-oxidant and anti-inflammatory properties, and studies have provided original observations on the role of oxidative stress and inflammation in the development of various renal diseases.

The dose of KAA in previous clinical studies was 600 mg TDS. The doses of N. sativa in various clinical studies were 2.5 mL oil twice daily, 3 g oil/day, 2 g powder of N. sativa seeds/day, 250 mg seeds twice daily, and N. sativa tea (hot water extract) 5 g/day. Hence, the dose of N. sativa oil we selected in our study was 2.5 mL/day, which lies between the minimum and maximum mentioned doses above, which was due to compromised renal status in patients with CKD.

On the basis of severity classification, the ADRs were mild in most of the cases (no hospitalization, no change of therapy, and no additional treatment were required). All the ADRs were of latent or subacute in onset on the basis of onset of action and no case belonged to the category of acute onset (within 60 min). The adverse drug events were possible (score = 1–4) in 12 cases and probable (score = 5–8) in 10 cases in control group (KAA) and possible (score = 1–4) in 10 cases and probable (score = 5–8) in seven cases in the test group (N. sativa oil-supplemented group along with KAA). On the basis of Naranjo’s Scale we did not find any serious adverse effects of N. sativa oil except only few cases experienced mild nausea in the beginning which disappeared in the 2nd week of study. Hence, the ADRs in both the groups might be the manifestations of the underlying renal pathology or due to other co-administered drugs in both the test and control groups.

**Conclusion**

N. sativa oil supplementation at a dose of 2.5 mL, p.o., once a day with KAA (600 mg tablet), three times a day, along with conservative management, is safe for use as an add-on therapy, and it improved renal functions significantly in patients with CKD, when compared to the control group having KAA at a dose of 600 mg tablet, three times a day, in addition to the conservative management of CKD patients.
It also proved that both drugs are acting by a different mechanism, as *N. sativa* is showing its add-on effects in addition to the effects shown by KAA. Further studies are needed to explore the efficacy and mechanism of action of this drug.

**Conflict of interest:** None declared.

**References**

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.
2. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: Approaches and initiatives—a position statement from kidney disease improving global outcomes. Kidney Int 2007;72:247-59.
3. Singh AK, Farag YM, Mittal BV, et al. Epidemiology and risk factors of chronic kidney disease in India—results from the SEEK (screening and early evaluation of kidney disease) study. BMC Nephrol 2013;14:114.
4. Kher V. End-stage renal disease in developing countries. Kidney Int 2002;62:350-62.
5. Qiu HY, Liu F, Zhao LJ, et al. Comparison of the effects of alpha-keto/amino acid supplemented low protein diet and diabetes diet in patients with diabetic nephropathy. Sichuan Da XueXueBao Yi Xue Ban 2012;43:425-8.
6. Prakash S, Pande DP, Sharma S, Sharma D, Bal CS, Kulkarni H. Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure. J Ren Nutr 2004;14:89-96.
7. El-Shamy KA, Mosa MM, El-Nabarawy SK, El-Qattan GM. Effect of Nigella sativa tea in type 2-diabetic patients as regards glucose homeostasis, liver and kidney functions. J Appl Sci Res 2011;7:2524-34.
8. Mohtashami R, Amini M, Huseini HF, et al. Blood glucose lowering effects of Nigella sativa L. seeds oil in healthy volunteers: A randomized, double-blind, placebo-controlled clinical trial. J Med Plants 2011;10:90-4.
9. Yesmin F, Rahman Z, Dewan JF, et al. Hepatoprotective role of aqueous and n-hexane extracts of Nigella sativa L. in experimental liver damage in rats. Asian J Pharm Clin Res 2013;6:205-9.
10. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
11. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
12. Gupta R. Trends in hypertension epidemiology in India. J Hum Hypertens 2004;18:73-8.
13. Jha V. ESRD in India and Pakistan 2013. Kidney Int Suppl 2013;3:157-60.
14. Jeloka TK, Upase S, Chitikeshi S. Monthly cost of three exchanges a day peritoneal dialysis is same as of thrice a week hemodialysis in self-paying Indian patients. Indian J Nephrol 2012;22:39-41.
15. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: Global dimension and perspectives. Lancet 2013;382:260-72.
16. Neuhäuser M, Ulm A, Leber HW, Schüttler G. Influence of essential amino acids and keto acids on protein metabolism and the anaemia of patients on chronic intermittent haemodialysis. Proc Eur Dial Transplant Assoc 1977;14:557-62.
17. Zaoui A, Cherrah Y, Alouai K, Mahassine N, Amarouch H, Hassar M. Effects of Nigella sativa fixed oil on blood homeostasis in rat. J Ethnopharmacol 2002;79:23-6.
18. Khan IA, Nasiruddin M, Haque SF, Khan RA. A randomized clinical trial to evaluate the efficacy and safety of α-keto amino acids supplementation in stage 3 and 4 patients of chronic kidney disease. Asian J Pharm Clin Res 2014;7:21-4.
19. Sayed-Ahmed MM, Nagi MN. Thymoquinone supplementation prevents the development of gentamicin-induced acute renal toxicity in rats. Clin Exp Pharmacol Physiol 2007;34:399-405.
20. Ansari ZM, Nasiruddin M, Haque SF, Khan RA. Evaluation of efficacy and safety of Nigella sativa oil supplementation in patients of chronic kidney disease. Asian J Pharm Clin Res 2016;9:107-10.
21. Toma CC, Olah NK, Vlase L, Mogoşan C, Mocan A. Comparative studies on polyphenolic composition, antioxidant and diuretic effects of Nigella sativa L. (Black Cumin) and Nigella damascena L. (Lady-in-a-Mist) seeds. Molecules 2015;20:9560-74.
22. Chang JH, Kim DK, Park JT, et al. Influence
of ketoanalogs supplementation on the progression in chronic kidney disease patients who had training on low-protein diet. Nephrology (Carlton) 2009;14:750-7.
23. Yusukswad M, Chaiyabutr N. Restoration of renal hemodynamics and functions during black cumin (Nigella sativa) administration in streptozotocin-induced diabetic rats. J Exp Pharmaco 2012;4:1-7.
24. Teplan V. Supplements of keto acids in patients with chronic renal failure. Nefroloji Dergisi 2004;13:3-7.
25. Chen N, Jin Y, Ren H, Xu J, Shen P, Huang X. Anti-inflammatory effects of low protein diet supplemented with keto-amino acid in the treatment of type 2 diabetic nephropathy. Kidney Res Clin Pract 2012;31:A24.
26. Bamosa AO, Kaatabi H, Lebdaa FM, Elq AM, Al-Sultanb A. Effect of Nigella sativa seeds on the glycemic control of patients with type 2 diabetes mellitus. Indian J Physiol Pharmacol 2010;54:344-54.
27. Dehkordi FR, Kamkhah AF. Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. Fundam Clin Pharmacol 2008;22:447-52.
28. Kaatabi H, Bamosa AO, Lebda FM, Al Elq AH, Al-Sultan A1. Favorable impact of Nigella sativa seeds on lipid profile in type 2 diabetic patients. J Fam Community Med 2012;19:155-61.
29. Ragheb A, Attia A, Eldin WS, Elbarbry F, Gazarin S, Shoker A. The protective effect of thymoquinone, an anti-oxidant and anti-inflammatory agent, against renal injury: A review. Saudi J Kidney Dis Transpl 2009;20:741-52.
30. Najmi A, Nasiruddin M, Khan RA, Haque SF. Effect of Nigella sativa oil on various clinical and biochemical parameters of insulin resistance syndrome. Int J Diabetes Dev Ctries 2008;28:11-4.
31. Heshmati J, Namazi N, Memarzadeh MR, Taghizadeh M, Kolahdooz F. Nigella sativa oil affects glucose metabolism and lipid concentrations in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Food Res Int 2015;70:87-93.
32. Shah AS, Khan GM, Badshah A, Shah SU. Nigella sativa provides protection against metabolic syndrome. Afr J Biotechnol 2012;11:10919-25.
33. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

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