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Alternative supplement for enhancement of reproductive health and metabolic profile among perimenopausal women: a novel role of *Nigella sativa*

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ABSTRACT

Objective(s): The aim of this open label crossover study was to investigate the effects of *Nigella sativa* on reproductive health and metabolic profile of perimenopausal women in Rawang, Malaysia.

Materials and Methods: Sixty nine perimenopausal women aged 45 to 65 were allocated into the experimental group treated orally with 1600mg/day of encapsulated pure powdered *N. sativa* compared to control groups treated with placebo for 12 weeks. At the end of study, participants underwent washout period for fourteen days before being crossed over and continued for another cycle of treatment. Participants were abstained from taking any other drugs, herbal preparations or food supplements throughout the study. Body weight, height, waist circumference, blood pressure, biochemical parameters and hormonal levels were measured at baseline and at the end of experiment for both cycles. Face to face interview was carried out at baseline and every week to check for compliance, minimize dropouts and to record reproductive health and quality of life indicators using Greene climacteric and SF-36 instruments.

Results: The treatment groups in both cycles showed significant improvement with reference to low density lipoprotein cholesterol and blood glucose ($P<0.05$). There were no significant differences between groups in total cholesterol, high density lipoprotein and triglyceride concentration. Treatment with *N. sativa* induced a significant reduction of prevalence and severity of menopausal symptomsas well as significant improvement in some components of quality of life ($P<0.05$).

Conclusion: These results suggested that treatment with *N. sativa* exert a therapeutic and protective effect by modifying weight gain, improving lipid profile and blood glucose as well as hormonal level which is believed to play an important role in the pathogenesis of metabolic syndrome during menopause.

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Introduction

Menopause is recognized by the cessation of menses for at least one year and, although it is not a disease, it is often accompanied by debilitating symptoms. Menopausal symptoms can affect women both physically and psychologically, and vary in frequency as well as intensity (1). Depending on the disorder of ovarian function and, therefore, lack of oestrogen in the postmenopausal period, symptoms such as hot flushes, irritability, sleeping disorders, fatigue, anxiety, loss of concentration are observed in the early period. Risk of coronary artery disease and incidence rate of osteoporosis increase due to the loss of protective effects of oestrogen will occur in the late period. These symptoms in the postmenopausal period adversely affect the quality of life (QOL) of woman (2). The impact of menopausal symptoms has gained in importance as the lifespan of women has increased throughout the world since women can expect to spend a significant portion of their lives after menopause (3). This period should be a highly productive time for women, and maintaining functional ability and a good QOL is of utmost importance. Accordingly, it is important to understand the QOL impacts of menopausal symptoms as well as the most recent therapeutic options of different approaches to managing symptoms (4).

Current treatments for symptoms of menopause include hormone replacement therapy (HRT) with conjugated equine estrogens and selective oestrogen receptor modulators (5).However, the standard practice of HRT is not free of risks or side effects and does not always alleviate the symptoms (6) and has been shown to increase the risk of stroke and cardiovascular disease (7). With concerns over the

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safety of long-term conjugated equine estrogens, women are seeking alternatives for the treatment of menopausal symptoms (8).The effects of complementary alternative medicines (CAMs) in preventing the postmenopausal symptoms as another aspect of treatment are widely accepted today. In the context of menopause, CAMs have the potential to alleviate symptoms as well as improve general health status and QOL.In the last years, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants (9).The treatment of choice in complementary medicine is supplementation with herbal remedies (10). The identification of an alternative agent, which has the beneficial effects of oestrogen but has low cancer risk and side effects, would, therefore, be of considerable value.

Despite a lack of data on the majority of CAM therapies for menopause, many women are seeking "natural" therapies as an alternative to relieve menopausal symptoms. A review showed that over $600 million is spent annually on CAM products for menopause (11). With some controversies regarding HRT and the risk of cardiovascular disease and breast cancer, there is more interest in alternative therapies that commonly include vitamins and minerals, soy isoflavones, herbs such as *Cimicifugaracemosa*, and custom compounded hormones. Micronized progesterone derived from plant sources and identical to physiologic progesterone has also been shown to be beneficial in relieving menopausal symptoms (12, 13). Numerous studies suggest that *Nigella sativa* (*N. sativa*) as an amazing and multidimensional herb has beneficial effects on various body systems (14-16) and according to its traditional use for promoting lactation and menstrual disorders; *N. sativa* isthought to be effective in hormonal deficiency such as menopausal symptoms.

Despite the wide use of *N. sativa* in clinical application and studies on its efficacy on animal reproductive systems (17, 18), the scientific literature on its efficacy and safety for the treatment of menopause is not available. The aim of this study, therefore, was to assess the effects of supplied product *N. sativa* capsule (BijirinHitam or Al-Habbatus As-Sauda') on menopausal symptoms and consequently quality of life among menopausal women suffering climacteric symptoms in an open label trial.

Materials and methods

Participants

Non-hysterectomized menopausal and perimenopausal women, aged between 45 and 65 years old, with complaints of climacteric symptoms were included. The women included in this study were recruited from urban areas of Rawang, Malaysia. No HRT had been given within the last 3-month period. Women taking any herbal and chemical drugs possibly affecting climacteric symptoms were excluded from the study. Subjects with a history of uncontrolled hypertension, stroke or transient ischemic attack, cancer diagnosed less than 5 years ago, or previous myocardial infarction were excluded. Other exclusion criteria were women currently using lipid-lowering drugs, anti-diabetic or anti hypertensive medications.

Study design

The aim of this study, an open label single arm comparative trial, was to compare the effect of l2-week treatment with *N. sativa* capsule or placebo in primenopausal women with climacteric symptoms. Sixty nine primenopausal women were enrolled into this study comparing the effects of *N. sativa* capsule and placebo on menopausal symptoms,psychological well being and QOL. Participants were first enrolled for the order of treatments and assigned to a 3-month treatment period with *N. sativa*, at a daily dosage of 1600 mg, as first drug. The capsules were manufactured in a local GMP compliant pharmaceutical company (SabitBananiSdnBhd, Malaysia). Study medication was taken twice daily, morning and evening. After completion of the 3-month period and, following by 2 weeks washout period, participants were assigned to a placebo (600 mg/day elemental Calcium Dietary Supplement) for another 3 months (Figure 1).Before the commencementof the study, the protocol of the study was approved by theClinical Research Ethics Committee of Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (UPM). All participants gave their written informed consent prior to the start of the study. Before inclusion in the trial, a general medical and gynecologic examination was performed, including weight, height, and heart rate, systolic and diastolic blood pressure. The general examinations were repeated biweekly. At baseline and after 12 weeks intervention, laboratory measures were taken. For the women who completed the study, a second assessment of FSH and E2 levels were done at the end of the study. Any events or side effects reported by the patient during the study were checked by general physician and graded according to severity (mild, moderate, and severe). Subjects were followed with weekly telephone calls and biweekly general examination during the treatments, to record adverse events and study compliance. Fortnightly check was conducted to ensure full compliance by subjects.

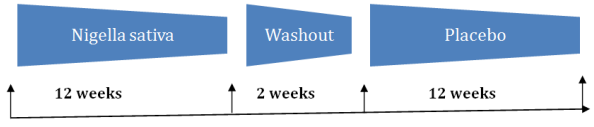

Figure 1. Study design of an open label single arm comparative trial (*Nigella sativa* vs. placebo) groups of premenopausal women

Clinical assessment

The primary endpoints for menopause-specific symptoms were evaluated with a Greene Climacteric Scale. Climacteric scale independently measures psychological, somatic and vasomotor symptoms; each symptom is rated by the subject according to its severity using a four point rating scale. The psychological, somatic and vasomotor scales are a sum of Greene Scale symptoms 1- 11, 12- 18 and 19-20, respectively. The psychological scale can be further subdivided to give measures of anxiety (a sum of symptoms 1-6) and depression (a sum of symptoms 7-11). In addition, symptom 21 is a probe for sexual dysfunction. The scale was completed at the start of the run-in period, at the initiation and after 12 weeks of treatment. After 2 weeks washout period, the scale was completed before second trial (placebo) and was repeated after 12 weeks treatment. Results were analyzed from women who had a complete set of Greene Scale recordings for all visits.

The secondary endpoint was the overall health-related QOL assessed using the standard SF-36 short-form health survey derived from the Medical Outcomes Study (19, 20). The SF-36 was chosen for its multidimensionality, brevity, and its previous successful application in a variety of conditions (21). Responses to the 36 items are categorized into 8 domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Scores range from 0 to 100 with higher scores indicating better states of health and QOL, and lower scores indicating poorer states of health. The SF-36 has been used as a clinical outcome indicator in menopausal symptoms treatment efficacy studies (22, 23) and monitoring QOL changes in menopausal women (24-26). To assess the response to the botanicals based on non-disease-specific but overall QOL in menopausal women with vasomotor symptoms, the SF-36 was evaluated at baseline and at 3 months.

Statistical analysis

Analysis of the primary and secondary end-point was performed using the SPSS 18 program. Primary outcome variable, improvement in symptom relief, expressed as the changes of the mean overall scores of the Greene Climacteric Scale and SF 36 index, were analyzed using paired Student's t-test for comparisons within the treatment group. Unpaired Student's t -test for independent samples was used to analyze the differences between the groups. The continuous secondary outcome variables (weight, height, BMI, waist/hip ratio) and other clinical parameters (fasting blood sugar, total cholesterol, LDL, HDL, triglyceride, creatinine, total billirobin) were also studied using the paired t - test for the evolution within the treatment groupand Student's t-test for independent samples wasused for the comparison between groups.

Table1 . Reasons for early discontinuation

Reasons for withdrown from study	No	%
Protocol violation	5	7.24
Adverse events (constipation after starting the placebo)	3	4.34
Unusual vaginal bleeding	2	2.89
Other reasons(went out for holidays abroad)	4	5.79
Total	14	20.28

Results

Out of 120 screened subjects, 69 eligible women were enrolled. Out of sixty nine women who agreed to participate in the trial, 55 initial recruits satisfied all inclusion and exclusion criteria and continued to the study until the end of trial. Fourteen subjects prematurely withdrew from the study because of protocol violation, adverse events, unusual vaginal bleeding and family holiday before the evaluation at the third month of the first study period (Table 1).

The characteristics of respondents are presented in Table 2. The ages of the subjects ranged from 37 to 71 years, with a mean of 50.1 years. Almost of the respondents were not menopause (65.2%) and majority of them have passed secondary school.

No clinically significant findings were found from the results of clinical parameters during treatment in both groups. Except that the significant changes of LDL mean scores were found between *N. sativa* and placebo (*P*=0.02). With comparisons of principal clinical parameters, no significant changes were

Table 2. Baseline demographic characteristics of respondents

	N (%)	Mean±SD	Range
Menopause woman			
Yes	24 (34.8)		
No	45 (65.2)		
Duration of menopause (years)		*7.0±12.5	0.75–32
<5	7 (29.2)		
5 – 9	8 (33.3)		
10 – 14	2 (8.3)		
≥15	7 (29.2)		
Age of menarche (years)		13.3±1.5	9–16
Ever use oral contraceptives			
Yes	24 (34.8)		
No	45 (65.2)		
Duration of oral contraceptives use (years)		*3.5±10	0.25–25
Number of children		3.6±1.8	0–9
None	1 (1.4)		
1-2	16 (23.2)		
3-4	33 (47.8)		
≥5	19 (27.5)		
Age (year)		50.1±7.6	37–71
<45	19 (27.5)		
45-54	31 (44.9)		
≥55	19 (27.5)		
Marital status			
Married	59 (85.5)		
Single	1 (1.4)		
Widowed	8 (11.6)		
Divorced/ Separated	1 (1.4)		
Highest education attained			
No formal education	3 (4.3)		
Primary school	14 (20.3)		
Secondary school	44 (57.8)		
College degree or higher	8 (11.6)		

Table 3. Clinical parameters before and after 12-weeks' treatment with *Nigella sativa* or placebo

	Nigella sativa			Control			Differences between groups
	Baseline	After 12 weeks	Mean change	Baseline	After 12 weeks	Mean change	
BMI	26.31 (4.89)	25.78 (4.73)	-0.53 * (1.10)	26.03 (4.66)	26.29 (4.87)	-0.28 (1.12)	NS
Waist/Hip ratio	0.82 (0.06)	0.80 (0.06)	-0.02 (0.05)	0.87 (0.06)	0.81 (0.06)	-0.006 (0.05)	NS
FBS	5.64 (1.64)	5.55 (0.87)	-0.09 (1.35)	5.65 (1.55)	5.61 (1.32)	-0.02 (1.78)	NS
Total cholesterol	5.82 (1.22)	5.56 (1.17)	-0.25 * (0.61)	5.84 (1.19)	5.76 (1.26)	0.08 (0.58)	NS
HDL	1.56 (0.38)	1.73 (0.47)	0.17 * (0.33)	1.52 (0.45)	1.58 (0.42)	0.08 (0.28)	NS
LDL	4.29 (5.28)	3.35 (1.09)	-0.93 (4.98)	4.30)5.12)	3.39 (1.25)	-0.91 (4.95)	*P*=0.02
TG	1.42 (0.84)	1.37 (0.75)	-0.05 (0.64)	1.41 (0.79)	1.45 (0.72)	0.04 (0.59)	NS
Creatinine	67.31 (24.87)	77.29 (27.87)	9.98 * (10.53)	65.76 (25.32)	69.72 (20.89)	4.96 (17.22)	NS
Total billirobine	12.80 (5.97)	11.27 (4.41)	-1.52* (3.41)	12.74 (5.36)	12.68 (5.97)	-0.61 (3.31)	NS
B/P systolic	122.32 (15.25)	117.63 (14.65)	-4.69 * (11.15)	121.42 (14.89)	118.18 (15.40)	3.23 * (12.16)	NS
B/P diastolic	79.07 (7.76)	73.96 (9.48)	-5.10 * (6.96)	78.42 (8.48)	74.50 (9.30)	-3.90 * (8.61)	NS

Data are presented as the Mean values (SD)
NS: not significant
* *P*<0.05 (paired t-test for the evolution within the treatment group)

Table 4. Quality of life as assessed by the GreeneClimacteric scale before and after 12-weeks' treatment with *Nigella sativa* or placebo

	Nigella sativa			Control			Differences between groups
	Baseline	After 12 weeks	Mean change	Baseline	After 12 weeks	Mean change	
Total score of GCS	16.29 (10.60)	11.81 (9.50)	-4.47 * (9.03)	15.12 (9.37)	15.90 (9.23)	0.78 (1.11)	*P*=0.024
Psychological score	8.49 (6.06)	5.80 (5.10)	-2.69 * (5.02)	7.81 (5.24)	8.14 (5.14)	0.32 (0.63)	*P*=0.018
Anxiety score	3.89 (3.38)	2.40 (2.94)	-1.49 * (2.90)	3.52 (2.94)	3.85 (2.85)	0.33 (1.62)	*P*=0.010
Depression score	4.60 (3.24)	3.40 (2.97)	-1.20 * (3.15)	4.29 (2.82)	4.25 (2.76)	-0.04 (1.24)	NS
Somatic score	6.11 (4.19)	4.78 (4.20)	-1.32 * (4.27)	5.76 (3.92)	6.05 (3.90)	0.29 (0.59)	NS
Vasomotor score	0.92 (1.19)	0.90 (1.19)	-0.02 * (1.42)	0.83 (1.21)	0.94 (1.22)	0.11 (0.36)	NS

GCS: Greeneclimacteric scale data are presented as the mean values (SD). NS: not significant
* *P*<0.05 (paired t-test for the evolution within the treatment group)

observed for the levels ofwaist/hip ratio, FBS, LDL and, triglyceride in *N. sativa* groups (before and after the treatment), but other parameters including BMI, total cholesterol, HDL, creatinine, total billirobine and blood pressure (systolic and diastolic) improved significantly from baseline (*P*<0.05). On the other hand within placebo group there were no significant mean changes from baseline except systolic and diastolic blood pressure (Table 3).

Treatment with *N. sativa* induced a significant reduction of prevalence and severity of menopausal symptoms. The mean total GreeneClimacteric Scores andthe mean scores of primary endpoints, psychologicaland somatic, decreased markedly with NStreatments. The significant changes of mean scoresin vasomotor symptoms and sexual dysfunctionwere found with the treatment of NS. No significant changes were found in Greene climacteric scale among the control group. In general, statisticallysignificant differences between treatments wereobserved in most of Greene climacteric scales, exceptfor depression, somatic and vasomotor score (Table 4).

From SF-36 components, four of the eight domains of health in response to 12 weeks treatment with NSimproved significantly (*P*<0.05), including; social function, role emotional, vitality and mental component summary. The mean changes in the four domains indicate improved overall health-related QoL with respect to social status and emotional health dimensions in the perimenopausal women. The changes in the other four domains were not significant. The inter-group comparison revealed the significant differences in some dimensions (*P*<0.05) including general health, role emotional, vitality, mental health and mental component summary (Table 5).

Discussion

Despite widespread use of alternative treatments, scientific evidence supporting the efficacy and safety of most complementary treatments for relief of

Table 5. Quality of life as assessed by the SF-36 Index before and after 12-weeks' treatment with *Nigella sativa* or placebo

	Nigella sativa			Control			Differences between groups
	Baseline	After 12 weeks	Mean change	Baseline	After 12 weeks	Mean change	
PF	27.92 (2.67)	27.38 (3.02)	-0.54 (3.16)	27.54 (2.26)	27.09 (2.22)	-0.45 * (1.01)	NS
BP	5.85 (0.40)	5.74 (0.69)	-0.10 (0.71)	5.72 (0.52)	5.61 (0.52)	0.10 (0.49)	NS
GH	8.85 (1.74)	9.16 (1.42)	0.31 (1.71)	8.61 (1.69)	8.38 (1.59)	-0.23 * (0.63)	*P*=0.008
RP	7.45 (1.52)	7.38 (1.69)	-0.07 (1.70)	7.27 (1.39)	7.07 (1.45)	-0.02 * (0.59)	NS
PCS	50.09 (4.67)	49.67 (4.21)	-0.41 (4.51)	49.16 (4.27)	48.16 (4.11)	-1.00 * (1.55)	NS
SF	4.43 (1.47)	3.98 (1.39)	-0.45 * (1.89)	4.27 (1.31)	4.10 (1.25)	-0.16 * (0.53)	NS
RE	12.69 (1.30)	13.29 (1.59)	0.60 * (1.47)	12.34 (1.35)	12.16 (1.25)	-0.18 * (0.47)	*P*=0.000
VT	14.58 (2.14)	15.23 (1.96)	0.65 * (2.49)	14.01 (1.91)	13.78 (1.92)	-0.23 * (0.71)	*P*=0.000
MH	17.78 (2.92)	18.96 (2.21)	1.18 (3.37)	17.14 (2.77)	16.76 (2.78)	-0.38 (0.99)	*P*=0.000
MCS	49.49 (4.41)	51.74 (3.45)	1.98 * (4.43)	47.78 (4.19)	46.81 (3.89)	-0.96 * (1.76)	*P*=0.000

Data are presented as the Mean values (SD). NS: not significant
P<0.05 (paired t -test for the evolution within the treatment group)
PF: physical function; RP: role physical; BP: bodily pain; GH: general health; PCS: Physical Components Summary; SF: social function; RE: role emotional; VT: vitality; MH: mental health; MCS: Mental components Summary

menopausal symptoms is sparse (27). Therefore, randomized controlled trials demonstrating the short- and long-term effects of these treatments are needed. The present study is the first controlled trial to compare the clinical effects of the *N. sativa*, and a placebo on climacteric symptoms in non-hysterectomizedperimenopausal women. This study proved clearly that *N. sativa* could help women with their menopausal problems. Moreover, *N. sativa* caused less unusual vaginal bleeding or spotting episodes and absence of breast tenderness during the study period. In this study, *N. sativa* showed significant improvements in overall symptomatic relief of the primary endpoint (total score of the Greene Climacteric Scale). Moreover, the significant reductions of psychological (anxiety, depression) and somatic symptom scores on the Greene Climacteric Scale were also noted.

The 3-month intervention period was used to assess changes, if any, produced by the *N. sativa* capsule (BijirinHitam or Al-Habbatus -Sauda')in menopausal subjects. Recent studies have used comparable short-term time periods to determine efficacy of therapies in menopausal subjects, including studies of CAM therapies for menopausal symptom control, such as phytoestrogens and isoflavones, and combination herbs (28, 29). Despite of preliminary nature of the pilot study, clinical measurement (e.g. weight, height, BMI, waist/hip ratio) and laboratory markers (e.g. fasting blood sugar, total cholesterol, LDL, HDL, triglyceride, creatinine, total billirobin) as well as qualitative endpoints (e.g. Greene Climacteric Scale and SF 36 Index) were examined.

As expected, the biochemical parameters such as total cholesterol, HDL, creatinine, total billirobine improve significantly in response to 12 weeks *N. sativa*treatment as well as some clinical measurement including BMI, systolic and diastolic blood pressure. Other studies on human and animal subjects consistently supported current study (14, 30-37). Ibrahim and his colleagues also reported improvement of lipid profile and blood glucose of menopausal women in response to 8 weeks supplementation with *N. sativa* capsule (38).

Randomized controlled trials in larger patient populations and longer intervention periods with positive and negative control groups will provide more evidence and better understanding of the value of *N. sativa* for controlling menopausal symptoms. With current concerns about the use of HRT to control menopausal symptoms, safer alternative choices are urgently needed. More extensive data on efficacy, safety, toxicity, and long-term consequences of botanicals, particularly*N. sativa,* focusing on quality assurance and quality control must also be evaluated.

Conclusion

Generally, the preliminary results suggested that *N. sativa* was a safe and efficacious therapy and might be an alternative choice for relief of climacteric symptoms in postmenopausal women who refuse or have contraindications for HRT. However, the exact efficacy and clinical roles of *N. sativa*have not been convincingly demonstrated in this study because of lack of the blinding approach and the lack of positive control group, and only the possibility of its efficacy has been raised. Therefore, a blinding trial with more patient numbers to evaluate the efficacy of *N. sativa* deserves further study.

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