CARDIOPROTECTIVE ACTION OF *NIGELLA SATIVA* SEEDS AND HONEY MIXTURE SUPPLEMENTATION

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Abstract
Hypercholesterolemia is one of the risk factors for cardiovascular disease (CVD). The effect of *Nigella sativa* (*N. sativa*) seeds or honey in modulating lipid profile has been widely studied. However, to date the study on its mixture is still limited to healthy adults. Therefore, this study was aimed to investigate the cardioprotective effects of *N. sativa* seeds and honey mixture on lipid profile modulation in healthy and also hypercholesterolemic subjects. Sixty-one subjects were assigned to control (n=20), healthy supplementation (n=20) and hypercholesterolemic supplementation (n=21) groups. Supplementation groups were administered with 50 mg/kg body weight the mixture daily for three months. The results demonstrated significant reductions in triglycerides (20.1%), ratio of TC:HDL-c (12.3%) and increased high density lipoprotein-cholesterol (15.3%), $p < 0.05$ for healthy subjects. Moreover, supplementation significantly decreased the total cholesterol (6.2%), triglycerides (13.3%), ratio of TC:HDL-c (19.5%) and increased high density lipoprotein-cholesterol (21.0%), $p < 0.05$ among hypercholesterolemic subjects. Based on the current findings, it seems that the mixture of *N. sativa* seeds and honey has beneficial therapeutic effects as cardioprotective supplement in dietary management of hypercholesterolemia.

Keywords: cardioprotective, hypercholesterolemia, lipid profile, *Nigella sativa*, honey

1. Introduction

Heart disease or cardiovascular disease (CVD) is a global of chronic human disease and over the past centuries, CVD has been remained as common public health problems throughout the world (Caterina et al., 2006). To date, CVD is still remains a leading cause of death in both developed and developing countries (WHO, 2011) and by 2020, it is predicted to be main causes of morbidity and mortality in most developing countries (Celermajer et al., 2012). In Malaysia, CVD has increased rapidly in recent years. It remains the number one killer disease since the last three decades (Mohamed et al., 2005). It is also the cause for 17% death in government hospital (National Heart Association, 2011). A study done by Liau et al. (2010) reported that the increasing burden of CVD in Malaysia is associated with a number of CVD risk factors. However CVD is a preventable disease and thus can be avoided through lifestyle changes, particularly in modification of CVD risk factors (Cheah et al., 2011).

Hypercholesterolemia is one of the prevalent risk factors for CVD and it is a modifiable risk factor. According to Ueshima et al. (2008), serum total cholesterol is a risk factor of coronary heart disease in Asian countries which is positively related to morbidity and mortality. The current management to modify the CVD risk factors is through medication by drugs usage. To date, many drugs (most popular are statins) have been introduced and are available for the prevention and treatment of nearly all CVDs events. However, a major problem with this kind of medication is prolonged use of drugs has been claimed for adverse effects (Golomb et al., 2004; Pahan, 2006). So, there has always been a need for seeking a natural remedy as an alternative source with no adverse effects which is also easy to prepare and its pharmacological properties are well recognized. Thus, the present study will report on the cardioprotective effects of *Nigella sativa* (*N. sativa*) seeds and honey mixture on CVD risk factor.

Many studies have been carried out on the utilization of *N. sativa* seeds and honey as natural sources in alternative medicine because of their beneficial therapeutic compounds impacts on CVD risk factors. The seed of *N. sativa* contains both fixed and volatile oils (Cheikh-Rouhou et al., 2007; Sultan et al., 2009) and they were rich with the sources of unsaturated fatty acids and quinones, respectively. It also has been shown to improve blood lipid profile in human studies (Ghurbakhshani et al., 2012; Mahmood et al., 2012; Sabzghabaee et al., 2012). Similarly, it has been reported that honey possesses beneficial effects on blood lipid profile (Yaghoobi et al., 2008; Mushtaq et al., 2011).

Previous studies have proven the cardioprotective effects of both *N. sativa* seeds and honey separately but with high dose of 2-18.4 g/day and 20-75 g/day, respectively. Following that, the present study was carried out to investigate the effects of *N. sativa* seeds and honey mixture with a mild dose, particularly on lipid profile. It is anticipated that the mixture could provide the same or better health effects. Yusof et al. (2012) investigated the effect of *N. sativa* seeds and honey mixture and the results demonstrated that *N. sativa* seeds and honey mixture produced hypolipidemic (decreased total cholesterol and triglycerides). The selected subjects were those the healthy with normal lipid profile. They were supplemented with the dose of 50 mg/kg body weight of *N. sativa* seeds and honey mixture. Thus, following this research findings, the present study also investigated the effect of *N. sativa* seeds and honey mixture with similar dose in modulating risk factor of CVD as primary and secondary prevention among the healthy and the hypercholesterolemic subjects.

2. Materials and Method

Sixty five male and female subjects or volunteers from Universiti Malaysia Terengganu (UMT) and UiTM (Terengganu), Kuala Terengganu Campus were selected and enrolled in this study. The subjects were visited by investigator to be informed about the purpose of the study and they were also provided with the subject information sheet. The subjects were selected with the following inclusion criteria: 25-58 years of age for both genders, free from chronic diseases for healthy subjects such as hypothyroidism, diabetes mellitus, gastrointestinal disorder, renal impairment or cardiac problem, not treated with drugs (lipid-lowering drugs, anti-diabetic, aspirin) and not consume any other dietary supplements, non-vegetarian, non-vigorous exerciser (not more than 3 x 30 minutes vigorous sessions per week), non-pregnant or lactating, non-heavy smoker (not more than 10 cigarettes per day), non-blood donor in the last 3 months, not planned to lose weight and not participated in a clinical trial for last 3 months. The sample size for this study was determined using the Altman's Normogram with assumption that the effect size was 1.1 and the experiment had a test power of 98%. This study was approved by the Committee of Post-graduate Research at UMT following the ethical consideration code for human.

The research work was conducted from May 2012 until October 2012. The eligibility of subjects was screened through Health and Lifestyle Questionnare and their baseline data was taken in the first visit and categorized into three different groups: control group was healthy subjects without supplementation (n = 20), healthy supplementation group was healthy subjects and supplemented with *N. sativa* seeds and honey paste mixture (n = 22) and hypercholesterolemic supplementation group was CVD risk subjects (hypercholesterolemia, n = 23) were supplemented with *N. sativa* seeds and honey paste mixture. They were required to consume the supplement daily according to the dosage instructed for three months (50 mg/kg body weight). For the control group, there was no placebo because of difficultly to mimic the paste- unique taste and aroma. During the intervention study or supplemental period, subjects' cooperation were needed to maintain their usual daily lifestyles and also avoid the consumption of any other dietary supplements. All subjects were followed-up every month to remind them consistenly to consume the paste given for three months. A written informed consents were obtained from them after subjects understood and voluntarily decided to participate in this study. The measurements of blood fasting for lipid profile including total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-c) and low density lipoprotein-cholesterol (LDL-c) were collected and measured before (at baseline) and after three months interval (at endline).

The baseline measurements were taken in the first visit done on June to July 2012. The data collection was carried out in the morning, where blood samples were taken using the finger prick skin punctured with disposable lancet after the subject had an overnight fasting for at least 10 hours. 40 μL of whole blood was collected using a capillary blood collector to determine all parameters blood lipid profile and analyzed using validated and standardized instruments. All the parameters of blood lipid profile of total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-c) and low density lipoprotein-cholesterol (LDL-c) in whole blood were measured directly using Lipid Panel Test Strips with the auto CardioChek P•A™ Analyzer (Polymer Technology System, USA) and classification of blood fasting total cholesterol (TC) was based on National Cholesterol Education Program Adult Treatment Panell III (NCEP, 2001). Based on this guideline, blood fasting total cholesterol which recorded blood reading > 5.2 mmol/L is classified as high risk for hypercholesterolemia. The endline data was then collected in the second visit done on September to October 2012. During this visit, subjects were required to return the remaining of *N. sativa* seeds and honey paste mixture and the amount left was

calculated as a measure of compliance. Subjects who consumed less than 90% of the supplement given were excluded from final analysis. Sixty-five subjects were recruited in the beginning, but only 61 subjects were used in the final analysis.

All data were analyzed where paired samples t-test was applied to determine differences in the values of baseline and endline intervention study within the group. The data were presented in mean (SD). For the variable whereby the criterion of normality was not met, the corresponding non-parametric tests, Wilcoxon Signed Rank test was used and data were presented in median (10th, 90th percentile). In all cases a value for $P \leq 0.05$ was taken to indicate a significant effect.

3. Results and Discussion

Four subjects were excluded from the final analysis because two of them were pregnant during the study and another two were due to lack of compliance (consumed less than 90%). Thus, the statistical analysis of the results was only done on 61 subjects (control group: n = 20, healthy supplementation group: n = 20 and hypercholesterolemic supplementation group: n = 21). Based on the amount of the returned *N. sativa* seeds and honey paste mixture for both supplemented group, compliance was high; 98.8 (2.66)% and no adverse effect as reported by subjects who fulfill the compliance required. The mean age (year) for control group was 34.5 (8.9), healthy supplementation group was 38.5 (8.1) and hypercholesterolemic supplementation group was 37.9 (9.4). The statistical analysis did not show any significant differences of age between three groups.

Lipid profile is a term referred to a pattern of lipids in the blood which consists of TC, TG, HDL-c and LDL-c. It has been noted that if a person has too much lipids in blood (hyperlipidemia), it leads to development of coronary heart disease (CHD) (Jain et al., 2007). Therefore, by modulating the lipid profile in blood is important way to prevent the CVD. The results obtained are presented in Table 1.

Table 1: Lipid profile at baseline, after three months of intervention and their percent change according to groups

Lipid parameter and trial group	Baseline	After three months	P value	Percent change
TC (mmol/L)				
Control	4.49 (0.57)	4.77 (0.71)	0.037□	6.9%
Healthy supplementation	4.69 (0.36)	4.66 (0.58)	0.923	-0.04%
Hypercholesterolemic supplementation	6.17 (1.06)	5.73 (0.71)	0.026□	-6.2%
HDL-c (mmol/L)				
Control	1.48 (0.44)	1.5 (0.42)	0.983	1.4%
Healthy supplementation	1.25 (0.36)	1.41 (0.37)	0.001□	15.3%
Hypercholesterolemicsupplementation	1.54 (0.45)	1.79(0.38)	0.001□	21.0%
LDL-c (mmol/L)				
Control	2.57 (0.61)	2.85 (0.77)	0.058	12.4%
Healthy supplementation	2.76 (0.41)	2.87 (0.44)	0.271	4.7%
Hypercholesterolemic supplementation	4.02 (0.97)	3.66 (0.68)	0.056	-6.7%
TG (mmol/L)				
Control	0.88 (0.58, 1.38)	0.85 (0.58, 1.67)	0.672	-7.5%
Healthy supplementation	1.35	0.99	0.001□	-20.1%

	(0.63, 2.63)	(0.55, 1.96)		
Hypercholesterolemic supplementation	1.09	0.79	0.001[□]	-13.3%
	(0.62, 3.53)	(0.55, 1.69)		
Ratio TC: HDL-c				
Control	3.0	3.25	0.075	4.4%
	(2.01, 5.14)	(2.20, 5.39)		
Healthy supplementation	3.9 (1.49)	3.5 (0.77)	0.013[□]	-12.3%
Hypercholesterolemic supplementation	4.1	3.1	0.000[□]	-19.5%
	(2.90, 5.98)	(2.62, 5.26)		

Key: TC= total cholesterol, TG= triglycerides, HDL-c= high density lipoprotein-cholesterol and I lipoprotein-cholesterol. Data are presented in mean (SD) or median (10th, 90th percentile).

[□] $p < 0.05$ indicate significant difference by
Paired t-Test

[□] $p < 0.05$ indicate significant difference by Wilcoxon Signed Rank Test

Based on Table 1, there was a significant increase in the level of TC in the control group at the end of intervention ($p < 0.05$) compared with baseline, from 4.49 (0.57) mmol/L to 4.77 (0.71) mmol/L and no other significant changes were seen in the other parameters of lipid profile. On the other hand, there were a significant reduction in TG and ratio of TC:HDL-c and also significant increase in HDL-c but no significant reduction in total cholesterol after three months in the healthy subjects supplemented with *N. sativa* seeds and honey mixture (as shown in Table 1). LDL-c increased but not significant ($p > 0.05$). The median score on TG decreased from 1.35 (0.63, 2.63) mmol/L at baseline to 0.99 (0.55, 1.96) mmol/L at the endline of study ($p < 0.05$). The mean score for ratio of TC:HDL-c was significantly decrease ($p < 0.05$) at three months compared with baseline, from 3.9 (1.49) to 3.5 (0.77). There was also a significant increase in HDL-c from 1.25 (0.36) mmol/L to 1.41 (0.37) mmol/L ($p < 0.05$).

The findings, as shown in Table 1, indicate that the *N. sativa* seeds and honey mixture also had a positive effects on lipid profile in hypercholesterolemic supplementation group after three months supplementation. The results showed significant reduction in TC, TG, ratio of TC:HDL-c and increase in HDL-c however there was no effect in LDL-c even though the level of LDL-c reduced by 6.7% when compared with baseline. There was a significant decrease in TC from 6.17 (1.06) mmol L to 5.73 (0.71) mmol/L, and significant increase in HDL-c from 1.54 (0.45) mmol/L to 1.79 (0.38) mmol/L ($p > 0.05$). The median scores of TG and ratio of TC:HDL-c decreased significantly from 1.09 mmol/L to 0.79 mmol/L and from 4.1 to 3.1, respectively. The findings showed a clear beneficial and more pronounced cardioprotective effects of *N. sativa* seeds and honey mixture in modulating the lipid profile.

The present findings in hypercholesterolemic supplementation group seem to be consistent with some previous studies done on *N. sativa* seeds/oil or honey which found that significant reduction in TC, TG, LDL-c and significant increase in HDL-c. In the latest study of Ghurbakhshani et al. (2012), supplementation with two spoons (approximately 18.4 g) of black seeds after breakfast daily among male and female hyperlipidemic patients (n = 30) age between 22 to 65 years for one month showed significant decreased in TC, LDL-c and enhanced HDL-c when compared with baseline (all significantly at $p < 0.001$). Mahmood et al. (2012) also demonstrated that after two months treatment with two tea spoons (approximately 9.0 g) of *N. sativa* seeds daily, hyperlipidemic patients (n = 25) showed a significant reduction in TC, TG, LDL-c and increased in HDL-c (all significantly at $p < 0.001$) as compared to patients who took

Gemfibrozil 600 mg twice daily. Sabzghabaee et al. (2012) conducted study on the effect of daily 2 g *N. sativa* crushed seeds among hyperlipidemia subjects (n = 37) for four weeks and observed the reduction in TC, TG and LDL-c (all significantly at $p < 0.001$) but it had no beneficial effects on HDL-c. However, Ibraheem (2011) found that TC, TG and LDL-c were not significantly affected by supplementation with *N.sativa* tablets (1200 mg/day) for two weeks in normal persons (n = 18, age 23-31 years). In addition, honey was also reported to have favorable effects on lowering TC, LDL-c and enhanced HDL-c (Chepulis & Starkey, 2008) and the antioxidant activity of honey has been suggested as beneficial to influence lipid metabolism (Nemoseck et al., 2011). Al-Waili (2004) observed the effects of 75 g of natural honey treatment in hyperlipidemic patients for 15 days and it was found that honey was capable to reduce TC and LDL-c significantly. Yaghoobi et al. (2008) also found that honey reduced TC, TG, LDL-c and enhanced HDL-c among obese patients after one month treatment with 70 g of natural honey. These results also in accordance with Mushtaq et al. (2011) whereby similar results were obtained on the effect of honey on lipid profile (reduction on TC, TG, LDL-c and increased HDL-c) in obese subjects after one month consumed 40 g honey dissolved in water with their regular meal. However, Hussain et al. (2012) reported no significant effect in the lipid profile among healthy postmenopausal Malay women after four months supplementation with Tualang honey (20 g/day).

The findings in the current study has been able to demonstrate that lower dose of honey used (approximately only 1.3 g/day) in combination with *N. sativa* seeds clearly proved to increase HDL-c significantly (by 21.0% in hypercholesterolemic subjects and 15.3% in healthy subjects) and decreased TC (by 6.2%), TG (by 13.3%) and LDL-c (by 6.7%) in hypercholesterolemic subjects while in healthy subjects only reduction in TG (by 20.1%) after three months supplementation was observed.

4. Conclusion

In summary, our results showed more beneficial effect on lipid profile modulation among hypercholesterolemic subjects as compared to healthy subjects and thus clearly suggesting that *N. sativa* seeds and honey mixture had a positive cardioprotective action in CVD management. This is an important finding for further research whereby it might be possible to use a different dosage of *N. sativa* seeds and honey mixture to identify the optimum dose by which can lowering lipid profile in order to prevent further CVDs events.

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