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Amira E Elfouly
Department of Family medicine, Faculty of medicine, Suez Canal University, Egypt

Mosleh A Ismail
Department of Family medicine, Faculty of medicine, Suez Canal University, Egypt

Hanan M Kamal
Department of Cardiology, Faculty of medicine, Suez Canal University, Egypt

Safwat A Ahmed
Department of Pharmacognosy, Faculty of Pharmacy, Suez Canal University, Egypt

Lamiaa E Fiala
(1) Department of Community Medicine, Faculty of Medicine, Suez Canal University, Egypt
(2) Department of Health Sciences, Faculty of Health & Rehabilitation Sciences, Princess Noura Bint Abdulrahman University, Riyadh, Saudi Arabia

Correspondence
Amira E Elfouly
Department of Family medicine, Faculty of medicine, Suez Canal University, Egypt

A randomized controlled trial measuring the effect of nigella sativa extract on lipid profile in adult patients with dyslipidemia attending family practice clinic, Suez Canal University Hospital, Egypt

Amira E Elfouly, Mosleh A Ismail, Hanan M Kamal, Safwat A Ahmed and Lamiaa E Fiala

Abstract
Background: Dyslipidemia is a risk factor for coronary heart disease (CHD), which is the leading cause of death. Although statins is mainstay therapy for dyslipidemia, it has many side effects, such as muscle weakness, pain, tenderness, stiffness. *Nigella sativa* is a herb with many pharmaceutical potential. The seeds of *N. sativa* plant have been used to promote health and fight disease for centuries, especially in the Middle East.
Objectives: To determine the effect of *Nigella Sativa* (black seed) extracts on the lipid profile among patients with dyslipidemia.
Methods: The study is double blinded trial that was conducted in Family practice clinic, 38 patients were recruited. 19 patients were included in intervention group and 19 in control group. Intervention group received their routine therapy for dyslipidemia (statins) in addition to crushed nigella sativa seeds daily for 6 weeks. Control group received their routine in addition to placebo. Baseline measurements and lipid profile were measured before trial and repeated after 6 weeks.
Results: Patients in intervention group had significantly lower waist circumference (p=0.039) and hip circumference (p=0.003) after receiving *N. Sativa*. Total cholesterol, LDL and Triglycerides show statistically significant differences ($p<0.05$) between the pre & post intervention measurement in intervention group. Favorable impact of N. sativa was noted on almost all laboratory in intervention group but the results were not statistically significant.
Conclusion: Adding N. sativa to routine therapy of dyslipidemia showed improvement on almost all variables, but not all results were statistically significant.

Keywords: Dyslipidemia, *N. sativa, statins*

1. Introduction
Dyslipidemia is an important major risk factor for coronary heart disease (CHD), which is the leading cause of death in most of countries. The World Health Organization estimates that dyslipidemia is associated with more than half of global cases of ischemic heart disease and more than 4 million deaths per year [1].
Substantial socioeconomic and demographic changes have taken place in countries of the Eastern Mediterranean region (EMR) over the past two decades. The population of this region has almost doubled, more people are living into older age, and the proportion of the urban population has been increasing [2].
Recent evidence suggests that lipid-lowering therapy reduces cardiovascular morbidity and mortality and causes regression of coronary atherosclerosis [3]. Serial studies using Intravascular Ultrasound (IVUS) showed that regression of coronary atherosclerosis induced by intensive statin therapy is related to the large reduction in low-density lipoprotein cholesterol [4]. The benefits of intensive statin therapy may also be due to increased high density lipoprotein cholesterol [5].
Alternative medicine has opened new door for the treatment of cardiometabolic disorders which has attained epidemic proportion throughout the world. *Nigella sativa* belonging to the buttercup family Ranunculaceae, is commonly known as black seeds. In South Asia, it is called Kalonji, its Arabic name is Habat-ul-Sauda and its English name is Black cumin. Nigella seeds have many pharmaceutical uses. The seeds have occupied special place for their medicinal value for centuries in the Middle East and Southeast Asia [6].

Dyslipidemia is a common risk factor for cardiovascular disease, the leading cause for morbidity and mortality among patients. *Nigella sativa* is an easily available and acceptable remedy to treat dyslipidemia and at a low cost. According to the above mentioned studies, there is an immense need to conduct the current study aiming to improve the quality of life of dyslipidemic patients by improving the management strategy of dyslipidemia.

2. Materials and methods

2.1 Study Setting and Subjects

We conducted a randomized clinical trial at the family practice clinic in Suez Canal University (SCU) Hospital, Ismailia, Egypt. This trial was conducted from February 2018 till August 2018, after being approved by the Medical Ethical Committee at Faculty of Medicine, Suez Canal University. In addition, an informed consent was obtained from each patient. The participants were aged between 40 and 75 years old diagnosed with dyslipidemia and presented to the clinic at SCU Hospital. The patients were included according to the 2013 guidelines of AAC/AHA guidelines [7].

2.1.1 The inclusion criteria

- Individuals with clinical Atherosclerotic Cardiovascular Diseases (ASCVD).
- Individuals with primary elevations of LDL–C >190 mg/dL.
- Diabetics aged 40 to 75 years with LDL– C 70 to189 mg/dL and without clinical ASCVD.
- Individuals without clinical ASCVD or diabetes with LDL–C 70 to189 mg/dL and estimated 10-year ASCVD risk >7.5%.

2.2 Study Procedure

We enrolled fourty patients in this trial. Patients were randomly allocated to two groups; the interventional and control groups, each group consisted of 20 patients. Data describing the socioeconomic status, education, occupation, and income were obtained from the participants. Then, all patients were subjected to full medical history taking and clinical examination. Patients in the interventional group received crushed *Nigella sativa* seed extracts, 1g capsule once daily, for 6 weeks and the anti-dyslipidemic drug (Atorvastatin) while Control comparator received Placebo which is dietary supplement (starch powder)1g capsule once daily, for 6 weeks and the anti-dyslipidemic drug (Atorvastatin)

2.3 Outcome measures

2.3.1 Primary Measures: The primary end point for the trial was serum LDL cholesterol concentration measured after six weeks of intervention.

2.3.2 Secondary Measures: Serum total cholesterol concentrations, Serum concentrations of HDL cholesterol, Serum concentrations of Triglyceride measured after six weeks of intervention.

2.4 Statistical Analysis

Statistical analysis had been performed using SPSS version 23 for windows software XP version. Data was presented using descriptive statistics in the form of frequencies and percentages for qualitative variables, means and standard deviations for quantitative variables. Independent student t test & Mann-Whitney U tests were used for comparison of continuous variables between study groups, and paired-sample student t test & Wilcoxon Signed Ranks Test were used for within-group analyses of change. The Chi-square (X^2 test) had been used to compare frequency ratios between groups. Whenever the expected values in one or more of the cells in a 2x2 tables was less than 5, Fisher exact test was used instead. Pearson's correlation coefficient was used to determine associations between different variables. P value of less than 0.05 had been considered statistically significant.

3. Results

Table (1) showing sociodemographic characteristics of patients in both groups. Age in both groups was comparable, with mean age 50.84 ± 7.52 years in intervention group and 56.26 ± 9.52 years in control group, females represented 89.5% of the intervention group, meanwhile females formed 94.7% of the control group. There was no significant difference between the two groups in the gender distribution (p=0.54). About 68.4%of patients in intervention group live in rural area as the same 68.4% of patients in control group live in urban area. Finally, there was no significant difference between the two groups in any of these characteristics except that higher family members significantly more prevalent in control group.

Table (2) shows socioeconomic characteristics of patients in both groups. The most frequent patient education level in intervention and control groups was illiteracy or being able to read and write only (63.2%) and (89.5%), respectively. Likewise, the most frequent spouse education level in intervention and control groups was illiteracy or being able to read and write only (47.4%) and (78.9%), respectively. Most patients were unemployed (housewives) (86.8%) while most of spouses are unskilled manual worker, Skilled manual worker or works in trades (68.4%).

Table (3) summarizes the medical history of patients in both groups. 78.9% of the patients are found to have diabetes and hypertension while 18.4% have diabetes only.

Table (4) shows clinical assessment of patients in both groups before intervention with nigella sativa and there was no statistically significant difference between the intervention group and control group in any of these clinical parameters ($p>0.05$).

Table (5) shows clinical assessment of patients in both groups after intervention with nigella sativa and there was no statistically significant difference between the intervention group and control group in any of these clinical parameters ($p>0.05$).

Table (6) shows Comparison between both groups regarding laboratory measures before intervention with nigella sativa. There was no statistically significant difference between the intervention group and control group in any of these laboratory measures ($p>0.05$).

Table (7) shows Comparison between both groups regarding laboratory measures after intervention with nigella sativa. There was no statistically significant difference between the intervention group and control group in any of these laboratory measures ($p>0.05$).

Table (8) summarizes the laboratory measures in the study group before and after receiving Nigella sativa seed extracts. Comparison shows that patients in the study group had significantly lower total cholesterol ($p<0.001$), LDL cholesterol (p=0.002) and triglycerides (p=0.002) after receiving Nigella sativa seed extracts.

Table (9) summarizes the laboratory measures in the control group before and after 6 weeks. Comparison shows that patients in the control group had significantly lower total cholesterol (p=0.007) and LDL cholesterol (p=0.027) after 6 weeks of follow up.

Table 1: Socio-demographic of the study groups.

SDC	Intervention group (N=19) (NO=%)	Control group (N=19) (NO=%)	Total (N=38) (N0=%)	Test value	p-value
Age (years), mean ± SD	50.84 ± 7.52	56.26 ± 9.52	53.55 ± 8.89	1.947	0.059[a]
Gender					
Male	2 (10.5)	1 (5.3)	3 (7.9)	0.36	0.54 [b]
Female	17 (89.5)	18 (94.7)	35 (92.1)		
Residency					
Rural	13 (68.4)	6 (31.6)	19 (50)	5.16	0.023[c]
Urban	6 (31.6)	13 (68.4)	19 (50)		
Number of family members					
< 5 members	14 (73.7)	5 (26.3)	19 (50)	8.53	0.004[c]
≥ 5 members	5 (26.3)	14 (73.7)	19 (50)		
Usual source of health care					
Covered by health insurance	17 (89.5)	18 (94.7)	35 (92.1)	0.362	0.9[b]
Uncovered by health insurance	2 (10.5)	1 (5.3)	3 (7.9)		

[a] values are based on independent student t-test. Statistical significance at $P<0.05$
[b] values are based on Fisher's Exact test. Statistical significance at $P<0.05$
[c] values are based on Chi-square test. Statistical significance at $P<0.05$

Table 2: Socio-demographic characteristics in both groups part 2 (N=38)

SDC	Intervention group (N=19) (NO=%)	Control group (N=19) (NO=%)	Total (N=38) (NO=%)	test value	p-value
Patient education					
Illiterate or read and write	12 (63.2)	17 (89.5)	29 (76.3)	3.686	0.151[a]
Primary or Preparatory	2 (10.5)	0	2 (5.3)		
Secondary or intermediate or university	5 (26.3)	2 (10.2)	7 (18.4)		
Spouse education				3.93	0.195 [a]
Illiterate or read and write	9 (47.4)	15 (78.9)	24 (63.2)		
Primary or Preparatory	3 (15.8)	1 (5.3)	4 (10.5)		
Secondary or intermediate or university	7 (36.8)	3 (15.8)	10 (26.3)		
Patient occupation					
Unemployed	15 (78.9)	18 (94.7)	33 (86.8)	3.117	0.23 [a]
Unskilled manual worker, Skilled manual worker or trades	3 (15.8)	0	3 (7.9)		
Professional	1 (5.3)	1 (5.3)	2 (5.3)		
Spouse occupation					
Unemployed	2(10.5)	0	2 (5.3)	2.048	0.484 [a]
Unskilled manual worker, Skilled manual worker or trades	13(68.4)	13 (68.4)	26 (68.4)		
Professional	4(21.1)	6 (31.6)	10 (26.3)		
Items owned by the family (Family possessions), mean± SD	7.53 ± 2.04	7.74 ± 1.85	5.18 ± 1.16	145.5	0.311 [b]
Crowding index					
≤ 1 person per room	16 (84.2)	9 (47.7)	25 (65.8)	5.73	**0.017** [c]
> 1 person per room	3 (15.8)	10 (52.6)	13 (34.2)		
Total SES[d] Score, mean ±SD	32.21 ± 12.25	27.78 ± 10.02	30 ± 11.26	149.5	0.37 [b]

[a] values are based on Fisher's Exact test. Statistical significance at $P<0.05$
[b] values are based on independent student t-test. Statistical significance at $P<0.05$
[c] values are based on chi-square test. Statistical significance at $P<0.05$
[d] socioeconomic status

Table 3: Comparison between intervention & control groups regarding their co-morbid diseases (N=38)

Variables	Intervention group (N=19) (NO=%)	Control group (N=19) (NO=%)	Total (N=38) (NO=%)
Chronic illnesses	19 (100)	19 (100)	38 (100)
Hypertension only	1 (2.6)	0	1 (2.6)
Diabetes only	4 (21.1)	3 (15.8)	7 (18.4)
Diabetes+ hypertension	14 (73.7)	16 (84.2)	30 (78.9)

Table 4: Comparison between intervention & control groups regarding pre-intervention clinical assessment : (N=38)

Baseline anthropometric Measurements	Intervention (N=19) mean ± SD	Control (N=19) mean ± SD	Total (N=38) mean ± SD	test value	p-value
Weight (kg)	88.74 ± 13.03	93.16 ± 19.88	90.95 ± 16.73	0.811	0.432 [a]
Height (cm)	157 (154- 160)	160 (154 – 163)	158 (154 – 160)	149.5	0.37 [b]
BMI (kg/m^2)	35.83 ± 5.28	37.04 ± 7.81	36.44 ± 6.60	0.559	0.58 [a]
Waist circumference (cm)	113.47 ± 10.11	114.79 ± 11.66	114.13 ± 10.78	0.372	0.712 [a]
Hip circumference (cm)	121.42 ± 11.66	122.89 ± 13.84	122.16 ± 12.65	0.355	0.725 [a]
Waist/hip ratio	0.94 ± 0.04	0.94 ± 0.04	0.94 ± 0.04	0.034	0.973 [a]

[a] values are based on Independent t-test. Statistical significance at $P<0.05$
[b] values are based on Mann-Whitney U test. Statistical significance at $P<0.05$
Parametric data were presented as mean ± standard deviation (SD), while non-parametric data were presented as median (25^{th} – 75^{th} percentile)

Table 5: Comparison between intervention & control groups regarding post intervention clinical assessment : (N=38)

Post-intervention anthropometric measurements	Intervention (N=19) mean ± SD	Control (N=19) mean ± SD	Total (N=38) mean ± SD	test value	p-value
Weight (kg)	88.05 ± 12.42	94.42 ± 20.84	91.24 ± 17.22	1.144	0.26 [a]
BMI (kg/m^2)	35.56 ± 5.10	37.51 ± 8.05	36.54 ± 6.72	0.891	0.379 [a]
Waist circumference (cm)	114 (104 -118)	116 (109 -118)	116 (105 -118)	165	0.665 [b]
Hip circumference (cm)	119.53 ± 10.99	123.79 ± 14.81	121.66 ± 13.04	0.344	0.733 [a]
Waist/hip ratio	0.94 ± 0.04	0.94 ± 0.05	0.94 ± 0.04	-0.172	0.865 [a]

[a] values are based on Independent student t-test. Statistical significance at $P<0.05$
[b] values are based on Mann-Whitney U test. Statistical significance at $P<0.05$
Parametric data were presented as mean ± standard deviation (SD), while non-parametric data were presented as median (25^{th} – 75^{th} percentile)

Table 6: Comparison between intervention & control groups regarding pre-intervention laboratory measures (N=38)

Pre-intervention Laboratory measures	Interventional group (N=19) mean ± SD	Control group (N=19) mean ± SD	Total (N=38) mean ± SD	Test value	p-value
Total cholesterol (mg/dl)	216.21 ± 53.12	198.32 ± 39.73	207.26 ± 47.15	-1.17	0.247 [a]
LDL cholesterol (mg/dl)	137.05 ± 46.90	120.58 ± 36.00	128.82 ± 42.07	-1.22	0.232 [a]
HDL cholesterol (mg/dl)	45.11 ± 9.77	42.79 ± 13.97	43.95 ± 11.95	-0.59	0.557 [a]
Triglycerides (mg/dl)	161 (110- 205)	145 (114 – 227)	145 (113 – 221)	168.5	0.729 [b]

[a] values are based on Independent t-test. Statistical significance at $P<0.05$
[b] values are based on Mann-Whitney U test. Statistical significance at $P<0.05$
Parametric data were presented as mean ± standard deviation (SD), while non-parametric data were presented as median (25^{th} – 75^{th} percentile)

Table 7: Comparison between intervention & control groups regarding post-intervention laboratory measures (N=38)

Post-intervention Laboratory measures	Intervention group (N=19) mean ± SD	Control group (N=19) mean ± SD	Total (N=38) mean ± SD	test value	p-value
Total cholesterol (mg/dl)	153 (125 – 205)	159 (148 –178)	158.5 (130.7 181.2)	158	0.525 [b]
LDL cholesterol (mg/dl)	75 (67 – 135)	95 (72 – 112)	86 (67 – 116)	156	0.488 [b]
HDL cholesterol (mg/dl)	44.53 ± 9.17	41.58 ± 11.80	43.95 ± 11.95	0.86	0.396 [a]
Triglycerides (mg/dl)	101 (88 – 184)	135 (118 –181)	123 (98.5 -181.7)	142	0.271 [b]

[a] values are based on Independent t-test. Statistical significance at $P<0.05$
[b] values are based on Mann-Whitney U test. Statistical significance at $P<0.05$
Parametric data were presented as mean ± standard deviation (SD), while non-parametric data were presented as median (25^{th} – 75^{th} percentile)

Table 8: Laboratory measures in the intervention group pre and post intervention (N=38)

Laboratory measures	Pre-intervention (N=19) mean ± SD	Post-intervention (N=19) mean ± SD	test value	p-value
Total cholesterol (mg/dl)	205 (173 – 264)	153 (125 – 205)	-3.74	<0.001 [a]
LDL cholesterol (mg/dl)	127 (108 – 175)	75 (67 – 135)	-3.09	0.002 [a]
HDL cholesterol (mg/dl)	45.11 ± 9.77	44.53 ± 9.17	0.362	0.722 [b]
Triglycerides (mg/dl)	161 (110 – 205)	101 (88 – 184)	-3.114	0.002 [a]

[a] values are based on Wilcoxon Signed Ranks Test. Statistical significance at $P<0.05$
[b] values are based on Paired t-test. Statistical significance at $P<0.05$
Parametric data were presented as mean ± standard deviation (SD), while non-parametric data were presented as median (25^{th} – 75^{th} percentile)

Table 9: Laboratory measures in the control group pre and post intervention (N=38)

Laboratory measures	Pre-intervention (N=19) mean ± SD	Post-intervention (N=19) mean ± SD	test value	p-value
Total cholesterol (mg/dl)	192 (173 – 228)	159 (148 – 178)	-2.697	**0.007** [a]
LDL cholesterol (mg/dl)	119 (99 – 146)	95 (72 – 112)	-2.213	**0.027** [a]
HDL cholesterol (mg/dl)	42.79 ± 13.97	41.58 ± 11.80	0.546	0.592 [b]
Triglycerides (mg/dl)	145 (114 – 227)	135 (118 – 181)	-1.75	0.08 [a]

[a] values are based on Wilcoxon Signed Ranks Test. Statistical significance at $P<0.05$
[b] values are based on Paired t-test. Statistical significance at $P<0.05$
Parametric data were presented as mean ± SD, while non-parametric data were presented as median (25^{th} – 75^{th} percentile)

4. Discussion

This trial evaluated the outcome of crushed nigella sativa seeds in improving the lipid measurements of dyslipidemic patients. Our study revealed that patients in the intervention group had lower levels after 6 weeks of intervention with 1gm nigella sativa compared to the control group but this difference was not statistically significant. The pre intervention results of the lipid profile in the current study showed that LDL concentration were (137.05 ± 46.90 versus 120.58 ± 36 in intervention &control groups respectively), total cholesterol (216.21 ± 53.12 versus 198.32 ± 39.73 in intervention & control groups respectively), HDL (45.11 ± 9.77 versus 42.79 ± 13.97 in intervention &control groups respectively) triglyceride (174.53 ± 93.39 versus 174.74 ± 75.06 in intervention &control groups respectively), the differences between both groups were statistically not significant.

The previous results of the current study were in partial agreement with the results of the study conducted in 2011 by Tasawar *et al*. [8] to determine the effects of *Nigella sativa* on lipid profile in patients having stable coronary artery disease and they measured the lipid profile results at baseline, after 2 months and after 6 months of the trial. Their baseline (pre-intervention) results were: LDL concentration (113.08±5.77 versus 105.37±7.43 in intervention &control groups respectively), total cholesterol (190.92±6.63 versus 173.77±6.75 in intervention &control groups respectively), HDL (40.85±0.78 versus 39.67±0.75 in intervention &control groups respectively) triglyceride (195.77±13.08 versus 160.75±9.88 in intervention &control groups respectively). Despite the lack of statistical significance of all lipid profile parameters reduction between current both groups, the current study reported favorable effect in the intervention group than in the control group in which the mean of these lipid parameters were (LDL 96.26 ± 59.21 versus 94.47 ± 38.20), (TC165.95 ± 56.64 versus 165.05 ± 42.97)' (HDL 44.53 ± 9.17 versus 41.58 ± 11.80) & (Triglcerides 141.42 ± 86.43 versus 143.05 ± 46.14) in intervention &control groups respectively. These results were in agreement with the study of Qidwai *et al*. [9] in which there were no statistically significant difference between both study groups, the lipid profile parameters after intervention were (Total cholesterol 188.95± 20.37 Versus 199.64 ± 27.30), (LDL 128.03 ±18.02 versus 133.21 ±20.90), (HDL 35.87± 8.48 versus 36.07± 9.13) & (Triglycerides 140.24 ±58.09 versus 157.76 ±90.71) in intervention &control groups respectively. The post intervention results of the current study were in disagreement with a lot of other studies that demonstrated statistically significant effect with nigella sativa in their intervention groups compared to control groups [10, 11, 12].

4.1 Limitations of the current study

The strengths of the present study were its prospective, randomized controlled double blinded design and compliance to medication, but this study also had some limitations as small sample size compared to other studies' sample size and intervention with nigella sativa as an add on drug to the recommended treatment of dyslipidemic patients (not a separate arm) so the effect of nigella sativa alone was not calculated.

5. Conclusions

The current study concluded that *N. sativa* was effective as an add on drug in the management strategy of patients with dyslipidemia and this improve the quality of life for these patients.

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