
**UNIVERSITI PUTRA MALAYSIA**

# *EFFECT OF NIGELLA SATIVA ON SELECTED MENOPAUSAL PARAMETERS IN OVARIECTOMIZED RATS*

**SAADAT PARHIZKAR**

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**DOCTOR OF PHILOSOPHY**
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**2009**

# EFFECT OF *NIGELLA SATIVA* ON SELECTED MENOPAUSAL PARAMETERS IN OVARIECTOMIZED RATS

**BY**

**SAADAT PARHIZKAR**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy**

**October 2009**

## DEDICATIONS

**Specially dedicated to,**

My beloved husband Mr. Mohammad Reza Nazari and my dear sons Reza, Pooya and Parsa for their invaluable support, love, patience and intellectual stimulation making my ambition and dreams come true.

And also dedicated to,

All people who were involved in my learning from the first step until present.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

**EFFECT OF *NIGELLA SATIVA* ON SELECTED MENOPAUSAL PARAMETERS IN OVARIECTOMIZED RATS**

By

**SAADAT PARHIZKAR**

**October 2009**

**Chairman: Associate Professor Dr. Latiffah A. Latiff, M.D (UKM)**
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Menopause is the condition when regular menstrual periods cease and may be accompanied by psychological and physical symptoms. This is due to ovarian failure and estrogen deficiency which will influence the quality of life. Hormone replacement therapy (HRT) is being used to relieve postmenopausal symptoms thereby improving the quality of life. Prolonged exposure to HRT, however, gives side effects. As such, Complementary and Alternative Medications (CAMs) is being used as an alternative to HRT. *Nigella sativa* (black seed) is used to treat various illnesses and improve health status. Its application in menopausal women however has never been scientifically evaluated.

Three experiments were conducted to investigate the effects of *Nigella sativa* (NS) in ovariectomized (OVX) rats (menopause-induced animal model). The first experiment was to determine the effect of *Nigella sativa* seeds on selected menopausal parameters (estrogen levels, uterine histological changes, vaginal epithelial cell cornification) and metabolic status (lipid profile, body weight and blood glucose level) of ovariectomized rats. Forty OVX rats were divided equally into 5 groups and supplemented for 21 days to one of the following treatments: conjugated equine estrogen (CEE, 0.2mg/kg), distilled water, *Nigella sativa*: low, medium and high doses (300, 600 and 1200 mg/kg). The second experiment was conducted to determine the effects of *Nigella sativa* extracts obtained by different methods of extraction on similar parameters as in experiment one with the exception of uterine histological study. Five groups of eight OVX rats each received of 300 mg/kg of different extracts of *Nigella sativa* (Supercritical Fluid Extraction (SFE), methanol and hexane extracts) or CEE (0.2mg/kg) or olive oil (1ml/day) for 21 days. The third experiment (consisted of two steps) was to determine the fatty acid composition of *Nigella sativa* and to investigate the effects of some of its ingredients on similar parameters as in experiment two. In step 1 of this experiment, various extracts of *Nigella sativa* were analyzed for their fatty acid composition. In step 2, three different chemical components of *Nigella sativa* (linoleic acid, 50 mg/kg; gamma linolenic acid, 10mg/kg; thymoquinone, 15mg/kg) were given to OVX rats. While CEE (0.2mg/kg) and olive oil (1ml/day) were supplemented to the control groups.

The results of the first experiment showed that CEE or *Nigella sativa* supplementation increased ($p<0.05$) uterine weight as compared to the controls (290-500 ± 0.01 vs

190±0.02 mg for NS and CEE vs control). These supplementations also induced histological changes in the uteri ($p<0.05$) similar to estrogen induced effect (Endometrial thickness: from 281±39 to 365±123 vs 251±107 µm for NS and CEE vs control). In addition, low dose of *Nigella sativa* supplementation was more effective in inducing the estrogenic-like effects as compared to medium and high doses. The second experiment showed that all extracts of *Nigella sativa* produced estrogen-like effects as compared to the control and the methanolic extract was the most effective (cornification of vaginal epithecell cell percentage 47.62%, 32.87%, 32.46% for methanol, hexane and SFE respectively vs 62% and 00% for positive and negative control respectively). In the third experiment, only linoleic acid showed significant ($p<0.05$) estrogen-like activities (cornification of vaginal cell percentage 37.92%, 9.50%, 14.62%, 62% for LA, GLA, TQ and CEE respectively vs 00% for control).

In this study, *Nigella sativa* showed estrogen-like effects on the physical, histological and biochemical parameters of OVX rats, thereby indicating the probable beneficial role for the treatment of postmenopausal symptoms. In conclusion, this study provides novel evidence in support of continuing action of the traditional use of *Nigella sativa* in menopausal women. The study also suggests the possibility of using *Nigella sativa* as an alternative to HRT for post menopause in human as indicated in animal model. Future studies are needed to elucidate the principles, mechanism and active ingredients of *Nigella sativa* on the mammalian reproductive systems.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**KESAN *NIGELLA SATIVA* KE TERHADAP TIKUSYANG TELAH DIAPUH MENOPOS DARI PARAMETER-PARAMETER TERTENTU**

Oleh

**SAADAT PARHIZKAR**

**Oktober 2009**

**Pengerusi: Profesor Madya Dr. Latiffah A. Latiff**

**Fakulti Perubatan dan Sains Kesihatan, UPM**

**dan Institut Biosains, UPM**

Menopos atau putus haid adalah keadaan di mana wanita berhenti dari mengalami haid, dan keadaan ini boleh diiringi oleh gejala psikologikal dan fizikal. Ini adalah disebabkan oleh kegagalan ovari dan penurunan pengeluaran estrogen yang sering menyebab berlakunya perubahan kepada kualiti hidup semasa. Terapi penggantian hormon (HRT) telah digunakan untuk mengurangkan gejala lepas menopos serta meningkatkan kesihatan wanita dan kualiti hidup mereka. Pendedahan berlanjutan kepada HRT walau bagaimanapun boleh memberi kesan yang negatif. Oleh yang demikian, perubatan komplementari pernah digunakan selain dari HRT. *Nigella sativa* (jintam hitam) telah digunakan untuk rawatan bagi pelbagai penyakit dan untuk mampu meningkatkan taraf kesihatan umum. Penggunaannya dalam wanita menopos walaubagaimanapun belum diuji secara saintifik.

Tiga ujian telah dijalankan untuk mengkaji kesan *Nigella sativa* pada haiwan menopos aruhan. Kajian pertama ialah untuk menentukan kesan pengambilan *Nigella sativa* dalam pelbagai dos terhadap ciri-ciri menopos terpilih dan status metabolik pada tikus-tikus. Sebanyak empat-puluh ekor tikus yang dibuang ovari (ovariectomized, OVX) dan parameter di bahagikan kepada 5 kumpulan (8 ekor tikus setiap kumpulan) dan diberi suplemen sama ada *Conjugated Equine estrogen* (CEE 0.2mg/kilogram) atau sukatan berbeza serbuk bijirin hitam *Nigella sativa* iaitu. dos rendah (300mg/kilogram), sederhana (600mg/kilogram) dan tinggi (1200mg/kilogram). Kajian kedua pula adalah bagi menentukan kesan-kesan pengambilan ekstrak minyak *Nigella sativa* melalui teknik *Supercritical Fluid Extraction (SFE)* dan ekstrak pelarut (methanol dan heksana), atau *Conjugated Equine Estrogen (CEE)* terhadap ciri-ciri menopos terpilih dan status metabolik tikus-tikus. Lima kumpulan tikus-tikus OVX dengan setiap satu kumpulan terdiri dari lapan ekor tikus diberi 300 mg/kilogram ekstrak berbeza *Nigella sativa* iaitu dari teknik *Supercritical Fluid Extraction(SFE)*, ekstrak pelarut metanol dan heksana atau CEE (0.2mg/kilogram). Kajian ketiga ialah bagi menentukan kandungan asid lemak dalam *Nigella sativa* iaitu asid linoleik (LA), asid gamma linolenik (GLA) serta sebatian minyak mudah meruap (volatile oil, thymoquinone TQ) dan mengenal pasti kesan sebatian-sebatian ini terhadap ciri-ciri putus haid terpilih dan status metabolik tikus-tikus teraruh menopos. Eksperimen ketiga mengandungi dua peringkat. Dalam peringkat 1, ekstrak pelbagai *Nigella sativa* dianalisis untuk menentukan kandungan asid lemak dan minyak meruap ruap (*volatile oil) Nigella sativa*. Dalam peringkat tikus OVX telah diberikan suplemen asid lemak (LA dan GLA) dan sebatian mudah meruap (TQ) yang terkandung dalam *Nigella sativa* dengan dos berikut: asid linoleik (50mg/kilogram), asid gamma linolenik (10mg/kilogram), dan thymoquinone (15mg/kilogram) atau

Conjugated Equine estrogen (0.2mg / kilogram) sebagai kawalan positif. Minyak zaitun (1ml/sehari) diberi sebagai kawalan negatif.

Keputusan bagi kajian pertama menunjukkan tikus-tikus yang menerima CEE dan peibagai dos *Nigella sativa*, mempunyai berat rahim yang lebih tinggi secara signifikan ($p<0.05$) berbanding kumpulan kawalan (290±0.01 -500±0.01 berbanding 190±0.02 mg untuk NS dan CEE berbanding kawalan). Suplementasi dengan *Nigella sativa* juga merangsang perubahan histologi menyerupai kesan estrogen pada lapisan endometrium rahim berbanding kumpulan kawalan (ketebalan endometrium: 281±39 dan 365±123 berbanding 251±107 µm untuk NS dan CEE berbanding kawalan). *Nigella sativa* pada dos yang rendah mampu mengaruh kesan seperti secara signifikan berbanding dos sederhana dan dos tinggi *Nigella sativa*. Kajian kedua pula menunjukkan ekstrak metanol *Nigella sativa* menunjukkan secara signifikan kesan estrogenik iaitu peningkatan peratus kornifikasi sel epitelium faraj dan peningkatan estrogen dan paras status metabolik berbanding heksana dan ekstrak dari SFE. Peratus kornifikasi sel faraj 47.62%, 32.87%, 32.46% untuk methanol, hexane dan SFE berbanding 62% dan 00% untuk masing-masing kawalan positif dan negatif). Kajian ketiga menunjukkan yang antara tiga sebatian aktif *Nigella sativa* [(asid linoleik (LA), asid gama linolenik(GLA) dan thymoquinone (TQ)], hanya LA mempunyai sifat menyerupai ($p<0.05$) kesan-kesan estrogenic. Peratus konifikasi sel faraj 37.92%, 9.50%, 14.62%, 62% masing-masing untuk LA, GLA, TQ dan CEE berbanding 00% kawalan.

Dalam kajian ini, tikus-tikus OVX yang diberi supplemen *Nigella sativa* telah menunjukkan kesan menyerupai kesan estrogen dari segi parameter fizikal, histologi dan

biokimia. Sehubungan itu kajian ini telah menunjukkan kemungkinan *Nigella sativa* boleh berperanan dan bermanfaat di dalam rawatan gejala menopos.

Sebagai kesimpulan, kajian ini menunjukkan beberapa bukti baru menukong kepada penggunaan herba tradisional seperti *Nigella sativa* sebagai salah satu pilihan terapi penggantian hormon estrogen. Kajian-kajian di masa hadapan adalah diperlukan untuk menjelaskan prinsip, mekanisme serta pengetahuan di peringkat molekular mengenai proses yang bertanggungjawab terhadap kesan *Nigella sativa* dan sebatian aktifnya ke atas sistem reproduksi mamalia.

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I certify that a Thesis Examination Committee has met on 26th October 2009 to conduct the final examination of **Saadat Parhizkar** on her thesis entitled **"Effect of *Nigella sativa* on selected menopausal parameters in ovariectomized rats"** in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the degree of Doctor of Philosophy.

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This thesis submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Date: 14 January 2010

## DECLARATION

I declare that this thesis is my original work except for quotations and citation which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.





**SAADAT PARHIZKAR**

Date: 5 February 2010

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| | |
|---|---|
| **AACE** | American Association of Clinical Endocrinologists |
| **ACOG** | American College of Obstetricians and Gynecologists |
| **ACUC** | Animal Care and Use Committee |
| **ADG** | Average Daily Gain |
| **AE** | Anestrus |
| **app** | Appendix |
| **ANOVA** | Analysis of Variance |
| **B.C.** | Before Christ |
| **BBT** | Basal Body Temperature |
| **BMD** | Bone Mass Density |
| **BS** | Black Seed |
| **BW** | Body Weight |
| **C** | Celsius/Centigrade |
| **cm.** | centimeter |
| **CAM** | Complementary and Alternative Medicine |
| **CE** | constant estrus |
| **CEE** | Conjugated Equine Estrogen |
| **CHD** | Coronary Heart Disease |
| **CLA** | Conjugated Linoleic Acid |
| **CM** | Cloroform-Methanol |
| **CRP** | C-reactive protein |
| **CSA** | Cross-Sectional Area |
| **CVD** | Cardiovascular disease |
| **CYP7$\alpha$** | Cholesterol 7$\alpha$-hydroxylase |
| **df** | Degree of Freedom |
| **DH2O** | Distilled Water |
| **DHEA** | Dehydroepiandrosterone |
| **DHEAS** | Dehydroepiandrosterone sulfate |
| **DHT** | Dihydrotestosterone |
| **DMRT** | Duncan Multiple Range Test |

| | |
|---|---|
| **DNA** | DeoxyriboNucleic Acid |
| **DPX** | Distyrene plasticizer xylene |
| **DSL** | Diagnostic Systems Laboratories |
| **DVT** | Deep Vein Thrombosis |
| **E1** | Estrone |
| **et al.** | et alia (Latin), which means "and others." |
| **E2** | Estradiol |
| **E3** | Estriol |
| **EPO** | Erythropoietin |
| **EPT** | Estrogen-Progestin Therapy |
| **ER** | Estrogrn Receptor |
| **ERs** | Estrogen Receptors |
| **ERT** | Estrogen replacement therapy |
| **ET** | Estrogen therapy |
| **FAME** | Fatty Acid Methyl Esters |
| **FBS** | Fast Blood Sugar |
| **FDA** | Food and Drug Administration |
| **FFA** | Free Fatty Acid |
| **Fig.** | Figure |
| **FHMS** | Faculty of Medicine and Health Sciences |
| **FMP** | Final menstrual period |
| **FPSK** | Fakulti Perubatan dan Sains Kesihatan |
| **FSH** | Follicle Stimulating Hormone |
| **FSH** | Follicle Stimulating Hormone |
| **G.** | Gauge |
| **GC-FID** | Gas Chromatography/Flame Ionization Detector |
| **GLA, γLA** | Gamma Linolenic |
| **GLM** | General Linear Model |
| **GnRH** | Gonadotropine releasing Hormone |
| **h** | Hour |
| **HDL** | High Density Lipoprotein |

| | |
|---|---|
| **HERS** | Heart and Estrogen-Progestin Replacement Study |
| **HRT** | Hormone replacement therapy |
| **HT** | Hormone Therapy |
| **IC50** | 50% Inhibitory Concentration |
| **i.e.** | id est (Latin), which means 'that is' |
| **IP** | Intraperitoneally |
| **IU** | International unit |
| **LA** | Linoleic Acid |
| **LDL-C** | Low Density Lipoprotein-Cholestrol |
| **LDL** | Low Density Lipoprotein |
| **LDLR** | Low Density Lipoprotein receptors |
| **LF** | Low Fat |
| **LH** | Luteinizing Hormone |
| **LHRH** | Luteinizing Hormone-Releasing Hormone |
| **MPA** | Medroxyprogesterone |
| **mRNA** | Messenger Ribonucleic Acid |
| **MPa** | MegaPascal (unit of pressure) |
| **MUFA** | Monounsaturated Fatty acid |
| **NAMS** | North American menopause Society |
| **NCCAM** | National Center for Complementary and Alternative Medicine |
| **NHLBI** | National Heart, Lung, and Blood Institute |
| **NHPs** | Nonhuman primates |
| **NS** | *Nigella sativa* |
| **NSB** | Non Specific Binding |
| **NSO** | *Nigella sativa* Oil |
| **NSW** | New South Wales |
| **OECD** | Organization for Economic Cooperation and Development |
| **OH** | Hydroxyl |
| **OVX** | Ovariectomized |
| **PD** | Persistent Diestrus |
| **PE** | Pulmonary Embolus |

| | |
|---|---|
| **$PGE_2$** | Prostaglandin E2 |
| **pmol/l** | Picomoles per Liter |
| **PPAR** | Peroxisome Proliferators-Activated Receptor |
| **PUFA** | Polyunsaturated Fatty Acid |
| **RCTs** | Randomized Clinical Trials |
| **REE** | Reduced Energy Expenditure |
| **RIA** | Radioimmunoassay |
| **RNA** | Ribonucleic acid |
| **rpm** | Revolutions (or rotations) per minute |
| **RR** | Relative Risk |
| **SAS** | Statistical Analysis Software |
| **SD** | Standard Deviation |
| **SERMs** | Selective estrogen-receptor modulators |
| **SFE** | Supercritical Fluid Extraction |
| **SHBG** | Sex Hormone-Binding Globulin |
| **SPSS** | Statistical Package for the Social Sciences |
| **SSRIs** | Selective Serotonin Reuptake Inhibitors |
| **STRAW** | Stages of Reproductive Aging Workshop |
| **TC** | Total Cholesterol |
| **TG** | Triglyceride |
| **TQ** | Thymoquinone |
| **TSFA** | Total Saturated Fatty acid |
| **TUFA** | Total unsaturated Fatty acid |
| **UPM** | Univerciti Putra Malaysia |
| **UV** | Ultraviolet |
| **VMS** | Vasomotor Symptoms |
| **VTE** | Venous Thromboembolism |
| **w/v** | Weight/volume |
| **WHI** | Women's Health Initiative |
| **WHIMS** | Women's Health Initiative Memory Study |
| **WHO** | World Health Organization |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background

The use of natural products with therapeutic properties is as ancient as human civilization and for a long time, mineral, plant and animal products were the main source of drugs used for reproductive purpose (Hernandez-Ceruelos *et al.*, 2002). Plants have always been a major source of nutrition and health care for both humans and animals. The writings on nutritional and medicinal plants started as early as before 1500 B.C. in Egypt, 800-400 B.C. in Indo-Pakistan, and 500 B.C. in China. In recent years, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants (Schwartsmann *et al.*, 2002). However, scientific research interest in medicinal plants received a thrust during the mid-1970s when World Health Organization (WHO) proposed the incorporation of traditional medicine into the health care system. In 1978, World Health Assembly called for a comprehensive approach to the medicinal plants that include the designation of research and training centers for the study and use of medicinal plants (Anwar, 2005).

The *Nigella sativa* (black seed*)* is a type of plant that belongs to the *Ranunculaceae* family (El-Dakhakhny *et al.*, 2000). It has been used as a herbal medicine for more than 2000 years. Ibn Sina (Avicenna 980-1037), is most famous for his publications called 'The Law of Medicine' regarded by many as the most famous book in the history of medicine, refers Black seed as the seed that stimulates the body's energy and helps recovery from fatigue or dispiritedness as well as gynecologic disorders (Sharafkhandy, 1990). It is also used as a food additive and flavoring agent in many countries. The black seed oil is reported to be beneficial due to its content of over a hundred components such as aromatic oils, trace elements, and vitamins (Ali and Blunden, 2003).

Recently, clinical and animal studies have shown that extract of the black seeds have many therapeutic effects such as immunomodulative (Hanafy and Hatem, 1991), antibacterial (Zaoui *et al.*, 2000), anti-tumor (Turkdogan *et al.*, 2001), diuretic and hypotensive (Kanter *et al.*, 2003), hepatoprotective and antidiabetic (Houghton *et al.*, 1995; Kanter *et al.*, 2003).

The seeds contain both fixed and essential oils, proteins, alkaloids and saponin. Much of the biological activity of the seeds has been shown to be due to thymoquinone, the major component of the essential oil which is also present in the fixed oil (Badary *et al.*, 2002). The pharmacological actions of the crude extracts of the seeds (and some of its active constituents, e.g. volatile oil and thymoquinone) that have been reported include protection against nephrotoxicity and hepatotoxicity induced by either disease or chemicals (Zaoui *et al.*, 2002).

Rhandhawa and Al-Ghamdi (2002) stated that the multiple use of *Nigella sativa* in folk medicine encouraged many investigators to isolate the possible active components and to conduct *in vitro* and *in vivo* studies on laboratory animals and human beings in order to understand its pharmacological actions. One of the components of fixed oils is the sterols. Sterols are steroids containing 27 or more carbon atoms with an OH [hydroxyl] group. A remarkable number of 23 sterols have been identified in the seed. As several of human and animal hormones also have steroidal structures, plant steroids with structural features which fit onto the hormone receptors can exert many bio-activities related to corticosteroids or the sex hormones. Because of the variety of steroidal structures present in the seed, the full extent of the seeds' action on the hormonal system can only be speculated upon at this stage (Norton, 1998).

*Nigella sativa* is also accepted in folk medicine as estrogenic activity which can help regulate menstrual cycles in women. Since estrogen plays an important role in regulating various body systems in the female, drastic change or reduction in estrogen levels can result in elevated blood pressure, increased glucose intolerance and dyslipidemia which may lead to development of metabolic syndrome. As a traditional medicine, *Nigella sativa* increases milk production and promotes menstruation in the female (Sharafkhandy, 1990); however there are no detail information on its effect on the reproductive system.

## 1.2 Problem Statement

Menopause is the period in a woman's life when hormonal changes cause menstruation to cease permanently (Andrews, 1995) and it is a natural part of the aging process. The World Health Organization (WHO) reported that by 2030, there will be 1.2 billion women at and over the age of 50. Therefore, although menopause seems like a natural process, it is a period that must definitely be followed and treated (Browngoehl, 2000). The experience of menopause varies greatly from one woman to another. For some, it is completely symptom free. Others may require assistance to cope with physical and psychological effects of menopause. For women requiring assistance, a range of options and supports are available such as lifestyle changes, medical treatments and complementary approaches (Bones, 2006).

According to WHO report (1996), at the end of the 19$^{th}$ century life expectancy for women was about 50 years, but nowadays it has risen to more than 80 years and in some countries such as Japan, women have a life expectancy of 86 years. The age of menopause, by contrast, has risen only slightly in this time, and occurs at about age 52. This means that in this day and age, women spend about one third of their life living in an estrogen-deficient state, which has far-reaching consequences for various organ systems and can result in a multitude of clinical problems. Clearly, the health concerns of menopause-aged women are rapidly becoming a public health priority (Lobo, 2000). Up to 75% of Malaysian women will experience five or more unpleasant menopausal symptoms such as atypical and classical symptoms during the menopausal transition (Dhillon *et al*., 2006).

Menopause, whether natural or surgically induced, is associated with elevated levels of circulating total cholesterol and LDL cholesterol (LDL-C), placing postmenopausal women at greater risk for coronary heart disease (CHD) (Fukami *et al*., 1995; Bruschi *et al*., 1996; Grodstein *et al.,* 1996; Sullivan and Newman, 1996). Women who develop menopause have to deal with hormonal changes that affect both their blood sugar levels and body weight gain. These changes are the consequences of the reduction in the level of circulating estrogen. The mechanism through which a reduced level of circulating estrogen elevates the plasma cholesterol level is poorly understood. Reductions in the activity of hepatic LDL receptors (LDLR) (Brown and Goldstein, 1980; Walsh *et al.,* 1991; Riedel *et al.,* 2003) and/or cholesterol 7α-hydroxylase (CYP7α) activity (Deliconstantinos and Ramantanis, 1982; Kushwaha *et al.,* 1991) are presumably involved.

Depending on the disorder of ovarian function and, therefore, lack of estrogen 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 estrogen will occur in the late period. These symptoms in the postmenopausal period adversely affect the quality of life of woman. If we assume menopausal age as beginning at 50, women will spend 1/3 of their lives with the pathological changes they are exposed to in the postmenopausal period (Vandenakker and Glass, 2002; Messinger, 2002).

Hormone replacement treatment (HRT) is used as a standard therapy in menopausal treatment (Teoman *et al.,* 2004). Estrogen replacement therapy (ERT) in postmenopausal women reduces the risk of CHD in part by modulating serum cholesterol (Contreras and Parra, 2000; Petteti, 2003). However, HRT and cholesterol-lowering pharmacologic agents may be accompanied by side effects. The National Heart, Lung, and Blood Institute (NHLBI) study suggest that HRT regimens not only lead to increased risk of adverse events, but also they seem to provide little or no protective effects (Zunin and Bregman, 2002). Current guidance from the US Food and Drug Administration (FDA) states that estrogen plus progestin or estrogen alone should be used at the lowest possible dose for the shortest period of time. However, even over short durations (up to 5 years), estrogen plus progestin or estrogen alone (in women with or without a uterus, respectively) increases the risks of stroke (Rossouw *et al.,* 2002; Anderson *et al.,* 2004) dementia (Shumaker *et al.,* 2004); in women who have not had a hysterectomy, estrogen plus progestin additionally increases the risks of thromboembolic disease, coronary events, and breast cancer (Sherman *et al.,* 2005). Such findings have serious health and financial implications for all women facing decisions about therapy for menopausal symptoms, and the health care system must accept the need to look into other therapies for women's needs.

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 quality of life. In relation to menopausal symptoms, studies have been undertaken on the clinical effectiveness of phytoestrogens (Albertazzi

*et al.*, 1998; Drapier Faure *et al.*, 2002; Van de Weijer and Barentsen, 2002) and herbal therapies such as Chinese herbs (Davis *et al.*, 2001), dong quai (Hirata *et al.*, 1997), and evening primrose oil (Chenoy *et al.*, 1994). Numerous studies suggest that *Nigella sativa* as an amazing and multidimensional herb that has beneficial effects on cholesterol metabolism by improving the effects that hypercholesterolemia exert (Haq *et al*., 1995; Bamosa, 1997; Buriro and Tayyab, 2007). On the other hand, based on its traditional use for promoting lactation and menstrual disorders, *Nigella sativa* is thought to be effective in improving hormonal deficiency such as menopausal symptoms. However *Nigella sativa* is quite safe and there is little concern about the side effects of excessive intake of *Nigella sativa* and the benefits out weigh its side effects. Due to probable risks of HRT and high cost of those treatments, herbal remedies particularly use of *Nigella sativa* may be a safe, cheap and effective treatment to control the symptoms of menopause.

**1.3 Scope of the study**

Menopause can represent a "choice point" or a preferred time for women to consider ways to improve their current health status and decrease the risk of long term illnesses (Mac Laren *et al.*, 2001; Taylor, 2001). Most women suffer from hormonal imbalances at some time during their reproductive, peri-menopausal and postmenopausal life. For the last decade or so, synthetic forms of hormone replacement therapy (HRT) have been the most prescribed treatment for peri-menopausal and postmenopausal women to reduce or eliminate uncomfortable symptoms that result from hormonal imbalances. However, the Women's Health Initiative (WHI) trial for HRT was terminated early

because of safety concerns and the Cancer Council of New South Wales (NSW) called for preventative hormone replacement to be suspended, because the study found that women were at greater risk of developing breast cancer and heart disease (Stapleton, 2008). As HRT was found to have treatment limitations and a higher risk to develop cancer, women are looking for other forms of treatment of menopausal symptoms and problems and they are turning to complementary and alternative medicine (CAM). The treatment of choice in complementary medicine is supplementation with herbal remedies (Boronditsky, 2000). The identification of an alternative agent, which has the beneficial effects of estrogen but has low cancer risk and side effects, would, therefore, be of considerable value.

In the context of menopause, Complementary and Alternative Medicines (CAMs) have the potential to alleviate symptoms as well as improve general health status. Yet few studies have been conducted on the use of CAMs among menopausal women, particularly the types, prevalence, and factors associated with CAM use. CAMs can be broadly grouped into CAM medications (ingestible) or therapies (non-ingestible) and include nutritional supplements, vitamins, and herbal supplements, as well as yoga, meditation, naturopathy, exercise, relaxation and deep breathing(Ivarsson *et al.*, 1998; Williamson *et al.*, 2002; Gorton, 1998; Chopin Luck, 2003; Younus *et al.*, 2003). The effect of nutritional supplements such as calcium on postmenopausal bone loss has also been explored (Aloia *et al.*, 1994). However, few studies have measured the use of CAMs in association with symptoms in menopausal women.

A number of studies have elucidated on the pharmacological action(s) of *Nigella sativa* (NS) seed extract or its active compound(s) on various body systems in vivo or in vitro. Conversely, among a long list of examples due to claimed usefulness in folk medicine; very few studies have reported the role of this versatile phytotherapeutic agent on the reproductive system.

Norton (1998) reported that *Nigella sativa* contains 23 different plant sterols. These sterols can fit onto the hormone receptors in the human body. This ability to fit onto the receptor sites may be useful in aging process particularly in relieving prostate inflammation and unpleasant menopausal symptoms. But, no data is available on the effects on female reproductive system, hormonal profile and unpleasant menopausal symptoms. Few studies that have reported its role in reproductive functions have focused on the male reproductive system. However, effect of *Nigella sativa* seeds on female reproductive functions remains largely unknown.

The studies on the effects of *Nigella sativa* on female reproductive system are very limited and almost all of them have focused on galactagogue effect or increasing milk production following *Nigella sativa* consumption. Furthermore, the subjects of all researches were normal animals and not ovariectomized (OVX) animals. The present study focuses on the other indices such as vaginal cytology, uterine changes such as uterine weight, uterine histology and metabolic status in response to *Nigella sativa* treatment in ovariectomized rats. Perhaps the same study in another experimental animal could address this issue. The findings may identify an effective and safe nutraceutical

product as food supplement which may be used to improve menopausal symptoms and metabolic changes after proving through necessitate researches on its efficacy and safety on other animal models. The purpose of the current study is to investigate the potential effect of *Nigella sativa* and some of its ingredients on the changes of menopausal characteristics of the ovariectomized rats as animal model of menopause. The menopausal characteristics included uterotrophic assay, uterine histological study, vaginal cytology, hormonal changes as well as metabolic status (Williamson and Okpako, 1996).

### 1.4 The use of rodents as an OVX model

The amount and types of research that can be conducted directly in women are extremely limited for ethical, practical, and financial reasons. Therefore, we must turn to animal models to shed light on the biology of menopause. Animal species that experience a similar menopausal process at a stage of their life history comparable to that in women presents an advantage because of the ability to utilize tighter control of genetic constitution and variation in experimental population and enable the researcher to perform invasive research under controlled experimental conditions. Whether a true animal model of human menopause exists will be clear only after extensive comparative studies were done. Nonhuman primate (NHP) species show substantial differences in reproductive and reproductive aging processes compared to humans, but some of these species, when ovariectomized, may provide appropriate models for postmenopausal health problems (Rodgers *et al*., 1973; Thorndike and Turner, 1998; Bellino, 2000).

Nonhuman primates (NHPs) hold great promise, because some species appear to undergo a process very similar to what women experience across menopause. Thus, it may be useful to consider nonhuman primate animal species as potential models for pathophysiological changes associated with loss of reproductive function (Bellino, 2000). However, some important differences, such as substantially shorter postmenopausal life span and differences in the timing of hormonal changes during the menopausal transition appear to exist.

Currently there is no single animal model that identically represents the stages of menopause in humans as a whole (Thompson *et al.*, 1995), although there are some available models that provide a relatively close comparison. Both small animals and large animals are used depending on which aspects of the menopausal condition are being studied. Such animals include rats, rabbits, and sheep.

Of these animal models, the ovariectomised (OVX) rat model remains the most popular choice as it has been validated to represent the most important clinical features of estrogen deficiency-induced in the adult human (An and Friedman, 1998; Namkung-Matthai *et al.*, 2001). It also offers certain advantages compared to the other animal models like rabbits and sheep. These include cost effectiveness and ease of handling and housing (An and Friedman, 1998). Because of these considerations, the OVX rat model is widely used for studies associated with the prevention and treatment of symptoms associated with estrogen deficiency (Kalu, 1991; Namkung-Matthai *et al.*, 2001; Hoegh-Andersen *et al.*, 2004). The ovariectomized (OVX) rat is a widely used model to study estrogen withdrawal and replacement because many phenomena in this

rat model are similar to those occurring in postmenopausal women (Van Linden *et al.*, 2006). This method was used to analyze physiological, biochemical as well as histological effects induced in blood, uterus and vagina after short term (3 weeks) supplementation with oral administration of *Nigella sativa* crude powder, its different extracts and some of its ingredients in OVX rats and compared them with those treated by either Conjugated Equine estrogen (CEE) or control group.

## 1.5 Objectives

### 1.5.1 General objective

The objective of this study was to investigate the effects of *Nigella sativa* seeds**,** oil and its fractions supplementation on metabolic status and selected menopausal parameters of ovariectomized rat.

### 1.5.2 Specific objectives

1. To determine the effect of *Nigella sativa* seeds on metabolic status and selected menopausal parameters of OVX rats by measuring their weight gain, lipid profile (including TC, TG, LDL and HDL) and blood glucose; serum estradiol, uterine histological changes and vaginal smear (vaginal cornified cells, endometrial and myometrial diameters, endometrial glands, epithelial cell height and uterine luminal dilatation).
2. To determine the effect of *Nigella sativa* oil fractions obtained by solvent extraction and supercritical fluid extraction (SFE), on metabolic status and selected menopausal parameters of OVX rats by measuring the weight gain, lipid profile (including TC, TG, LDL and HDL), blood glucose; serum estradiol and vaginal smear (vaginal cornified cells).
3. To determine the effect of some fractions of *Nigella sativa* on metabolic status and selected menopausal parameters of OVX rats by measuring the weight gain,

lipid profile (including TC, TG, LDL and HDL), blood glucose ; the serum estradiol, and vaginal smear (vaginal cornified cells).

### 1.6 Research Hypothesis

- *Nigella sativa* seeds can improve selected menopausal parameters of OVX rats by increasing serum E2, vaginal cornified cells, endometrial and myometrial diameters, endometrial glands, epithelial cell height and uterine luminal dilatation.
- *Nigella sativa* seeds, oil and its fractions can improve metabolic status of OVX rats by decreasing serum glucose, triglyceride, total cholesterol, low density lipoproteind, weight and increasing high density lipoprotein.
- *Nigella sativa* oil and its fractions can improve selected menopausal parameters of OVX rats by increasing serum E2 and vaginal cornified cells.
- Selected ingredients of *Nigella sativa* have estrogen-like effects which improve selected menopausal parameters of OVX rats by increasing serum E2 and vaginal cornified cells.
- Selected ingredients of *Nigella sativa* have estrogen-like effects that improve metabolic status of OVX rats by decreasing serum glucose, triglyceride, total cholesterol, low density lipoprotein, weight and increasing high density lipoprotein.

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