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# Inhibition of MAO and GABA: Probable mechanisms for antidepressant-like activity of *Nardostachys jatamansi* DC. in mice

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Ethanolic extract (100, 200 and 400 mg/kg, po) of *N. jatamansi* administered for 14 successive days to Swiss young albino mice (either sex) produced significant antidepressant-like effect in both tail suspension and forced swim tests. The efficacy of the extract was found to be comparable to imipramine (15 mg/kg, po) and sertraline (20 mg/kg, po). Ethanolic extract (200 mg/kg, po) did not show any significant change on locomotor activity of mice as compared to control; hence it did not produce any motor effects. Further, the extract decreased the whole brain MAO-A and MAO-B activities as compared to control, thus increased the levels of monoamines. The antidepressant effect of the extract was also significantly reversed by pretreatment of animals with baclofen ($GABA_B$ agonist); when tested in tail suspension test. The results suggested that the antidepressant-like effect of the extract may also be due to interaction with $GABA_B$ receptors, resulting in decrease in the levels of GABA in mouse brain. Thus, the extract may have potential therapeutic value for the management of mental depression.

**Keywords**: Depression, Forced swim test, GABA, Monoamine oxidase, *Nardostachys jatamansi*, Tail suspension test

Depression, the most common form of affective disorder, may range from a very mild condition, bordering on normality to severe depression (also called psychotic depression) accompanied by hallucinations and delusions. According to World Health Organization estimation, 121 million people worldwide suffer from mental depression. The high prevalence of suicide in depressed patients (up to 15%) coupled with complications arising from stress and its effects on the cardiovascular system have suggested that it will be the second leading cause of death by the year 2020[1]. In spite of the availability of antidepressant drugs like tricyclic antidepressants, selective reversible inhibitors of monoamine oxidase-A (MAO-A), selective serotonin reuptake inhibitors (SSRIs) and selective nor-adrenaline reuptake inhibitors (SNRIs), depression continue to be a major medical problem[2]. Therefore, research for new antidepressants with greater effectiveness without any (or with least) adverse effects is still desirable. Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. Further, the use of alternative medicines is increasing worldwide day by day. *Hypericum perforatum*, a well known plant has been proven to be effective antidepressant in clinical studies[3]. Thus there is a constant need to identify newer natural antidepressants with greater efficacy, and to explore their potential over synthetic antidepressants.

In light of the above information, *Nardostachys jatamansi* DC (Family: Valerianaceae), was selected for evaluating its antidpressant activity due to its traditional use in the management of psychosomatic and mental disorders in the Indigenous system of medicine. In very small doses, it soothes the nervous system and induces tranquility in mind. It is a nervine tonic and also exhibits anxiolytic, tranquilizing, nootropic and psychotropic effects. It gives quick relief in the management of epilepsy, agitative psychosis, maniac psychosis, syncope and hysteria[4,5]. It has been claimed to possess sedative[6], anticonvulsant[7], antiparkinsonian[8], memory-enhancing[9], anti-ischemic[10], antiarrhythmic[11,12], hypolipidaemic[13], cardioprotective[14], antioestrogenic[15], hepatoprotective[16], antiasthmatic[17], antifungal[18], nematicidal[19] and antibacterial activities[20]. Chemically, jatamansi contains sesquiterpenoids like jatamansone (valeranone), spirojatamol, patchouli

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alcohol, norseychelanone, jatamol A and B; lignans and neolignans (e.g. virolin, pinoresinol, 1-hydroxypinoresinol), jatamansic acid, terpenic coumarins like oroselol and jatamansin[21,22].

Therefore, the present study has been undertaken to investigate the effect of *N. jatamansi* extract on depression in mice employing FST and TST; and to explore the possible underlying mechanisms of antidepressant-like activity.

## Materials and Methods

*Animals*—Swiss albino mice of either sex, weighing around 20-25 g were purchased from Disease Free Small Animal House, Chaudhary Charan Singh Haryana Agricultural University, Hisar, India. Male and female animals were housed separately in groups of 6 per cage (polycarbonate cage size: 29×22×14 cm) under laboratory conditions with alternating light and dark cycle of 12 hr each. The animals had free access to food and water. The animals were kept fasted 2 hr before and 2 hr after drug administration. The animals were acclimatized for at least 5 days before behavioral experiments which were carried out between 0900 and 1700 hrs. The experimental protocol was approved by Institutional Animals Ethics Committee and animal care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, Govt. of India (Registration No. 0436).

*Drugs and chemicals*—Sertraline hydrochloride (Aurobindo Pharma Ltd., Hydrabad, India), baclofen and imipramine hydrochloride (Sigma-Aldrich, St. Louis, USA); Tween 80 (Loba Chemie, Mumbai, India); Tris (hydroxymethyl)aminomethane, Folin-ciacalteu's reagent (Sd Fine-Chem Ltd., Mumbai, India), di-sodium hydrogen phosphate (Merck Ltd, Mumbai, India), sodium di-hydrogen orthophosphate, sucrose (Qualigens Fine Chemicals, Mumbai, India), EDTA di-sodium salt, 5-hydroxy tryptamine creatine sulphate, benzylamine (Hi-Media Laboratories Pvt. Ltd., Mumbai, India), bovine serum albumin (Spectrochem Pvt. Ltd., Mumbai, India) were used in the present study.

*Collection of plant material*—The dried rhizomes of jatamansi were purchased from the commercial market, New Delhi and were authenticated as *Nardostachys jatamansi* DC from Raw Materials Herbarium and Museum, NISCAIR, New Delhi (voucher specimen number 741/58).

*Preparation of ethanolic extract*—The dried rhizomes of *N. jatamansi* were coarsely powdered. About 500 g of powdered drug was extracted with 95% ethanol using Soxhlet apparatus at 78°C till siphoning solution became colorless. The extract was concentrated by distillation and dried using water bath. The dried extract was chocolate brown in color and the yield was 4.33%. The extract was stored in an air tight container and kept in a refrigerator.

*Preliminary phytochemical screening*—For preliminary phytochemical screening, ethanolic extract was tested for the presence of alkaloids, glycosides, carbohydrates, sterols, phenolic compounds and tannins, flavonoids, saponins, proteins and amino acids following the standard procedures.

*Vehicle*—The extract was emulsified in 10% v/v Tween 80. Imipramine, sertraline and baclofen were separately dissolved in normal saline (0.9% NaCl). Volume of administration by oral route and ip injection was 10 ml/kg for each mouse.

### Laboratory models employed for the evaluation of antidepressant-like activity

*Tail suspension test* (*TST*)—Tail suspension test, commonly employed behavioral model for screening antidepressant-like activity in mice, was first given by Steru *et al*[23]. The test was conducted as followed earlier[24,25]. Animals were moved from their housing colony to laboratory in their own cages and allowed to adapt to the laboratory conditions for 1-2 hr. Briefly, each mouse was individually suspended to the edge of a table, 50 cm above the floor, by adhesive tape placed approximately 1 cm from the tip of the tail. Each animal under test was both acoustically and visually isolated from other animals during the test. The total period of immobility was recorded manually for 6 min. Animal was considered to be immobile when it didn't show any body movement, hung passively and completely motionless. The test was conducted in a dim lighted room and each mouse was used only once in the test. The observer, recording the immobility of animals, was blind to the drug treatments given to the animals under study.

*Forced swim test (FST)*—Forced swim test, the most frequently used behavioral model for screening antidepressant-like activity in rodents, was first proposed by Porsolt *et al*[26-28]. The procedure was same as followed previously[24,25]. Animals were moved from their housing colony to laboratory in

their own cages and allowed to adapt to the laboratory conditions for 1-2 hr. Briefly, mice were individually forced to swim in open glass chamber (25 × 15 × 25 $cm^3$) containing fresh water to a height of 15 cm and maintained at 26°±1°C. At this height of water, animals were not able to support themselves by touching the bottom or the side walls of the chamber with their hind-paws or tail. Water in the chamber was changed after subjecting each animal to FST because "used water" has been shown to alter the behavior[29]. Each animal showed vigorous movement during initial 2 min period of the test. The duration of immobility was manually recorded during the next 4 min of the total 6 min testing period. Mice were considered to be immobile when they ceased struggling and remained floating motionless in water, making only those movements necessary to keep their head above water. Following swimming session, mice were towel dried and returned to their housing conditions. The test was conducted in a dim lighted room and each mouse was used only once in the test[30,31]. The observer, recording the immobility of animals, was blind to the drug treatments given to the animals under study.

*Measurement of MAO-A and MAO-B activities*—On 14th day, mice were sacrificed after 6 min exposure to FST, and the brain samples were collected immediately on an ice plate. The collected brain samples were washed with cold 0.25*M* sucrose-0.1*M* Tris-0.02*M* EDTA buffer (*p*H 7.4) and weighed. The whole procedure of brain isolation was completed within 5 mins[32,33]. Mouse brain mitochondrial fractions were prepared following the procedure of Schurr and Livne[32]. The MAO activity was assessed spectrophotometrically[2,33,34]. Briefly, the buffer washed brain sample was homogenized in 9 volumes of cold 0.25*M* Sucrose-0.1*M* Tris-0.02*M* EDTA buffer (*p*H 7.4) and centrifuged twice at 800 *g* for 10 min at 4°C in cooling centrifuge (Remi Instruments, Mumbai, India). The pellet was discarded. The supernatant was then centrifuged at 12000 *g* for 20 min at 4°C in cooling centrifuge. The precipitates were washed twice with about 100 ml of sucrose-tris-EDTA buffer and suspended in 9 volumes of cold sodium phosphate buffer (10 m*M*, *p*H 7.4, containing 320 mM sucrose) and mingled well at 4°C for 20 min. The mixture was then centrifuged at 15000 *g* for 30 min at 0°C and the pellets were re-suspended in cold sodium phosphate buffer. The protein concentration was estimated by Lowry method using bovine serum albumin as standard[35]. The assay mixture contained 100 µl of 4 m*M* 5-hydroxytryptamine and 100 µl of 0.1 *M* benzylamine as the specific substrate for MAO-A and MAO-B respectively, 150 µl solution of mitochondrial fraction and 2.75 ml sodium phosphate buffer (100 m*M*, *p*H 7.4).

For estimating MAO-B activity, 2.75 ml sodium phosphate buffer (100 m*M*, *p*H 7.4) and 100 µl of 0.1 *M* benzylamine were mixed in a quartz cuvette which was then placed in double beam spectrophotometer (Systronics 2203, Bangalore, India). This was followed by the addition of 150 µl solution of mitochondrial fraction to initiate the enzymatic reaction and the change in absorbance was recorded at wavelength of 249.5 nm for 5 min against the blank containing sodium phosphate buffer and benzylamine.

For estimating MAO-A activity, 2.75 ml sodium phosphate buffer (100 m*M*, *p*H 7.4) and 100 µl of 4 m*M* 5-hydroxytryptamine were mixed in a quartz cuvette which was then placed in double beam spectrophotometer (Systronics 2203, Bangalore, India). This was followed by the addition of 150 µl solution of mitochondrial fraction to initiate the enzymatic reaction and the change in absorbance was recorded at wavelength of 280 nm for 5 min against the blank containing sodium phosphate buffer and 5-HT.

*Measurement of locomotor activity*—To rule out the effects of extract on immobility period, horizontal locomotor activities of control and test animals were recorded for a period of 10 min using Medicraft Photoactometer, Model No. 600-4D (INCO, Ambala, India). The photoactometer consisted of a square arena (30 × 30 × 25 cm) with wire mesh bottom, in which the animal moves. Six lights and six photocells were placed in the outer periphery of the bottom in such a way that a single mouse can block only one beam. Technically its principle is that, a photocell is activated when the rays of light falling on the photocells are cut off by animals crossing the beam of light. As the photocell activated, a count is recorded. The photocells are connected to an electronic automatic counting device which counts the number of 'cut offs'.

**Experimental protocols**

Animals were divided into 19 groups of a minimum of 6 mice each. The experimental protocol was divided into the following groups:

*Using TST*

Group 1: Control group: 10% v/v Tween 80 was administered orally for 14 consecutive days and on 14th day, 60 min after the administration; immobility period was recorded in TST.

Group 2 and 3: Imipramine (15 mg/kg) and Sertraline (20 mg/kg) respectively were orally administered for 14 successive days and on 14th day, 60 min after the administration; immobility period was recorded in TST.

Group 4, 5 and 6: Ethanolic extract (100, 200 and 400 mg/kg, po respectively) was administered for 14 successive days and on 14th day, 60 min after the administration, immobility period was recorded in TST.

Group 7 (Baclofen control): Vehicle (10% v/v Tween 80) was administered orally for 14 consecutive days and on 14th day, after 45 min of vehicle treatment; baclofen (10 mg/kg, ip) was injected. After 45 min of injection, the animals were subjected to TST.

Group 8: The extract (200 mg/kg, po) was administered for 14 consecutive days. On 14th day, after 45 min of extract treatment; baclofen (10 mg/kg, ip) was injected and the animals were subjected to TST after 45 min of the injection.

*Using FST*

Group 9 to 14 were similar to group 1 to 6 as mentioned under TST except that the immobility period was recorded using FST. Thus, group 9 was similar to group 1; group 10 was similar to group 2 and so on.

*Estimation of MAO-A and MAO-B*

Group 15: Vehicle (10% v/v Tween 80) was administered orally for 14 successive days and on 14th day, 60 min after the administration; the animals were subjected to FST for 6 min, and immediately brain samples were collected. MAO-A and MAO-B levels were measured in the brain samples.

Group 16: Imipramine (15 mg/kg, po) was administered orally for 14 successive days and on 14th day, 60 min after the administration; the animals were subjected to FST for 6 min, and immediately brain samples were collected. MAO-A and MAO-B levels were measured in the brain samples.

Group 17: The extract (200 mg/kg, po) was administered orally for 14 successive days and on 14th day, 60 min after the administration; the animals were subjected to FST for 6 min, and immediately brain samples were collected. MAO-A and MAO-B levels were measured in the brain samples.

*Measurement of locomotor activity*

Group 18: Vehicle (10% v/v Tween 80) was administered orally for 14 successive days and on 14th day, 60 min after the administration; locomotor activity was measured.

Group 19: The extract (200 mg/kg, po) was administered for 14 consecutive days and on 14th day, 60 min after the administration; locomotor activity was measured.

*Statistical analysis*—All the results were expressed as mean ± SE. The data of all the groups were analyzed using one-way ANOVA followed by Dunnett's t-test using the software Sigma-Stat 3.5. The data for locomotor activity scores was subjected to Student's unpaired t-test. In all the tests, the criterion for statistical significance was $P<0.05$.

## Results

*Phytochemical screening*—The results of phytochemical screening indicated the presence of alkaloids, carbohydrates, sterols, saponins, phenolic compounds and tannins in ethanolic extract.

*Effect of the extract on immobility periods in TST and FST*—Ethanolic extracts (100, 200 and 400 mg/kg, po) administered for 14 successive days to mice significantly decreased the immobility periods in both TST and FST. The dose of 200 mg/kg of the extract showed most potent antidepressant-like effect as indicated by the highest decrease in the immobility period in both TST and FST. Imipramine (15 mg/kg, po) and sertraline (20 mg/kg, po) administered for 14 successive days to mice significantly reduced the immobility periods in both TST and FST as compared to control, indicating significant antidepressant-like activity (Tables 1 and 2). Baclofen (10 mg/kg, ip) alone significantly increased the immobility period as compared to control group in TST. Pretreatment of animals with baclofen significantly reversed the decrease in immobility time elicited by the extract (200 mg/kg) in TST (Table 1).

*Effect of the extract on whole brain MAO levels*—Ethanolic extract (200 mg/kg, po) of *N. jatamansi* administered for 14 consecutive days to mice, significantly reduced the brain MAO-A and MAO-B levels as compared to the respective vehicle treated groups. The efficacy of the extract, towards these

Table 1—Effect of ethanolic extract of *N. jatamansi* (NJE) alone and its combination with baclofen on immobility period of mice using tail suspension test
[Values are mean ± SE from 6 animals in each group]

| Group No. | Treatment | Oral dose (mg/kg) × 14 days | Immobility period (sec) |
|---|---|---|---|
| 1 | Vehicle | — | 166.5 ± 7.9 |
| 2 | Imipramine | 15 | 112.8 ± 3.9* |
| 3 | Sertraline | 20 | 79.8 ± 6.4* |
| 4 | NJE | 100 | 131.5 ± 12.7* |
| 5 | NJE | 200 | 120.5 ± 13.5* |
| 6 | NJE | 400 | 131.5 ± 7.7* |
| 7 | Vehicle + Baclofen | 10 | 231.8 ± 7.2* |
| 8 | Extract + Baclofen | 200 + 10 | 178.5 ± 9.5# |

Data were analyzed by one-way ANOVA followed by Dunnett's t-test.
F (7, 40) = 26.47; $P< 0.001$
$P$ values: < 0.05; when compared with *vehicle treated group
# extract treated group (NJE-200)

Table 2—Effect of ethanolic extract of *N. jatamansi* (NJE) on immobility period of mice using forced swim test
[Values are mean ± SE from 6 animals in each group]

| Group No. | Treatment | Oral dose (mg/kg) × 14 days | Immobility period (sec) |
|---|---|---|---|
| 9 | Vehicle | — | 158.2 ± 5.1 |
| 10 | Imipramine | 15 | 109.8 ± 7.7* |
| 11 | Sertraline | 20 | 106.6 ± 4.9* |
| 12 | NJE | 100 | 110.3 ± 5.3* |
| 13 | NJE | 200 | 111.0 ± 2.3* |
| 14 | NJE | 400 | 120.5 ± 6.7* |

Data were analyzed by one-way ANOVA followed by Dunnett's t-test.
F (5, 30) = 12.26; $P< 0.001$
*$P < 0.05$

parameters, was found to be comparable to imipramine (Table 3).

*Effect on locomotor activity*—Ethanolic extract (200 mg/kg, po) administered for 14 successive days did not show any significant change in the locomotor activity (709.5±29.6) of mice as compared to the vehicle treated group (737.3±50.1).

## Discussion

In the present study, ethanolic extract (100, 200 and 400 mg/kg, po) administered for 14 successive days to mice, produced significant antidepressant-like effect in both TST and FST and their efficacies were found to be comparable to imipramine (15 mg/kg, po) and sertraline (20 mg/kg, po). TST and FST are two of the most commonly used behavioral tests in rodents for evaluating drugs having antidepressant-like activity[23,26-28]. These tests are quite sensitive and relatively specific to all major classes of antidepressants.

The antidepressant-like effect of ethanolic extract of *N. jatamansi* seems not to be associated with any motor effects since it did not show any significant change in locomotor functions of mice as compared to control. It confirms the assumption that the antidepressant-like effect of the extract is specific and not the false positive. The precise mechanisms by which the extract produced antidepressant-like effect are not completely understood. However, the present investigations demonstrated that the antidepressant-like effect of the extract (200 mg/kg) was significantly reversed by pretreatment of the animals with baclofen ($GABA_B$ agonist), when tested in TST. This suggested that ethanolic extract might produce antidepressant-like effect by interaction with $GABA_B$ receptors. There are two GABA hypotheses of the antidepressants action: an increase in $GABA_A$ neurotransmission or a decrease in $GABA_B$

Table 3—Effect of ethanolic extract of *N. jatamansi* (NJE) and imipramine on brain MAO-A and MAO-B activities
[Values are mean ± SE from 6 animals in each group]

| Group No. | Treatment | Oral dose (mg/kg) × 14 days | MAO-A activity (U/g protein) | MAO-B activity (U/g protein) |
|---|---|---|---|---|
| 15 | Vehicle | — | 55.5 ± 2.3 | 50.9 ± 1.9 |
| 16 | Imipramine | 15 | 28.9 ± 6.6* | 40.3 ± 1.5* |
| 17 | NJE | 200 | 37.3 ± 2.8* | 38.9 ± 2.6* |

Data were analyzed by one-way ANOVA followed by Dunnett's t-test.
F (2, 15) = 9.743; $P< 0.01$ (for MAO-A)
F (2, 15) = 9.970; $P< 0.01$ (for MAO-B)
*$P < 0.05$

neurotransmission which may contribute to action of antidepressants[36]. Thus, $GABA_B$ receptor antagonism may serve as a basis for the generation of novel antidepressants[37].

Further, the extract significantly reduced the mouse whole brain MAO-A and MAO-B activities as compared to control, hence exerted antidepressant-like action by inhibiting the metabolism of monoamines. MAO regulates the metabolic degradation of catecholamines, serotonin and other endogenous amines in central nervous system. Inhibition of this enzyme causes a reduction in metabolism and subsequent increase in the concentration of biogenic amines. This was also supported by the literature, where 15 days treatments of alcoholic (95%) extract of *N. jatamansi* to Wistar male albino rats significantly increased the brain levels of monoamines[38]. Antidepressant-like action of the extract might be due to the presence of active compound – jatamansone.

In conclusions, the present results suggest that ethanolic extract of *N. jatamansi* produced antidepressant-like effect in mice when tested in FST and TST; probably by inhibiting MAO-A and MAO-B, and through interaction with GABAergic receptors. The efficacy of the extract was comparable to that of imipramine and sertraline. Thus, the extract may have potential therapeutic value for the management of mental depression.

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