



Antidepressant-like effects of an apolar extract and chow enriched with *Nepeta cataria* (catnip) in mice

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Abstract

Nepeta cataria (catnip) is a plant used in pet toys and to treat human diseases. Catnip has also been used in the treatment of some depressive disorders. In this paper, we studied the antidepressant, anxiogenic, and motor activity effects of acute and repeated feeding of chow enriched with 10% *N. cataria* leaves and the acute and repeated administration of apolar and polar extracts of *N. cataria* leaves in male mice. The results showed that repeated feeding and acute and repeated administration with the apolar extract reduced immobility in the behavioral despair test but did not alter elevated plus maze and open-field parameters. Acute feeding and the acute and repeated administration of the polar extracts of *N. cataria* leaves did not alter the behavior of mice. These data suggest that *N. cataria* has antidepressant properties. Moreover, this antidepressant activity was present in the apolar extract. **Keywords:** open field, elevated plus maze, behavioral despair test.

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Introduction

Nepeta cataria (catnip or catmint) belongs to the mint family (Lamiaceae; Adiguzel et al., 2009). *Nepeta* is a genus composed of perennial or annual herbs with a cosmopolitan distribution in Asia, Europe, and North Africa. *N. cataria* has long been used in North American popular medicine and in teas, dyes, and infusions. *Nepeta* species are widely used because of their antispasmodic, expectorant, diuretic, antiseptic, febrifuge, antitussive, and antiasthmatic effects (Smitherman, Janisse, & Mathur, 2005). Moreover, the fresh or dried plant, juice, and extract can induce extreme pleasure manifestations in cats.

For these reasons, *N. cataria* is also used in pet toys (Hatch, 1972).

Furthermore, several reports attribute the antidepressant and anxiolytic properties to *N. cataria* plants or its components (Bhat & Moskovitz, 2009; Cauffield & Forbes, 1999; Zeichen, Gargiulo, Carena, & Bindstein, 2004). However, the antidepressant effects of *N. cataria* have not been replicated in other studies (e.g., at different ages in children, adolescents, and the elderly; Frazer, Christensen, & Griffiths, 2005; Jorm et al., 2006). Because of these discrepancies, we tested the possible antidepressant-like effects of *N. cataria* in animal models that evaluate antidepressant drugs.

A previous study from our group showed that long-term treatment with commercial products containing *N. cataria* produces antidepressant-like effects without interfering with general activity observed in an open field (OF) and the elevated plus maze ([EPM]; Bernardi, Spinosa, Sender, Górnica, & Massoco, 1998). The present study replicated these experiments using the leaves of *N. cataria* because commercial products can contain a mixture of other plants, and the effects cannot be exclusively attributed to *N. cataria*. Moreover, the apolar and polar leaf extract effects were studied to investigate the fraction that contains the active components responsible for the behavioral effects.

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The behavioral despair test (BDT), EPM, and OF test were employed to assess the antidepressant-like, anxiolytic-like, and motor effects, respectively, of *N. cataria* in mice.

Methods

Animals

Three hundred male BALB/c mice from our colony, weighing 25–30 g, were used. The animals were housed in groups of five in polypropylene cages (38 × 32 × 16 cm) at a controlled room temperature (22 ± 2°C), humidity (65–70%), and artificial lighting (12 h/12 h light/dark cycle, lights on at 6:00 a.m.) with free access to filtered water. The mice used in this study were maintained in accordance with the guidelines of the Committee on the Care and Use of Laboratory Animal Resources of the School of Veterinary Medicine, University of São Paulo, Brazil. These guidelines are similar to those of the National Institutes of Health, Bethesda, MD. The experiments were performed in accordance with good laboratory practice protocols and quality assurance methods.

Botanical material collection and *N. cataria*-enriched chow and extract production

Nepeta cataria L. (Lamiaceae) was collected in Rua Serra Azul, 308, Piracicaba, SP, Brazil (specimen no. 001/205). Specimens were identified by botanist Oriana Favero, Ph.D., from the Universidade Presbiteriana Mackenzie. A voucher specimen was deposited in the Herbário Municipal de São Paulo (collection no. PMSP8986).

After collection, the leaves (3.195 kg) were completely dried in an air circulation stove at 40°C, ground in a hammer mill to a final four-mesh granulometry, and mixed with regular powdered chow in a 10% proportion. According to the American Institute of Nutrition, the chow used in this study, which was mixed with 10% *N. cataria* leaves, maintained the minimal amounts of essential nutrients recommended in the AIN-93G diet formulated for the adequate development of rats (Reeves, Nielsen, & Fahey, 1993).

The air-dried leaves of *N. cataria* (approximately 700 g) were individually macerated with n-hexane and ethanol. After solvent evaporation under reduced pressure, 23.5 g (3.3%) of the n-hexane extract (apolar) and 15.1 g (2.2%) of the ethanol extract (polar) were obtained.

Treatments

Male mice were fed acutely or repeatedly with chow enriched with 10% *N. cataria* leaves. The control groups received regular chow (Nuvital, Nuvital Company, São Paulo, Brazil), which was balanced and specific to laboratory animals, without the plant leaves during the same period. Moreover, the apolar and polar extracts of *N. cataria* leaves were administered acutely or repeatedly

per os to other groups of mice (48 mg/kg). The control groups for the apolar and polar extracts were administered with oil and saline, respectively (0.1 ml/10 g, *per os*).

Furthermore, one positive control group received the antidepressant imipramine (30 mg/kg; i.p., imipramine hydrochloride diluted in physiological saline). Another positive control group received diazepam (Cristália do Brasil S/A, 1 mg/kg/day; i.p., diluted in physiological saline).

The behavioral effects of *N. cataria*-enriched chow and the apolar and polar extracts were evaluated by the BDT, EPM, and OF test. Animals in the control and experimental groups were observed alternately in each experiment during the light phase of the cycle between 2:00 p.m. and 5:00 p.m.

Behavioral despair test

The BDT was previously described by Porsolt, Bertin, and Jalfre (1977). Mice were individually placed in a cylinder (40 cm height, 22 cm diameter) containing 15 cm water (22°C) from which they could not escape. Two sessions were performed on 2 consecutive days. In the first session (training session), mice were gently placed in the water and kept in the cylinder for 10 min. In the second session (test session), the latency to the first bout of immobility and the duration of immobility were measured. The minimal duration of a bout of immobility was set at 1 s. An immobile mouse was considered a mouse without active behaviors (i.e., struggling, swimming, and jumping) that remained passively floating or made the minimal movements necessary to maintain the nostrils above the water. The water of the cylinder was changed between sessions.

Elevated plus maze

The EPM has been described in detail elsewhere (Hogg, 1996; Rodgers, Cao, Dalvi, & Holmes, 1997). Briefly, the apparatus consisted of two open arms (35 × 5 cm) and two closed arms (30 × 15 cm) that extended from a common central platform (5 × 5 cm). The floor and walls of each arm were made of wood and painted white with an acrylic washable covering. The entire maze was elevated to a height of 50 cm above floor level as described by Lister (1987). Testing was conducted in a quiet room illuminated only by a dim light. To begin a test session, mice were placed in an open arm facing the center of the maze. An entry into an arm was defined as the placement of all four paws over the line marking that area. The number of entries into and time spent on the open and closed arms were recorded during a 5 min test session. The maze was wiped clean with a 5% alcohol solution between each trial.

Open field test

To determine the motor effects of *N. cataria* extracts, general activity was directly assessed through behavioral observation in an OF. The arena consisted of a circular

wooden arena as suggested by Broadhurst (1960). The background was divided into three concentric circles that were subdivided by straight segments into 19 roughly equal areas. This arena was inside a wooden case 48 cm above the floor. For the observations, each animal was individually placed in the center of the arena, and the following parameters were measured over a period of 5 min: locomotion frequency (number of floor units entered with both feet), rearing frequency (number of times the animal stood on its hind legs), and immobility time (the number of seconds the mouse was immobile). The device was cleaned with a 5% alcohol/water solution before placement of the animals to eliminate possible bias effects caused by odor clues left by the previous mice.

Experiment 1: Behavioral effects of acute feeding with chow enriched with 10% *N. cataria* leaves

Eighty male mice were food-deprived for 8 h and then received the enriched (10% *N. cataria* leaves) or normal rodent chow for 2 h. Immediately after these treatments, 30 previously trained mice were divided into three equal groups (control, experimental, and imipramine) and tested in the BDT. Another 30 male mice were divided into three equal groups (control, experimental, and diazepam) and tested in the EPM. Twenty male mice were divided into two equal groups (control and experimental) and were observed in the OF test. Food consumption was measured.

Experiment 2: Behavioral effects of repeated feeding with chow enriched with 10% *N. cataria* leaves

Sixty male mice were fed for 7 days with the enriched chow (10% *N. cataria* leaves) or the normal rodent chow. These animals were divided into six equal groups (three experimental and three control groups) and behaviorally tested in the BDT, EPM, and OF test. Food consumption was also measured during treatment.

Experiments 3 and 4: Behavioral effects of acute administration of *N. cataria* leaf apolar and polar extracts

One hundred twenty male mice were food-deprived for 8 h. These animals were divided into six equal groups (three experimental and three control groups) and behaviorally tested in the BDT, EPM, and OF test. The mice in the experimental groups received the apolar or polar extract of *N. cataria* (48 mg/kg, *per os*) and were observed in the OF and EPM 15 min after treatments. This dose was calculated based on the daily consumption of the enriched food chow (4.5 g/day/10% of plant), the extract yield, and the mean mouse body

weight. The mice tested in the BDT received the apolar or polar extract *per os* 15 min before the test session.

Experiments 5 and 6: Behavioral effects of repeated administration of *N. cataria* leaf apolar and polar extracts

Forty male mice were divided into two experimental (apolar and polar extracts) and two control (vehicles) groups. The mice in the experimental groups received 48 mg/kg *per os* of the *N. cataria* leaf apolar or polar extracts once per day for 7 days. The BDT was performed 15 min after the last extract administration.

Statistical analysis

The results are expressed as mean \pm SEM. Data from two groups were compared using Student's *t*-test. Three or more group data were analyzed using one-way analysis of variance (ANOVA) followed by the Bonferroni test. In all cases, the results were considered significant with $p < .05$. Statistical analyses were performed using GraphPad InStat version 3.01 software (GraphPad, San Diego, CA).

Results

No behavioral effects in the BDT, EPM, and OF test were observed in the enriched chow (10% *N. cataria* leaves) acute feeding group compared with the control group. However, mice treated with imipramine presented a higher latency to the first immobility in the BDT compared with the control group, showing that the BDT was effective in revealing antidepressant effects. Furthermore, mice treated with diazepam prior to the EPM test presented an increased number of entries into and time spent on the open arms and a reduced number of entries into and time spent on the closed arms, revealing the efficiency of this animal model (Table 1).

Figure 1 shows that repeated feeding with the enriched chow (10% *N. cataria* leaves) reduced the immobility time of mice in the BDT ($p < .0007$). However, no differences were observed in the latency to the first immobility between groups ($p > .326$). No differences were observed in the enriched chow (10% *N. cataria* leaves) repeated feeding group in the EPM or OF test (Table 1).

No differences were observed in food consumption in the enriched chow (10% *N. cataria* leaves) acute feeding group (4.5 ± 0.3 g for the control group and 4.4 ± 0.3 g for the experimental group; $p < .05$). During repeated feeding, control mice were fed 4.5 ± 0.4 g/day, and the experimental mice were fed 4.6 ± 0.30 g/day in the beginning and up to 6.7 ± 0.34 g/day on the last day of treatment. A two-way ANOVA revealed significant differences between treatments ($F [6, 126] = 5.76$; $p < .0001$) and days of

Table 1. Effects of acute and repeated feeding of chow enriched with 10% *N. cataria* leaves and acute and repeated administration of the apolar and polar extracts of *N. cataria* leaves in the behavioral despair test, elevated plus maze, and open field test in male mice ($n = 10$ for both the groups, mean \pm SEM). Data from two groups were compared using Student's *t*-test. Three-group data were analyzed using one-way ANOVA followed by the Bonferroni test. In all cases, the results were considered significant with $p < 0.05$. Columns with different letters mean significant differences.

Experiment	Parameters	Control group	Catnip group	Imipramine/ Diazepam group
	<i>Behavioral despair</i>			
	Latency to 1st immobility	98.80 \pm 15.36 a	105.90 \pm 21.08 a	230.00 \pm 12.50 b
	Immobility (s)	137.20 \pm 33.11	110.68 \pm 18.70	65.00 \pm 2.00
	<i>Elevated plus maze</i>			
Acute feeding with chow en- riched with 10% <i>N. cataria</i> leaves	No. of open arm entries	9.31 \pm 0.90 a	8.10 \pm 1.01 a	19.22 \pm 2.92 b
	Open arm time (s)	78.20 \pm 7.80 a	74.13 \pm 11.32 a	191.20 \pm 17.20 b
	No. of closed arm entries	14.80 \pm 0.70 a	13.80 \pm 1.40 a	10.22 \pm 0.89 b
	Closed arm time (s)	168.00 \pm 10.32 a	175.5 \pm 15.77 a	95.20 \pm 9.20 b
	<i>Open Field</i>			
	Locomotion frequency	128.90 \pm 6.00	160.00 \pm 8.00	-
	Rearing frequency	4.00 \pm 3.00	4.80 \pm 2.30	-
	Immobility (s)	29.50 \pm 16.00	19.00 \pm 17.00	-
	<i>Elevated plus maze</i>			
Repeated feeding with chow en- riched with 10% <i>N. cataria</i> leaves	No. of open arm entries	6.70 \pm 0.80	6.70 \pm 0.82	-
	Open arm time (s)	61.30 \pm 9.45	62.10 \pm 7.20	-
	No. of closed arm entries	15.30 \pm 0.90	14.12 \pm 0.85	-
	Closed arm time (s)	178.90 \pm 10.20	184.56 \pm 11.00	-
	<i>Open Field</i>			
	Locomotion frequency	140.20 \pm 8.41	158.00 \pm 10.00	-
	Rearing frequency	4.80 \pm 2.50	5.30 \pm 3.80	-
	Immobility time (s)	30.00 \pm 12.00	28.00 \pm 14.00	-
	<i>Elevated plus maze</i>			
Acute administra- tion of <i>N. cataria</i> apolar extract	No. of open arm entries	2.90 \pm 1.10	2.55 \pm 0.45	-
	Open arm time (s)	132.40 \pm 16.85	75.60 \pm 25.01	-
	No. of closed arm entries	3.60 \pm 0.81	3.50 \pm 1.10	-
	Closed arm time (s)	231.10 \pm 8.20	251.00 \pm 13.12	-
	<i>Behavioral despair</i>			
	Latency to 1st immobility	100.00 \pm 3.20	98.00 \pm 3.00	-
	Immobility time (s)	155.00 \pm 5.00	156.00 \pm 3.00	-
	<i>Elevated plus maze</i>			
Acute administra- tion of <i>N. cataria</i> polar extract	No. of open arm entries	2.90 \pm 1.10	2.45 \pm 1.00	-
	Open arm (s)	132.40 \pm 16.85	130.20 \pm 13.70	-
	No. of closed arm entries	3.60 \pm 0.81	3.90 \pm 0.96	-
	Closed arm time (s)	231.10 \pm 8.20	216.21 \pm 6.90	-
	<i>Open Field</i>			
	Locomotion frequency	85.20 \pm 2.73	71.10 \pm 5.56	-
	Rearing frequency	23.10 \pm 1.86	22.60 \pm 2.65	-
	Immobility time (s)	65.00 \pm 8.26	72.00 \pm 4.40	-
	<i>Elevated plus maze</i>			
Repeated admin- istration of <i>N.</i> <i>cataria</i> apolar extract	No. of open arm entries	2.80 \pm 1.11	2.60 \pm 0.50	-
	Open arm time (s)	134.40 \pm 16.85	72.80 \pm 25.01	-
	No. of closed arm entries	3.80 \pm 0.86	3.40 \pm 1.03	-
	Closed arm time (s)	240.20 \pm 7.15	268.00 \pm 14.98	-

Table 1. (continued)

		<i>Behavioral despair</i>			
		Latency to 1st immobility	101.00 ± 3.00	99.00 ± 2.50	-
		Immobility time (s)	158.00 ± 5.00	155.00 ± 3.00	-
		<i>Elevated plus maze</i>			
Repeated ad- ministration of <i>N. cataria</i> polar extract	No. of open arm entries	2.80 ± 0.33	2.50 ± 0.98	-	
	Open arm time (s)	133.22 ± 15.20	129.35 ± 12.80	-	
	No. of closed arm entries	3.85 ± 0.92	3.96 ± 0.98	-	
	Closed arm time (s)	220.20 ± 7.33	215.22 ± 6.89	-	
		<i>Open Field</i>			
		Locomotion frequency	125.00 ± 22.33	121.30 ± 21.34	-
		Rearing frequency	4.22 ± 4.10	4.40 ± 2.65	-
		Immobility time (s)	31.29 ± 15.75	28.00 ± 16.00	-

treatment ($F [1, 126] = 63.62; p < .0001$) and an interaction between factors ($F [6, 126] = 4.84; p < .0002$).

Figure 2 shows the general activity observed in the OF test in mice treated acutely with *N. cataria* leaf apolar extracts. Compared with the control groups, mice treated with the apolar extract had decreased locomotor activity and rearing frequency ($p < .0001$ and $p = .0042$, respectively). Moreover, the immobility time increased in these animals ($p = .0038$).

Figure 3 shows the data from the BDT in mice treated acutely or repeatedly with *N. cataria* leaf apolar extracts. The immobility time in the BDT decreased in mice treated acutely (Fig. 3A, $p < .0001$) and repeatedly (Fig. 3B, $p < .001$) with the apolar extract. Moreover, repeated administration with the apolar extract decreased the latency to the first immobility (Fig. 3B, $p < .0001$). However, acute and repeated administration with the *N. cataria* leaf apolar extracts did not modify the EPM parameters (Table 1).

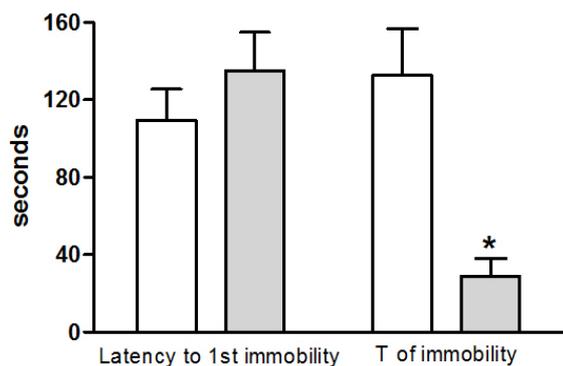


Figure 1. Effects of repeated feeding (7 days) of chow enriched with 10% *N. cataria* leaves in the behavioral despair test in mice. The latency to the first bout of immobility and the duration of immobility were measured. Open bars, Control group; gray bars, experimental group (chow enriched with *N. cataria*). Values are expressed as mean ± SEM. * $p < 0.001$, compared with the control group (Student's *t*-test). $n = 10$ per group.

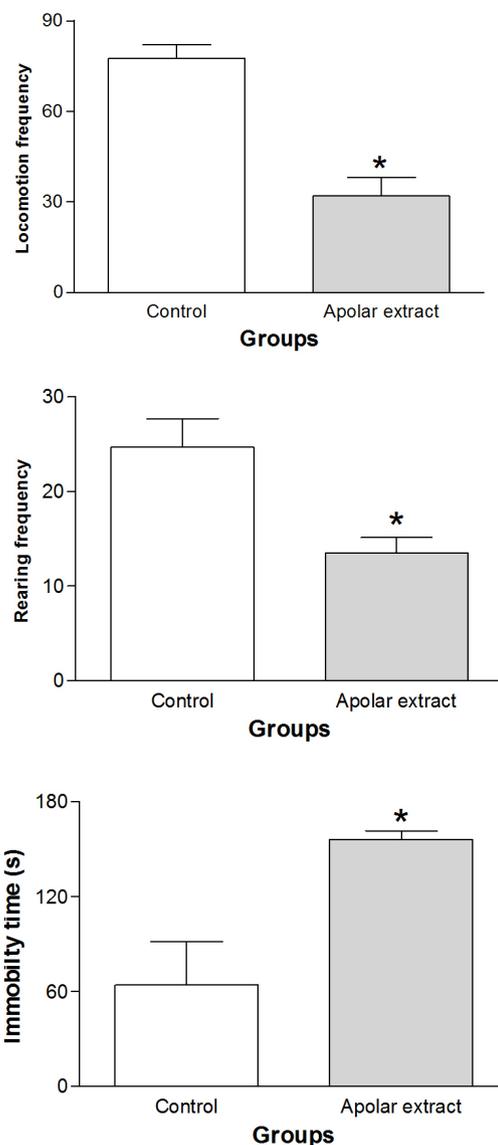


Figure 2. Effects of acute administration of the *N. cataria* leaf apolar extract (48 mg/kg) on open-field behaviors in mice. Locomotion, rearing frequency, and immobility time were measured. Values are expressed as mean ± SEM. * $p < 0.05$, compared with the control group (Student's *t*-test). $n = 10$ per group.

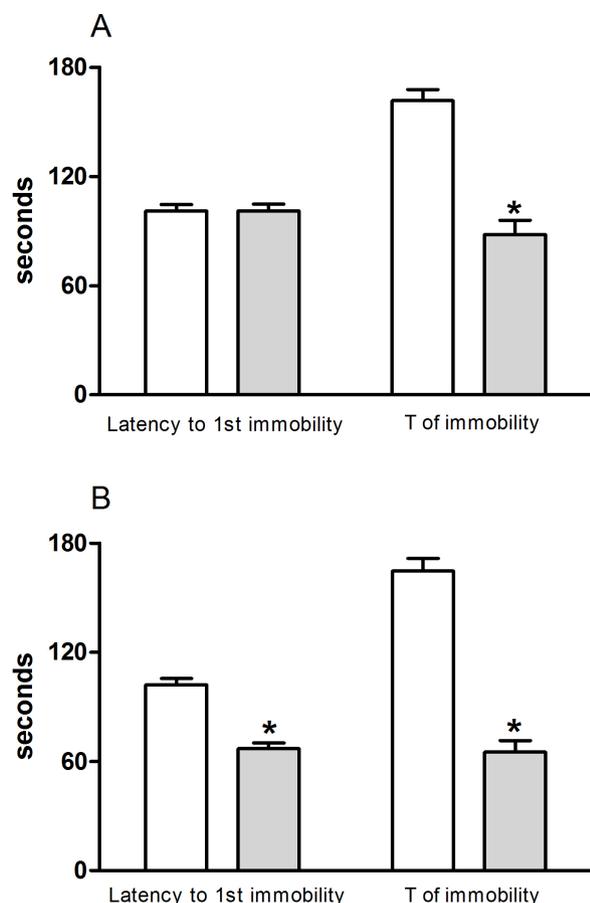


Figure 3. Effects of (A) acute and (B) repeated administration (7 days) of *N. cataria* leaf apolar extract in the behavioral despair test in mice. The latency to the first bout of immobility and the duration of immobility were measured. Open bars, control group; gray bars, apolar extract of *N. cataria*. Values are expressed as mean \pm SEM. * $p < 0.001$, compared with the control group (Student's *t*-test). $n = 10$ per group.

No behavioral effects in the BDT, EPM, and OF test were observed with acute or repeated administration of *N. cataria* leaf polar extract compared with the control group (Table 1).

Discussion

Among all of the animal models, the BDT remains one of the most widely used tools for screening antidepressants (Borsini & Meli, 1988; Petit-Demouliere, Chenu, & Bourin, 2005). When forced to swim in a restricted space, rats and mice will rapidly cease attempts to escape and become immobile (Castagne, Porsolt, & Moser, 2009). Porsolt, Anton, Blavet, and Jalfre (1978) showed that immobility was mainly reduced by antidepressant agents, despite some cases of false positive results (e.g., with antihistamines and psychostimulants; Bourin, 1990). This forced-swim immobility has been referred to as “behavioral despair,” which might be considered an acute depressive reaction in response to inescapable swimming (Porsolt et al., 1978; Porsolt, Bertin, Blavet, Deniel, & Jalfre, 1979).

The repeated feeding of chow enriched with 10% *N. cataria* leaves and the acute or repeated administration of *N. cataria* leaf apolar extracts induced some behavioral changes associated with the antidepressant response. In fact, these treatments reduced the time of immobility vs. the control group in the BDT. Additionally, repeated administration with the apolar extract reduced the latency to immobility. The present data suggest that these treatments induced a behavioral profile that was similar to antidepressant drugs.

Several central nervous system effects related to antidepressants have been described for *N. cataria*. Cauffman and Forbes (1999) reported that the *N. cataria* leaf is used as a dietary supplement for the treatment of depression, anxiety, and sleep disorders. Additionally, Bhat and Moskovitz (2009) showed that *N. cataria* is effective in the treatment of stress, tension, and insomnia. Comparing the *N. cataria* and *Melissa officinalis* effects, these plants have similar pharmacological profiles as central nervous system antidepressants (Zeichen et al., 2004).

Interestingly, nepetalactone, a major constituent of the essential oil of another *Nepeta* (*N. ratanjensis*), inhibits the monoamine oxidase (MAO) B enzyme *in vitro* and moderately inhibits MAOA, similar to the first antidepressant MAO inhibitors (MAOIs; Tovilović, Tomić, Mišić, & Grubišić, 2005). The essential oil isolated from this plant does not show a significant antidepressant effect, probably because inhibition of MAOA, but not MAOB, is primarily responsible for the behavioral antidepressant effects.

The repeated apolar extract treatment reduced both the time and latency to immobility in the BDT, similar to the antidepressant fluoxetine, which is a selective serotonin reuptake inhibitor (Cryan & Lucki, 2000).

Acute feeding with chow enriched with 10% *N. cataria* leaves and the acute or repeated administration of *N. cataria* leaf polar extracts did not induce an antidepressant- or anxiogenic-like effect or locomotor disturbances in mice. However, the use of imipramine or diazepam as a positive control in our behavioral tests showed the reliability of these models in our experiments.

Locomotor disturbances affect the performance of several behaviors. Moreover, some psychostimulants are considered potential false positives because they are active in the BDT but are not recognized as clinically effective antidepressants (Castagne et al., 2009). Acute apolar extract treatment reduced OF behavior in mice but not the latency to first immobility in the BDT. These contradictory results could be explained by the differences between the two behavioral methods employed here. General activity in the OF measures various behavioral parameters, among which are those related to emotional, exploratory, and motor behaviors.

The first exposure of the animal to the OF has a more marked emotional component than the remaining aspects of exposure (Batatinha, de Souza-Spinosa, & Bernardi, 1995; Lazarini, Uema, Brandao, Guimaraes, & Bernardi, 2000; Massoco, Silva, Gorniak, Spinosa, & Bernardi, 1995; Moniz, Bernardi, & Spinosa, 1994). Thus, the decreased general activity observed in mice with acute treatment of the apolar extract could be a consequence of an increased emotional state. However, the lack of effect of the apolar extract in the EPM suggests that the reduction in OF parameters was not the result of increased emotionality but rather reduced exploratory activity. These facts also exclude any locomotor disturbances in the antidepressant studies (i.e., BDT).

In this respect, Rabbani, Sajjadi, and Mohammadi (2008) studied the anxiolytic effect of another plant of the *Nepeta* genus (*N. persica*). The authors employed the hydroalcoholic extract of the aerial parts of this plant and found that 50 mg/kg, i.p., had anxiolytic-like effects with less sedative and hypnotic effects than diazepam and caused nonspecific stimulation at 100 mg/kg. However, a previous study by our group using commercial products of *N. cataria* (Massoco et al., 1995) suggested an amphetamine-like effect (i.e., psychostimulant properties). Thus, we examined the effects of acute and repeated feeding of chow enriched with 10% *N. cataria* leaves and apolar and polar leaf extracts in a behavioral model of anxiety, the EPM. Data from all of the EPM studies failed to show anxiolytic- or anxiogenic-like effects of the plant or its extracts when the data of the experimental and control groups were compared.

In the present study, repeated feeding with *N. cataria* increased food consumption. These data may indicate that *N. cataria* was more appetitive or even induced hyperphagia.

In conclusion, the present study indicated that chow enriched with 10% *N. cataria* and the apolar extract have antidepressant properties, especially after repeated administration. In this respect, antidepressant drugs are well known to be effective after long-term treatment (Moreno, R.A., Moreno, & Soares, 1999). Additionally, this study indicated that the active principles responsible for the antidepressant-like effects of *N. cataria* are present in the apolar extract. These findings corroborate reports of *N. cataria* for the treatment of depressive disorders as a complementary and alternative medicine. Moreover, the results suggest that an effective treatment should be with the apolar extract using repeated administration.

Future studies are planned to evaluate the effects of long-term (21 day) feeding and long-term apolar extract administration. Moreover, identifying the substance or substances responsible for the antidepressant effects of *N. cataria* will be interesting.

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