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Original article

Hydroalcoholic Extract of *Avena sativa* Exerts Antidepressant-like Effects Through the Monoaminergic System

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Abstract

Background and objectives: Previous research has demonstrated the antidepressant potential of *Avena sativa*; however; its mode of action is still unknown. Hence, the role of the monoaminergic system in the antidepressant-like activity of *A. sativa* was investigated by using the tail suspension test in the present study. **Methods:** The mice intraperitoneally (i.p.) received the hydroalcoholic extract of *A. sativa* (50, 100, and 200 mg/kg) 30 min before the tail suspension test. The participation of the monoaminergic system in the antidepressant-like activity of *A. sativa* (200mg/kg) was assessed by administration of several receptor antagonists, 60 min before the administration of the extract in the test. Moreover, the effect of *A. sativa* on animals' locomotion was examined by using open-field test. **Results:** All doses of the *A. sativa* extract caused a significant antidepressant-like effect ($p<0.001$) in the tail suspension test, without any significant change in the mice locomotion in the open-field test ($p>0.05$). In addition, pre-treatment of the animals with sulpiride, haloperidol, SCH23390, *p*-chlorophenylalanine, ketanserin, WAY100135, reserpine, yohimbine, and prazosin abolished the antidepressant-like activity of *A. sativa*. Furthermore, the joint administration of sub-effective doses of *A. sativa* with fluoxetine and imipramine produced a synergistic antidepressant-like effect. **Conclusion:** *Avena sativa* induced an antidepressant-like effect in tail suspension test that is dependent on the monoaminergic system; however; clinical studies are required for showing the beneficial effects of the extract in humans.

Keywords: antidepressant-like effect; *Avena sativa*; mice; monoaminergic system; tail suspension test

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Introduction

Depression is a disorder that afflicts a considerable part of people all over the world [1]. On the other hand, as reported by WHO, about 3.8% of the population experience depression, including 5% of adults (4% and 6% among men and women, respectively), and 5.7% of adults older than 60 years old. Approximately 280 million people suffer from depression worldwide [2]. Common symptoms of depression are low mood and anhedonia, which can end in suicide [3]. Depression is an important neurological disease that threatens human health and quality of

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life [4]. The etiology and pathophysiology of depression are still unknown, owing to its involvement of multiple brain circuits that make the pathophysiology very complex [5]. Several studies have reported involvement of the monoaminergic system in the pathophysiology of depression. On the other hand, studies have reported the key function of the serotonergic, dopaminergic, and noradrenergic neurotransmitter systems in the pathogenesis of depression [6-10]. In this regard, most of the standard antidepressants (such as imipramine and fluoxetine) act by increasing the bioavailability of these monoamines.

Despite the development of those standard antidepressants, depression treatment still fails to lead clinical remission in lots of patients. Furthermore, many patients still display intolerance or refractory responses to these agents [11]. Moreover, they also cause side effects such as sexual impotence, agitation, insomnia, and weight gain [12]. Hence, novel medications with lower risk are required for the treatment of depression. Natural products are important medical sources used for the treatment of many psychological diseases, including depression. Previous studies have reported the antidepressant potential of medicinal plants in animal models [13-16].

Oat (*Avena sativa* L.*)* is a plant whose consumption has increased owing to its unsaturated fatty acids, phenolic compounds, and dietary fiber [17,18]. Studies have reported its positive effects on the nervous and brain systems. A study showed that administration of oat modulated cerebro-electrical activity [19]. Additionally, studies have shown that the hydroalcoholic extract of *Avena sativa* has positive effects on attenuating morphine withdrawal signs in mice [20]. Apart from these findings, earlier studies from several laboratories, including our laboratory have demonstrated the antidepressant potential of *A. sativa* [21,22]; however; the mode of action is still unknown. Hence, the role of monoaminergic systems in the antidepressant potential of *A. sativa* was investigated in the present research.

Material and Methods

Ethical considerations

The care and treatment were conducted based on the Ethical Committee of Islamic Azad Tehran Medical Sciences University, Pharmacy and Pharmaceutical Branches Faculty (ethical approval code: IR.IAU.PS.REC.1402.034).

Chemicals

SCH23390, sulpiride, p-chlorophenylalanine (pCPA), WAY100635, ketanserin and reserpine (from Sigma-Aldrich, USA), haloperidol (Exir Co., Iran), prazosin (Razak Co., Iran) yohimbine (Iran Daru Pharmaceutical Co., Iran), fluoxetine (Jalinous Pharmaceutical Co., Iran) and imipramine (Marham Darou Co., Iran) were used in the study.

Plant material

Oat extract [Ethanol (60): water (40)] was purchased ready-made (Bath No. S1201) from Giah Essence Phytopharm Co. (Gorgan, Iran). According to the analysis report sheet of the seeds extract, the dry residue after evaporation of the solvent and polysaccharides content were 2-3 g/100 mL and 46-54 mg/100 mL, respectively.

Animal study

All the drugs were administrated by intraperitoneal (i.p.) route, but SCH23390 was administrated by subcutaneous (s.c.) route. All the agents were dissolved in normal saline (0.9%) and 5 % Tween 80 and administrated at a volume of 10 mL/kg. A control group received normal saline with 5 % Tween 80 as the vehicle. The doses of *A. sativa* [21,22] and the drugs [15,16] uses were selected on the basis of literature data and previous studies.

A total of 168 male NMRI mice, six weeks of age, (26±2 g) were purchased from the Razi Institute (Tehran, Iran) and fed with commercial mice pellet and water ad libitum. The animals were kept under a lighting program of 12 h lightness and 12 h darkness. All the efforts were considered to minimize pain and stress in the mice.

Tail suspension test (TST)

The TST was conducted as reported by Steru et al. [23]. In this test, 70 cm metal bars were vertically fixed and connected with a 50 cm string. The animals were fixed to the string with a tape positioned approximately 1 cm from the tip of the tail. The animal first tried to escape but ultimately became completely immobile, passive, and unresponsive. The immobility time was recorded by a chronometer for 4 min after 2 min for accumulation. The decrease in immobility

time was considered the antidepressant activity. Doses of 50, 100 and 200 mg/kg of the hydroalcoholic extract of *A. sativa* were administrated to mice in three groups of six mice per group. Other groups were administrated with 1) vehicle (10 mL/kg), 2) fluoxetine (20 mg/kg) and 3) imipramine (30 mg/kg) [20,21].

Open-field test (OFT)

The OFT was conducted as reported by Brown et al. [24]. To reduce the number of animals used, the OFT was performed 5 minutes before the TST. In summary, 50, 100 and 200 mg/kg of the hydroalcoholic extract of *A. sativa* were administrated to mice in three groups and six mice per group. They were transferred into the center of the Plexiglas box in order to find the center of the box, 1h after the pre-treatment. Crossing and rearing numbers were recorded for 4 min, after 1 min of accumulation.

Investigation of the mechanisms of *A. sativa* extract in the monoaminergic system

The involvement of the dopaminergic system

To elucidate the possible involvement of the dopaminergic system, SCH23390 (as dopamine D_1 receptor antagonist, 0.05 mg/kg), sulpiride (as dopamine D_2 receptor antagonist, 50 mg/kg) and haloperidol (as non-selective dopamine receptor antagonist, 0.2 mg/kg) were administrated, respectively [15,16]. The agents were injected and the *A. sativa* extract (200 mg/kg) and/or vehicle (10 mL/kg), were administered after 15 min. The mice were exposed to the TST, 1 h after the administration of the extract and vehicle.

Involvement of the noradrenergic system

To elucidate the involvement of the noradrenergic system, prazosin (as an α_1 adrenoreceptor antagonist, 1 mg/kg) and yohimbine (as an α_2 adrenoreceptor antagonist, 1 mg/kg) were administrated, respectively [15,16]. The agents were injected and the *A. sativa* extract (200 mg/kg) and/or vehicle (10 mL/kg) were administrated after 15 min. The mice were submitted to the TST, 1h after the administration of the *A. sativa* extract and vehicle.

Involvement of the serotonergic system

To elucidate the involvement of the serotonergic system, WAY100135 (a selective 5-HT_{1A} receptor antagonist, 10 mg/kg) and ketanserin (a selective $5HT_{2A/C}$ receptor antagonist, 5 mg/kg) were administrated, respectively [15,16]. The mice were exposed to the TST, 1 h after the administration of the *A. sativa* extract (200 mg/kg) and vehicle. The pCPA (a blocker of serotonin synthesis, 150 mg/kg) was daily administrated for three consecutive days [15,16]. Fifteen minutes after the last injection, the extract and vehicle were administrated, and the mice were submitted to the TST, 1 h after the administration of the extract and vehicle.

Effects of reserpine on the antidepressant effect of the *A. sativa* extract in the TST

The mice were administrated with reserpine (as vesicular monoamines deplete, 2 mg/kg) [15,16], and treated with the *A. sativa* extract (200 mg/kg) and/or vehicle (10 mL/kg) 4 h after the administration of reserpine. The mice were submitted to the TST, 1 h after the administration of the extract and vehicle.

Effects of co-administration of the *A. sativa* extract with sub-effective doses of common anti-depressants

Conventional anti-depressants of imipramine and fluoxetine were individually administrated at a sub-effective dose of 5 mg/kg and the *A. sativa* extract was administrated after 15 min at a dose of 50 mg/kg [15,16]. The mice were submitted to the TST, 1 h after the administration of the extract.

Statistical analysis

The data were firstly investigated for normality status. Since the data were normal, parametric tests were used. The data were analyzed by one-way or two-way analysis of variance. Where significant differences were observed between groups, Tukey's HSD post-hoc test was used. The data were analyzed by Graph Pad Prism (version of 9.0); data are presented as mean ± standard error of mean (SEM).

Results and Discussion

The groups of mice treated with *A. sativa* extract (50, 100, and 200 mg/kg), fluoxetine (20 mg/kg) and imipramine (30 mg/kg) showed a significant ($p=0.001$) decline in duration of immobility time compared to control mice (Figure 1). On the other hand, hydroalcoholic extract of *A. sativa* Showed a promisingly antidepressant efficacy in TST. The results showed that only the high dose (200 mg/kg) of extract reduced immobility time,

stronger than fluoxetine ($p<0.001$). But, doses of 50 and 100 mg/kg of extract weaker than imipramine reduced immobility time ($p<0.001$). The most effective dose of *A. sativa* (200 mg/kg) was used to evaluate the mechanism(s) of action. The results are similar to other studies that showed plant derivations have antidepressant-like effects in animal models of depression [13-16]. The behavioral problems are the common symptoms of major depression, and they have a close relation to committing suicide. To mimic behavioral problems in humans, the forced swimming test and TST are still used as behavioral tests of animal models of major depression [23,25]. In the current study, we used the TST and showed that the acute administration of the extract decreased immobility time.

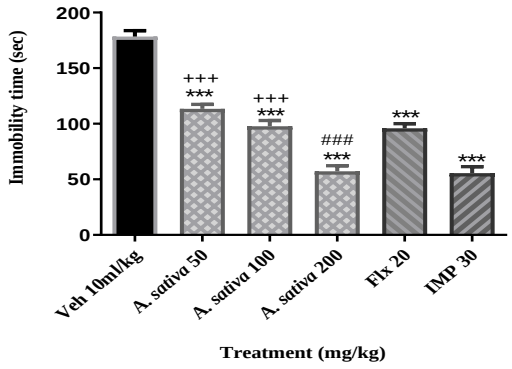

Figure 1. The effects of the *Avena sativa*, fluoxetine (Flx) and imipramine (IMP) on the immobility time in tail suspension test; the data are reported as mean ± SEM; ***: significant difference compared to control group; $^{+++}$: significant differences compared to IMP group; $^{###}$: significant difference compared to Flx group

As shown in Figure 2, the different doses of *A. sativa* extract (50-200 mg/kg) did not affect the number of crossing ($p=0.320$) and rearing ($p=0.776$) in the OFT. The OFT shows the psychomotor stimulant activity in an animal model [24]. The decrease in immobility time as a result of *A. sativa* extract cannot be attributed to any psychostimulant effects.

According to Figure 3, pre-treatment of animals with dopaminergic system antagonists including SCH 23390 ($p=0.001$), haloperidol ($p=0.001$), and sulpiride ($p=0.001$) could block the antidepressant-like effect induced by the *A. sativa* extract (200 mg/kg) in the TST. On the other hand, the results showed possible involvement of the D_1 and D_2 receptors in the antidepressant-like effect. Hence, the dopaminergic system could partly involve in the antidepressant-like effect of *A. sativa* extract. The dopaminergic system is known to be involved in depression in humans, motivation, and attention [26,27]. The hypo-dopaminergic condition has a closed relation with depression [26]. Wong et al. reported the involvement of wild green *A. sativa* extract by the dopaminergic system in cognitive performance [28].

Our results illustrated that pretreatment of the animals with WAY100135 ($p=0.001$), pCPA ($p=0.001$) and ketanserin ($p=0.001$) reversed the antidepressant-like effect of *A. sativa* extract (200 mg/kg) in TST (Figure 4). It means that *A. sativa* extract shows antidepressant-like effects by the modulation of the serotonergic system. The serotonergic system was introduced as one of the main neurotransmitters in depression because it is involved in some signs of severe depression [29].

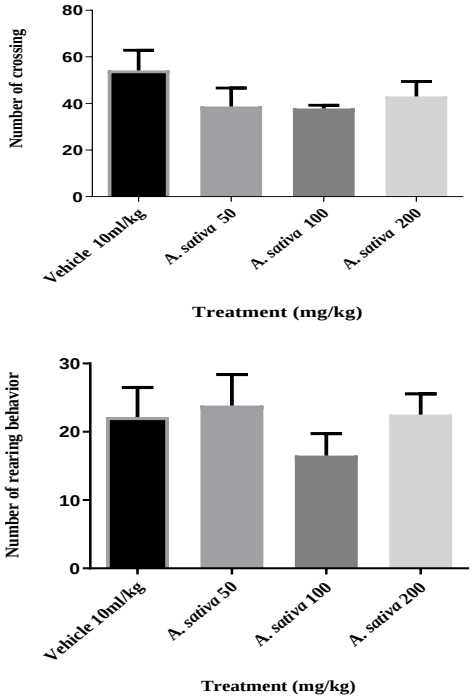

Figure 2. The results for the number of crossings and rearing in the open-field test

The 5-HT1A receptors are directly involved in the clinical effect of antidepressants, [30] because of their position on the soma and dendrites of 5-HT neurons in the dorsal raphe and the release of 5-HT [31]; 5-HT2 receptors are positioned in the brain regions that are involved with etiology of depression [32]. No previous study has reported the effects of the *A. sativa* extract on the serotonergic system and this research has reported the effects for the first time.

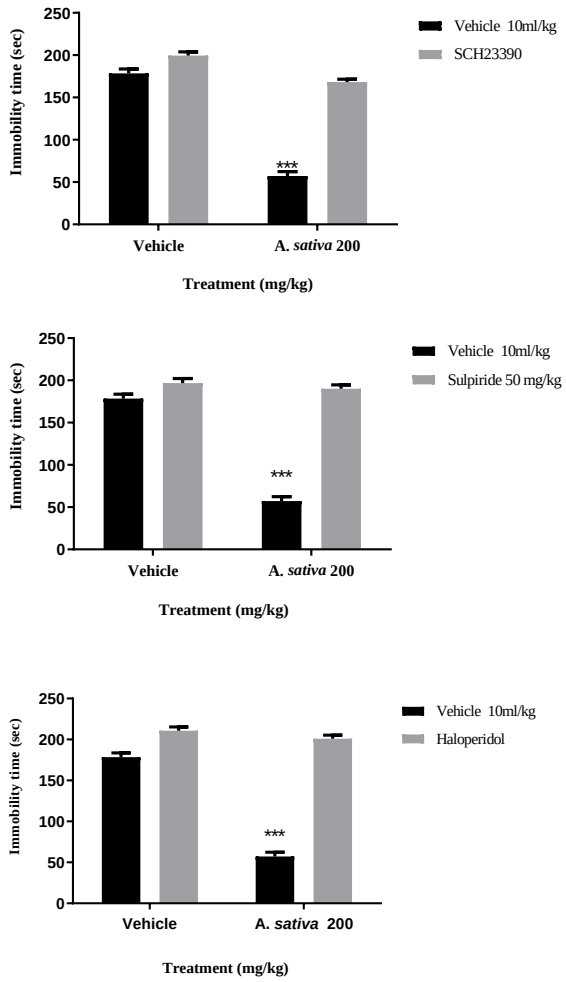

Figure 3. The results of the pre-treatment of dopaminergic system antagonists on the antidepressant-like effect induced by the *Avena sativa* extract in tail suspension test; the data are reported as mean ± SEM; ***: significant differences compared to control group

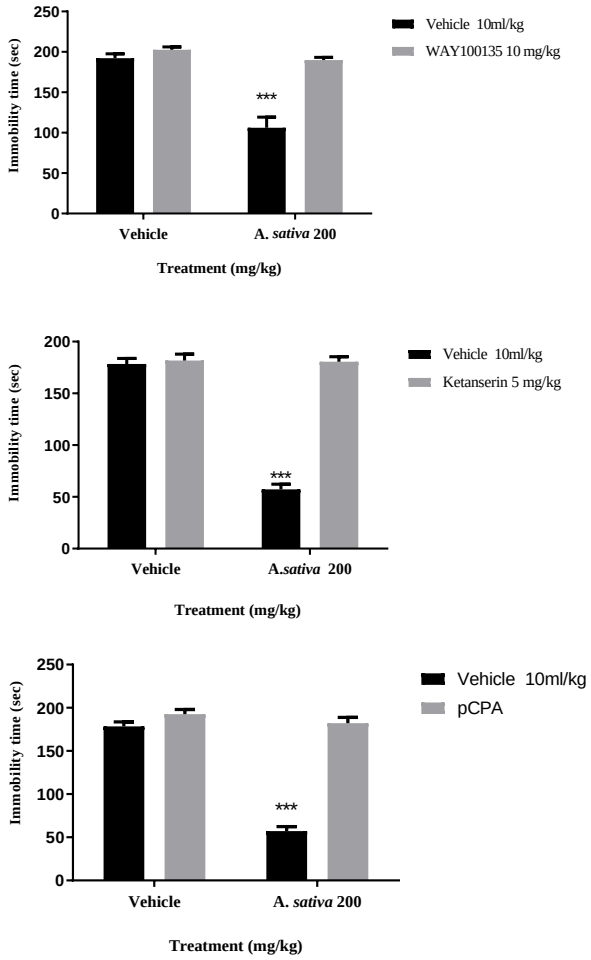

Figure 4. The results for the pre-treatment of serotonergic system antagonists on the antidepressant-like effect induced by *Avena sativa* extract in tail suspension test; data are reported as mean ± SEM; ***: significant differences compared to control group

As shown in Figure 5, pre-treatment of the mice with prazosin (p=0.001), and yohimbine (p=0.001) reversed the antidepressant-like effect of *A. sativa* extract (200 mg/kg) in TST. On the other hand, the results showed that the extract performed an antidepressant-like effect by modulation in the noradrenergic system. Studies have reported the involvement of the noradrenergic system in the pathogenesis of depression in humans [33,34] and animals [35,36].

In another set of experiments, the pre-treatment of animals with reserpine (p=0.001) also blocked the antidepressant-like effect of *A. sativa* extract (200 mg/kg) in TST (Figure 6). It confirms the involvement of monoaminergic system on the antidepressant-like effects of *A. sativa.*

Apart from these findings, our results demonstrated that the joint administration of a sub-effective dose of *A. sativa* extract (50 mg/kg) with fluoxetine (p=0.001) and imipramine (p=0.001) could potentiate the effects (Figure 7) showing a synergism interaction between the extract with sub-effective doses of common anti-depressants. Hence, the results show that sub-effective doses of conventional antidepressant drugs and the *A. sativa* extract might act in one way and/or improve others.

Conclusions

Our results documented the antidepressant-like effect of *A. sativa* extract in TST. It induced the effects partly by modulation of dopaminergic (D_1 and D_2 receptors), serotonergic (5-HT1A, 5-

HT2A receptors), and noradrenergic (α_1 and α_2 adrenoceptors) systems. *Avena sativa* could potentiate the antidepressant-like effect of fluoxetine and imipramine, proposing that this species might improve the efficiency of these antidepressants. However, clinical studies are required for showing the beneficial effects of the extract in humans.

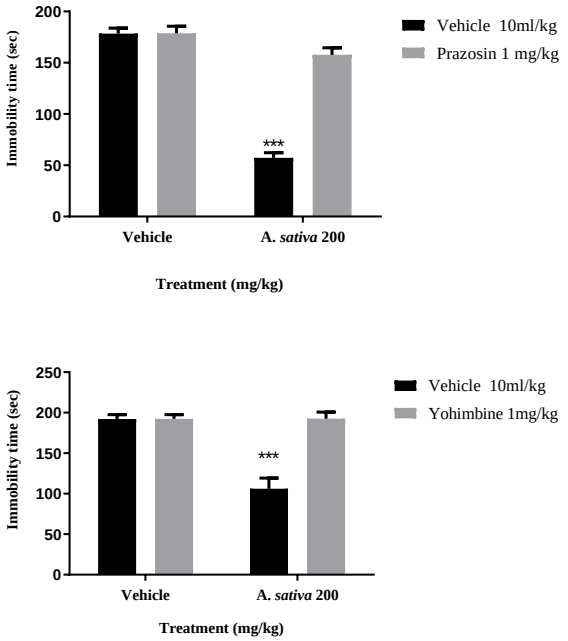

Figure 5. The results of pre-treatment of noradrenergic system antagonists on the antidepressant-like effect induced by the *Avena sativa* extract in tail suspension test; data are reported as mean ± SEM; ***: significant differences compared to control group.

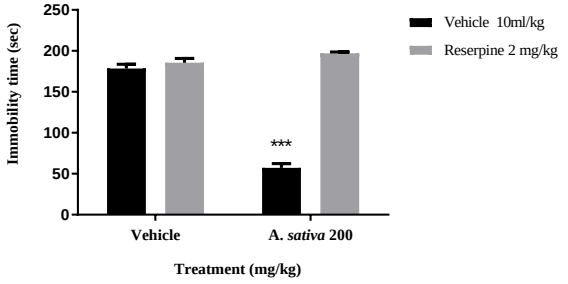

Figure 6. The results of the pre-treatment of reserpine on the antidepressant-like effect induced by the *Avena sativa* extract in tail suspension test; data are reported as mean ± SEM; *** significant differences compared to control group

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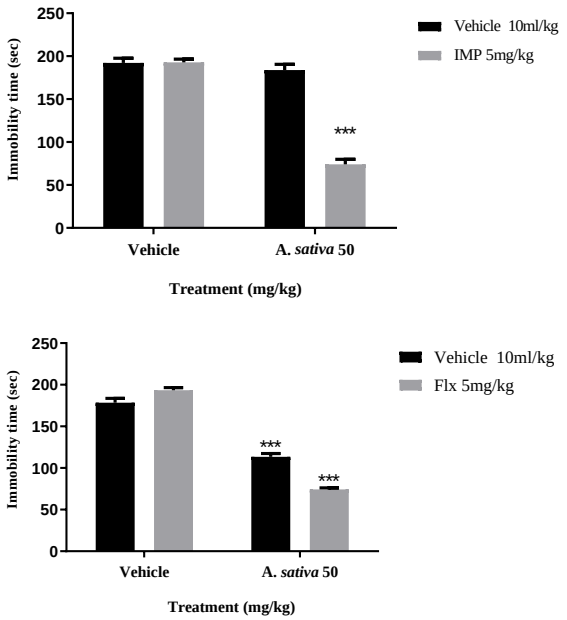

Figure 7. The effects of the sub-effective doses of fluoxetine (5 mg/kg, i.p.) and imipramine (5 mg/kg, i.p.) on the sub-effective dose of the *Avena sativa* extract (50 mg/kg) in tail suspension test in the mice; data are reported as mean ± SEM; ***: significant differences compared to control group

Author contributions

Zahra Mousavi, Saeid Abbasi Maleki, and Saeed Mohammadi Motamed designed and supervised the research and prepared the manuscript; Hamid Arraey performed the experiments and collected data. All authors have read and given their consent to the final manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

Flx: fluoxetine; 5-HT: 5-hydroxytryptamine; IMP: imipramine; i.p.: intraperitoneally; NMRI: National Maritime Research Institute; pCPA: p-chlorophenylalanine; SEM: standard error of mean; s.c.: subcutaneous; TST: tail suspension test; WHO: World Health Organization