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The effect of *Morinda officinalis* How, a Chinese traditional medicinal plant, on the DRL 72-s schedule in rats and the forced swimming test in mice

Zhong-Qi Zhang*, Li Yuan, Ming Yang, Zhi-Pu Luo, Yi-Min Zhao

Division of Psychopharmacology, Beijing Institute of Pharmacology and Toxicology, 27 Taiping Road, Beijing, 100850, China

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Abstract

The present study observed the antidepressant-like action of the medicinal plant *Morinda officinalis* in the differential reinforcement of low rate 72-s (DRL 72-s) schedule, a behavioral screen selective and sensitive to antidepressant drugs, and the forced swimming test, a well-known animal model of depression. In the DRL 72-s schedule in rats, the plant extract (25–50 mg/kg), similar to clinically effective antidepressant drug desipramine (5–10 mg/kg), significantly reduced response rate and efficiency ratio while at the same time increasing reinforcement rate. In the forced swimming test in mice, the plant extract (50 mg/kg), like the effect of desipramine (20 mg/kg), also elicited a significant reduction in the duration of immobility. A tendency to this phenomenon could be seen at the dose of 100 mg/kg. Meanwhile, the plant extract, in the effective doses for the forced swimming test, had no effects on spontaneous motor activity in mice. These findings provide further support for the conclusion that *M. officinalis* extract possesses the antidepressant effect.

Keywords: *Morinda officinalis*; Desipramine; Forced swimming test; Operant behavior; Antidepressant effect

1. Introduction

At present, all kinds of clinically used antidepressants have a slow onset of action and do not improve all patients. In addition, most of them have undesirable side effects. Thus, there is an absolute need for new antidepressants. Apparently, in China, screening agents from traditional medicinal herbs will be an important way to obtain new antidepressants because China has plentiful herbal resource. *Morinda officinalis* How (family Rubiaceae) is a plant extensively used as a Yang-tonic agent for about 2000 years in China (Chen, 1988). The plant grows in humid areas of southeast China. In a screening program designed to detect activity on the central nervous system, the crude extract of the roots of *M. officinalis* How was found to increase markedly the content of monoamine transmitters in the in vivo brains of reserpinized mice [e.g. both hippocampal norepinephrine (NE) and 5-hydroxytryptamine (5-HT) contents were increased over 30%] and in the meantime to improve body signs induced by reserpine (unpublished observations). From these findings, we speculated that *M. officinalis* extract may have an antidepressant-like action. Soon afterwards, we examined the effect of the ethanolic extract of *M. officinalis* in animal models of depression such as forced swimming tests and learned helplessness paradigm, finding that the extract induced significant reductions in the duration of immobility and in the number of escape failures (Zhang et al., 2000, 2001a). Furthermore, in an open small-sample clinical trial, the extract was found to improve symptoms of patients with depression (Liang, 1998). Very obviously, these results support our earlier speculation. In order to evaluate further the antidepressant-like effect of *M. officinalis*, the present study was to observe behavioral changes after treatment with the aqueous extract of *M. officinalis* in the differential reinforcement of low rate 72-s (DRL 72-s) schedule in rats and forced swimming test in mice.

* Corresponding author. Tel.: +86-10-68156771 (H)/66874606 (O); fax: +86-10-68211656.

E-mail address: zzhongqi@yahoo.com.cn (Z.-Q. Zhang).

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2. Methods

2.1. Animals

Male Kuming mice ($n = 148$) weighing 18–22 g and male Wistar rats ($n = 15$) weighing 180–220 g (Experimental Animal Center, AMMS, Beijing) were used in these experiments. They were group housed under following laboratory conditions: temperature 21 ± 2°C, humidity 40–60%, 12:12-L/D cycle, lights on at 08:00 h. Mice had free access to water and food pellets. The rats were also allowed free access to water but were food deprived, with access to food restricted to 4-g food pellets/100-g rat body weight after each behavioral session, during behavioral training days (Mondays–Fridays). On nontraining days (weekends), rats were allowed to free access to food pellets until Sunday morning. Food was withdrawn on Sundays (approximately 24 h prior to training on Mondays). Animals were treated in accordance with the current law and the NIH Guide for Care and Use of Laboratory Animals.

2.2. Preparation of the aqueous extract of M. officinalis

The dried roots of *M. officinalis* were purchased from Xiamen botanical garden, Fujian Province, and identified in Beijing Tongrentong Pharmaceutical Group, where a voucher specimen was deposited. The dried roots (5 kg) were pulverized and macerated at room temperature with 95% ethanol in water (15 l) for 6 days then filtered. The filtrate obtained was dried, suspended in water and partitioned with $CHCl_3$, ethyl acetate and *n*-butanol in turn. The dried extracts were obtained after evaporation of solvents, including $CHCl_3$ fraction 19 g, ethyl acetate fraction 6 g, *n*-butanol fraction 42 g and aqueous layer fraction 545 g. The aqueous extract was used in the present study. It mainly consisted of nystose (8.49% of total aqueous extract), 1F-fructofuranosylnystose [*O*-β-D-fructofuranosyl-([2 → 1]-*O*-β-D-fructofuranosyl)$_3$α-D-glucopyranoside; 5.83%], inulin-type hexasaccharide [IHS; *O*-β-D-fructofuranosyl-([2 → 1]-*O*-β-D-fructofuransyl)$_4$α-D-glucopyranoside; 12.08%] and inulin-type heptasaccharide [*O*-β-D-fructofuranosyl-([2 → 1]-*O*-β-D-fructofuransyl)$_5$α-D-glucopyranoside; 28.27%]. These compounds were identified by chemical and spectroscopic methods.

2.3. DRL 72-s

2.3.1. Apparatus

Four identical operant conditioning chambers (Med Associates, East Fairfield, VT) were used for DRL behavioral testing. Each chamber was equipped with two response levers, a pellet dispenser, a pellet delivery trough with light and photocell across the opening, a houselight and two stimulus lights over each lever. Only left lever and left stimulus light were active during each behavioral session. Response on right lever had no effect throughout the experiment. Chambers were connected to a microcomputer via a Med interface. Data acquisition was programmed using the MED-PC software system (Med Associates).

2.3.2. Procedure

Each rat was initially trained under a fixed-ratio, fixed-time 1-min schedule for food reinforcement until lever pressing behavior had been established. The rats were then shifted to a DRL 18 s schedule where food was delivered only when the inter-response time was 18 s or longer. After 4 weeks (20 sessions), the schedule requirement was increased to 72 s (DRL 72-s). The rats were trained under the DRL 72-s schedule for approximately 16 weeks until stable performance was achieved: the standard error of the mean total reinforcement rate was less than 10% around the corresponding mean during the last five consecutive sessions (not including data collected from Monday) and the number of reinforcers obtained during each of these sessions was not less than seven. Following this, the rats received drug administration. Experimental sessions were run from Monday to Friday. Test sessions were conducted on Tuesdays and Fridays, while control sessions were conducted on Thursdays. Each session lasted 1 h.

2.4. Forced swimming test

This test was performed as the original method described by Porsolt et al. (1977). Mice were placed individually and forced to swim for 6 min in a Plexiglass cylinder (25 cm in height, 15 cm in diameter), which was filled to a height of 12 cm with water maintained at 25 °C. The total duration of immobility in the last 4-min period was recorded by an observer unaware of the drug treatment. A mouse was considered immobile when it remained floating in the water, without struggling, making only very slight movements necessary to keep its head above water. Each animal was used only once. The percent reduction in the duration of immobility of test animals was calculated compared to the vehicle (VEH) condition.

2.5. Locomotor activity (LA)

LA of mice was monitored via a VIDEOMEX-V (Columbus Instruments, Columbus, OH). The distance traveled and time ambulated during 10 min in the open field (35 × 30 × 25 cm) were automatically recorded. Each mouse was tested individually and used only once.

2.6. Drug administration

Both *M. officinalis* extract and desipramine-HCl (Sigma) were freshly prepared in distilled water each day before testing. The extract (DRL-72 s: VEH, 12.5, 25, 50 and 100 mg/kg, $n = 7$; FST: VEH, 25, 50, 100 and 200 mg/kg, $n = 30, 14, 13, 13$ and 7; LA: VEH, 25, 50, 100 and 200 mg/kg, $n = 10$) and desipramine (DRL 72-s: VEH, 2.5, 5.0, 10 and

20 mg/kg, $n=7$; FST: VEH, 20 mg/kg, $n=30$ and 21) were given intraperitoneally in a volume of 2 (rats) or 10 ml/kg (mice) 30 min prior to the test. Doses of both drugs were administered in ascending order in DRL 72-s.

2.7. Data analysis

Data were presented as means ± S.E.M. FST and LA results were analyzed by one-way analysis of variance (ANOVA). The DRL experiment results were analyzed by repeated-measures ANOVA. Post hoc individual comparisons were made for each drug dose with control group using Dunnett's t test (two-tailed).

3. Results

3.1. Effect of M. officinalis extract on DRL 72-s behavior of rats

The effects of both *M. officinalis* extract and desipramine on DRL 72-s behavior in rats were shown in Table 1. Desipramine produced overall significant decreases in response rate [$F(3,24)=8.08$, $P<.001$] and efficiency ratio (responses/reinforcers) [$F(3,24)=5.53$, $P<.01$]. Dunnett's t tests revealed significant effects ($P<.01$) at the 5-and 10-mg/kg doses. The highest dose of desipramine (20 mg/kg) also produced decreases in response number and efficiency ratio but, as stated in Table 1, was not included in the statistical analysis. Desipramine also produced a significant increase in reinforcement rate compared with the VEH treatment [$F(3,24)=3.17$, $P<.05$]. Dunnett's t tests revealed significant effects at doses of 5 ($P<.01$) and 10 mg/kg ($P<.05$). *M. officinalis* extract had a similar profile as desipramine, that is, the extract produced an overall significant decrease in response number [$F(3,24)=6.45$, $P<.01$] and efficiency ratio [$F(3,24)=6.36$, $P<.01$] while at the same time increasing the rate of reinforcement [$F(3,24)=6.45$, $P<.01$]. Post hoc comparisons revealed significant effects ($P<.01$) at the 25- and 50-mg/kg doses. However, when extract's dose reached 100 mg/kg, both response rate and reinforcement rate were decreased.

Table 1
Effects of desipramine or the extract of *M. officinalis* on DRL 72-s schedule

Treatment (mg/kg)		Reinforcers per hour	Responses per hour	Efficiency ratio[a]
VEH		14.7 ± 1.3	95.8 ± 6.1	6.8 ± 0.7
Desipramine	2.5	18.6 ± 1.9	93.7 ± 7.7	5.8 ± 1.2
	5.0	21.4 ± 2.4**	70.1 ± 5.4**	3.4 ± 0.5**
	10.0	20.4 ± 1.0*	62.6 ± 3.6***	3.1 ± 0.3**
	20.0	7.1 ± 1.8	13.8 ± 3.0	1.5 ± 0.4
VEH		13.4 ± 1.2	105.0 ± 5.5	8.3 ± 1.0
Extract	12.5	14.4 ± 2.0	94.4 ± 5.9	7.9 ± 1.6
	25	19.1 ± 1.1**	70.3 ± 9.8**	3.8 ± 0.6**
	50	20.8 ± 1.1**	68.8 ± 8.7**	3.3 ± 0.5**
	100	5.7 ± 1.4	11.7 ± 3.8	2.4 ± 0.4

Treatments were performed 30 min intraperitoneally before the 1-h test session. Three of the seven rats tested failed to respond at the 20-mg/kg dose of desipramine. Four of the seven rats tested also failed to respond following administration of the 100-mg/kg dose of the extract. Data from the 20-mg/kg dose of desipramine and 100-mg/kg dose of the extract were excluded from the statistical analyses. All values are the means ± S.E.M. for each measure.

[a] Efficiency ratio = responses/reinforcers.

* $P<0.05$, significant difference from respective VEH treatments.

** $P<0.01$, significant difference from respective VEH treatments.

*** $P<0.001$, significant difference from respective VEH treatments.

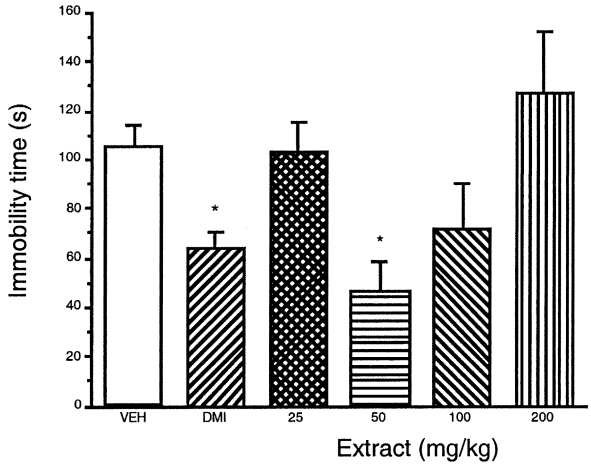

Fig. 1. Effects of desipramine and the extract of *M. officinalis* on immobility in the forced swimming test. Mice were administered VEH, desipramine (20 mg/kg ip) or extract (25–200 mg/kg ip). Values represent means ± S.E.M. of 7–30 mice per group. Immobility time of VEH animals = 104.9 ± 9.3 s. The respective mean ± S.E.M. percent reduction in immobility time is 40 ± 6.0 and 55 ± 11.5 for desipramine at 20 mg/kg and extract at 50 mg/kg. * $P<.05$, significant difference from VEH treatment.

3.2. Effects of M. officinalis extract in the forced swimming test in mice

Fig. 1 showed the effect of *M. officinalis* extract and desipramine on the duration of immobility. The extract produced a overall significant decrease in the duration of immobility in the forced swimming test in mice [$F(5,92)=5.11$, $P<.001$]. Post hoc comparison revealed that the 50-mg/kg dose of the extract produced a significant decrease (55%, $P<.05$) in the duration of immobility compared with the VEH treatment. A tendency to this phenomenon could be seen at the dose of 100 mg/kg. However, the extract at the low dose (25 mg/kg) or high dose (200 mg/kg) exhibited no behavioral effects. Under the same experimental conditions, desipramine (20 mg/kg) also produced a significant reduction (40%, $P<.05$) in the duration of immobility time in contrast to the VEH animals.

3.3. Effect of M. officinalis extract on LA in mice

In view of the fact that a reduction in the duration of immobility in the forced swimming test can also be

Table 2
Effect of the extract of *M. officinalis* on LA

Treatments (mg/kg)		Time ambulatory (s)	Distance traveled (cm)
VEH		419.0 ± 22.3	1921.5 ± 233.8
Extract	25	433.5 ± 16.1	2090.6 ± 210.7
	50	433.0 ± 22.1	2035.4 ± 210.7
	100	404.1 ± 22.1	1950.1 ± 208.7
	200	408.6 ± 37.2	1873.1 ± 242.9

Treatments were performed 30 min before LA was measured. LA was assessed for 10 min. Data represent the mean ± S.E.M. of 10 mice per group.

elicited by drugs, which induce hyperactivity, the influence of the extract on the LA was therefore assessed in the present study.

The extract had no effects on the LA in the open field in the dose ranges of 25–100 mg/kg [$F(4,45) = 0.30$, n.s. for time ambulatory; $F(4,45) = 0.16$, n.s. for distance traveled; Table 2]. These results suggest that the ability of the extract to reduce the duration of immobility in the forced swimming test is not due to an increase in motor activity.

4. Discussion

The DRL 72-s operant schedule has been generally considered to be a behavioral screen selective and sensitive to classical and novel antidepressants (Andrews et al., 1994; Marek and Seiden, 1988; Marek et al., 1989; McGuir and Seiden, 1980; O'Donnell and Seiden, 1982, 1983; Seiden et al., 1985; Sokolowski and Seiden, 1999; Van Hest et al., 1992; Zhang et al., 2000, 2001b), although the specificity of the method has been disputed (Jakson et al., 1995, Pollard and Howard, 1986). In the present study, clinically effective antidepressant desipramine (5.0 and 10 mg/kg) markedly increased reinforcement rate and decreased response rate in the DRL-72 s schedule. Thus, the present study used DRL 72-s schedule as a method of further evaluating the antidepressant-like effect of *M. officinalis* extract. After treatment with *M. officinalis* extract, DRL 72-s behavior of rats was very similar to the response pattern after treatment with desipramine. For example, the magnitude of the effect of both drugs on reinforcement rate and response rate had no apparent difference. The low doses had no effects on DRL behavior, whereas after treatment with intermediate doses, reinforcement rate increased and response rate decreased, consistent with an antidepressant effect. However, the high-dose exposures disrupted performance in the DRL 72-s schedule and the reasons of which remain unclear. These findings are very similar to the results after treatment with antidepressant drugs fluoxetine or sertraline (Sokolowski and Seiden, 1999).

The FST is a widely used animal model that detects antidepressant activity of new compounds. A reduction in the duration of immobility of animals in the FST reflects their antidepressant-like performance. In the present study, both the plant extract and desipramine significantly reduced the duration of immobility in mice. Furthermore, the reduction in the duration of immobility produced by *M. officinalis* extract was not due to an increase in general activity, as *M. officinalis* extract did not alter LA.

It is apparent that the behavioral effect of *M. officinalis* extract on the forced swim test performance follows an U-shaped dose–response function because only the intermediate dose (50 mg/kg) shortened the duration of immobility.

Taken together, it was shown that treatment with *M. officinalis* extract increased reinforcement rate and decreased response rate in the DRL 72-s schedule and reduced the duration of immobility in the FST. It may be concluded from these findings that *M. officinalis* extract possesses antidepressant effect.

The main constituents of *M. officinalis* extract are inulin-type oligosaccharides, which include nystose, 1F-fructofuranosylnystose, IHS and inulin-type heptasaccharide (see Methods). Our earlier unpublished observations found that the crude extracts of *M. officinalis* possessed no antidepressant action when the content of inulin-type oligosaccharides in *M. officinalis* was extremely low and it was difficult to quantified them. In order to understand the relationship between the content of inulin-type oligosaccharides in *M. officinalis* extracts and the effective doses for antidepressant action, we incorporated the recent reports (Zhang et al., 2000, 2001a,b) and the present study and further found that an increase in the content of inulin-type oligosaccharides in *M. officinalis* extracts was followed by a decrease in the effective doses for antidepressant action. In the meantime, there was no apparent difference in the magnitude of the antidepressant activity between extracts containing inulin-type oligosaccharides ranging from 40% to 75%. The active moieties obtained from *M. officinalis* also had profiles similar to the extracts. For example, the magnitude of the antidepressant activity in DRL 72-s for IHS appeared no difference when compared with those found in the aqueous extract in the present study. However, the effective doses of the antidepressant activity of IHS decreased to 5–10 mg/kg (Zhang et al., 2001a,b), comparable to the effective doses of desipramine in DRL 72-s. These data demonstrate that the antidepressant activity has been improved after bioassay directed fractionation and that the pharmacological effect of *M. officinalis* extract may be ascribed to inulin-type oligosaccharides.

Recently, an open small-sample clinical trial (Liang, 1998) showed that *M. officinalis* extract improved the symptoms of patients with mild to moderate depression and that this product was remarkably safe, devoid of major side effects typical for tricyclic antidepressant (TCA) or for the specific serotonin reuptake inhibitors (SSRI; Pinder, 1997). The generally good tolerability of *M. officinalis* extract is in agreement with the results of the toxicological studies conducted in animals (unpublished reports). For example, the rat maximal tolerable oral single dose of *M. officinalis* extract is higher than 15,080 mg/kg. After repeated administration of *M. officinalis* extract at three

dose levels (150, 600 and 2400 mg/kg po once daily) for 13 consecutive weeks, the rats of either sex have not shown any apparent toxicological signs. In a pilot study (Liang, 1998), *M. officinalis* extract was found to possess immunomodulation activity, which may be a unique advantage of *M. officinalis* extract in the treatment of depression because the immunological function seems to be abnormal in some subtypes of depression (Gold et al., 1986; Lamberts, 1986; Stokes and Sikes, 1987). Based on the findings of the present and the abovementioned studies, in combination with behavioral and biochemical data in earlier reports (Cai et al., 1996), it seems likely to conclude that *M. officinalis* extract may be a prospective and clinically effective antidepressant agent. A randomized double-blind controlled clinical trial of *M. officinalis* extract is in progress.

The mechanisms by which *M. officinalis* extract produced antidepressant effect still remain unclear. However, *M. officinalis* extract was found to bind selectively to 5-HT1A receptor and to protect cultured cortical and hippocampal cells from neuronal lesion induced by 5,7-dihydroxytryptamine (5,7-DHT) and to increase brain NE and 5-HT contents in olfactory bulbectomized rats (unpublished data). Moreover, all of the abovementioned pure compounds isolated from *M. officinalis* extract significantly increased the 5-HT-induced head twitches in mice (Cai et al., 1996). In light of these data, we suggest the antidepressant effect could at least partly be linked to the improved effect of *M. officinalis* extract on the functional deficiencies of 5-HT transmitter system at the neuron level.

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