March 2001

# Bronchodilator, spasmolytic and calcium antagonist activities of Nigella sativa seeds (Kalonji): a traditional herbal product with multiple medicinal uses

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# Bronchodilator, Spasmolytic and Calcium Antagonist Activities of Nigella Sativa seeds (Kalonji): a traditional herbal product with Multiple Medicinal Uses

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## Abstract

**Objective:** The seeds of Nigella sativa locally known as "Kalonji" has been used in traditional medicine for the treatment of a variety of diseases including diarrhoea and asthma. The crude extract of N. sativa seeds (Ns.Cr) was studied in vitro for its possible spasmolytic and bronchodilator activities to rationalize the folkloric uses.

**Methods:** Isolated rabbit jejunum and guinea-pig tracheal preparations were set up in Tyrode's and Kreb's solutions respectively and aerated with 5% $CO_2$ in oxygen. Isotonic and isometric responses were measured on Bioscience oscillograph and Grass polygraph respectively.

**Results:** The Ns.Cr caused a dose-dependent (0.1 - 3.0 mg/ml) relaxation of spontaneous contractions in rabbit jejunum. Ns.Cr also inhibited K+-induced contractions in a similar dose range, suggestive of calcium channel blockade (CCB). This effect was confirmed when pretreatment of the tissue with Ns.Cr, produced a dose-dependent shift in the Ca++ dose-response curves to the right similar to that of verapamil, a standard calcium channel blocker. In guinea-pig trachea, it caused relaxation of carbachol-, histamine- or K+-induced contractions indicating CCB. Activity-directed fractionation revealed that the CCB activity is concentrated in the petroleum ether fraction, which was found to be approximately 10 times more potent than the crude extract both in jejunum and tracheal preparations.

**Conclusion:** These data indicate that the crude extract of Nigella sativa seeds exhibits spasmolytic and bronchodilator activities mediated possibly through calcium channel blockade and this activity is concentrated in the organic fraction. Its usefulness for diarrhoea and asthma in traditional medicine, appears thus to be based on a sound mechanistic background (JPMA 51:115;2001).

## Introduction

Nigella sativa Linn. belongs to family Ranunculaceae. The herb is widely grown in different parts of the world and its seeds are used as condiment. In south Asia it is known as "Kalonji" and its Arabic name is "Habat-ul Sauda"[1]. In the Western world, it is known as "Black cumin"[2]. In the traditional system of medicine, it is recommended in a wide range of ailments including, asthma, chronic headache, migraine, chest congestion, dysmenorrhoea, infections (both fungal and bacterial), obesity, paralysis, hemiplegia, back pain, rheumatism, hypertension and GI problems, like dyspepsia, flatulence and diarrhoea[1,3]. It has also been used as stimulant, diuretic, emmenagogue, lactagogue and anthelmintic. Its use in asthma and eczema has also been recognized worldwide[4].

Phytochemical studies on seeds revealed the presence of volatile oil (1.5%), fixed oil (37.5%) nigellin, melanthin and arabic acid[1], and thimoquinone[5]. The volatile oil consists mainly of carvone (45-60%), carvene and cymene[1] and thymoquinone[6]. Pharmacological effects of the isolated alkaloids from N. sativa seeds viz. nigellidine, nigellimine and nigellicine have not been reported.[7-9]

The popularity of the plant was highly enhanced by the ideological belief in the herb as a cure for multiple diseases. In fact, this plant has occupied special place for its wide range of medicinal value in the Islamic civilizations. Due to the sayings of Holy Prophet, Muhammed (peace be upon him) that the plant is full of medicinal value[10], it gained immense popularity.

Consequently, Kalonji has been extensively studied particularly in the Islamic world, which justifies its broad traditional therapeutic value. It was found to have antimicrobial[11,12], anthelmintic[13,14], wound healing[15], antioxytocic[16], antilipaemic[17,18], antiplaque[19], CNS depressant and analgesic[20], antifertility[21], anticancer[22-25], antiulcer[26], post-coital contraceptive[27], antiimplantation[28], histamine release inhibitor[29], antihypertensive[6], antiinflammatory[30], antidiabetic[31] antispasmodic and renal protective properties[32].

However, the plant has not been studied to provide the scientific basis for its use in asthma or diarrhoea. In this investigation, we provide evidence that the crude extract of Nigella sativa seeds contains calcium channel blocker(s), which may explain some of its traditional therapeutic uses, viz, diarrhoea, asthma and hypertension. Furthermore, activity-directed fractionation revealed that the activity reported in the crude extract might be due the presence of active principle(s) concentrated in the petroleum fraction and the further studies in collaboration of chemists are likely to yield interesting results.

## Material and Methods

### Drugs and Chemicals

The following reference materials were obtained from the Sigma Chem. Co. St. Louis, USA: acetylcholine chloride, carbachol (carbamylcholine chloride), histamine phosphate and verapamil hydrochloride.

### Plant material, extraction and fractionation

The seeds of Nigella sativa were purchased from the local market of Karachi, authenticated with the help of a botanist (Afzal Rizvi) at the Hamdard University, Karachi and the sample voucher has been submitted at the herbarium of the University. Seeds were ground to powder and soaked in 70% aqueous-methanol for three days and filtered. This procedure was repeated twice on the residue. All the filtrates were combined and concentrated under reduced pressure on a rotary evaporator below 40°C. The brownish black crude extract, yielding about 11% was coded as Ns.Cr.

Ns.Cr was subjected to activity-directed fractionation by dissolving the crude extract in minimal amount of distilled water and successively extracted with different solvents of increasing polarity (Petroleum ether, Ethyl Acetate and Butanol) as shown in Scheme 1. The yields of different fractions were calculated as 1.98% of petroleum ether (Ns.Pet), 4.77% of ethyl acetate (Ns.EtAc), 22.09% of butanol (Ns.But) and 71.16% of aqueous (Ns. Aq) fractions.

### Animals

Rabbits (1.5-2.0 kg) and guinea pigs (500-600 g) of local breed and either sex, housed at the Animal House of the Aga Khan University, Karachi, were used for this study. Animals had free access to water but food was withdrawn 24 hours prior to experiment in case of rabbit for the use of jejunum. Rabbits were sacrificed by blow on the back of the head and guinea pigs were sacrificed by cervical dislocation.

### Rabbit jejunum

Spasmolytic action of the plant materials was studied by using isolated rabbit jejunum as described previously[33]. Segments of jejunum (2 cm) were suspended in Tyrode's solution bubbled with a mixture of 95% oxygen and 5% carbon dioxide and maintained at 37°C. The composition of the Tyrode's solution in mM was: KCl 2.68, NaCl 136.9, $MgCl_2$ 1.05, $NaHCO_3$ 11.90, $NaH_2PO_4$ 0.42, $CaCl_2$ 1.8, and glucose 5.55. Intestinal responses were recorded isotonically using BioScience transducers and an oscillograph. Each tissue was allowed to equilibrate under the 1 g resting tension for at least 30 min before the addition of any drug. Under these experimental conditions, rabbit jejunum exhibited spontaneous, rhythmic contractions and allowed the test of relaxant (spasmolytic) activity directly without the use of an agonist.

### Guinea-pig trachea

Bronchodilator activity was studied by using guinea-pig tracheal strip preparations as described previously[34]. Tracheal strip preparations were set up in Kreb's solution of the following composition in mM: NaCl, 118.0; KCl, 4.7; $MgSO_4$, 1.64; KH2$PO_4$, 1.2; D-glucose, 5.55; $NaHCO_3$, 25.0 and $CaCl_2$, 2.5. A basal tension of 2g was applied to each tissue and the tissue was allowed to equilibrate at least for two hours. Under these experimental conditions, the tissue behaved as quiescent preparation. Carbachol, histamine and K+ were used as bronchoconstrictors, which produced sustained contractions and the relaxant activity of both crude extract and the petroleum fraction was assessed by adding the test materials in a cumulative fashion[35].

### Calcium antagonist activity

For the determination of calcium antagonist activity, both preparations were used and $K^+$ was used to depolarize the preparations as described by Farre et al[36]. $K^+$ (50 mM) was added to the tissue bath, which produced a sustained contraction. Plant extract was then added in a cumulative fashion to obtain concentration-dependent inhibitory responses. The relaxation of intestinal preparations, pre-contracted with $K^+$(50 mM) was expressed as percent of the control response mediated by $K^+$. Contraction of smooth muscle induced by high $K^+$(>30 mM) is known to be mediated, via influx of $Ca^{++}$ from extracellular fluid and the substance, which inhibits this contraction, is considered to act through blockade of voltage dependent slow calcium channels[37].

To confirm the calcium antagonist activity of test substances, rabbit jejunum was used, as it was relative quick in responding to drugs. The tissue was allowed to stabilize in normal Tyrode's solution, which was then replaced with $Ca^{++}$-free Tyrode's solution containing EDTA (0.1 mM) for 30 min, in order to remove calcium from the tissues. This

solution was further replaced with K+-rich and $Ca^{++}$-free Tyrode's solution, having the following composition in mM: KCl 50, NaCl 91.04, $MgCl_2$ 1.05, $NaHCO_3$ 11.90, $NaH_2PO_4$ 0.42, glucose 5.55 and EDTA 0.1. Following an incubation period of 30 min, control dose-response curves (DRCs) of $Ca^{++}$ were obtained. When the control DRCs of $Ca^{++}$ were found superimposable (usually after two cycles), the tissue was pretreated with the test substance for 60 min to test the possible calcium channel blocking effect. The DRCs of $Ca^{++}$ were repeated in the presence of different concentrations of the test material.

## Results

The Nigella sativa seeds have been traditionally used in a variety of diseases including diarrhea, asthma and hypertension. Its antihypertensive action has been confirmed in a recent study[6], while there is no report available for the antidiarrhoeal and antiasthmatic activities. In view of its folkloric use in diarrhoea, the plant extract was tested for its possible spasmolytic activity in a spontaneously contracting gut preparation (rabbit jejunum). It caused a dose-dependent (0.1 - 3.0 mg/ml) suppression of spontaneous contractions thus showing spasmolytic activity (Figure 1). This figure also shows the dose-dependent (0.03 - 0.3 mg/ml) spasmolytic effect of the petrolium ether fraction, which was found the most potent fraction as a result of activity-directed fractionation (Scheme 1). The butanol fraction was found least active and the ethyl acetate

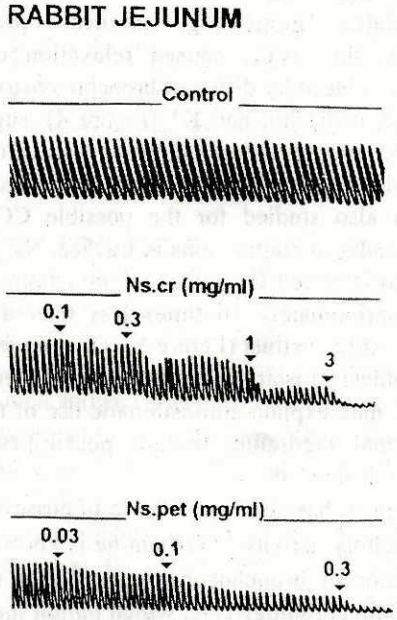
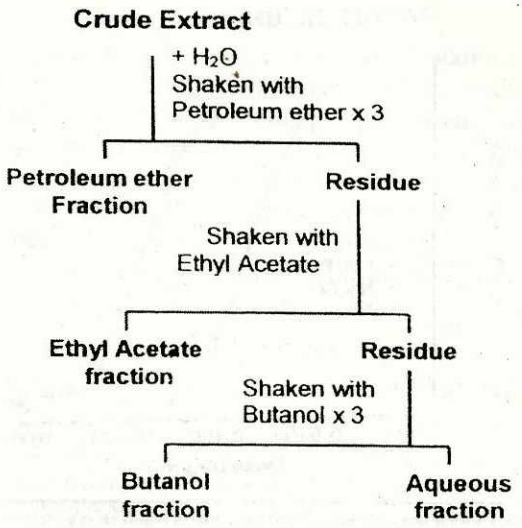



Figure 1. Tracings from a typical experiment, showing the effect of the aqueous-methanol extract of Nigella sative seeds (Ns.Cr) and its petrolium ether fraction (Ns.Pet) on spontaneous contractions of rabbit jejunum. Plant materials were administered by a cumulative method; the concentrations listed are final bath concentrations.




**Fractionation of *Nigalla sativa* crude extract**

Scheme 1.

fraction occupying intermediate position in potency for spasmolytic activity. Aqueous fraction was found devoid of any spasmolytic activity, instead, mild spasmogenic activity was unmasked, which was atropine insensitive (data not shown). The spasmolytic activity has also been reported in an earlier study, which is of preliminary nature and the activity-directed fractionation has also not been carried out.

To elucidate its possible mechanism involved in spasmolytic action, $K^+$ (50 mM) was added to the tissue bath, which caused a sustained contraction. The plant extract was then added to the tissue bath to obtain dose-dependent inhibitory responses and the combined data of different experiments is shown in Figure 2. The crude extract (Ns.Cr.) caused inhibition of $K^+$-induced contraction in a similar concentration range (0.1-3.0 mg/ml). Similarly, Ns.Pet. fraction also caused a dose-dependent (0.03 - 0.3 mg/ml) inhibition of $K^+$-induced contractions being approximately 10 times more potent than the crude extract.

The contractions induced by high $K^+$ (>30 mM) are dependent upon entry of $Ca^{++}$ into the cells through voltage-dependent calcium channels36 (Bolton, 1979) and a substance which inhibits K+-induced contractions is, therefore, considered to be a calcium channel blocker[38]. Thus, inhibition of high $K^+$ (50 mM)-induced contractions of rabbit jejunum by the plant extract or its active fraction (Ns.Pet) may reflect restricted $Ca^{++}$ entry via calcium channels. This hypothesis was further confirmed when pretreatment of the tissue with Ns.Cr or Ns.Pet caused a dose-dependent rightward shift in the dose-response curves of $Ca^{++}$, constructed in the $Ca^{++}$ free solution (Figure 3). This figure also shows the dose-response curves of calcium

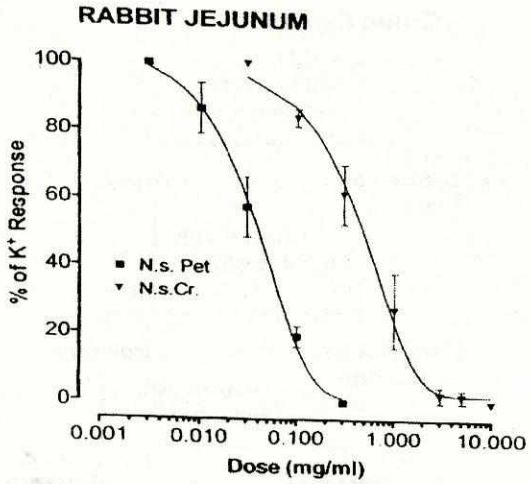



Figure 2. Comparison of the aqueous-methanol extract of Nigella sative seeds (Ns.Cr) and its petroleum ether fraction (Ns.Pet) for their inhibitory effect on K+-induced contractions in rabbit jejunum. The contractions induced by K+ (50 mM) were taken as control (100 % response). Ns.Pet elicited inhibitory response at doses about 10 times less than of the Ns. Cr.

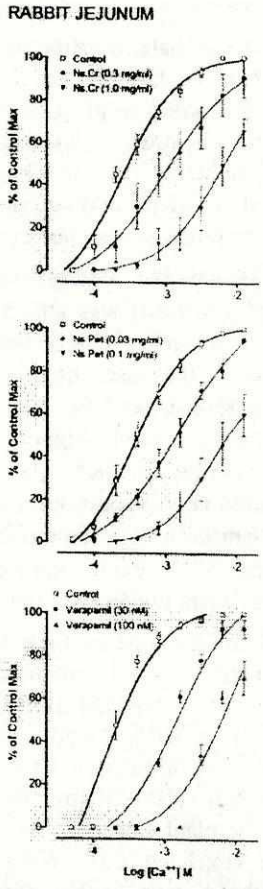



Figure 3. Comparison of the aqueous-methanol extract of Nigella sative seeds (Ns.Cr) and its petrolium ether fraction (Ns.Pet) and verapamil for their inhibitory effect on Ca++. An equilibrium period o30 min was used for each dose of the test materials before the re-determination of Ca++ dose-response curves. Pretreatment of the tissue with plant materials caused displacement of Ca++ dose-response curves to the right, similar to that by verapamil, a known calcium antagonist.

in the absence and presence of different concentrations of verapamil, a standard calcium channel blocker[39]. Both verapamil and the test materials caused dose-related displacement of the Ca++ curves.

## Discussion

Calcium antagonists form an important therapeutic group, which is particularly employed in the treatment of different cardiovascular diseases[40]. The common characteristic of these drugs is their dose-dependent inhibition of the slow entry of calcium and their capacity for reversal of this effect by calcium ions[38]. The observed effect of the Ns.Cr and Ns.Pet fraction of the plant extract to inhibit Ca++ entry followed by being displaced with a high concentration of Ca++ confirms the presence of calcium antagonist(s), which is/are concentrated in the organic fraction.

Interestingly calcium channel blockers (CCBs) are known to be effective in controlling diarrhoea through their spasmolytic action[41] and the presence of CCBs in the Nigella sativa seeds may be responsible for its traditional use as an anti-diarrhoeal. The plant is also known to have anti-microbial activity against a wide range of organisms[11,12] and this property may be a of added value, particularly in infective diarrhoea.

Calcium channel blockers have been shown to be effective in asthma[42,43]. Based on its traditional use in asthma and the CCB activity reported in this study, the plant extract was studied for its possible bronchodilator action using isolated guinea-pig tracheal preparations. Interestingly, the Ns.Cr. caused relaxation of tracheal contractions induced by different bronchoconstrictors, such as histamine, carbachol and $K^+$ (Figure 4), suggestive of non-specific bronchodilator action mediated possibly through calcium channel blockade. Consequently, the Ns.Pet was also studied for the possible CCB activity against K+-induced contractions in trachea. Ns. Pet, like in jejunum also inhibited $K^+$-induced contractions in trachea, at doses approximately 10 times less than those found effective for crude extract (Figure 5). This suggests that the CCB constituent(s) is/are concentrated in this fraction and this activity may explain anti-asthmatic use of the plant in the traditional medicine, though possibility of other mechanisms also exists.

The plant has also been shown to possess histamine release inhibitory activity[29]. Histamine is known to be the main mediator of bronchoconstriction[44] and the agents, such as sodium chromoglycate, which inhibit the release of histamine are considered useful particularly as preventive measure in patients with chronic asthma. Such activity reported in this plant may be of additional benefit in asthma.

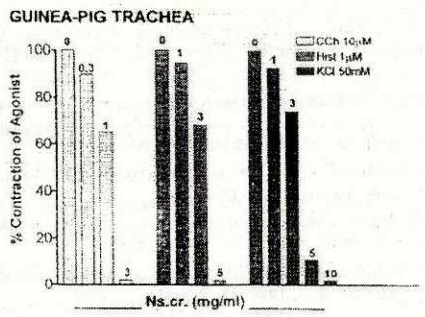



Figure 4. Comparison of the inhibitory response of the aqueous-methanol extract of Nigella sative seeds (Ns.Cr) against contractions induced by histamine (Hist.), carbachol (CCh) and K+ in guiea-pig trachea. Ns.Cr caused a dose-dependent inhibitory effect against all agonists used in a similar concentration range.

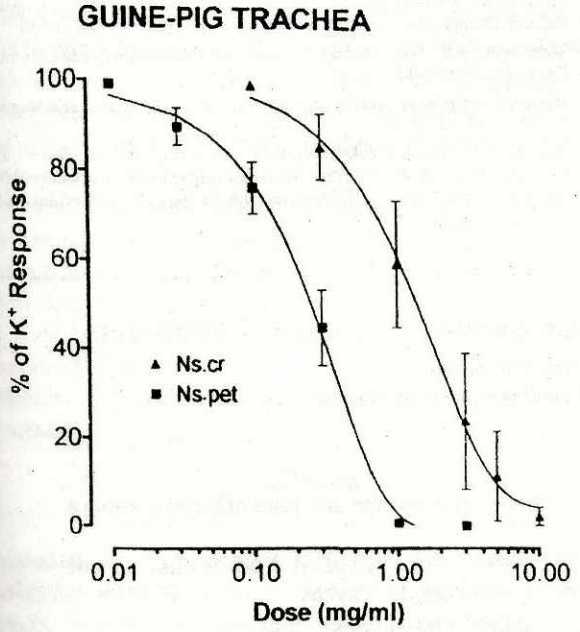



Figure 5. Comparison of the aqueous-methanol extract of Nigella sative seeds (Ns.Cr) and its petrolium ether fraction (Ns.Pet) for their inhibitory effect on K+-induced contractions in guinea-pig trachea. The contractions induced by K+ (50 mM) were taken as control (100 % response). Ns.Pet elicited inhibitory response at doses about 10 times less than of the Ns. Cr.

The plant has been traditionally used to treat hypertension and this effect was confirmed in a recent study[6], which showed that the volatile oil of Nigella sativa seeds lowers blood pressure possibly through central mechanism involving muscarinic and 5-HT receptor activation. Calcium antagonists are well known to be effective in treating hypertension[41] and the presence of such constituent(s) in the crude extract (non-volatile part) reported in this study thus provide a complimentary mechanism of lowering blood pressure acting at the peripheral level. It is not uncommon that the antihypertensive drug therapy in modern medicine involves use of multiple drugs acting at different sites[39].

These data indicate that the Nigella sativa seeds (Kalonji) contain calcium channel blocking constituent(s) thereby exhibiting spasmolytic and bronchodilator activities, which is/are concentrated in the petroleum ether fraction. The presence of CCB activity may partly explain the usefulness of the plant in different diseases, like diarrhoea, asthma and hypertension. Furthermore, presence of the multiple constituents acting mostly at different sites makes the plant versatile in its therapeutic success.

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# A Survival Analysis of Metastatic Breast Cancer in Pakistani Patients

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## Abstract

**Objective:** To determine the overall survival of metastatic breast cancer in the Pakistani patients and compare it with published information.

**Method:** The design was a retrospective analysis of metastatic breast cancer patients from breast cancer database. A total of 137 patient based information was available for review and analysis.

**Results:** An overall median survival of 2.83 years was noted in metastatic breast cancer patients.

**Conclusion:** This survival figure in this study compares favorably to those published in the literature (JPMA 51:120;2001).

## Introduction

Metastatic breast cancer (MBC) or stage IV breast cancer is a major medical problem, which is not curable with the currently available therapies[1]. Besides medical issues a significant amount of time, emotional energy and financial resources are required for its management. Therefore decision making is a medical challenge in such cases. The medical oncologist is helped in managing MBC by the knowledge of individual disease characteristics, which are known to be of prognostic significance in such a setting. Race and ethnic origin are recognized as significant prognostic factors for the outcome of many diseases including breast cancer[2]. In the United States, black populations do worse stage for stage, than the white women with breast cancer[3,4]. Breast cancer tends to present at a more advanced stage in Pakistan than what is seen the West. Factors, which contribute to the advanced stage of presentation, include poor socioeconomic circumstances, social taboos and a general lack of education leading to poorl treatment choices. Additionally the biological nature of the disease in Pakistan may be different from that reported in the literature[5]. The factors, which may contribute to these differences, include race, ethnicity, nutritional factors and perhaps interfamily marriages.