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The anti-inflammatory, analgesic and antipyretic activity of *Nigella sativa*

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Abstract

The aqueous extract of *Nigella sativa* (*N. sativa*) was investigated for anti-inflammatory, analgesic and antipyretic activities in animal models. The extract has an anti-inflammatory effect demonstrated by its inhibitory effects on Carrageenan induced paw edema. It also produced significant increase in the hot plate reaction time in mice indicating analgesic effect. However, *N. sativa* crude suspension had no effect on yeast induced pyrexia. This study therefore, supports its use in folk medicine both as analgesic and anti-inflammatory agent and calls for further investigations to elucidate its mechanism of action.

Keywords: *N. sativa*; Anti-inflammatory; Analgesic; Folk medicine

1. Introduction

Nigella sativa (N. sativa) is a herbaceous plant known locally (in Saudi Arabia) as the black seed and is commonly used as a natural food additive. Traditionally these seeds are also used for the prevention and cure of many ailments in the Middle East and South East Asia. The principal active ingredient isolated from the volatile oil of *N. sativa* is thymoquinone (Mahfouz and El-Dakhakhany, 1960).

N. sativa has been reported to exhibit many pharmacological effects including antibacterial activity (Topozada et al., 1965), and has been shown to increase bile secretion in dogs and uric acid in rats as well as protect guinea pigs against histamine induced bronchospasm (El-Dakhakhany, 1982). The fatty and petroleum extracts shortened bleeding time and inhibited fibrinolytic activity in rabbits (Ghoneim et al., 1982). El-Tahir et al. (1993a) reported that the volatile oil of *N. sativa* causes dose-dependent increase in the respiratory rate and intracranial pressure of urethane-anesthetized guinea pigs. They also reported reduced heart rate and blood pressure (El-Tahir et al., 1993b). Significant reduction in blood glucose and cholesterol levels in humans was also reported by Bamosa et al. (1997). Furthermore, *N. sativa* seeds were found to enhance immunity by increasing T_4: T_8 ratio as well as natural killer cell activity (Elkadi and Kandil, 1986). Anticancer activity was reported against malignant cells in mice (Salomi et al., 1991) and in humans (Salomi et al., 1992, Worthen et al., 1998). In spite of the large number of pharmacological studies carried out world wide on *N. sativa* seeds, scrutiny of published articles showed that there is a need to investigate its anti-inflammatory activity. This study is therefore, aimed to find out if *N. sativa* seeds possess any anti-inflammatory, analgesic or antipyretic activities in experimental animals.

2. Material and methods

2.1. Animals and preparations

Albino Wistar rats and Albino Swiss mice of either sex fed on standard chow diet and water were ob-

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tained from the Animal House, King Faisal University. Dry *N. sativa* seeds were purchased from a local market in Dammam, Saudi Arabia. 12.5 g of the seeds was ground and added to 100-ml distilled water at room temperature to prepare a crude suspension a few minutes before each experiment.

2.2. Anti-inflammatory

Inflammation was produced in the rats using 0.05 ml of 1% Carrageenan sodium salt (BDH; Winter et al., 1962). Carrageenan was injected into the right hind foot of each rat under the plantar aponeurosis. Each rat in

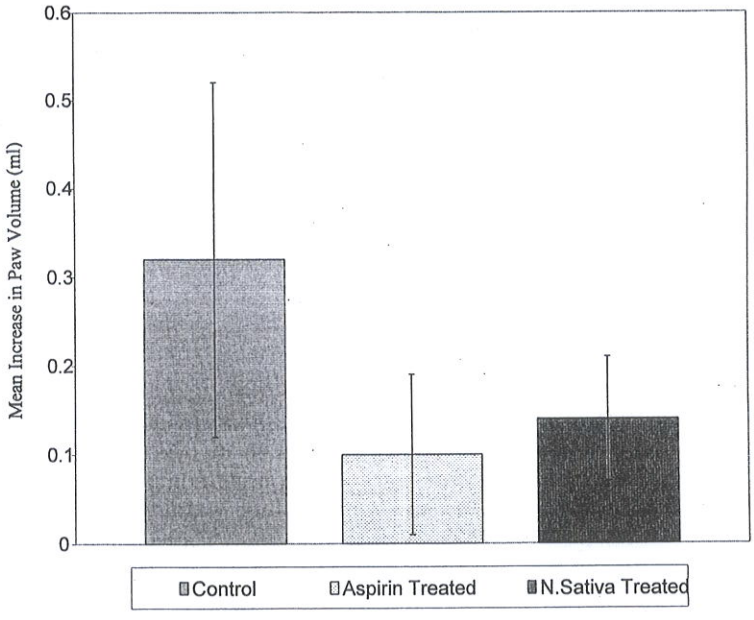

Fig. 1. Mean increase in paw volume ± S.D. induced by Carrageenan in *N. sativa* treated animals compared to Control and Aspirin treated groups.

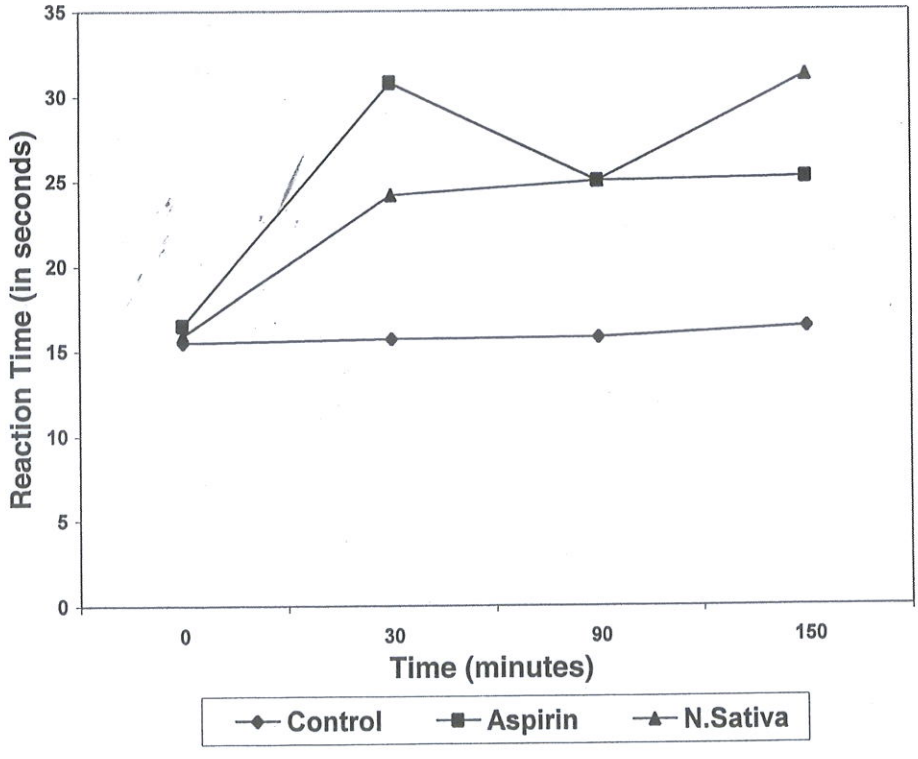

Fig. 2. Effect of *N. sativa* 500 mg/Kg; Aspirin 100 mg/Kg and Control Group on hot plate reaction time in mice.

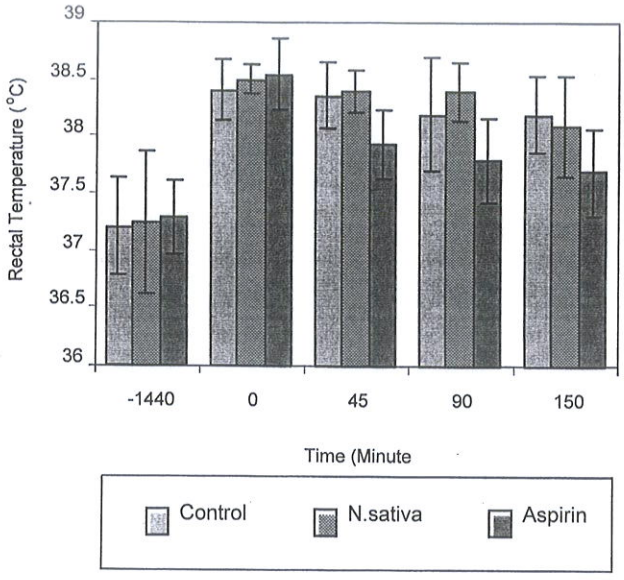

Fig. 3. Effect of *N. sativa* 500 mg/Kg on yeast induced pyrexia in rats compared to the Control and Aspirin groups.

the experimental group (eight rats) was treated orally with 500 mg/kg-body weight of *N. sativa* seeds 1 h before the Carrageenan injection. The standard reference group was treated orally with 100 mg/kg body weight of aspirin aqueous solution while the control group was given normal saline. Measurements of foot volume were performed by the displacement technique using a calibrated glass tube immediately before and 3 h after the injection of Carrageenan. Inhibitory activity was calculated using the following formula:

$$\text{Percentage inhibition} = 100\left(1-\frac{a\text{-}x}{b\text{-}y}\right),$$

where 'a' is the mean paw volume of treated rats after Carrageenan injection, 'x' is the mean paw volume of treated rats before Carrageenan injection, 'b' is the mean paw volume of control rats after Carrageenan injection and 'y' is the mean paw volume of control rats before Carrageenan injection.

2.3. Analgesic activity in mice

The hot plate method described by Turner (1965) was used to evaluate the analgesic activity. The animals were dropped gently on a plate maintained at 53 ± 0.5°C. Reaction time was taken as the interval between the instant the animal reaches the hot plate till the moment the animal licks its forepaws or jumps out. Measurements were carried out 5 min before and 30, 90 and 150 minutes after oral administration of *N. sativa* seeds crude suspension (500 mg/kg body weight). The control group was given 1 ml normal saline while the standard reference group was treated with 1 ml (100 mg/kg body weight) aqueous solution of aspirin. Each result was calculated as the means of three readings.

2.4. Antipyretic activity in rats

Three groups of rats (12 in each group) were injected subcutaneously with 10 ml/kg-body weight 15% yeast solution to induce pyrexia. The rectal temperature of each animal was recorded before and 24 h after the yeast injection. Thereafter, the test group was treated orally with 1 ml (500 mg/kg-body weight) crude suspension of *N. sativa*. The control group was given 1 ml normal saline and the standard reference was treated with 1 ml (100 mg/kg body weight) aqueous solution of aspirin. Post treatment rectal temperature of each animal was recorded at 45, 90 and 150 min. Each result was calculated as the mean of three readings.

2.5. Statistical methods

The data obtained were computed using SPSS software and later analyzed using ANOVA of variance. The Duncan test with significance level of 0.05 between means was used.

3. Results

The study of the acute anti-inflammatory test showed that *N. sativa* produced a significant ($P = 0.018$) reduction at 3 h in Carrageenan induced paw edema when compared to the control group. This anti-inflammatory effect is comparable to that produced by aspirin Fig. 1.

Results of analgesic study showed that *N. sativa* increases animal reaction time to hot plate. At 30 min, the mean reaction time for *N. sativa* group was 24.2 ± 5.8 seconds compared to 15.3 ± 3.8 and 30.8 ± 13.7 s for the control and aspirin treated groups respectively. The difference between the mean reaction time of *N. sativa* treated group and the control group was statistically significant ($P = 0.001$) but comparable to that of aspirin treated animals. At 90 min the mean reaction time for *N. sativa* and aspirin groups were the same and significantly greater ($P = 0.002$) than that seen with the control group. At 150 min, the mean reaction time for *N. sativa* is longer (31.2 ± 10.4) than that of aspirin (25.2 ± 9.7) but the difference was not statistically significant. However, the reaction time for both groups remained significantly greater than that of the control ($P = 0.001$) (Fig. 2).

The antipyretic study showed that *N. sativa* is not effective when compared to aspirin (Fig. 3). At 45 and 90 min post treatment, the temperatures of aspirin treated group was significantly ($P = 0.02$ and 0.013, respectively) less than that of the control and *N. sativa* treated animals. Although, same pattern were observed after 150 min, the differences were not statistically significant.

4. Discussion

The results showed that *N. sativa* has an anti-inflammatory action comparable to that of 100 mg/kg aspirin as documented by the lack of increase in paw volume after administration of carrageenan. Furthermore, *N. sativa* induces analgesic effect comparable to that of aspirin, but it does not have anti-pyretic activity.

The anti-inflammatory effect of *N. sativa* presented in this study is consistent with the inhibitory effects of thymoquinone and other components of the seeds on many inflammatory mediators. For example, Chakravarty (1993) demonstrated the inhibition of histamine release from mast cells by the *N. sativa*-derived nigellone. Furthermore, Houghton et al. (1995) have shown that both the crude fixed oil of *N. sativa* and pure thymoquinone inhibited cyclooxygenase and 5-lipoxygenase pathways of arachidonate metabolism in rat peritoneal leukocytes. The effect was demonstrated via the dose-dependent inhibition of the formation of thromboxane B_2 and leukotriene B_4. They also showed that the inhibition of eicosanoid generation by the fixed oil of *N. sativa* was greater than that produced by thymoquinone and concluded that this might explain why whole *N. sativa* is useful in the treatment of rheumatism and related inflammatory diseases. The anti-inflammatory effect was confirmed by the study of Mutabagani and El-Mahdy (1997) in rats. However, their study was not extended to investigate the analgesic and antipyretic effect of *N. sativa*.

The analgesic effect of *N. sativa* has not been previously reported and the mechanism by which it occurs is not fully understood. Inhibition of prostaglandin may not be the main factor but one of several possibilities. Indeed, Haq et al. (1995) have reported increased secretion of the cytokines IL-1beta and IL-8 by whole *N. sativa* in culture medium with non-activated peripheral blood mononuclear cells. Both agents are important in eliciting the pain of inflammation and liberate the release of prostaglandins (Insel, 1996).

The absence of *N. sativa*-antipyretic effect suggests again that the constituents of these seeds may not inhibit the synthesis of prostaglandins.

In conclusion, the pharmacological activities of *N. sativa* support its use in folk medicine to reduce pain and inflammation but further studies are needed to elucidate the exact mechanism by which the *N. sativa* inhibits inflammation and pain.

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