Therapeutic evaluation of Kalonji (Nigella sativa) in dyslipidemia - A randomized control trial

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ABSTRACT

Dyslipidemia is one of the most common risk factors of cardiovascular diseases. An increased level of cholesterol is responsible for atherogenesis, which ultimately leads to the development of cardiovascular, cerebrovascular, and peripheral vascular diseases. According to a survey report, 36.3% patients are dyslipidemic; therefore, the problem is increasing day by day as a huge cause of morbidity and carries economic burden for society. These days, dyslipidemia is treated using lipid-lowering agents with lifestyle intervention; however, lipid-lowering agents produce various side effects. In Unani system of medicine, several drugs are used as lipid-lowering agents, which are comparatively safe. However, such drugs are still not validated on scientific parameters. Thus, a clinical trial was conducted with the objective to evaluate the efficacy and safety of Unani drugs in the management of dyslipidemia.

The study was designed as single-blind, randomized with standard control. Thirty patients of dyslipidemia were selected and randomly assigned to control and test groups, the test group comprising 20 patients and the control group comprising 10. The test group received the powder of Kalonji in the form of capsule (two capsules twice a day) and the control group received Lipotab(R) (two tablets once a day for 60 days). All the patients were assessed on subjective and objective parameters. The result was analyzed statistically using appropriate statistical tests.

The test drug shows significant results on few subjective and objective parameters in comparison to the control drug. Overall, improvement was observed in the test group without any clinically and statistically significant side effects or toxicity. The compliance to the treatment was found good.

The study revealed that the comparative analyses of both test and control drugs were not statistically significant, but improvements in subjective and objective parameters were present in both groups.

Key words: Dyslipidemia, Nigella sativa, Kalonji, Unani system of medicine, Lipotab

INTRODUCTION

Dyslipidemia is a metabolic disorder of lipid and lipoproteins. Lipids are a group of heterogeneous metabolically active substances constantly moving in the circulation and existing in the state of dynamic equilibrium between peripheral tissue, gastrointestinal tract, and liver. They are classified as polar and non-polar depending on their solubility in aqueous environment; triglycerides and cholesterol esters are non-polar lipids, while free cholesterol and phospholipids are incorporated with a specific protein, i.e., apoprotein. These apoproteins constitute the surface layer of triglyceride and cholesterol ester, and form a complex molecule called lipoproteins (1).

An estimated 15% of patients with premature coronary artery disease have familial hypercholesterolemia (FHCL) (2). FHCL is found worldwide. Heterozygous FHCL occurs in about 1 in 500 persons worldwide (1-5). Familial hypertriglyceridemia occurs in about 1 in 500 persons (5). Familial combined hyperlipidemia occurs in about

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1 in 200 persons worldwide. Polygenic hypercholesterolemia is relatively common, occurring up to 5% of the general population (1-5).

Prevalence of dyslipidemia varies according to the age, sex, race, geographical conditions, and association with other diseases. The age group of 30-40 years has a tendency of high prevalence, and above 60 years it becomes markedly high. Men are more prone to dyslipidemia than are women; rural population has less prevalence of this disease than has urban population in India. The prevalence of dyslipidemia with other disease association is high, i.e., diabetes, obesity, renal disease, and liver disease (6-9).

In Unani system of medicine, there is a concept of Quwate Tabaiyah, which serves the functions of nutrition, growth, and reproduction in the body, and expels out Fuzlat (waste products) from the body. Liver is the chief organ of Quwate Tabaiya. Quwate Ghazia (nutritive faculty) is one of the types of Quwate Tabaiya that is responsible for ingestion, digestion, absorption, transformation, and assimilation of Ghiza (food) and excretion of waste products. Quwate Ghazia is served by four kinds of subordinate faculties. Hazme Kabidi is one of the parts of Quwate Hazma, i.e., the type of subordinative faculty of Quwate Ghazia. It is aimed at benefitting the liver cells and the entire body (10).

Dyslipidemia as such has not been described in Unani literature, but it may be interpreted with the abnormalities of the entire mechanism of Hazme Kabidi. There are three conditions that affect Hazme Kabidi, i.e., Baroodat-e-jigar: first, hindrance in the digestion of Ghiza (food) that reaches liver from intestine; second, obstruction by viscous matter or any inflammation that causes partial digestion of nutrients, and third, nutrition resulting from alteration in quantity or quality (Kammiyat and Kaifiyat) of food (11).

Unani system of medicine has recommended a number of drugs; Har in Mizaj (hot temperament) modulates liver functions. Some of the Unani drugs are also scientifically reported to have lipid-lowering effects, which include guguli pid (Cammiphora mukul), alfalfa (Medicago sativa), Asian ginseng (Panax ginseng), fenugreek (Trigonella foenum graecum), garlic (Allium sativum), onions (Allium cepa) (12), turmeric (Crucuma longa), lilly of the valley (Convallaria majalis), and black cumin (Nigella sativa), etc. (13).

MATERIALS AND METHODS

The present clinical study was conducted in the Hospital of National Institute of Unani Medicine, Bangalore. Before embarking on patients, a comprehensive protocol was chalked out with the ethical clearance for biomedical research from institutional ethical committee of the institute. After the ethical clearance, a clinical study was started by enrolling eligible patients from the OPD (Out-door patients) and IPD (In-door patients) of National Institute of Unani Medicine into test and control groups by random allocation. This study was conducted from October 2010 to March 2012.

The patients were selected on the basis of subjective parameters, i.e., palpitation, joints pain, increasing body weight, breathlessness, and xanthelasma or any one of these, and then subjected to lab investigations and electrocardiography (ECG). During the selection procedure, a complete history including interrogation; general, physical and systemic examinations; past reports, family history, personal history, and socioeconomic history were recorded (Table 1). If the patients were not diagnosed by objective parameters but simultaneously fulfilled other obligatory terms of inclusion criteria, they were enrolled in the study after obtaining a written voluntary consent.

Patients who gave written consent to participate voluntarily were included and randomly allocated into two groups by using computer-generated random table; 20 patients were included in the test group and 10 patients in the control group. The patients below 35 and above 65 years of age were excluded from the study, as they came under the exclusion criteria. Further, the patients who failed to provide the signed and informed consent and who did not attended the follow-up regularly for the diseases like pregnancy, lactating women, sever cardiovascular diseases, renal diseases, liver diseases, AIDS, tuberculosis, diabetes mellitus, hypothyroidism were also excluded. Total cholesterol, serum triglyceride, High Density Lipoproteins (HDL), Low Density Lipoproteins (LDL), Hemoglobin% (Hb), Total Leucocytes Count (TLC), Differential Leucocytes Count (DLC), Erythrocyte Sedimentation Rate (ESR), Fasting Blood Sugar (FBS) and Post-prandial Blood Sugar (PPBS), Kidney Function Test (KFT), Liver Function Test (LFT), Urine Routine and Microscopic [urine (R/M)], and ECG were carried out to confirm the diagnosis, to exclude and to find out the lipid profile.

The powder of test drug (Kalonji) was given in the form of capsules to the test group patients. The drug was provided

TABLE 1: Demographic data.

	Test group n=20	Control group n=10
Age		
35-42	10	3
43-50	1	3
51-58	2	3
59-65	7	1
Total	20	10
Gender		
Male	14	7
Female	6	3
Total	20	10
Dietary habits		
Mixed diet	18	8
Vegetarian	2	2
Total	20	10
Socioeconomic status		
Upper (I)	1	1
Upper middle (II)	5	4
Lower middle (III)	11	3
Upper lower (IV)	3	2
Lower (V)	0	0
Total	20	10

by the pharmacy of National Institute of Unani Medicine. The powdered drug was filled in gelatin capsules; each capsule had a capacity for 500 mg of powder. Every patient was given 2 g of Kalonji powder in four capsules; two capsules twice a day just after meal for the period of 60 days (14). The control drug Lipotab (Hamdard Dawa Khana, New Delhi) was given in the dose of two tablets once a day just after the meal for the period of 60 days. The patients were assessed every fortnightly. The assessment of efficacy in the test group and the control group was based on subjective and objective parameters like palpitation, breathlessness, joint pain, increasing body weight, and xanthelesma. Objective parameters were total serum cholesterol, triglycerides, and HDL and LDL cholesterol. Subjective parameters were assessed at every visit, while objective parameters before and after the completion of trial. An arbitrary grading scale was adopted for the assessment of subjective parameters in both test and control groups.

The safety of the treatment was assessed by clinical assessment at every visit of follow-up and biochemical assessment, such as Hb%, TLC, DLC, ESR, FBS and PPBS, KFT, LFT, Urine (R/M), and ECG, before and after the treatment. Any adverse event or reaction appearing during the study either in the test group or in the control group was recorded. Appropriate statistical tests were carried out to analyze the data using Instat graph pad, and the difference in the treatment groups were considered significant at $p<0.05$.

RESULTS

The statistical test used was Friedman test, with post-test for intragroup comparison and Kruskal-Wallis test with Dunns multiple comparison tests for intergroup comparison. a) $p<0.05$ with respect to control day 0, b) $p<0.001$ with respect to test day 0. Intergroup comparison, $p>0.05$ (Table 2).

The statistical test used was paired t test for intragroup comparison, and one-way ANOVA with post-test was used for intergroup comparison, a) $p>0.05$ with respect to the control group day 0, b) $p<0.01$ with respect to test day 0. Inter group comparison, $p=0.0461$ (Table 3).

DISCUSSION

In this study, a maximum 13 (43.33%) patients aged 35-42 years, 4 (13.33%) patients aged 43-50 years, 5 (16.67%) in 51-58 years, and 8 (26.67) patients aged 59-65 years were included. This data shows that dyslipidemia is more prevalent in the age group of 35-42 years, and over 60 years (Table 1). This is in conformity with the study by Swami AM et al. who concluded that the prevalence of dyslipidemia is high in 31-40 years of patients6and by Estari M et al who observed that the prevalence of dyslipidemia over the age 60 years is also high (7).

TABLE 2: Effect of drugs on subjective parameters in dyslipidemic patients (Median scores with ranges in bracket).

Group	Palpitation		Breathlessness		Joints pain		Xanthelesma	
	Before Tt.	After Tt.	Before Tt.	After Tt.	Before Tt.	After Tt.	Before Tt.	After Tt.
Control n=10	2{1,3}	1{0,1}[a]	3{2,3}	1{0,2}[a]	2{0,3}	0.5{0,2}[a]	0{0,3}	0{0,3}
Test n=20	2{0,3}	1{0,1}[c]	2{2,3}	1{0,1}[c]	3{0,3}	1{0,2}[c]	0{0,0}	0{0,0}

Table 3: Effect of drugs on objective parameters in dyslipidemic patients (Mean ± SEM in bracket).

Group	Cholesterol		Triglyceride		HDL-C		LDL-C		Cholesterol/HDL (Ratio)	
	Before Tt.	After Tt.	Before Tt.	After Tt.	Before Tt.	After Tt.	Before Tt.	After Tt.	Before Tt.	After Tt.
Control n=10	219.6 ± 9.89	213.1 ± 11.16[a]	221.6 ± 27.74	175.5 ± 23.43[a]	44.3 ± 3.15	45.1 ± 2.74[a]	142.4 ± 9.54	133.7 ± 9.32a	5.10 ± 0.31	4.84 ± 0.32[a]
Test n=20	223.2 ± 6.98	194.85 ± 7.33[b]	209.4 ± 20.3	196.6 ± 18.28[b]	43.05 ± 1.52	38.7 ± 1.07[b]	127.8 ± 7.90	116.7 ± 6.95[b]	5.18 ± 0.21	5.09 ± 0.21[b]

According to dietary distribution, 26 (86.67%) patients had a mixed diet habit and only 4 (13.33%) patients were vegetarian (Table 1). Consuming more fatty diet is a factor of dyslipidemia. Stephen JM and Maxine AP suggested that more fatty diet causes lipoprotein disorders (15).

The present result on palpitation, breathlessness, joints pain, and xanthelasma reveals that the test drug has a significant result on all subjective parameters except xanthelasma. The high level of lipoproteins develops cardiovascular disease symptoms and peripheral vascular symptoms. The exact mechanism of the action of N. sativa is not known; however, in other studies by Tasawar Z, Siraj Z, Ahmad N, and Mushtaq H, it was reported that the volatile oil of Nigella has two main constituents, i.e., nigellone and thymo quinone, which play a key role in heart disease prevention by their antioxidant activity (16). The unsaponifiable matter of the fixed oil has a marked depressant effect and produces bradycardia. Ahmad J and Ali R suggested that spasmolytic and bronchodilator activities are found in the crude extract of N. sativa due to the presence of anticholinergic property (18). CRC Hand Book of Medicinal Spices by Duke, James A (19) suggested that the cardiovascular activity of volatile oil lowered the heart rate dose, which had a significant effect on intratracheal pressure.

Serum cholesterol was assessed before treatment and after the treatment in both test and control groups. The difference of Mean±SEM in the control group at the 60th day with respect to the control day 0 was found not significant ($p>0.05$); while in the test group, a comparison at the 60th day with respect to the test day 0 was significant ($p<0.01$). The test drug exhibited significant reduction in serum cholesterol, and intergroup comparison was statistically significant ($p = 0.0461$) in favor of the test group.

The Mean SEM score for serum triglyceride was assessed before and after the treatment (Table 3). The difference of Mean±SEM in the control group at the 60th day with respect to the control day 0 was found significant ($p<0.05$); while in the test group, a comparison at the 60th day with respect to dthe test day 0 was not significant ($p>0.05$). The result revealed that the control drug has an effect on serum triglyceride, while there was no effect of the test drug. The intergroup comparison was not significant ($p = 0.6270$).

HDL cholesterol was assessed before and after the treatment in both test and control groups (Table 3). The difference of Mean±SEM in the control group at the 60th day with respect to the control day 0 was not significant ($p>0.05$); while in the test group, a comparison at the 60th day with respect to the test day 0 was significant ($p<0.05$). The intergroup comparison was not significant ($p = 0.0644$). The present data exhibited a reduction in HDL cholesterol by the test drug; while there was no significant difference between test and control drugs.

LDL cholesterol was assessed before and after the treatment in both test and control groups (Table 3). The difference of Mean±SEM in the control group at the 60th day with respect to the control day 0 was not significant ($p>0.05$); while in the test group, a comparison at the 60th day with respect to the test day 0 was not significant ($p>0.05$). The intergroup comparison was not significant ($p=0.2024$). Statistically, both test and control drugs showed no effect on LDL level; however, a reduction was seen according to the investigation report in the level of LDL cholesterol.

The ratio of cholesterol and HDL (cholesterol/HDL) before and after the treatment was assessed; Mean±SEM was calculated in both test and control groups. The Mean±SEM score of the control group was (5.10±0.31) and (4.84±0.32) on the baseline and the 60th day, respectively. In the test group, the Mean SEM score was (5.18±0.21) and (5.09±0.21) on the baseline and the 60th day, respectively (Table 3). The difference between the intragroup comparison was not

significant ($p>0.05$) in the control group as well as in the test group with respect to the baseline. The intergroup comparison was also not significant ($p>0.05$).

In this study, Kalonji was found to have effect on almost all parameters, but a statistically significant result was obtained only on total cholesterol and HDL cholesterol. However, the extract of N. sativa was found to have effect on lipid profile; it decreased intracellular cholesterol due to an upregulation of LDL receptors (20). The supplementation of N. sativa seed has a favorable effect on lipid profile; this may be due to the possible choleretic activity. The choleretic function of N. sativa is either by reducing the synthesis of cholesterol through hepatocytes or by decreasing the fractional reabsorption of cholesterol through small intestine (Buriro MA, Tayyab M, 2007) (21). N. sativa is effective in lowering the cholesterol level and improving the lipid profile; the possible mechanism may be either inhibiting cholesterol synthesis or stimulating bile acid excretion. It is known that both effects would lead to a decrease in serum cholesterol. Another mechanism proposed that N. sativa increases the production of LDL receptors (Ahmad Najami 2008) (22). In one of the studies, it was suggested that hypolipidemic effect of Nigella sativa is due to anorexic property.

Harrisons Internal medicine recommended the normal ratio of cholesterol and HDL as 4.52. In this study, the ratio was not statistically significant between before and after the treatment in the intragroup and the intergroup.

CONCLUSION

The overall effect of the Kalonji was found quite encouraging in the treatment of dyslipidemia. Marked improvement in subjective parameters, like palpitation, breathlessness, and joints pain, and reduction was seen in objective parameters, like cholesterol, triglyceride, and HDL cholesterol, were observed. Both test and control drugs had same effects on subjective and objective parameters. Statistically no side effect was observed in the test group; compliance to the treatment was found good. These results concluded that the test drug was quite safe in the treatment of dyslipidemia.

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