Effect of *Nigella sativa* Seed Extract for Hypertension in Elderly: a Double-blind, Randomized Controlled Trial

Aulia Rizka, Siti Setiati, Aida Lydia, Esthika Dewiasty

Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Aulia Rizka, MD, PhD. Division of Geriatric Medicine, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: dr. auliarizka@yahoo.co.id.

ABSTRAK

Latar belakang: *ekstrak biji Nigella sativa (NS) pada penelitian in vivo menunjukkan potensi sebagai anti hipertensi karena memiliki efek diuretik, meningkatkan produksi Oksida Nitrit dan menghambat overaktivitas sistem saraf simpatis, sehingga potensial digunakan sebagai obat anti hipertensi pada pasien usia lanjut. Penelitian ini bertujuan untuk mengetahui pengaruh pemberian ekstrak biji NS pada perubahan tekanan darah sistolik (TDS) dan tekanan darah diastolik (TDD) pasien usia lanjut dengan hipertensi.* ***Metode:*** *dilakukan uji klinis acak tersamar ganda mulai Juni hingga September 2011 terhadap 76 pasien usia lanjut dengan hipertensi di tiga poliklinik di RS Cipto Mangunkusumo Jakarta Indonesia. Dengan alokasi tersamar, subyek dibagi menjadi kelompok yang mendapat kapsul berisi ekstrak biji NS 300 mg sebanyak 2 kali sehari selama 28 hari dan kelompok yang mendapat plasebo. Tekanan darah (TD) diukur pada hari ke-1 dan ke-28. Dilakukan analisis dengan uji-t tidak berpasangan untuk melihat perbedaan tekanan darah pada kedua kelompok setelah intervensi dengan prinsip analisis intention to treat.* ***Hasil:*** *dari 85 subjek yang memenuhi kriteria awal, didapatkan 76 subjek yang sesuai kriteria penelitian dan dirandomisasi menjadi dua kelompok, masing-masing terdiri dari 38 subjek. Pada akhir pengamatan, TDS kelompok NS turun dari 160,4 (SD 15,7) menjadi 145,8 (SD 19,8) mmHg and pada plasebo turun dari 160,9 (SD 16,3) menjadi 147,53 (SD 22,0) mmHg (p=0,36). TDD pada kelompok NS turun dari 78,3 (SD 11,9) menjadi 74,4 (SD 8,2) dan pada kelompok plasebo turun dari 79,0 (SD 12,4) menjadi 78,2 (SD 8,9) mmHg. Efek simpang yang dilaporkan adalah dispepsia pada 6 subjek (15,7%), mual pada 3 subjek (7,8%) dan konstipasi pada 2 subjek (5,2%). Tidak didapatkan gangguan elektrolit, gangguan fungsi ginjal, hati, maupun hipotensi ortostatik.* ***Kesimpulan:*** *meskipun menunjukkan kecenderungan penurunan tekanan darah, Nigella sativa belum terbukti dapat menurunkan tekanan darah pasien usia lanjut dengan hipertensi.*

Kata kunci: *Nigella sativa, hipertensi, usia lanjut.*

ABSTRACT

Background: *Nigella sativa (NS) seed extract shows diuretic activity, inhibits sympathetic nervous system overactivity and increases the production of Nitric Oxide in in vivo studies, thus it has a potential use as an adjuvant antihypertensive for elderly population. This study aimed to determine the effect of Nigella sativa seed extract to systolic blood pressure (SBP) and diastolic blood pressure (DBP) of elderly patients with hypertension.* ***Methods:*** *a double-blind, randomized controlled trial was conducted on elderly subjects with hypertension in three outpatient clinics in Cipto Mangunkusumo National Hospital Jakarta Indonesia from June to September 2011. Subjects were divided into intervention group given 300 mg Nigella sativa seed extract twice daily for 28 days and into another group which was given placebo. Blood pressure were measured on day 1 and 28. Intention*

to treat analysis using unpaired t-test to compare blood pressure after intervention between the two groups was performed. ***Results:*** *of a total of 85 patients, 76 subjects fulfilled the study criteria and were randomized into 2 groups, with 38 subjects in each group. Both groups were comparable in all important prognostic factors. The mean systolic blood pressure of the NS group was decreased from 160.4 (SD 15.7) mmHg to 145.8 (SD 19.8) mmHg, and from 160.9 (16.3) mmHg to 147.53 (SD 22.0) mmHg in the placebo group (p=0.36). The mean diastolic blood pressure in the NS group was decreased from 78.3 (SD 11.9) to 74.4 (SD 8.2) mmHg, and from 79.0 (SD 12.4) to 78.2 (SD 8.9) in the placebo group (p=0.35). Reported adverse events include dyspepsia in 6 subjects (15.7%), nausea in 3 subjects (7.8%), and constipation in 2 subjects (5.2%). No electrolyte abnormalities, liver and renal toxicities, or orthostatic hypotension were observed.* ***Conclusion:*** *although a trend towards a slight decrease in blood pressure was observed, Nigella sativa has not been proven to be effective in reducing blood pressure in elderly patients with hypertension.*

Keywords: *Nigella sativa, hypertension, elderly.*

INTRODUCTION

To date, hypertension remains a major health problem in various countries. The financial burden, both direct and indirect, caused by hypertension is substantial. With cardiovascular complications that often follows, hypertension remains the number one cause of death in the elderly.[1,2] Results from Riset Kesehatan Dasar (Indonesian Basic Health Research) reporting that the prevalence of hypertension in Indonesia is 63.5% in populations aged 65-74 years old and 67.2% for those aged 75 years or more.[3] Despite this high prevalence, control of hypertension remains very poor in this population.[4] With the increase of elderly population in Indonesia which is predicted to reach 414% within 35 years, this problem becomes more important.[5]

The importance in decreasing blood pressure in elderly patients has been proven by a meta-analysis on seven large scale clinical trials involving a total of 1,670 patients. The analysis concluded that a decrease in blood pressure in patients aged over 60 years will reduce mortality and cardiovascular events significantly within the next 4.5 years.[6] Reducing 10 mmHg of systolic blood pressure or 5 mmHg of diastolic blood pressure at the age of 65 means reducing the risk of myocardial infarction by 25%, reducing the risk of stroke by 40%, and reducing the risk of congestive heart failure by 50%.[7]

Nigella sativa, which is known in Indonesian as jinten hitam (black cumin) or habatussauda, is a dicotyledon from the family Ranunculaceae which has been used to resolve various diseases since hundreds of years ago.[8] Experimental studies on animal models have proven that the biological effects of *Nigella sativa* including its effect in diuresis, decreasing sympathetic activities, and improving lipid profile, are potentially beneficial for the treatment of hypertension.[9-11] In relation to the rigidity of arteries, which is a pathogenesis characteristic of hypertension in the elderly, *Nigella sativa* also increases the production of nitrite oxide which may inhibit the rigidity of arteries.[11]

Previous clinical trials by Dehkordi[12] and Qidwai[13] involving adult patients with hypertension were unable to show conclusive results. To our knowledge, no clinical trial has been able to prove the efficacy of *Nigella sativa* in elderly with hypertension, therefore we wished to perform a clinical trial to prove its efficacy in decreasing blood pressure in this specific population.

METHODS

This study was a double-blind, controlled, randomized clinical trial aimed to investigate the role of Nigella sativa in decreasing the blood pressure of elderly patients with hypertension. This study was conducted in June – September 2011 at the Geriatric Outpatient Clinic, Renal-Hypertension Outpatient Clinic, and Internal Medicine Outpatient Clinic of the Faculty of Medicine of the University of Indonesia/Cipto Mangunkusumo National Hospital. The inclusion criteria were patients aged ≥60 years with hypertension (SBP>140 mmHg and or DBP>90

mmHg). The exclusion criteria were patients with decreased renal function (Glomerular Filtration Rate <30 ml/m^3), decreased liver function (increased SGPT over 2 times the upper normal limit), severe dementia, depression, orthostatic hypertension, malignant hypertension, having consumed more than three antihypertensive agents at maximum dose and refusing to participate in the study.

In order to calculate the minimum sample size required to acquire a difference in mean blood pressure after the intervention between the intervention and control groups, the sample size formula for independent numerical data was used, with standard deviation data taken from Qidwai's study.[13] Differences deemed significant were 10 mmHg for SBP (systolic blood pressure) and 5 mmHg for DBP (diastolic blood pressure), with α=0.05 and power 80%. The minimum sample size required was 64 subjects.

Subjects were randomized into two groups, in which one group received Nigella sativa and another group received placebo at the time of visit. Allocation concealment was also performed. Each patient received 2 capsules per day for 28 days. Patients in the treatment group received capsules containing a dose of 300 mg Nigella sativa extracts, whereas patients in the placebo group received capsules of similar color, weight, and smell containing flour. Both the investigator and study subjects had no knowledge of the randomized allocation (i.e. double-blind).

Patients were allowed to consume antihypertensive medications previously taken. Lifestyle, dietary habits (including salt, fat, and vegetable intake), smoking habits, exercising habits, and other supplementation usage were continued normally. In order to ensure that the drugs were taken by the patients, they were packaged in plastic which needed to be torn before consumption and was counted during examination on the 28th day. Furthermore, a family member or caregiver would be asked to ensure that the drugs were consumed properly and to mark a tick on the drug consumption form. Prior to drug administration, patients underwent interview, physical examination (including body mass index and blood pressure) and laboratory examination. Blood pressure measurement was performed using validated BP monitor (Omron, Kyoto Japan). On day 28, the patient would revisit the clinic for another round of interview, physical examination, and laboratory examination. Patients were deemed to have completed the study if they were present at the examination on day 28 and have consumed all of the drugs with the assigned dose.

Characteristics (especially characteristics which may potentially affect the decrease in blood pressure such as age, drugs consumed and duration of hypertension) in each of the Nigella sativa and placebo group were presented as means with standard deviation for numerical variables or as a proportion if the variables were categorical. A difference in blood pressure between the Nigella sativa and placebo group after the intervention were analyzed with unpaired t-test or its alternatives. All analysis would apply a significance level of 5%, in conjunction with its 95% confidence interval. Analysis at the end of the study were performed under the intention to treat analysis principles.

This study was performed conforming to the Helsinki declaration, Guideline for Good Clinical Practice from ICH Tripartite and consistent with the rules of clinical trials in Indonesia. Written consent had been obtained from each subject and the protocol of this study had approved by local independent ethical committee, numbered 283/PT02.FK/ETIK/2011.

RESULTS

Between July and September 2011, 76 hypertension patients fulfilled the study subject selection criteria. The patients then received drugs according to codes listed on a previously determined randomization table. At the start of the study, there were 38 subjects who were given *Nigella sativa* and the remaining 38 subjects were given placebo. As many as 7 subjects (9.2%), which consisted of 5 subjects receiving *Nigella sativa* and 2 subjects receiving placebo did not complete the study due to nausea (4 subjects; 5.2%), emergency surgery for abdominal trauma (1 subject; 1%), and forgetfulness (2 subjects; 2.6%). A total of 69 patients completed of the study, consisting of 33 subjects in the *Nigella sativa* group and 36 subjects in the control group

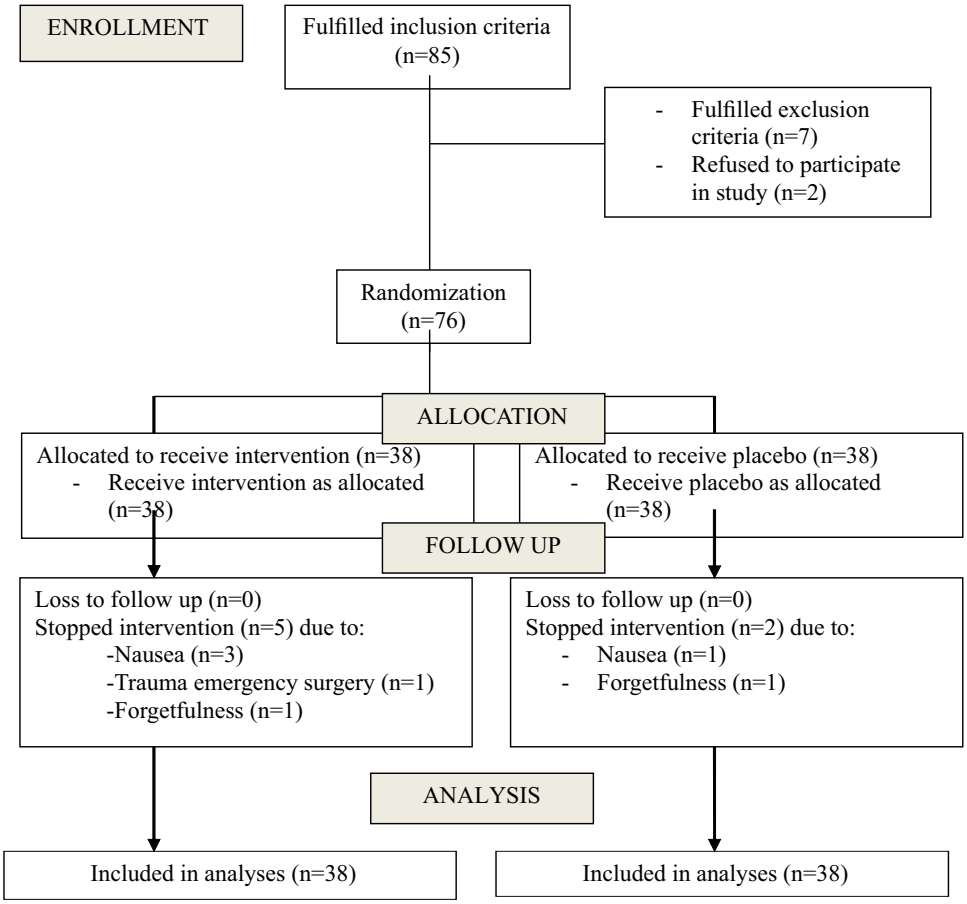

Figure 1. Study flowchart

as presented in **Figure 1**. Patients who completed the study declared that they have consumed all the drugs on the previously assigned dose. Gastrointestinal disorders in the form of nausea and gastric discomfort were reported in six subjects receiving *Nigella sativa*, one of whom experienced vomiting without signs of dehydration, and two others reported difficulty in defecation.

As presented in **Table 1**, subject characteristics were comparable across all considered prognostic factors. At the end of the study, a repeat blood pressure measurement was performed and a tendency towards a reduced SBP was observed. This was clinically important but not statistically significant (p=0.36), as presented in **Table 2**. No significant decrease in DBP (p=0.35) was observed in the group receiving *Nigella sativa*, as presented in **Table 3**.

DISCUSSION

Subject characteristics in this study differs relatively from that of a study by Kamso, et al.[14] involving 565 elderly patients with hypertension, who were randomly selected from patients of a Public Health Centers in Special Capital Region of Jakarta, Indonesia. Although most of the subjects were females, similar to that of Kamso's study, the mean age in this study was significantly higher (72 years old in the intervention group and 73.8 years old in the control group compared to 65.9 years old in Kamso's study). Mean SBP in this study was also much higher which was 160.4 mmHg in the intervention group and 160.9 mmHg in the control group compared to 141 mmHg in the Kamso study.

To date, only two studies were known to have investigated the effects of *Nigella sativa* on blood pressure, the studies of Dehkordi and Qidwai, both observed the young adult population.[12,13]

Table 1. Baseline study subjects characteristics

Variables	*Nigella sativa* (n=38)	Placebo (n=38)
Male, %	13 (34)	8 (21)
Age (years), mean (SD)	72 (5.9)	73.8(6.8)
Education ≤ middle school, %	8 (21)	10 (26)
Duration of HT <5 years, %	21 (55)	22 (57.9)
BMI (kg/m^2), mean (SD)	24.5(3.5)	24.2(5.2)
SBP (mmHg), mean (SD)	159.4 (15.7)	160 (16,3)
DBP (mmHg), mean (SD)	78.7 (10.9)	79.2 (12.8)
Isolated Systolic Hypertension, %	23 (60)	25 (65)
Grade 1 HT, %	8 (21)	9 (24)
>2 types antihypertensive agents, %	6 (15.7)	8 (21)
Routine consumption of antihypertensive agents	33 (86.8)	32 (84.2)
Type of antihypertensive agent		
- ACE inhibitor, %	10 (26)	8 (21)
- Angiotensin receptor blocker, %	8 (21)	6 (15.7)
- Calcium channel blocker, %	5 (13.1)	4 (10.5)
- Diuretics, %	0 (0)	1 (2)
- Combination of ACE inhibitor and calcium channel blocker, %	7 (18.4)	9 (24)
- Combination of angiotensin receptor blocker and calcium channel blocker, %	2 (5.2)	1 (2)
- Combination of ACE inhibitor, calcium channel blocker, and beta blocker, %	4 (10.5)	5 (13.1)
- Combination of ACE inhibitor, calcium channel blocker, and alpha blocker, %	2 (5.2)	3 (7.9)
> 6 total drugs consumed, %	8 (21)	7 (18.4)
Routine NSAID use, %	2 (5.2)	3 (7.9)
Routine steroid use, %	0 (0)	0 (0)
Alcohol consumption >1 glass a day, %	0 (0)	0 (0)
Salt consumption >1 tsp./day, %	10 (26)	13 (34.2)
Smoking >10 cigarettes a day	1 (2)	1 (2)
Routine exercise <2x a week @ 30 minutes, %	25 (65)	23 (63)
Coffee consumption >2 cups a day, %	0 (0)	0 (0)
Diabetes Mellitus, %	13 (34.2)	14 (36.8)
Dyslipidemia, %	2 (5)	1 (2.6)
Albumin (mg/dL), mean (SD)	4.2 (0.37)	4.1 (0.39)
Creatinine (mg/dL), mean (SD)	0.85 (0.17)	0.91 (0.17)
SGPT (mg/dL), mean (SD)	19.5 (6.4)	21.22 (8.3)
Proteinuria more than +1, %	4 (10.5)	6 (15.7)

Table 2. Effects of *Nigella sativa* to systolic blood pressure

	Before treatment mmHg (SB)	After treatment mmHg (SB)	Delta (mmHg)
Nigella sativa (n=33)	160.4 (15.7)	145.8 (19.8)	14.6
Placebo (n=36)	160.9 (16.3)	147.53 (22.0)	13.3
		P=0.36*	

* unpaired t-test

Table 3. Effects of *Nigella sativa* to dyastolic blood pressure

	Before treatment mmHg (SB)	After treatment mmHg (SB)	Delta (mmHg)
Nigella sativa (n=33)	78.3 (11.9)	74.4 (8.2)	3.9
Placebo (n=36)	79.0 (12.4)	78.2 (8.9)	0.8
		P=0.35*	

* unpaired t-test

Qidwai's study observed blood pressure as a secondary outcome with the primary outcome being lipid profile.[13]

There were two important points found in this study. Firstly, the administration of *Nigella sativa* seed extract with a dose of 300 mg twice a day for 28 days in elderly patients with hypertension could not significantly reduce SBP and DBP. A study by Dehkordi[12] tested the effects of *Nigella sativa* on mild hypertension in young adult subjects produced statistically significant decrease in blood pressure with 2 mmHg decrease in SBP after a 2x200 mg dose regimen for 4 weeks. The Qidwai study used a 2x500 mg dose for 6 weeks and displayed higher SBP reduction (5.16 mmHg), although it has poor internal validity with a high dropout percentage, reaching 42%, due to low compliance.[13] The findings of the current study differ from the other two studies performed in a young adult population. The lack of therapeutic effects from *Nigella sativa* in this study compared to placebo appears to be unrelated to the dosage or duration, considering that the blood pressure was clinically reduced. One explanation for this is the rigidity of arteries, which is an important part of the pathogenesis of hypertension in the elderly, impedes the activity of *Nigella sativa* in reducing blood pressure. Although *Nigella sativa* was found to improve hypertension through inhibition on alpha adrenoceptors after sympathetic stimuli, increasing the production of nitrite oxide, anti-inflammatory activities, and anti-sclerotic effects in in vivo studies performed on animals, it appears that those various mechanisms weren't able to improve the rigidity of arteries in the elderly.

Another possible explanation is that sex characteristic of study subjects, which was dominated by females, plays a role in impeding the effect of *Nigella sativa* in reducing blood pressure. Blood pressure in elderly women has been known to be harder to control compared to elderly men.[15] Data from NHANES noted that the difficulty of controlling blood pressure in female patients stems from the higher prevalence of other cardiovascular risk factors in women, such as central obesity, increased total cholesterol level, and low LDL (low density lipoprotein) level.[16]

This study also found that *Nigella sativa* had no influence on diastolic blood pressure. As previously noted, most subjects suffer from Isolated Systolic Hypertension, a condition where the systolic blood pressure is high with normal or low diastolic blood pressure. The rigidity of arteries present in the elderly is a good explanation of that concept, while normal or even low DBP may be caused by the inability of the aorta or other arteries to enlarge during systole and contract during diastole, making it hard for DBP to increase.

Although gastrointestinal adverse events were not severe and most were resolved with the administration of proton pump inhibitors and increased intake of fiber consumption, they were quite bothersome for elderly patients considering their physiologically decreased meal intake compared to younger patients. These gastrointestinal disorders may potentially decrease fluid intake even further which will increase the risk of dehydration.

Gastrointestinal disorders were not reported in the Dehkordi[12] and Qidwai[13] studies on young adult patients. The difference in subject characteristics may explain the occurrence of said gastrointestinal adverse events. Elderly patients also often consume other medications which may cause dyspepsia, such as NSAIDs, steroids, or anti-platelet related to their comorbidities. Comorbidities such as diabetic gastroparesis, worsens the symptoms of patients with previous history of dyspepsia due to medication. Although packaged in capsules, interactions between this medication and *Nigella sativa* in the stomach with delayed emptying movements may have triggered dyspepsia. No side effects on the liver and kidney were found, similar to findings of the Dehkordi and Qidwai studies.[12,13]

The advantages of this study lies in its design (randomized, double-blind clinical trial), which is the best for experimental studies, and in it being the first clinical trial investigating the effects of *Nigella sativa* in the elderly. This study is also the first one to confirm that *Nigella sativa* has no therapeutic effects in elderly patients with hypertension.

The limitations of this study lies in the fact

that the blood pressure measurements were only performed at the start and the end of intervention without any measurements taken between the two points in time. As a result, blood pressure fluctuations were not evaluated. Another limitation is the relatively short duration of study.

CONCLUSION

Despite showing a clinically significant decrease in systolic blood pressure, *Nigella sativa* has not been proven to improve hypertension in the elderly. *Nigella sativa* also has not been proven to reduce diastolic blood pressure in elderly patients.

REFERENCES

1. Bayley K, Grossardt B, Graves J. Novel use of Kaplan Meier methods to explain age and gender differences in hypertension control rates. Hypertension. 2008;51:841-47.
2. Centers for Disease Control and Prevention. Racial/ethnic disparities in prevalence, treatment, and control of hypertension in the United States, 1999-2002. MMWR Morb Mortal Wkly Rep. 2007;54:7-9.
3. Departemen Kesehatan Nasional. Riset Kesehatan Dasar 2007 [internet]. Jakarta: Badan Penelitian dan Pengembangan Kesehatan Departemen Kesehatan; 2008 [cited on May 10th 2011]. Downloaded from http://kgm.bappenas.go.id/index.php?hal=13&keyIdHead=10.
4. Gunawan D, Setiati S. Proporsi hipertensi pada usia lanjut dan faktor-faktor yang mempengaruhi keterkontrolannya [Thesis]. Jakarta: Universitas Indonesia: 2010.
5. Soejono CH. Pengkajian paripurna pada pasien geriatri. In: Sudoyo AW, Setyohadi B, Alwi I, Kolopaking MS, Setiati S, editors. Buku ajar ilmu penyakit dalam. 4th ed. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam; 2006. p.1425.
6. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev. 2009;4:CD000028.
7. Chobanian A, Bakris G, Black H, Cushman W, Green L. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treament of High Blood Pressure. Hypertension. 2003;42:1206-52.
8. Salem ML. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. Int. J. Immunopharmacol. 2005; 5:1749–70.
9. Nader MA, el Agami DS, Suddek GM. Protective effects of propolis and thymoquinone on development of atherosclerosis in cholesterol-fed rabbits. Arch Pharm Res. 2010;337:637-43.
10. ElTahir K, Ashour MM, al-harbi MM. The cardiovascular actions of the volatile oil of the black seed (*Nigella sativa*) in rats: elucidation of the mechanism of action. Gen Pharmacol. 1993;24(5):1123-31.
11. Ubru U, Burak U, Yusuf S, Reyhan B, Arif K, Faruk TH. Cardioprotective effects of *Nigella sativa* oil on cyclosporine A-induced cardiotoxicity in rats. Basic Clin Pharmacol Toxicol. 2008;103(6):574-80.
12. Dehkordi F, Kamkhah A. Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. Fundamental and Clin Pharmacol. 2008;22:447-52.
13. Qidwai W, Hamza H, Qureshi R, Gilani A. Effectiveness, safety, and tolerability of powdered *Nigella sativa* (Kalonji) seed in capsules on serum lipid levels, blood sugar, blood pressure, and body weight in adults: Results of a randomized, double-blind controlled trial. J Altern Compl Med. 2009;15:639-44.
14. Kamso S, Rumawas J, Lukito W, Purwantyastuti. Determinants of blood pressure among Indonesian elderly individuals who are of normal and overweight: a cross sectional study in an urban population. Asia Pac J Clin Nutr. 2007;16(3):546-53.
15. Lloyd Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. JAMA. 2005;294:466-72.
16. Ong KL, Tso AW, Lam KS, et al. Gender difference in blood pressure control and cardiovascular risk factors in Americans with diagnosed hypertension. Hypertension. 2008;51:1142-8.