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Penile erection responses of *Nigella sativa* seed extract on isolated rat corpus cavernosum

M Aminyoto*¹ and S Ismail^{2,3}

¹Department of Community Medicine, Faculty of Medicine, Mulawarman University, Jl. Kerayan Kampus Gn. Kelua, Samarinda, Indonesia

²Research Center on Drugs and Public Health, University of Mulawarman, Jl. Kerayan Kampus Gn. Kelua, Samarinda, Indonesia

³Pharmacology Laboratory, Faculty of Medicine, Mulawarman University, Jl. Kerayan Kampus Gn. Kelua, Samarinda, Indonesia

*Corresponding author: meiliati.aminyoto@gmail.com

Abstract. *Nigella sativa* L. (NS) from Ranunculaceae family is known as black cumin in Indonesia. The seed has been used as an aphrodisiac in ethnobotanical studies and reported to have pharmacological activities such as antihypertensive through the relaxant effect of vascular smooth muscles but the direct effect to the blood vessels of the corpus cavernosum is still unknown. The purpose of this study was to examine the response of NS seed extract on penile erection in vitro. NS seeds were macerated in ethanol solvent for three days in room temperature and repeated for two times. Penile erection responses was assessed using isolated rat corpus cavernosum in Krebs-Henseleit solution, temperature 37°C, pH 7.4, aerated with carbogen gas. After acclimation, corpus cavernosum was contracted with a phenylephrine solution. Ethanolic extract of NS seeds or control solution were given after reaching the plateau phase of the highest contraction. This study showed that the contraction response of the corpus cavernosum decreased after addition of NS extract and this action was increased with the addition of the extract concentration. This study concluded that NS seed ethanol extract affects the penile erection response directly through the relaxation of blood vessels in the corpus cavernosum.

1. Introduction

Nigella sativa L. (NS) from Ranunculaceae family is well known in Southern Europe, North Africa, Middle East, Middle Asia and Far East as a natural remedy for several disorders. The seed also called as black seed, black cumin, habbatussauda, habbatul barakah. In Indonesia, it also calls as jintan hitam. Many studies have been conducted on the effect of *Nigella sativa* seed extract on various body systems and reported on several pharmacologic activities including anti-hypertensive, anti-inflammatory, antimicrobial, antidiabetic, antihistaminic, insulinotropic, hepatoprotective, antiulcer, and bronchodilator. Most of the pharmacological properties of the *Nigella sativa* seed extract mainly due to quinine constituents, which the major one is thymoquinone. The seed also contain essential oil, protein, alkaloids and saponin [1,2]

Nigella sativa seed extract also reported to have benefits in male infertility. The increased levels of testosterone and follicle stimulating hormone (FSH) in testicular tissue after *Nigella sativa* seed extract administered have been shown to increase sperm concentration, enhancing reproductive performance, sperm motility and sperm quality [3].



Aphrodisiac is any food or drug that arouses sexual desire, increases pleasure and sexual performance. These substances are derived from plants, animals or minerals [4]. Medicinal plants that act as aphrodisiac have a potential to use in the treatment of erectile dysfunction. Erectile dysfunction can cause relationship difficulties among the couples, characterized by inability to develop or maintain an adequate erection of the penis [5].

World Health Organization (WHO) have been reported that traditional medicine or non-conventional medicine is found in almost every country in the world with an increasing number of users and facilities. Even in some countries where the conventional health-care system is quite well established, more than 70% of the population still commonly use traditional medicine [6]. The demand of herbal medicine is increasing because they are considered safer and well tolerated compared to the allopathic drugs [7]. Therefore, it is necessary to scientifically study on the herbal or traditional medicine in order to develop an evidence based medicine.

There is currently not much evidence regarding the effects of *Nigella sativa* seed as an aphrodisiac. Thus, the primary endpoint of this research was to examine the response of *Nigella sativa* seed extract on penile erection in vitro.



Figure 1. *Nigella sativa* seed

2. Material and Methods

2.1. Study design

This study was conducted as a post-test only control group trial. All the experimental procedures were conducted in Pharmacology Laboratory, Faculty of Medicine, Mulawarman University. Ethical approval was granted by the Health Research Ethics Committee, Faculty of Medicine, Mulawarman University with the reference number 211/KEPK-FK/XI/2016.

2.2. Sample preparation

Nigella sativa seeds were purchased from a local herbal shop in Samarinda, East Kalimantan Province. Identification of *Nigella sativa* seeds was done by plant taxonomists from the Faculty of Forestry, Mulawarman University (reference 78/UN17.4.3.08/LL2016).

2.3. Sample maceration and extraction

The seeds were ground into powder then added to the macerator. One part of the seed powder was diluted with 10 parts of absolute ethanol solvent. It was soaked for 6 hours and stirred occasionally with an orbital shaker 20 rpm for 10 minutes then stayed for three days in room temperature. The maceration solution was filtered using Whatman filter paper. All the process was repeated two times. The macerates were collected and evaporated with rotavapor vacuum, temperature 50°C, which yields a concentrated extract. The extract was dried by putting into a dessicator containing blue silica gel in an oven with temperature 50°C for one week [8].

2.4. Animal maintenance and preparation

This study used isolated rat corpus cavernosum to prove the efficacy of *Nigella sativa* seed extract as an aphrodisiac. The rats were euthanized by overdose ketamine injection then their penis excised. Dorsal penile vein and spongiosae tissues were removed carefully. Strips of corpus cavernosum were mounted in organ bath containing physiologic solution (Krebs-Henseleit) at 37°C temperature, pH 7.4, continuously aerated with carbogen gas and connected to an isometric transducer (resting tension 250 mg).

After 60 minutes stabilization period, corpus cavernosum was contracted with 10 μ M phenylephrine solution to test the smooth muscles integrity. The smooth muscles considered in a good condition if there was a contraction response. Then it rinsed with the physiologic solution every 15 minutes until the muscle tone back to the basal condition. Further, corpus cavernosum were induced by the addition of 10 μ M phenylephrine. After reaching the plateau tonic phase, corpus cavernosum was exposed to the cumulative concentrations of *Nigella sativa* seed extract (0.03, 0.1, 0.3, 1, and 3 mg/ml). Same amount of solvent solution were used as a control. The resulting relaxation of the smooth muscle was recorded and evaluated. The same protocol was repeated 5 times. Negative results indicate a relaxation activity and otherwise a positive value indicates contraction activity.

2.5. Statistical analysis

Data obtained were analyzed using the Statistical Package for the Social Sciences (SPSS) software. Activity of the smooth muscles are expressed as mean \pm SE and showed in dose response curve. All the data examined with the t-test after assessed as normal distributed and normal variance. Significance was set at $p < 0.05$.

3. Results and Discussion

Extract of *Nigella sativa* seed have vasodilation activity to the corpus cavernosum characterized by negative contraction percentage. The expected effect of *Nigella sativa* seed extract addition to the isolated rat corpus cavernosum was a vasodilation of blood vessels to prove that *Nigella sativa* seed extract effective as an aphrodisiac to maintain penile erection. The percentage of corpus cavernosum contraction response after given *Nigella sativa* seed extract is shown in table 1. Positive values indicated the opposite effect than expected resulting the flaccid state of the penis. Vasodilation activity was initially recorded at the concentration level 0.1 mg/ml with the percentage contraction value -1.57 ± 0.81 and this effect was strengthened with the addition of cumulative dose. Significant differences between the effects of *Nigella sativa* seed extracts compared to control solution were also found starting from the organ exposure to concentration level 0.1 mg/ml ($p < 0.05$). Emax value was obtained from the experimental data -23.84 ± 1.24 ($p < 0.05$).

Table 1. Contraction response percentage of corpus cavernosum after exposed to NS seed extract

Concentration of extract (mg/ml)	Contraction percentage of control solution (Mean \pm SE)	Contraction percentage of NS seed extract (Mean \pm SE)
0.03	2.18 ± 0.32	1.02 ± 0.78
0.1	1.45 ± 0.37	$-1.57 \pm 0.81^*$
0.3	0.31 ± 0.44	$-5.27 \pm 0.52^*$
1	-0.75 ± 0.43	$-9.92 \pm 0.69^*$
3	-1.82 ± 0.53	$-16.10 \pm 0.90^*$

n=5 rats . Statistical analysis with *t*-test. *significantly different compared to control

Figure 2 shows the corpus cavernosum contraction activity dose response curve of *Nigella sativa* seed extract compared to control solution at the same concentration. Increased concentrations of control fluid or solvent may result in a mildly negative contraction percentage, -1.82 ± 0.53 at the concentration

3 mg/ml, meaning that the solvent causing mild vasodilation of the blood vessels within the rat corpus cavernosum.

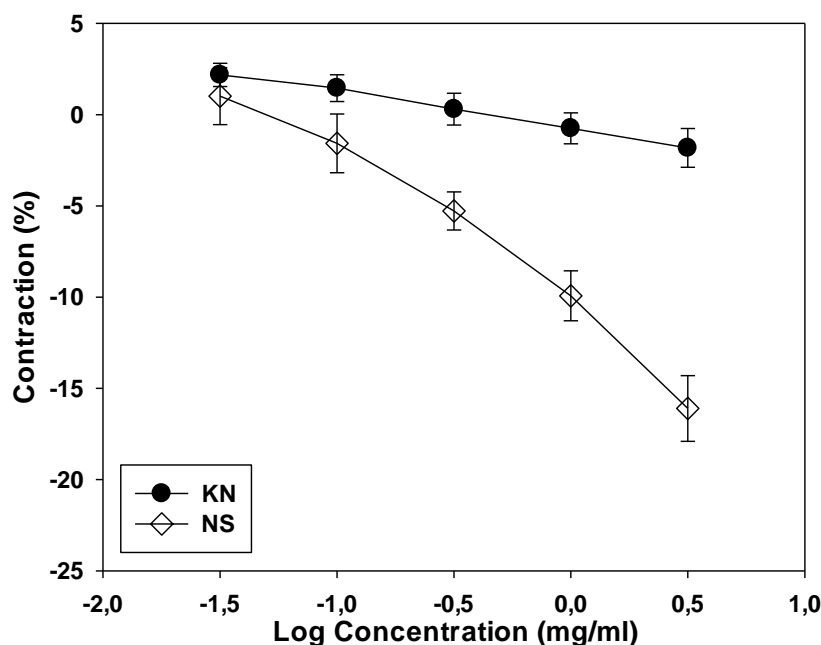


Figure 2. Dose-response curve of *Nigella sativa* seed extract and control solution effects to the corpus cavernosum contraction

Our results confirmed negative contraction response of the penile after administration of *Nigella sativa* extract. Mechanism of action of vasodilation in the corpus cavernosum needs further investigation whether influenced by vascular endothelium via eNOS (endothelial nitric oxide synthase) or by inhibition of phosphodiesterase enzyme. Activation of eNOS by an agonist in the vascular endothelium will release nitric oxide (NO) which can diffuse easily into the smooth muscle of the blood vessels that present in the corpus cavernosum of the penis. NO will activate GC (guanylate cyclase) then GC are responsible for the conversion of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). cGMP stimulates calcium ions release out from the blood vessel smooth muscle resulting the penile relaxation. NO can also be release if there is sexual stimulation or the effect of some drugs [9].

Decreased calcium ions in the blood vessel smooth muscle within the corpus cavernosum can also because of the inhibition of phosphodiesterase enzyme (PDE). This enzyme plays role to convert cAMP (cyclic adenosine monophosphate) or cGMP into AMP or GMP. Inhibition to this enzyme will cause cGMP levels remain high then the blood vessels in corpus cavernosum remains in relaxation state allowing more blood filled into the corpus cavernosum, the penis will remain erect or increasingly tense [9-11].

Several studies on *Nigella sativa* seeds related to its benefit on male infertility, none as we know have studied the direct effect on penile erection. *Nigella sativa* have been reported increasing reproductive parameters (seminiferous tubules thickness and diameters, account of spermatogonia, primary and secondary spermatocytes, spermatids, free spermatozoa, account of sertoli and Leydig cells, diameter of Leydig cells and the height of epithelial cells entirely covered epididymal caudal), stimulates testosterone and follicle stimulating hormones as well as protein concentration. The results need to be confirmed with further experimental study as this was set in vitro [12].

4. Conclusion

The present results confirmed that *Nigella sativa* seed extract affects the penile erection response directly through the relaxation of the blood vessels in the corpus cavernosum of male rats. This result may support the use of *Nigella sativa* seed as sexual enhancing remedies. Further investigations are required to explore the mechanism of action of *Nigella sativa* seed as an aphrodisiac.

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