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The Interaction Between The Volatile Oil of The Black Seed (Nigella sativa) And Morphine Reinforcing Effects In Place Preference Conditioning

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Abstract

The aim of this study was to examine the ability of the volatile oil (V.O.) of Nigella sativa to interact with the effect of morphine in a Place Preference Conditioning procedure. This is based on the findings of a number studies that some of the constituents of Nigella sativa were found to have similar effects as morphine, effects such as its analgesic and its anti-anxiety effects. Additionally, it was suggested that V.O. share with morphine a common site of action on the 5-HT system. Thus, twenty four male Albino Wistar rats were divided into two groups, the first one (the experimental group) was injected with a dose of 30 microgram/kg V.O, before being administered a dose of 5mg/kg of morphine and subjected to four-day conditioning sessions on a Place Preference Conditioning procedure. The second group (the control group) was treated the same except that V.O. was substituted with saline. Results showed that although there was clear conditioning effect for morphine, no interaction was found between V.O. and morphine. Results were discussed in terms of the low V.O. dose used in the present study.

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The black seed (known by other names as black cumin or black caraway) is a substance that is used as herbal medicine or herbs that is added to some dishes in the Middle East and some parts of Asia. It is cultivated from the fruit capsule of the plant Nigella Sativa Linnaeus. In recent years there has been a rising interest in the black seed for its therapeutic effect. It has been claimed that the oil of the black seed is effective in the treatment of a wide range of illnesses, including cough and bronchial asthma if taken orally (Mahfouz & El-Dakhakny, 1960) and it was found to be effective in relieving toothache if applied to the affected tooth (Hashim & El-Kiey, 1962). It was found that the oral intake of the black seed oil can induce stimulation of appetite, expulsion of intestinal worms and stimulation of milk production (Chopra et al.,1956; Nadkarni 1976). Ashour (1991) reported that administration of the black seed volatile oil to rats have resulted in a decrease in the arterial blood pressure and body temperature and also an increase in respiratory rate with an accompanying bronchoconstriction.

Other researchers have looked into the effect of the Nigella sativa on the central nervous system and specifically, its pain suppressing effect. Abdel-Fattah et. al. (2000), examining the antinociceptive effects of Nigella sativa oil and its major component thymoquinone have reported that the p.o. administration of Nigella sativa oil (50–400 mg/kg) dose-dependently suppressed the nociceptive response in the hot-plate test, tail-pinch test, acetic acid-induced writhing test and in the early phase of the formalin test. The systemic administration (2.5–10 mg/kg, p.o. and 1–6 mg/kg, i.p.) and the i.c.v. injection (1–4 μg/mouse) of thymoquinone attenuated the nociceptive response in not only the early phase but also the late phase of the formalin test. Naloxone injected s.c. (1 mg/kg) significantly blocked Nigella sativa oil- and thymoquinone-induced antinociception in the early phase of the formalin test. The authors also found that the antinociceptive effect of morphine was significantly reduced in thymoquinone- and Nigella sativa oil-tolerant mice, but not vice versa. Al-Naggar et. al. (2001) have conducted pharmacological studies on the aqueous and methanol extracts of defatted Nigella sativa L. seeds to evaluate their effects on the central nervous system (CNS) and on analgesic activity. The observations suggest that the two extracts of Nigella sativa possesses a potent CNS and analgesic activity (depressant action

especially in the case of the methanolic extract). In a different study, Al-Ghamdi (2001), has investigated the aqueous extract of Nigella sativa analgesic activities in mice, and found that the extract has produced significant increase in the hot plate reaction time in mice indicating an analgesic effect.

Although the mechanisms by which the Nigella sativa act and its site of action of is not clear yet, Ashour (1991) suggested that at least some of the actions of Nigella sativa volatile oil (V.O.) on the cardiovascular system of rats and the rectal temperature of the mouse were mediated by the release of central 5-HT. This suggestion was supported by findings that this V.O effect was blunted by the 5-HT and histamine H1 receptor blocker cyporoheptadine (Niemegeers et al. 1982).

Findings from other studies have supported the hypothesis that the Nigella sativa act through the modulation of the 5-HT system. Hosseinzadeh et. al.(2005) have reported that Intracerebroventricular administration of thymoquinone, the major constituent of Nigella sativa seeds, suppresses epileptic seizures in rats, and that pretreatment with naloxone, the 5HT antagonist antagonized the prolongation of tonic-clonic seizure latency as well as the reduction in seizure duration induced by thymoquinone.

Finally, a number of Nigella sativa seed constituents (aqueous extract, fixed oil, volatile oil, and major constituents of the volatile oil) were found to have anti-anxiety effects in mice using the Y-maze and hole-board tests as models for the exploration –induced anxiety, and the waterlick test as a model for the conflicting-induced anxiety (Raza et. al., 2006). Keeping in mind that anxiety reduction is a well known effect of morphine (Le Merrer, 2006), these finding lend further support to the hypothesis that Nigella sativa and morphine might have a common site of action.

Based on the above findings that the oil exerts some of its effects through the interaction with the 5-HT system, it is speculated in the present study, that pretreatment with the volatile oil of Nigella sativa (V.O.) will modulate the reinforcing effects of morphine. This assumption is warranted by findings reported by a number of researcher that the central 5HT system is involved in the reinforcing action of morphine (Vadawy & Evan, 1983; Nomikos and Spyraki,1988; Spyraki et. al., 1988; Carboni et al. 1989; Higgins et. al. 1992; Suzuki et al. 1995).

The role of 5HT in the reinforcing effects of morphine:

The reinforcing effects of psychoactive drugs is thought to be highly related to its abuse potential, in that the higher the rewarding effect of the drug is the more possibility of the drug misuse (Kollins, 2003). This principle applies to morphine amongst a wide range of other substances.

Although the reinforcing effects of morphine is thought to be mediated through the activation of the central endogenous opioid system (Biala and Langwinski 1996), some researchers have demonstrated good evidence that the central 5HT system might also be involved in this effect (Vadawy & Evan, 1983; Nomikos 1988 ;Nomikos and Spyraki,1988; Spyraki et. al., 1988; Carboni et al. 1989; Higgins et. al. 1992; Suzuki et al. 1995). Spyraki et. al., (1988) have suggested that 5-hydroxytryptamine (5-HT)-containing neurons of the nucleus accumbens of male rats were a component of the neural circuitry that mediates the rewarding properties of morphine. Nomikos and Spyraki (1988) have found that pretreatment with ritanserin, a 5-HT-sub-2 antagonist, has attenuated the Place Preference Conditioning (PPC)(see below) effect of morphine. Higgins et. al. (1992) have also found that pretreatment with the selective 5-hydroxytryptamine-sub-3 (5-HT-sub-3) antagonists MDL72222 and ondansetron (0.01 mg/kg sc) before morphine significantly antagonized the PPC effect to this treatment. The chronic administration of, morphine sulfate (0.1-0.4 mg/ml) to male Wistar rats enhanced brain 5-HT synthesis, whereas subsequent withdrawal caused an inhibition (Vadawy & Evan, 1983) .

Using a different procedure, Will et. al. (2004) have found that pretreatment with an intra-DRN microinjection of the 5-HT1A agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT, 1.0 μg/0.5 μ1) either before inescapable shock or before morphine (3.0 mg/kg, SC) injections during PPC testing, has completely blocked the effect of the stressor induced potentiation of morphine effect on PPC. Furthermore, examining the effects of the high-efficacy 5-hydroxytryptamine (5-HT)-sub(1A) receptor agonist (F 13640) Colpaert et. al. (2006) have found that treatment with (F13640) both prevented and reversed the conditioned place aversion induced by naloxone (0.04 mg/kg i.p.) in morphine-infused rats. Finally, Vekshina and Khristolyubova (1992) have observed changes in the properties of brain 5-HT receptors in the offspring of rats consuming morphine over a long period of time.

Based on the evidence sited above, it seems that both the Nigella sativa and morphine exert their action through modulation of the central 5-HT system. Thus, the present study aims at examining the behavioral effects of the volatile oil of Nigella sativa (V.O.) on the reinforcing effect of morphine, using the Place Preference Conditioning (PPC) procedure.

Place Preference Conditioning (PPC):

Drugs reinforcing effects may be assessed using an experimental procedure known as Place Preference Conditioning (PPC). In this procedure animals are administered reinforcing agents and placed in a distinct environment, and on other occasions they are administered saline and placed

in a different environment. In a later drug free-test when animals are given a choice between the two environments they would spend more time in the drug paired one. This is taken as an indication of the reinforcing effects of the drug, and is being used as a measure of the abuse potential of that drug (Kollins, 2003; Brado and Bevin, 2000). PPC have been demonstrated with a number of potentially abused substances including morphine (Blander et al. 1984; Mucha & Iversen 1984), cocaine (Suzuki & Misawa 1995) , amphetamine, THC (Lepore et al. 1995) and LSD (Parker 1996). Drug induced PPC is based on Classical Conditioning principle, that is when a primary reinforce (the drug) is paired with a neutral stimulus (i.e.,the experimental context) this latter stimulus will acquire the conditioned reinforcing effects of the drug. These conditioned reinforcing effects, are thought to be capable of eliciting an operant approach response or place preference (Tzschentke, 1998; Bardo and Bevins, 2000).

The aim of the following experiment is to explore the interaction between V.O. and morphine using a PPC procedure. It is expected that pretreatment with V.O. will potentiate the place preference conditioning effects of morphine, in that rats pretreated with V.O. will spend more time in the morphine-paired environment, than those who did not receive V.O. before morphine.

Materials and Methods

Animals: Twenty four male Wistar rats weighing 250-300 grams were brought into the labs of the psychology department and housed individually in steel cages furnished with saw dust, in a thermo regulated room (22°C). They were kept on 12:12 hr dark/light cycle 8:00 am to 8:00 pm, Food and water were available ad lib. Rats were handled for two weeks prior to the start of the experiment.

Drugs and substances: Immediately before the start of the experimental procedure, fresh Nigella Sativa was purchased at the local market and brought to the labs of the college of pharmacology at King Saud university, where the volatile oil (V.O.) was extracted and stored in the refrigerator in small glass containers. The V.O. was suspended in olive oil (1ml olive oil/30μl) injected to rats i.p. in doses of 30μl/kg of body weight. Morphine su (Mallinckrodt Inc., Paris, Kentucky) obtained through the college of Medicine at King Saud university, was dissolved in saline and injected subcutaneously in a dose of 5mg/kg of body weight.

Apparatus: The PPC apparatus was made of transparent Plexiglas and plywood. Four two-compartment chambers were used. The two compartments were equal in size, each measured 25X30X25 cm rectangular shape, and were separated by a guillotine door, and covered with transparent tops. The two compartments had different visual and tactile properties: the

floor of compartment A was furnished with black wire mesh and the floor of compartment B was furnished with sandpaper.

Pre-conditioning test : On the day before the start of the experiment, the guillotine door separating the two conditioning compartments was removed and rats were placed above the line separating the two compartment, facing the back of the chamber, and allowed to move freely between the two compartment for 15 min. Rats were videotaped for later analysis of their movements.

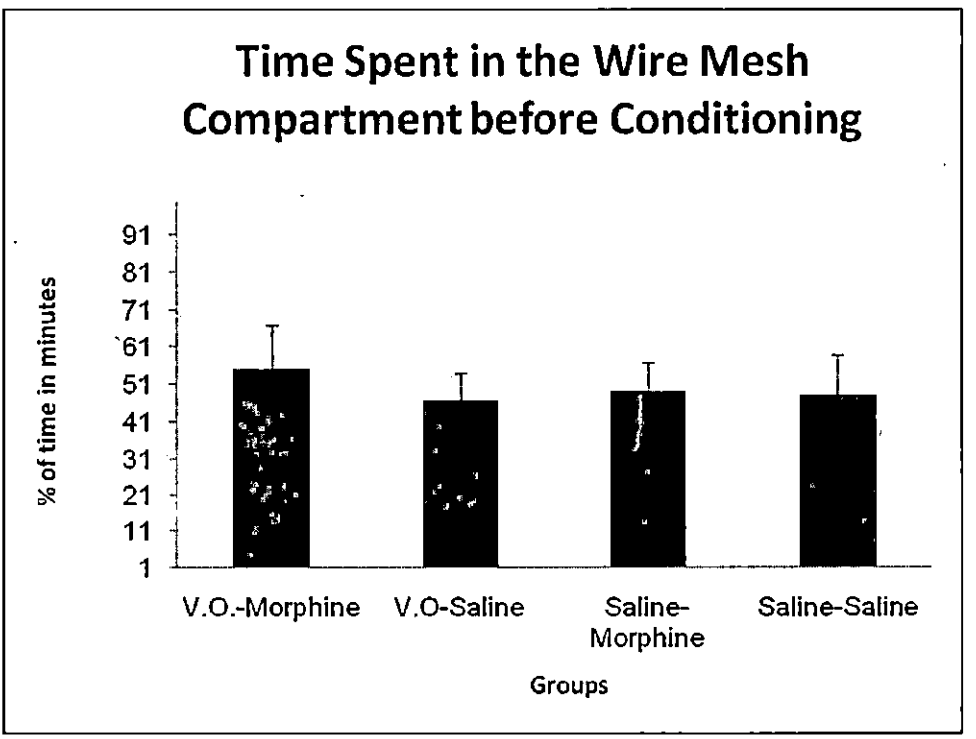

Fig. 1.

The mean percentage of time spent by each group in the wire mesh compartment during the pretest before the start of the conditioning trials (n=6 rats in each group).

As shown in Fig.1, all groups of rats spent almost equal time in each conditioning compartment. A oneway anova comparing the average percentage of time of all groups showed no significant difference between any of the groups.

Table 1. Results of a oneway anova on the percentage of time spent by each group in the conditioning compartments, prior to conditioning.

Groups	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
V.O.-Morphine	6	55.00	11.84	4.83	42.57	67.43	33.33	66.67
V.O.-Saline	6	46.67	7.31	2.99	38.99	54.34	34.00	54.00
Saline-Morphine	6	49.00	7.95	3.25	40.65	57.35	40.00	60.00
Saline-Saline	6	48.22	10.64	4.34	37.06	59.39	32.00	60.67
Total	24	49.72	9.53	1.95	45.70	53.75	32.00	66.67

Conditioning phase:

On day 1 of the conditioning procedure, the guillotine door separating the two compartment was put in place. Animals were divided into two equal groups matched according to weight; V.O-group and saline-group. Rats in the V.O.-group (n=12) were injected i.p. with 30μl/kg of V.O. and 30 min later half of the subjects in this group (n=6) were injected with 5 mg/kg morphine and immediately half of them (n=3) were placed, individually, in the wire mesh-floor compartment and the other half were placed in the sandpaper-floor compartment. The other half of the V.O.-group were injected with saline and, again, half of them were placed in wire mesh-floor compartment and the other half were placed in the sandpaper-floor compartment for 30 min. The other 12 rats in the saline-group were treated in the same manner except that saline injections were substituted for the V.O. injections. Injections and placement were counterbalanced between and within groups. On day 2 of the conditioning procedure, the order of substance given and compartments placement was reversed. Subjects that were administered morphine injections and placed in the wire mesh-floor compartments on day 1 of the experiment, were administered saline on this day and placed in the sandpaper-floor compartments, and those that previously administered morphine injections before being placed in the sandpaper compartments were administered saline injections, on this day and placed in the wire mesh compartments. The experiment was run in a two four-day conditioning cycles, separated by a conditioning test. So that each animal would have received two pairings with morphine and two pairings with saline, and then tested for conditioning, before receiving two more pairings with morphine and another two pairings with saline. Thus, at the end the experiment each group had four pairings with morphine and four pairings with saline. Conditioning trials and testing were run on Tuesdays and Thursdays of each week in the order of one trial per day.

Tests

Both the mid and the post-conditioning tests were run exactly in the same manner as the preconditioning test. The degree of conditioning was calculated by recording the percentage of time (in minutes) the rat spent in each compartment. An entry was recorded if the front legs of the rat were in the compartment.

Data analysis:

The time spent in the drug paired compartment during the PPC tests was expressed as percentage of time spent in each compartment, and the data were analyzed using SPSS statistical package. T-tests were run to compare the percentage of time spent in the designated compartment by each group. Statistical differences at $P< 0.05$ were considered significant.

Results

As shown in Fig. 2, the average percentage of time spent by different groups in the drug-paired and the vehicle-paired compartments was variable, being the highest for the group that were administered saline before the morphine injection (the Saline-Morphine group). The lowest was that of the group that received two saline injections (the Saline-Saline group).

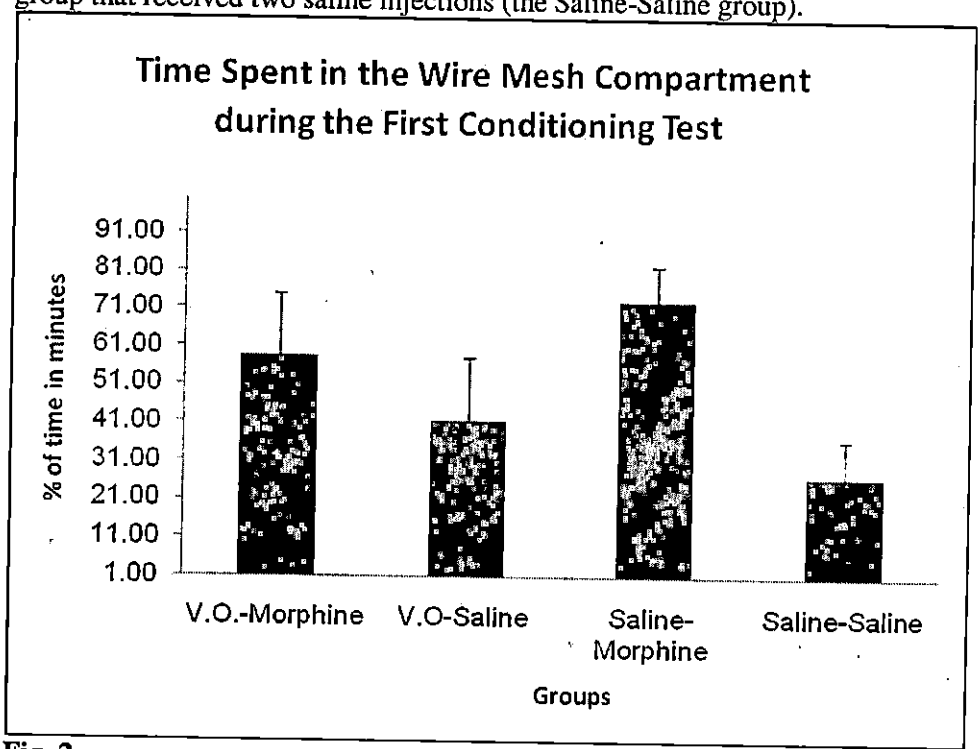

Fig. 2.

The mean percentage of time spent by each group in the designated compartment (n=12) during the first post conditioning test. Small bars represent the standard deviation.

A oneway repeated measures anova revealed that the differences among groups were significant (Table. 2) A paired samples t-test showed that the time spent in the drug-paired compartment by the V.O.-Saline group was significantly more than that of the Saline-Saline group, ($t = 2.44$, $df = 11$, $p < .033$, two-tailed).

Table 2. Results of a oneway repeated measures anova on the percentage of time spent by each group in the conditioning compartments, after the first conditioning phase.

Source	TypIII Sum of Squares	df	Mean Square	F	Sig
Groups	14186.88	3	4728.96	25.61	0.00
Error (Groups)	6092.48	33	184.62		
Intercept	2700.00	1	2700.00	698.13	0.00
Error	42.54	11	3.87		

This is an indication that the V.O. might have a conditioning effect that is similar to the effect of morphine. On the other hand, a paired samples t-test showed that the time spent in the drug-paired compartment by the group that had a saline injection before morphine (the Saline-Morphine group) was significantly more than the one that received V.O. injection before morphine (the V.O.-Morphine group), ($t = 2.44$, $df = 11$, $p < .033$, two-tailed). These results could be interpreted as an indication that the administration of the V.O. before the morphine injection has retarded the development of PPC, and it runs counter to expectations. Therefore, in an effort to reach a firm conclusion, it was decided to resume the conditioning trials for 4 more days, and then run another conditioning test.

As shown in Fig. 3, the second conditioning test results showed no difference between the V.O.-Morphine group and the Saline-Morphine group, in the percentage of time spent in the drug-paired compartment . Thus, running the conditioning trials for a couple more days has diminished the difference between these two groups. However, the difference was large between these two groups and the other two saline groups.

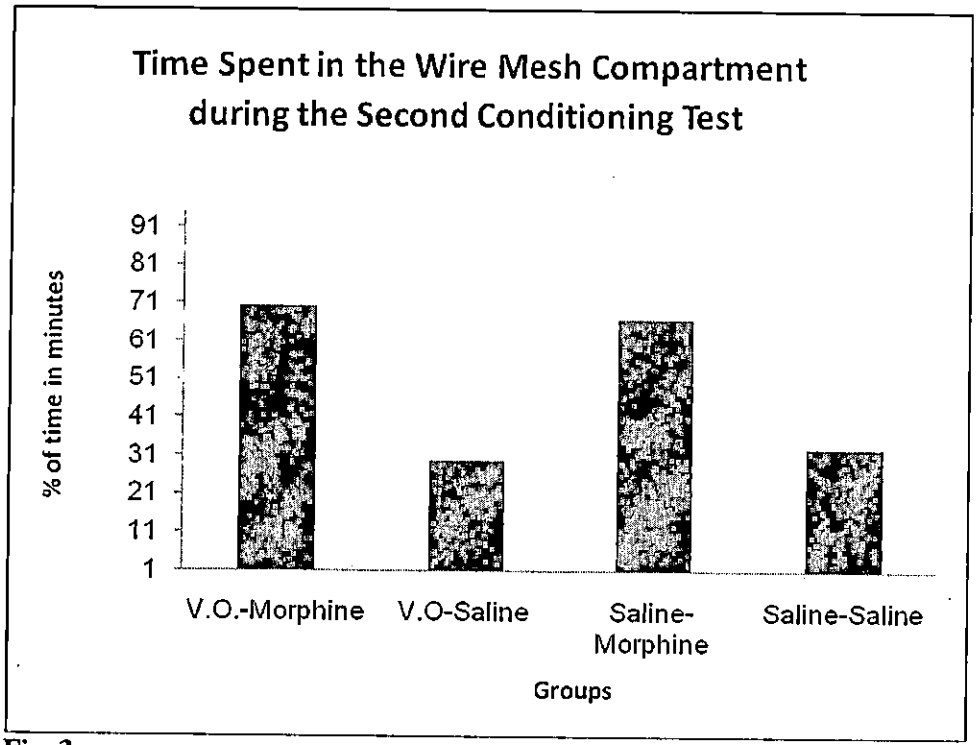

Fig. 3.

The percentage of time spent by each group in the drug-paired compartments (n=12) during the second post conditioning test. Small bars represent the standard deviation.

A repeated measure oneway anova revealed a significant group effect(Table.3).

Paired samples t-test revealed that there was a significant difference between the V.O.-Morphine group and V.O.-Saline group ($t = 6.39$, $df = 11$, $p < .0005$, two-tailed), as well as between Saline-Morphine group and the V.O.-Saline group ($t = 8.48$, $df = 11$, $p < .0005$, two-tailed), in the percentage of time spent in the drug-paired compartment. Furthermore, there was no difference between the Saline-Saline and the V.O.-Saline groups in the percentage of time spent in the drug-paired compartment. Taken together, the results of the second conditioning test seem to indicate that although conditioning to the effect of morphine was evident, there was no evidence of an interaction between V.O. and morphine in the development of PPC.

Table 3. Results of a repeated measures anova on the percentage of time spent by each group in the conditioning compartments, after the second conditioning phase.

Source	TypIII Sum of Squares	df	Mean Square	F	Sig
Groups	16694.82	3	5564.94	27.49	0.00
Error (Groups)	6681.64	33	202.47		
Intercept	120000.00	1	120000.00	352.70	0.00
Error	3742.52	11	340.23		

Discussion

The overall results of the study showed that the V.O. did not interact in any way with the effect of morphine, nor had it any effect of its own on PPC. This is indicated by the fact that administration of a V.O. dose of 30μl/kg before the morphine injection did not alter conditioning to the reinforcing effect of morphine. This is despite the fact that when the V.O. was administered by itself during the first test, it did show some conditioning effect. The disappearance of the V.O. effects, during the second conditioning test, might be attributed to the low V.O. dose (30μl/kg) used in this study. The V.O. dose used here was based on that used by Ashour (1991) in which this very dose (administered i.v.) resulted in a decrease in the arterial blood pressure and body temperature and an increase in respiratory rate with an accompanying bronchoconstriction. El-Tahir et. al. (1993) have also reported that 4-32 μl/kg, delivered intravenously, increased dose-dependently the respiratory rate and the intratracheal pressure, in a urethane-anaesthetized guinea-pig. Furthemore, doses as low as 10 and 20 μl/ear of the black cumin seed essential oil was found to reduce croton oil-induced oedema in mice (Hajhashemi et. al., 2004). Nevertheless, other studies that looked into the effect of the Nigella sativa have used larger doses that ranged from 1-400 mg/kg, as well as different routs of administration (p.o., i.p., and i.c.v) in which the substance was found to result in alteration to the physiological responses in these studies (Al-Ghamdi, 2001; Al-Naggar et. al., 2001;Abdel-Fattah et. al., 2000).

Since all studies sited in this paper have not looked into the behavioral effects of the V.O. (as in this study), but rather focused on the physiological responses to the substance, it remains a possibility that an increase in the V.O. dose might have shown different behavioral effects. Thus, future behavioral studies examining the effects of Nigella sativa, amongst other issues, should address the effects of different doses and different routes of administration.

Although administering V.O. before hand did not potentiate the morphine

conditioning effect during PPC, the data of the first conditioning test showed that when rats were administered V.O. only without morphine, they did show some preference for the V.O. associated compartment. This was indicated by comparing the results of the experimental group that was administered V.O. then 30 min later received saline (V.O.-Saline group) and the group that was administered saline then 30 min later received another saline injection (Saline-Saline group) before being placed in the conditioning compartment. However, although the observed conditioning effect of V.O. was not in the same magnitude as the morphine's effect, it was there, and it remains a possibility that the V.O. might have some conditioning effects of its own. This suggestion is supported by the Raza et. al. (2006) report in which a number of Nigella sativa constituents was found to have anti-anxiety effects.

Nevertheless, the data also showed that V.O.'s effect was not additive with the effect of morphine since it did not increase its conditioning effect. This might be taken as an indication that V.O. exerts its reinforcing effect via adifferent mechanisms than morphine. This hypothesis is supported by the report of Hajhashemi et. al. (2004), in which he found that although the black cumin essential oil produced a significant analgesic and anti-inflammatory effects, these effects could not be reversed by the opioid antagonist nalaxone.

Alternatively, the small conditioning effect to the V.O. associated compartment, that has been observed during the first conditioning test, might be due to the antinociceptive effects of the Nigella sativa. That is, when rats are subjected to the stressful injection procedure and the pain associated with the insertion of the needle, the effect of all this might have been reduced by the analgesic effects of Nigella sativa. Consequently, rats chose the compartment that was not associated with stress (the V.O.-paired one). This antianalgesic effects of Nigella sativa was reported earlier to have counteracted the stress induced in a number of experimental procedures, including the hot plate-test, the tail-pinch test, the acetic acid-induced writhing test and the formalin test (Al-Naggar et. al. 2001; Al-Ghamdi, 2001; Abdel-Fattah et. al., 2000). The disappearance of this effect on the second test might be attributed to the development of tolerance to this effect. This suggestion, however, remains to be pure speculation that needs to be substantiated by further testing.

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التفاعل بين الزيوت الطيارة للحبة السوداء والتأثير التعزيزي للمورفين باستخدام طريقة إشراط تفضيل المكان

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كان الهدف من هذه الدراسة هو اختبار قدرة الزيوت الطيارة للحبة السوداء (Nigella sativa) على التفاعل مع تأثير المورفين باستخدام طريقة إشراط تفضيل المكان. اعتمدت الدراسة على ما توصل إليه عدد من الدراسات السابقة من وجود تشابه بين تأثير المورفين وبعض مكونات الحبة السوداء، مثل التأثير المضاد للألم والتأثير المضاد للقلق. إضافة إلى ذلك فإن بعض الباحثين قد أشار إلى أن الحبة السوداء والمورفين لربما يستثيرون نفس مناطق السيروتونين (5-HT) في الجهاز العصبي.أجريت الدراسة على أربعة وعشرين جرذاً من فصيلة (Albino Wistar) تم تقسيمهم إلى مجموعتين، تم حقن إحداهما (المجموعة التجريبية) بجرعة مقدارها ٣٠ ميكروجرام لكل كيلوجرام من الزيوت الطيارة للحبة السوداء قبل أن تحقن بجرعة مقدارها ٥ ملجرام لكل كيلوجرام مورفين ثم تخضع لأربعة جلسات إشراطية باستخدام طريقة إشراط تفضيل المكان. أما المجموعة الأخرى (المجموعة الضابطة) فقد تم حقنها بمحلول ملحي (saline) بدلاً من زيوت الحبة السوداء، وفيما عدا ذلك تمت معاملتها بالمثل. أظهرت النتائج تأثير إشراطي واضح للمورفين، ولكن بالرغم من ذلك لم يظهر أي تفاعل بين زيوت الحبة السوداء وتأثير المورفين. تمت مناقشة النتائج في ضوء الجرعة المنخفضة للزيوت الطيارة للحبة السوداء التي استخدمت في هذه الدراسة.