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EVALUATION OF SYNERGIC ANTIDEPRESSANT ACTIVITY OF *NARDOSTACHYS JATAMANSI* WHEN GIVEN ALONG WITH IMIPRAMINE IN WISTER ALBINO RATS AND SWISS ALBINO MICE

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ABSTRACT: Background: Depression is affecting around 5% of the population. In the traditional systems of medicine, many plants and formulations have been used to treat depression for thousands of years. **Objectives:** This study evaluated the synergic effect of Hydro-alcoholic extract of Rhizomes of *Nordostachys jatamansi* DC Per Se with combination with Imipramine in Wistar, albino rats, and swiss albino mice normal groups. **Materials and Method:** Animals of either sex were selected and randomly divided into a test group. Jatamansi extract 10:1 and imipramine dissolved in distilled water were used. Animals were tested for forced swimming test, tail suspension test, and locomotor after given test drug. **Results:** *Nardostachys jatamansi* DC, when given to rats, showed a dose-dependent increase in the number of rotations during forced swimming tests in rats. *Nardostachys jatamansi* DC, when given to mice dose-dependent statistically significant decrease in immobility time, swimming time, and climbing observed. When given along with a combination of imipraine it shows a statistically significant difference in the result, confirmed that it could have synergistic antidepressant activity. When used for locomotor activity in mice, none of the test drugs significantly increase or decrease the locomotor activity. **Conclusion:** Jatamansi showed antidepressant-like properties in various tests conducted on rats and mice. It showed a statistically significant result with increasing dose and had a synergic effect when given along with imipramine.

INTRODUCTION: "Depression let's talk" is the slogan for World Health Day 2017. Depression is an extremely common illness affecting people of all ages, genders, different socioeconomic groups, and religions in India and all over the world. Globally, an estimated 322 million people were affected by depression in 2015. Depression contributes to a significant disease burden at national and global levels.

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At the individual and family level, depression leads to poor quality of life, causing huge social and economic impact. Depression is one of the two diagnostic categories that constitute common mental disorders (CMDs), the other being anxiety disorder. Both are highly prevalent across the population (hence they are considered "common") and impact on the mood or feeling of affected persons.

Depression includes a spectrum of conditions with episodes, illnesses, and disorders that are often disabling in nature, vary in their severity (from mild to severe) and duration (from months to years), and often exhibit a chronic course that has a relapsing and recurring trajectory over time [1].

India is home to an estimated 57 million people (18% of the global estimate) affected by depression. With India witnessing significant changes (including globalization, urbanization, migration, and modernization) that is coupled with the rapid sociodemographic transition, depression is likely to increase in the coming years.

Globally, the proportion of the population with depression is estimated to be 4.4%. It is more common among females (5.1% vs. 3.6%), with a peak in the 55–74 year age group in both sexes. Among the WHO Regions, the prevalence varies from as low as 2.6% among males in the Western Pacific Region to 5.9% among females in the African Region [1]. *Nardostachys jatamansi,* also called nard, nardin Spikenard, and muskroot is a flowering plant of the Valerian family that grows in Nepal, China, and India. The plant grows to about 10-60 cm in height and has pink, bell-shaped flowers. It is found at an altitude of about 17000 ft [2]. Herbal preparation provides new insight into the treatment of depression. Many herbal preparations are proven to possess antidepressant activity [3].

MATERIALS AND METHOD: The study was conducted at the laboratory of the Department of Pharmacology, Government Medical College, Bhavnagar, after institutional animal ethical committee approval (IAEC approval no, 46/2016).

The animal handling was performed according to guidelines of the committee for the purpose of control and supervision of experiments on animals, New Delhi. Swiss albino mice of 3-4 months of age of either sex weighing 24-30 grams were used in this study. All the animals were acclimatized to the laboratory conditions at least one day prior to the experiments. Food was withdrawn 12 h before the experiments. Each animal was used only once. Jatamansi extract 10:1 and Imipramine hydrochloride dissolved in distilled water were used in the study. The dose of Jatamansi was calculated by using data from ancient medical literature, considering the median dose of 200 mg/kg and 400 mg/kg were taken as a low dose and high dose, respectively. Imipramine hydrochloride dose used for swimming test 10.5 mg/kg for rats and mice, for tail suspension test and locomotor activity in mice 15 mg/kg. Forced swimming test Apparatus with activity wheel was used for swimming test for Rat, borosilicate glass cylinder was used for forced swimming test forrat and mice, and tail suspension test assembly used for tail suspension test in mice, for measurement of locomotor activity in mice digital photoactometer was used.

Animals were grouped, with each group has six animals. Group1: vehicle control group, distilled water group 2: *Nardostachys jatamansi* low dose, Group 3: *Nardostachys Jatamansi* high dose Group 4: Imipramine hydrochloride Group 5: Imipramine hydrochloride ± Nardostachys Jata-mansi. In rats, for all the groups of animals, vehicle and test drugs were administered orally for 14 days. After 60 min of administration on the 14th-day number of rotations in the water wheel was conducted.

In mice for all the groups of animals, vehicle and test drugs were administered orally for 24 h, 5 h, and 1 h before the test. Period of immobility, swimming, and climbing was then digitally recorded by the camera and then analyzed. Statistical analysis of data was carried out by one-way ANOVA followed by Tuckey-Kramer multiple comparison test. Forced swimming test performed for rats using glass jar showed a statistically significant decrease in immobility in test group rats with Imipramine ($p<0.01$), Jatamansi high as well dose ($P<0.01$) and combination of Imipramine with Jatamansi ($p<0.05$).

RESULTS:

TABLE 1: EFFECT OFTEST DRUGS ON NUMBER OF ROTATION IN FORCED SWIMMING TEST WITH ACTIVITY WHEEL IN RATS (N=6 IN EACH GROUP)

Group	Treatment	Dose (mg/kg) Once a Day	No. of Rotations (Mean±SEM)
1	Vehicle control	2.5 ml	10.6 ± 0.5
2	Imipramine	10.5 mg	49.5 ± 0.7
3	Jatamansi	125 mg	34.1 ± 0.9
4	Jatamansi	320 mg	55.0 ± 1.1
5	Imipramine + Jatamansi	10.5 mg ± 320 mg	102± 8.3

Table 1 showing test group showed a significant increase in the number of rotations in forced swimming test in rats with Imipramine ($p<0.01$), Jatamansihigh as well as low dose ($P<0.01$) and combination of Imipramine with Jatamansi ($p<0.05$).

TABLE 2: EFFECT OF TEST DRUGS ON IMMOBILITY, SWIMMING AND CLIMBING TIME IN FORCED SWIMMING TEST IN MICE (N= 6 IN EACH GROUP)

Group	Treatment	Dose (mg/Kg)	Immobility time (sec) Mean± SEM	Swimming time (sec) Mean± SEM	Climbing time (sec) Mean± SEM
1	Vehicle control	2.5 ml	220.3 ± 5.8	51.3 ± 5.7	29.6 ± 4.0
2	Imipramine	15 mg	105.0 ± 5.6	83.6 ± 2.2	125.5 ± 11.0
3	Jatamansi	200 mg	100.0 ± 4.7	73.6 ± 6.1	90.3 ± 7.2
4	Jatamansi	400 mg	141.6 ± 8.6	124.5 ± 9.1	75.2 ± 5.6
5	Imipramine± Jatamansi	15 mg ± 400 mg	62.3 ± 7.7	145.1 ± 6.0	94.0 ± 9.3

Table 2 showing a statistically significant decrease in immobility time, swimming time, and climbing time in mice treated with Imipramine ($P<0.01$), Jatamansi high as well as low dose($P<0.01$) and combination of Imipramine with Jatamansi ($p<0.05$)

TABLE 3: EFFECT OF TEST DRUGS ON TIME OF IMMOBILITY IN TAIL SUSPENSION TEST IN MICE (N=6 IN EACH GROUP)

Group	Treatment	Dose (mg/kg)	Immobility time (sec) Mean ± SEM
1	Vehicle control	2.5 ml	172.0 ± 7.1
2	Imipramine	15 mg	75.1 ± 7.0
3	Jatamansi	200 mg	94.0 ± 4.0
4	Jatamansi	400 mg	61.8 ± 1.9
5	Imipramine + Jatamansi	15 mg ± 400 mg	38.5± 3.8

As shown in **Table 3**, during tail suspension test performed in mice, time of immobility is significantly reduced in treatment group Jatamansi alone ($p<0.05$) as well as with Imipramine + Jatamansi combination ($p<0.001$)

TABLE 4: EFFECT OF TEST DRUGS ON LOCOMOTOR ACTIVITY IN PHOTOACTOMETER IN MICE (N=6 IN EACH GROUP)

Group no.	Treatment groups	Dose (mg/kg)	Total count (sec) Mean ± SEM
1	Vehicle control	2.5 ml	118.3 ± 10.2
2	Imipramine	15 mg	108.6 ± 10.9
3	Jatamansi	200 mg	120.6 ± 16.5
4	Jatamansi	400 mg	123.0 ± 14.0
5	Imipramine + Jatamansi	15 mg ± 400 mg	129.0 ± 15.5

Table 4 showing the result of the locomotor activity of mice using a digital photoactometer. There was not any statistical significance found among any of the groups. None of the test drugs significantly increase or decrease locomotor activity.

DISCUSSION: In the systems of traditional medicine, numerous plants and formulations have been used to take care of depression for thousands of years. We have reported the antidepressant activity of Jatamansi. In our study, Jatamansi showed antidepressant-like properties in various tests conducted on rats and mice. It showed a statistically significant result with increasing dose and had a synergic effect when given along with Imipramine. The present study, both acute and chronic models with two different species of animals (Wister albino rats) and (Swiss albino mice) used as each has its own peculiarities. *Nardostachys jatamansi* DC, when given to rats as monotherapy in dose of 125 mg/kg and 300 mg/kg showed a dose-dependent increase in the number of rotation during forced swimming test in rats. During the forced swimming test in a glass jar, statistically significant decrease in immobility was observed. *Nardostachys jatamansi* DC, when given to mice dose-dependent statistically significant decrease in immobility time, swimming time, and climbing was observed. When given along with a combination of Imipramine it shows a statistically significant difference in the result, confirmed that it could have synergistic antidepressant activity. When used for locomotor activity in mice, none of the test drugs significantly increase or decrease the locomotor activity, confirms that assumption that the antidepressant-like effect of Jatamansi is specific and not false positive. Antidepressant effect on forced swimming model of depression provides a rapid and reliable behavior screening test for anti-depressants. The model is valid for a broad spectrum of antidepressants, mainly including tricyclics and MAO inhibitors, which significantly decreased immobility time in FST [4]. Immobility is thought to reflect either a failure to persist in escape directed behavior after persistent stress or the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli [5]. Several antidepressants

reduce the immobility after forced swimming [6]. In the present study, Jatamansi significantly decreased the immobility time of mice in FST and is comparable with standard anti-depressant drug imipramine. The observed effect may be attributed to the blockage of 5 -HT reuptake or MAO inhibition. AmitkumarMongaetal[7] studied that jatamansi [200 and 400 mg/kg, p.o] produced significant [P<0.001] antidepressant-like effect in normal and sleep-deprived mice in both TST and FST, and their efficacies were found to be comparable to imipramine [10 mg/kg, p.o].

It did not show any significant change in locomotor functions of mice as compared to normal control. However, it significantly [P<0.01] improves the locomotor activity in case of sleep deprivation which is comparable to normal control. Swati Hardainiyan *et al*., [8] observed the mean duration of immobility in mice by forced swimming test using Immipramine Hydrochloride was 90.2 ± 1.77 sec, by tail suspension test 94.4 ± 1.66 sec. Habibur Rahman *et al.,* [9] in their study, concluded that methanolic extract of *Nardostachys jatamansi* DC, has dose-dependent antidepressant activity and can also be used in patients suffering from depression due to sleep disturbances. In a study of Banda Deepa *et al.*, [10]. The electron beam radiated mice treated with *Nardostachys jatamansi* ethanolic root extract has shown a significant reduction in the duration of immobility (in seconds) in both the tests on comparing with non treated electron beam radiated mice. Dhingra D *et al.,* [11] observed 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 a 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.

CONCLUSION: Jatamansi possesses both anxiolytic and anti-depressant activity and which is comparable with the standards. Being a polyherbal formulation, the observed activity profile may be attributed to one or more bioactive principles present in the different plants of this formulation. However, further studies are required to know the exact mechanism. Jatamansi is an important medicinal plant mentioned in the Ayurveda and Unani system used for the treatment of various diseases. The different studies done on animals provide a significant effect on the different activities mentioned in the traditional treatise. *N. jatamansi* also has many properties with no animal study, which provide the researchers to do research on those activities to serve humanity. We recommend further research elucidate the mechanism of action involved in the antidepressant activity of Jatamansi.

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CONFLICTS OF INTEREST: There are no conflicts of interest.

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