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Effect of *Nigella Sativa* on Blood Lipids in Normal Rats

Abstract: We have studied the effect of *Nigella Sativa* seeds on the blood levels of cholesterol, triglycerides, HDL and LDL in white albino rats. A total of 200 rats, 150 experimental and 50 controls, were included in the study. Six doses of *N. Sativa* were used (50, 100, 200, 300, 400 and 500 mg/day/200g rat). Each dose was given for five durations: 1, 4, 7, 10, and 14 days.

Generally all doses of *N. Sativa* produced significant reduction in the blood level of all parameters studied. There was no linear dose or time dependent effect of *N. Sativa* on these parameters. The effect of *N. Sativa* started after 4 days and continued, with some swings, for the rest of the duration. The effective dose of *N. Sativa* seemed to lie between 100–400mg. It is concluded that *N. Sativa* has a hypocholesterolemic effect. Therefore, we recommend further research on the effect of *N. Sativa* in related diseases in humans and animals.

Keywords: *Nigella Sativa*, Blood lipids, Rats, Saudi Arabia

تأثير الحبة السوداء على الدهون في الفئران

باسل عبدالرحمن الشيخ ، عبدالله عمر باموسي ، زبيده علي هوساوي
المستخلص: تمت دراسة تأثير الحبة السوداء على مستويات الدم للكوليسترول والجليسيرينات الثلاثية والبروتين الدهني عالي الكثافة والبروتين الدهني منخفض الكثافة في الفئران. أشتمل البحث على (200) فأر وضع (150) منها في عينة الاختبار و(50) في العينة الضابطة. استخدم في البحث 6 جرعات من الحبة السوداء كالتالي: (50 ، 100 ، 200 ، 300 ، 400 ، 500 ملغم / اليوم / فأر) وأعطيت كل جرعة لخمس فترات مختلفة (1 ، 4 ، 7 ، 10 ، 14 / يوم). أحدثت الحبة السوداء انخفاضا ملحوظا في مستويات الدم لجميع أنواع الدهون ولكن لم يظهر بأن لهذا الانخفاض علاقة خطية بالجرعة أو الفترة الزمنية. لقد ظهر تأثير الحبة السوداء بعد مرور أربع أيام وأستمر التأثير مع بعض التراجع في جميع الفترات. وقد أوضحت الدراسة الى أن الجرعة الفعالة تقع ما بين (100 - 400 ملغم). يستنتج من الدراسة بأن للحبة السوداء تأثير مخفض للدهون، وعليه توصي الدراسة بعمل مزيد من البحوث حول تأثير الحبة السوداء في الأمراض ذات العلاقة بالدهون في الإنسان والحيوان.

كلمات مدخلة: الحبة السوداء، مستويات الدم، بروتين دهني، فئران، السعودية.

Introduction

The black seed (*Nigella Sativa*) is a type of plant which belongs to the Ranunculaceae family (Saad, 1975). It has been used as an herbal medicine for more than 2000 years. It is also used as a food additive and flavor in many countries. *N. Sativa* volatile oil has been recently shown to possess 67 constituents, many of which are capable of inducing beneficial pharmacological effects in humans (Aboutabl *et al.* 1986).

N. Sativa has been reported to possess many pharmacological effects including a hypotensive

effect (El-Tahir *et al.* 1993), enhancement of immunity by increasing the T4:T8 ratio and natural cell activity (Elkad & Kandil, 1986), as well as the phagocytic activity of macrophages (Ali and Erwa 1993). *N. Sativa* also possesses anti-bacterial activity (Topozada, 1965) and anti-tumour activity (Salami *et al.* 1992). A hypoglycemic effect of *N. Sativa* was also reported both in animals (Al-Hader *et al.* 1993) and in humans (Bamosa, 1997).

Research on the effect of *N. Sativa* on blood lipids is limited. In a human study, a significant decrease in blood cholesterol was observed by the end of the first week of daily treatment with 2gm *N. Sativa* seeds (Bamosa, 1997). El-Zawahry (1997) reported an increase in serum total lipids and triglycerides and a decrease in total LDL cholesterol and LDLC/HDL ratio in rats which received daily doses of 36mg of *N. Sativa* seeds for 6 weeks. However, results of large doses of *N. Sativa* (10% of diet) on rats were mostly opposite to those of the low dose.

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The aim of this study was to investigate the effects of *N. Sativa* on the blood lipids of normal rats and to find out the optimum dose and duration for such effects.

Materials and Methods

A total of 150 experimental and 50 control white female albino rats, weighing 200 ± 20 g, were included in the study. The experimental group were divided into 6 sub-groups of 25 rats each, receiving doses of *N. Sativa* of 50, 100, 200, 300, 400 and 500mg/day respectively. Each dose was mixed with flour, making a dough weighing around 2.5g before feeding. Each dose group was divided into 5 duration subgroups of 5 rats each, in which the feeding of *N. Sativa* continued for 1, 4, 7, 10 and 14 days respectively. All experimental animals were allowed free access to normal food and water. Control animals were given dough weighing around 2.5g daily and allowed free access to normal food and water. They were divided into 5 duration subgroups of 10 rats each and each served as controls for one of the different durations to which the tested groups were subjected to (1, 4, 7, 10 and 14 days respectively) regardless of the dose of *N. Sativa*. Food was allowed to all rats around 8:00 a.m. in order to avoid the effect of diurnal variation.

After 2 hours of fasting, a sample of blood was obtained at 10.00 a.m. from each rat, both experimental and control at the end of each duration. The blood was extracted from the abdominal aorta, following abdominal incision, after anesthetizing the animal with 1.25mg/kg phenobarbitone.

From each blood sample, total cholesterol, triglyceride and high and low density lipoproteins (HDL, LDL) were measured spectrophotometrically utilizing enzymatic methods and a spectrophotometer (Spectronic Instruments, USA) and standard kits (BioMerieux, France).

The mean of each blood parameter from each experiment group was compared to its corresponding parameter in the control groups using unpaired student's t-test. Two-way analysis of variance, one-way analysis of variance and Duncan multiple range tests were also carried out. The level of statistical significance was P value < 0.05.

Results

All animals tolerated the five doses of *N. Sativa* used and none of them showed any sign of discomfort or toxicity in the entire duration of the study.

- Effect of *N. Sativa* feeding on total blood cholesterol level

All *N. Sativa* doses had no effect on cholesterol level when given for one day. The 50 and 100mg doses produced a clear and significant reduction only after 14 days. Feeding with 200, 300 and 400mg resulted in a significant decrease in cholesterol level in the remaining four duration groups. The 500mg dose produced a significant reduction in cholesterol level in only the 4 and 10 day groups. (Table 1)

Table 1. Changes in cholesterol level (mg/dl) in normal rats treated with different doses of *Nigella Sativa* seeds given for different durations compared with control.

Animal groups	Sample size	Dose mg/day	DURATION									
			1 Day		4 Days		7 Days		10 Days		14 Days	
			Mean \pm SD	P-value	Mean \pm SD	P-value	Mean \pm SD	P-value	Mean \pm SD	P-value	Mean \pm SD	P-value
Control	50*	0	70.4 \pm 10.0	-	63.1 \pm 10.0	-	70.2 \pm 12.0	-	62.2 \pm 9.0	-	69.3 \pm 9.6	-
Experimental	150**	50	64.8 \pm 8.4	0.308	62.4 \pm 6.0	0.830	58.4 \pm 3.3	0.049	60.2 \pm 11.0	0.714	48.0 \pm 8.6	0.001
		100	64.6 \pm 9.0	0.302	59.6 \pm 5.0	0.441	59.0 \pm 6.0	0.077	58.2 \pm 9.4	0.441	38.6 \pm 6.0	<0.001
		200	76.0 \pm 8.3	0.245	45.6 \pm 6.2	0.004	38.0 \pm 5.0	<0.001	42.6 \pm 7.2	0.001	31.8 \pm 4.7	<0.001
		300	64.4 \pm 4.5	0.234	38.6 \pm 2.0	<0.001	38.2 \pm 4.3	<0.001	36.8 \pm 6.6	<0.001	33.8 \pm 5.0	<0.001
		400	77.8 \pm 7.0	0.170	36.0 \pm 3.0	<0.001	48.0 \pm 10.3	0.003	37.4 \pm 4.2	<0.001	46.6 \pm 5.2	<0.001
		500	78.8 \pm 35.0	0.099	37.4 \pm 5.0	<0.001	65.2 \pm 7.4	0.405	45.0 \pm 7.7	0.003	60.4 \pm 3.6	0.051

*10 animals for each of the five durations regardless of the dose (a total of 50 control animals).

** 5 animals for each of the five durations of each dose (a total of 150 tested animals).

• Effect of *N. Sativa* feeding on blood triglyceride level

The one-day treatment with all doses of *N. Sativa* produced no significant effect on blood triglyceride levels. Generally, all doses thereafter produced highly significant reductions in triglyceride levels.

Exceptions to that included the 300 and 400mg doses in the 7 day group and the 500mg dose in the 14 day group. The blood triglyceride levels exhibited an upward swing on the 7th day of treatment with three doses (300, 400 and 500mg). (Table 2).

Table 2. Changes in triglyceride levels (mg/dl) in normal rats treated with different doses of *Nigella Sativa* seeds given for different durations compared with control.

Animal groups	Sample size	Dose mg/day	DURATION									
			1 Day		4 Days		7 Days		10 Days		14 Days	
			Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value
Control	50*	0	79.3±12.6	-	55.6 ±5.7	-	78.0±15.3	-	65.0 ±1.0	-	78.9±12.0	-
Experimental	150**	50	67.0±15.0	0.120	53.2 ±5.6	0.454	44.6±15.0	0.001	35.8 ±9.1	0.054	38.6±7.4	0.001
		100	76.0 ±8.0	0.618	42.0 ±5.6	0.001	36.0±12.5	0.001	45.4 ±5.0	0.001	29.0±7.3	<0.001
		200	75.0±11.3	0.532	39.2 ±3.0	0.001	41.2±12.5	<0.001	37.2 ±6.0	0.001	30.0±7.3	<0.001
		300	69.4±13.0	0.178	37.4 ±3.5	<0.001	73.2 ±3.0	<0.504	34.6 ±5.4	<0.001	35.4±10.0	<0.001
		400	75.0±14.0	0.557	33.0 ±4.0	<0.001	69.9 ±6.0	0.246	32.0 ±4.8	<0.001	61.0±3.8	0.006
		500	67.2±12.0	0.097	36.8 ±3.7	<0.001	61.4 ±4.6	0.036	39.2 ±3.4	0.001	73.4±9.0	0.375

*10 animals for each of the five durations regardless of the dose (a total of 50 control animals).

** 5 animals for each of the five durations of each dose (a total of 150 tested animals).

• Effect of *N. Sativa* feeding on HDL level

No effect of significance was seen following one day of administration on any of the different doses of *N. Sativa*. The 50 and 100mg doses produced, however, significant reduction in HDL which persisted in the four remaining duration groups and

was greatest in the 14 day group. Rats treated with 200 and 300mg *N. Sativa* showed a significant reduction in HDL in the 7 and 14 day groups, but the reduction in the 10 day group was non-significant. The 400 and 500mg doses started to produce a significant reduction in HDL after 7 days and persisted thereafter. (Table 3)

Table 3. Changes in HDL level (mg/dl) in normal rats treated with different doses of *Nigella Sativa* seeds given for different durations compared with control.

Animal groups	Sample size	Dose mg/day	DURATION									
			1 Day		4 Days		7 Days		10 Days		14 Days	
			Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value
Control	50*	0	44.0±12.0	-	34.2 ±8.0	-	43.6 ±7.4	-	42.4 ±4.0	-	50.0±9.8	-
Experimental	150**	50	50.4±10.0	0.324	31.8 ±4.4	0.042	29.2 ±6.6	0.002	32.4 ±3.9	0.001	18.2±6.8	<0.001
		100	42.2±10.4	0.780	30.6 ±4.0	0.022	27.4 ±6.6	0.001	37.0 ±2.5	0.017	13.8 ±5.2	<0.001
		200	46.4±14.2	0.735	30.6 ±3.4	0.021	15.4 ±4.9	<0.001	36.0 ±4.3	0.014	13.2 ±3.1	<0.001
		300	53.0±10.6	0.179	32.4 ±4.8	0.058	13.4 ±4.3	<0.001	36.8 ±6.1	0.067	12.8 ±2.0	<0.001
		400	51.4±11.7	0.275	36.2 ±3.0	0.265	12.2 ±3.2	<0.001	34.4 ±5.6	0.007	29.6 ±7.2	0.006
		500	51.0 ±9.7	0.278	37.2 ±4.6	0.402	17.0 ±3.1	<0.001	34.2 ±3.2	0.002	52.2±18.9	0.048

*10 animals for each of the five durations regardless of the dose (a total of 50 control animals).

** 5 animals for each of the five durations of each dose (a total of 150 tested animals).

• Effect of *N. Sativa* feeding on LDL level

No significant effect on LDL level was observed one day following feeding rats with different doses of *N. Sativa*. All doses produced highly significant reduction in LDL level in the 4, 7 and 14 day duration groups, with the exception of the 50mg

dose in the 4 day group and 500mg dose in the 14 day group. An upward swing in the level of LDL was noticed in the 10 day group receiving the doses of 50, 100 and 200mg. In animals receiving 400 and 500mg, the level of LDL was higher in the 14 day groups as compared to the 4, 7 and 10 day groups.(Table 4)

Table 4. Changes in LDL level (mg/dl) in normal rats treated with different doses of *Nigella Sativa* seeds given for different durations compared with control.

Animal groups	Sample size	Dose mg/day	DURATION									
			1 Day		4 Days		7 Days		10 Days		14 Days	
			Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value
Control	50*	0	43.5 ±8.0	-	31.0 ±4.5	-	47.5 ±9.0	-	24.5 ±4.0	-	40.2±8.0	-
Experimental	150**	50	41.8 ±7.4	0.708	25.2 ±7.2	0.055	12.8 ±5.4	<0.001	26.4 ±2.7	0.355	15.4 ±5.6	<0.001
		100	41.8±10.6	0.704	22.6 ±3.9	0.002	12.4 ±1.5	<0.001	21.2 ±3.3	0.133	12.0 ±2.2	<0.001
		200	46.0 ±5.0	0.555	20.6 ±6.6	0.001	12.0 ±4.2	<0.001	19.6 ±4.8	0.054	10.0 ±2.0	<0.001
		300	47.8±10.0	0.391	20.0 ±3.4	<0.001	14.4 ±4.2	<0.001	17.2 ±4.6	0.007	8.4 ±1.1	<0.001
		400	39.8±11.0	0.478	20.2 ±3.0	<0.001	20.2 ±7.9	<0.001	17.2 ±4.8	0.008	23.4 ±8.2	0.002
		500	43.8 ±9.0	0.950	25.0 ±4.4	0.019	31.6 ±8.5	0.006	23.4 ±3.4	0.604	39.6 ±7.7	0.892

*10 animals for each of the five durations regardless of the dose (a total of 50 control animals).

** 5 animals for each of the five durations of each dose (a total of 150 tested animals).

• Effect of *N. Sativa* on HDL/LDL and HDL/total cholesterol ratios

N. Sativa feeding tended to produce elevation in the HDL/LDL ratio in most doses and duration studied; however, the increment was not significant

in the majority of cases (Table 5). The effect of *N. Sativa* on the HDL/total cholesterol ratio was not consistent (Table 6). While 300 and 400mg doses produced significant elevation in 4 and 10 day groups, most doses in the 7 and 14 day groups gave significant reduction.

Table 5. The ratio between HDL/LDL on different doses of *Nigella Sativa* fed for the five durations on blood glucose.

Animal groups	Sample size	Dose mg/day	DURATION									
			1 Day		4 Days		7 Days		10 Days		14 Days	
			Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value
Control	50*	0	1.08±0.5	-	1.2 ±0.2	-	1.0 ±0.30	-	1.8 ±0.4	-	1.4 ±0.4	-
Experimental	150**	50	1.3 ±0.5	0.507	1.3±0.3	0.471	2.7 ±1.2	0.001	1.2 ±0.1	0.013	1.2 ±0.6	0.343
		100	1.0 ±0.1	0.768	1.5 ±0.3	0.073	2.2 ±0.5	<0.001	1.7 ±0.2	0.838	1.5 ±0.4	0.970
		200	1.0 ±0.3	0.762	1.5 ±0.3	0.032	1.6 ±0.8	0.044	1.9 ±0.3	0.588	1.4 ±0.5	0.593
		300	1.2 ±0.4	0.620	1.7 ±0.3	0.006	1.0 ±0.3	0.612	2.3 ±1.0	0.105	1.1 ±0.2	0.189
		400	1.4 ±0.6	0.311	1.8 ±0.4	0.001	0.9 ±0.3	0.401	2.2 ±0.9	0.238	1.3 ±0.3	0.270
		500	1.2 ±0.2	0.713	1.6 ±0.4	0.059	0.6 ±3.0	0.009	1.5 ±0.4	0.234	1.3 ±0.2	0.021

*10 animals for each of the five durations regardless of the dose (a total of 50 control animals).

** 5 animals for each of the five durations of each dose (a total of 150 tested animals).

Table 8. Level (mean \pm SD) of different lipids in rats treated with *Nigella Sativa* for different durations regardless of doses.

Dose	Cholesterol	Triglyceride	HDL	LDL	HDL/Cholesterol	HDL/LDL
1 Day (n=40)	71.00 \pm 9.45	73.55 \pm 12.42	47.80 \pm 11.21	43.50 \pm 8.50	0.68 \pm 0.19	1.15 \pm 0.39
4 Days (n=40)	50.73 \pm 13.38	44.10 \pm 9.80	33.40 \pm 4.60	24.45 \pm 6.10	0.73 \pm 0.24	1.47 \pm 0.35
7 Days (n=40)	55.90 \pm 14.57	60.25 \pm 19.20	25.23 \pm 13.51	24.80 \pm 15.90	0.45 \pm 0.18	1.35 \pm 0.88
10 Days (n=40)	50.58 \pm 13.06	46.68 \pm 14.14	36.95 \pm 5.25	21.80 \pm 4.91	0.77 \pm 0.22	1.80 \pm 0.60
14 Days (n=40)	49.73 \pm 15.60	53.15 \pm 22.57	30.00 \pm 18.73	23.65 \pm 14.65	0.53 \pm 0.27	1.32 \pm 0.36
Sig. of F	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Discussion

Our results indicate that *N. Sativa* seeds have a promising reduction effect on the blood levels of cholesterol, triglycerides and LDL in normal rats. The results, however, fail to show a linear consistent dose or time dependent effect of *N. Sativa* on the various parameters studied. The effective dose range of *N. Sativa* lies between 100-400mg/200grat/day for most parameters studied. Findings of significant interactions between the dose and duration in all measured lipids rule out the independent effect of the dose regardless of duration or the independent effect of duration regardless of the dose on these parameters. Although the maximum effect of a particular dose could sometimes occur before 2 weeks, it is best to complete the treatment for 14 days to ensure maximum effect. The higher doses of *N. Sativa*, particularly 500mg, tended to lose their effect after 2 weeks of daily treatment. A similar finding was observed in our previous study in humans (Bamosa *et al.* 1997), which may support the possibility that the dose used in the human study (2g/day) was also high. The swings observed in certain parameters during the 2 weeks of treatment with some doses are hard to explain. One plausible explanation for these swings could be attributed to the heterogeneity of animals, as different animals were used for groups of different duration. If this is true, then either self control or increasing the sample size of each duration group might minimize such swings. Another possible explanation is that the swings are due to triggering of a body compensatory mechanism that overcomes the reducing effect of the drug and thereafter raises the blood level towards the baseline till it is stopped by a negative

feedback mechanism, and then the drug resumes its effect and the level goes down again. It would be interesting to see whether such phenomenon exists after repeating the same study on animals with abnormalities in these parameters. However, such swings warn researchers to exercise caution in interpreting an effect of a single dose of *N. Sativa* used for one duration.

N. Sativa seeds produced a highly significant reduction in blood cholesterol. Similar findings were found in other studies both in rats (El-Zawahry, 1997) and in humans (Bamosa *et al.* 1997). *N. Sativa* seeds contain various chemical substances which have been reported to possess hypocholesterolemic effect. These include linoleic acid (ethyl and methyl esters) and linolenic acid (ethyl ester) present in volatile oil (Lindsey *et al.* 1990; Woollett *et al.* 1992), thymoquinone and thymohydroquinone in volatile oil (El-Dakhakhany, 1965; Faidley *et al.* 1990), Saponins (Malinow *et al.* 1981, Topping *et al.* 1980, Harwood, 1993) and sterols in fixed oil of the seed (Mattson *et al.* 1982, Vahouny *et al.* 1983 & Heineman *et al.* 1986). Our finding that *N. Sativa* produced highly significant reductions in triglycerides seems conflicting with El-Zawahry (1997). Differences in the dose and duration, between the two studies, could account for such a contradiction. The questions that might arise include what the effective ingredients and possible mechanisms are. Certain reports had shown that polyunsaturated fatty acid, highly present in *N. Sativa* seeds, are capable of reducing triglycerides (Mattson and Grundy, 1985; Ventura *et al.* 1989). It is thought that increasing length and unsaturation of fatty acids, as is the case in *N. Sativa*, reduce their esterification into triglycerides (Fernandez *et al.*

1992, Woollett *et al.* 1992). Furthermore, the fiber content of the seeds (5% of weight) may reduce fat absorption through the intestine (Ikeda *et al.* 1989), and therefore, may contribute partly to the reduction effect on triglyceride.

The previously mentioned ingredients of *N. Sativa* that are capable of reducing cholesterol could also be responsible for the observed reduction in LDL and HDL. Several findings of the present study indicate that *N. Sativa* is a potential drug in preventing and decreasing or completely reversing atherosclerotic changes in vessels. These findings include a decrease in total cholesterol, a decrease in triglycerides and the tendency to elevate HDL/LDL ratio. Indeed, it has been shown that feeding with 36mg *N. Sativa* for 6 weeks prevented atherosclerotic changes in senile rats and also produced regression and healing of atherosclerotic changes induced by feeding a hyperlipidemic diet (El-Zawahry, 1997).

Conclusion

Nigella Sativa produced a significant reduction in the blood level of cholesterol, triglyceride, HDL and LDL in albino rats. The effect started after 4 days and looked to be neither dose nor time dependent.

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