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Antidepressant Activity of *Nardostachys jatamansi* Extract in Animal Models of Depression

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Authors' contributions

This work was carried out in collaboration among all authors. The concept of study was developed by authors MOI and FS. Author FS performed herbal extraction, experimental work, drafted the document and interpreted the results. Author MOI critically reviewed the article and finalized the results. Finally reviewed and approved by author ZM. Data analysis was performed by author FA. All authors read and approved the final manuscript.

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ABSTRACT

Background: Depression refers to a wide range of mental health problems characterized by the loss of interest in routine activities, low mood and a range of associated emotional, cognitive, physical and behavioral symptoms. It is one of the major causes of mortality as tendency of suicidal attacks are exhibited in these patients. The diagnosis of depressive patients is very complicated in many cases and they do not respond to rational clinical prescription. In traditional medicine, *Nardostachys jatamansi* has been used as stimulant, antispasmodic, laxative and antiepileptic in ayurvedic and unani systems of medicine. The objective of our study was to evaluate and compare the antidepressant activity of *N. jatamansi* extract with fluoxetine in animal models of depression.
Methodology: It was a preclinical experimental study in which Total 100 BALB/c mice divide into 14 groups i.e. Group 1 & 2 control 0.9% NaCl i.p for forced swimming test (FST) and tail suspension test (TST) respectively, Group 3 & 4 Fluoxetine 0.5 mg/kg i.p for FST and TST respectively, Group 5, 6 & 7 of *N. jatamansi* 125, 250 and 500 mg/kg respectively for FST, Group 8, 9 & 10 *N. jatamansi* 125, 250 and 500 mg/kg respectively for TST, Group 11 *N. jatamansi* (most

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effective dose) for Locomotor Test, Group 12 NaCl 0.9% for Yohimbine Potentiation Test (YPT), Group 13 Fluoxetine 0.5 mg/kg for YPT and Group 14 Received extract of *N. jatamansi* (most effective dose) for YPT. Antidepressant activity of *N. jatamansi* extract at different doses after induction of depression via FST and TST was recorded. Moreover the antidepressant effect was confirmed by locomotor test. YPT was also applied to comment on possible underlying mechanism.

Results: In our study 250 mg/kg and 500 mg/kg doses of *N. jatamansi* showed significant reduction in immobility time when compared to controls and 500 mg/kg showed significant reduction as compared to group given fluoxetine in FST model. All the groups in TST model showed significant reduction in immobility time when compared to controls and fluoxetine given group. *N. jatamansi* at the dose of 500 mg/kg was found to be most effective in both the models. No significant change in locomotor activity was found in locomotor test. The percentage mortality of 50% was observed in *N. jatamansi* group using yohimbine potentiation test.

Conclusion: In our study *Nardostachys jatamansi* showed significant reduction in immobility time when compared to controls and fluoxetine.

Keywords: Depression; Nardostachys jatamansi; extract; fluoxetine.

1. INTRODUCTION

Depression remains to be a prevalent psychological condition, which is widely seen in general medical settings and is expected to become global by year 2030 [1,2]. The literal meaning of depression is a level below the surface. If a person is depressed he or she feels sad. Persistent depression and lack of focus in activities that are usually enjoyed by an individual for at least two or more weeks are identified. Unfortunately this mental problem is gradually on a rise and afflicts all socioeconomic levels. It has become a challenge for low-income countries where only a low percentage of gross domestic products are allocated on health services [3]. The World Health Organization (WHO) has rated depression as the fourth leading cause of failure worldwide [4] and predicts that it will be the second leading cause of morbidity by 2020 [5,6]. Globally, the total number of people with depression was estimated to exceed 300 million in 2015 equivalent to 4.4% of the world's population [7]. WHO also stated that depression is more common among females (5.1%) than males (3.6%) [7].

Depression refers to a wide range of mental health problems characterized by the loss of interest in ordinary activities, low mood and a range of associated emotional, cognitive, physical and behavioral symptoms [8]. It leads to a much greater deterioration in fitness than the major chronic physical conditions such as angina, hypertension, asthma and diabetes [9]. This psychological disease can be long lasting or recurrent, substantially impairing an individual's ability to function at work or school or cope with daily life stress [7]. It is the one of the major causes of mortality as tendency of suicidal attacks are exhibited in these patients. In the year 2015, it is estimated that 788000 people died due to suicide worldwide; many more than this number attempted suicide [7]. The diagnosis of depressive patients is very complicated in many cases and they respond sub-optimally to rational prescription. Multiple groups of drugs are available for the treatment of depression that include tricyclic antidepressants (TCAs), mono amine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and atypical drugs [10]. Among these drugs SSRIs and SNRIs are most frequently used in clinical settings. Modern psychiatric practice has seen the rise and fall of mentioned antidepressant agents specially due to their unpredictable therapeutics, side effects and interactions [11]. To date, the efficacy of the drugs for depression is very limited so the need for newer, better-tolerated and more efficacious treatment is required [12].

Phytomedicine is reviving and herbs play a vital role in numerous disorders including depression. According to a WHO survey, about 60% of the world's population depends on some types of conventional medicines, primarily herbs [13]. *Nardostachys jatamansi* is a popular plant, belongs to family Valerianaceae. It is commonly known as Indian spikenard and found in Himalayas. Rhizomes occurs in short pieces, has dark grey color and typical smell. Leaves are sessile and ovate. Flowers are dark–pink in color [14]. Its rhizomes are used in traditional medicines as stimulant, antispasmodic, laxative

and antiepileptic therapeutic effect in ayurvedic and unani systems of medicine [15]. Rat brain treated with root extract of *N. jatamansi* showed an overall increase in the levels of central monoamines and inhibitory amino acids, including a change in the levels of serotonin, 5-hydroxyindole acetic acid, gamma-amino butyric acid, and taurine [12]. The aim of our study was to evaluate and compare the antidepressant activity of *N. jatamansi* extract with fluoxetine in animal models of depression.

2. METHODOLOGY

It was a preclinical animal experimental study conducted at Ziauddin University Karachi from November 2019 to February 2020 after approval from animal ethics committee (ERC protocol number 2019-001). Total of 100 male BALB/c mice weighting 20-30gm were used in the study. Depression model was induced by performing Forced swimming test (FST), Tail suspension test (TST) while Locomotor test (LT) and yohimbine potentiation tests (YPT) were performed to validate antidepressant effect [16,17]. The drugs were administered to the animals as per defined guidelines. Results were analyzed by SPSS version 20. All the numeric variables were expressed as mean ± standard deviation (SD). After checking out the normality by Shapiro-wilk test and QQplot and homogeneity through Levene's test, analysis of variance (ANOVA) was applied for finding difference between FST and TST. Student's paired *t* test was applied to analyze the significant difference in locomotor test. P value less than 0.05 was considered significant.

2.1 Procedure

Animals were kept under standard conditions with normal light cycle (12 hours light/ dark) with free access to food and water. Mice were housed in plastic cages in groups of 6 animals per cage and wooden chips were used as bedding material. Prior to the experiment, animals were acclimatized with the environment for few days. All animals were dealt according to International Standards for the Use and Care of laboratory Animals set by National Institute of Health (US) [18].

2.2 Collection and Extraction of *Nardostachys jatamansi*

Rhizomes of *N. jatamansi* were purchased from the local market of Karachi. They were cleaned and adherent sand and dust particles were removed. It was dried and made into a coarse powder with the help of electric grinder (Moulinex AR1100). The powder extract of plant materials were mixed with 70% ethanol (Merck, Pakistan). The maceration was repeated 3 times to exhaustively extract the plant material. Extract was filtered by using Whatmann No. 1 filter paper and further extract by using a rotary evaporator (BUCHI, Switzerland) in a water bath set at 40°C [19]. The crude extract was placed open in a ventilated room to let them dry for 6-7 days to get free from solvent and dried completely. Dried extract from plant was packed in glass bottle with proper labeling. The extract then was stored in a refrigerator at 4°C until use [20]. *N. jatamansi* extract was emulsified in control vehicle (10%DMSO) for intraperitoneal administration (i.p.: 0.2 mL/20 g, mice).

2.2.1 Forced swimming test

Mice were placed individually in a glass tank (Height = 45 cm and Width =17 cm) filled with water to a height of 15 cm and temperature was maintained at 25C. Each session was of 6

Chart 1. Animal grouping

Group 1	Received (0.9% NaCl i.p) served as Control Group for FST
Group 2	Received NaCl 0.9% served as Control Group for TST
Group 3	Received Fluoxetine 0.5mg/kg for FST
Group 4	Received Fluoxetine 0.5mg/kg for TST
Group 5, 6 and 7	Received extract of *N.Jatamansi* 125, 250 and 500mg/kg respectively for FST
Group 8, 9 and 10	Received extract of *N.Jatamansi* 125, 250 and 500mg/kg respectively for TST
Group 11	Received extract of *N.Jatamansi* (most effective dose) for Locomotor Test
Group 12	Received NaCL 0.9% for Yohimbine Potentiation Test
Group 13	Received Fluoxetine 0.5mg/kg for Yohimbine Potentiation Test
Group 14	Received extract of *N.Jatamansi* (most effective dose) for Yohimbine Potentiation Test

n=6 for (FST and TST) and n= 10 for (YPT and LT)

minutes duration, divided into pretest (the first 2 min) and test (the remaining 4 min). Vehicle control 0.9% NaCl i.p in Group 1 and fluoxetine (0.5 mg/kg i.p) was administered in Group 3. ethanolic extract of *N. jatamansi* (125, 250, 500 mg/kg i.p) administered in Group 5, 6 and 7 respectively. After 1 hour of the treatment, mice were forced to swim under similar conditions as described above. The duration of immobility time was recorded for a period of 4 minutes and animals were considered immobile when it remained floating with all four limbs motionless [21,22].

2.2.2 Tail suspension test

Mice were given (0.9% NaCl) Group 2 and ethanolic extract of *N. jatamansi* (125, 250, 500 mg/kg) for Group 8, 9 and 10 and fluoxetine (0.5 mg/kg) Group 4 intraperitoneally. After 1 hour of the treatment, mice were suspended on the edge of the table by using adhesive tape placed approximately 1 cm from the extremity of the tail, 35 cm above the ground and the duration of immobility time was recorded for the period of 6 minutes. Mice were considered immobile when they hung passively motionless [23]. The percent reduction in the immobility time of the test animals were calculated as compared to the control animals.

2.2.3 Locomotor test

Locomotor activity of the animals were monitored via open-field apparatus. An individual mouse was treated with 0.9% NaCl intraperitoneally 1 hour before the observations. The animal was placed in open field test [24], 15 min prior to the observations for acclimatization. Ten minutes locomotor counts were noted for the period of 100 minutes and the mean of ten readings were calculated (control counts). After 24 hours, the same animals were given ethanolic extract of *N. jatamansi* (most effective dose) for Group 11 were administered intraperitoneally to animals at the same time under similar conditions and locomotor counts will be recorded as described above (test counts). Test count of each dose will be compared with its respective control [25].

2.2.4 Yohimbine potentiation test

A single mice was administered 0.9% NaCl (Group 12), most effective dose of ethanol extract of *N. jatamansi* (Group 14) and 0.5 mg/kg of fluoxetine (Group 13) intraperitoneally. A group of ten animals were used in a single session for same treatment. After 30 minutes, all the animals were given a subcutaneous injection of yohimbine at the dose of 30 mg/kg [26]. Mortality was observed after 24 hours and the percent mortality of the test animals was compared with the control animals.

3. RESULTS

In FST, group 1 (Control) showed significant reduction in immobility time when compared with group 3, 5, 6 and 7 and p–value was observed to be less than 0.05 as shown in Table 1. *N. jatamansi* groups 5, 6 and 7 showed reduction in immobility time as compared to fluoxetine group and significant reduction in immobility time was observed with group 7 (p-value= 0.031) as displayed in Fig. 1.

In TST, comparison of group 2 (Control) with groups 4, 8, 9 and 10 showed significant reduction in immobility time and p–value was observed to be less than 0.05 as shown in Table 2. Comparison of fluoxetine (group 4) with *N. jatamansi* groups 8, 9 and 10 showed significant reduction in immobility time (p-value= 0.001 in all 3 groups). Fig. 3 depicts the comparison of fluoxetine using TST.

In intra group comparison of *N. jatamansi* at different doses, we observed that the most effective dose was 500 mg/kg in both FST and TST as shown in Figs. 2 & 4 respectively.

Pre and post analysis of locomotor activity with most effective dose of *N. jatamansi* (500 mg/kg) exhibited non-significant difference when compared to controls as shown in Table 3.

Table 1. Mean ± SD of control, experimental drug and extracts after FST

NaCl (control) Group 1	Group	Test compounds in mg /kg	Mean immobility time in secs	p-value
	3	Flouxetine 0.5	108.83 ± 12.891	.002*
	5	*N. jatamansi* 125	120.67 ± 12.863	0.056
152.5 ± 11.879	6	*N. jatamansi* 250	120.67 ± 27.792	0.047*
	7	*N. jatamansi* 500	74.67 ± 29.351	0.001*

Table 4 showed the percentage mortality in 30% and 50% with group 13 and 14 yohimbine potentiation test which was respectively.

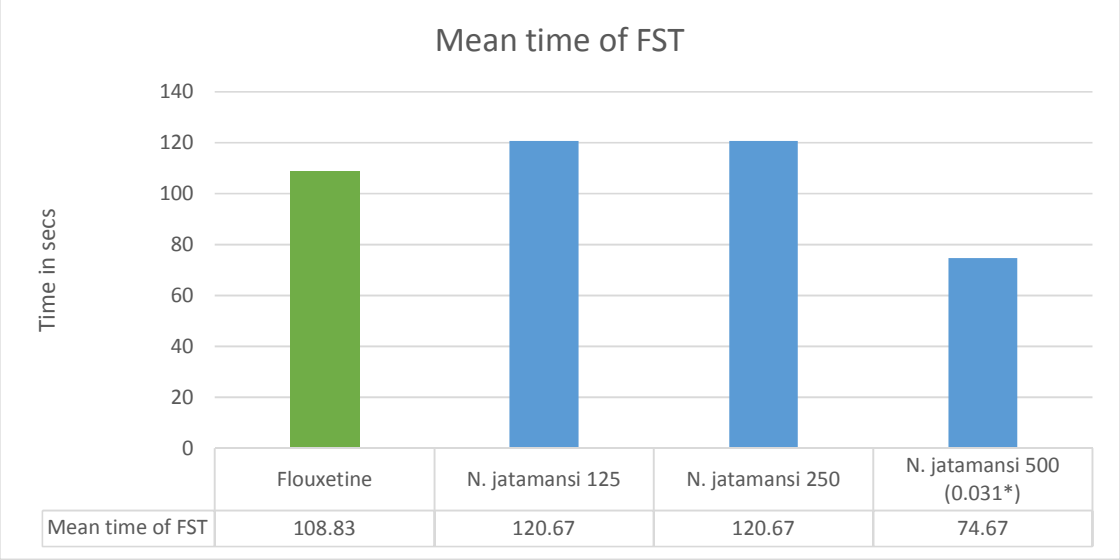

Fig. 1. Comparison of fluoxetine with *Nardostachys jatamansi* at different doses after FST

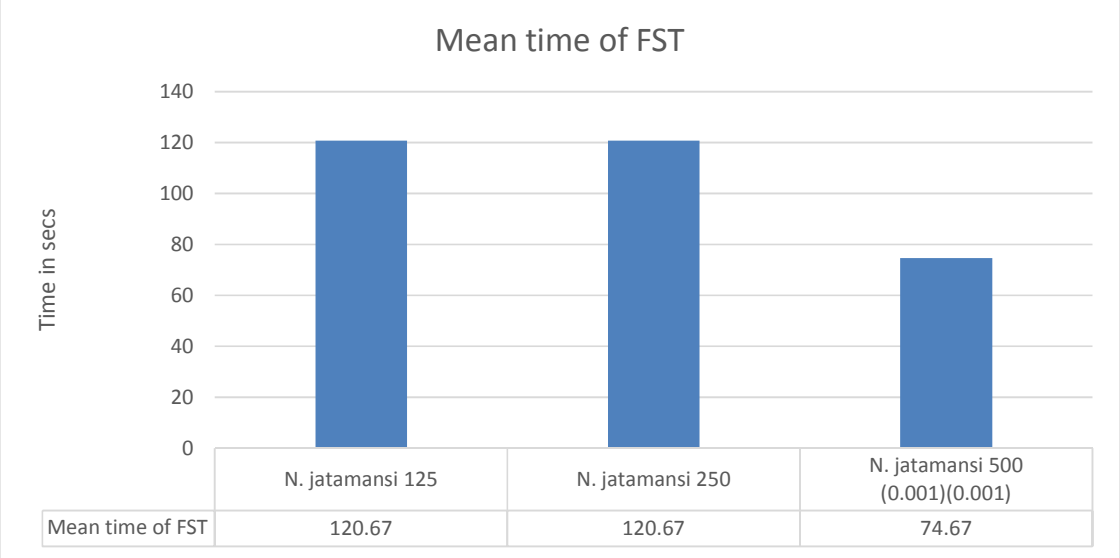

Fig. 2. Intra group comparison of *Nardostachys jatamansi* at different doses after FST

Table 2. Mean ± SD of control, experimental drug and extract after TST

NaCl (control) Group 2	Group	Test compounds in mg /kg	Mean immobility time in secs	p-value
	4	Flouxetine 0.5	199.33 ± 11.860	0.014*
	8	*N. jatamansi* 125	116.33 ± 21.584	0.001*
256.33 ± 41.254	9	*N. jatamansi* 250	127.83 ± 29.329	0.001*
	10	*N. jatamansi* 500	79 ± 30.080	0.001*

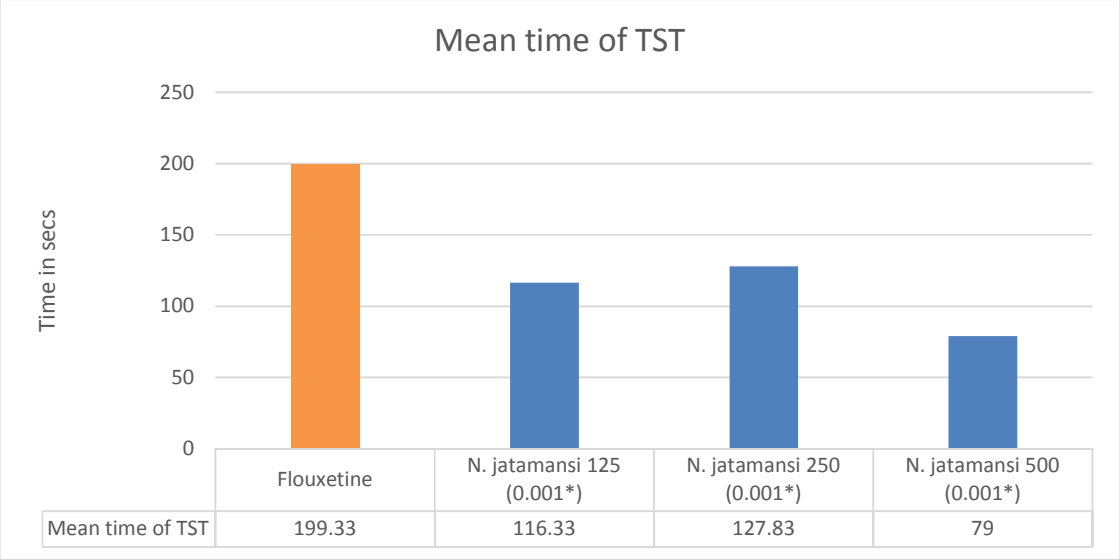

Fig. 3. Comparison of fluoxetine with *Nardostachys jatamansi* at different doses after TST

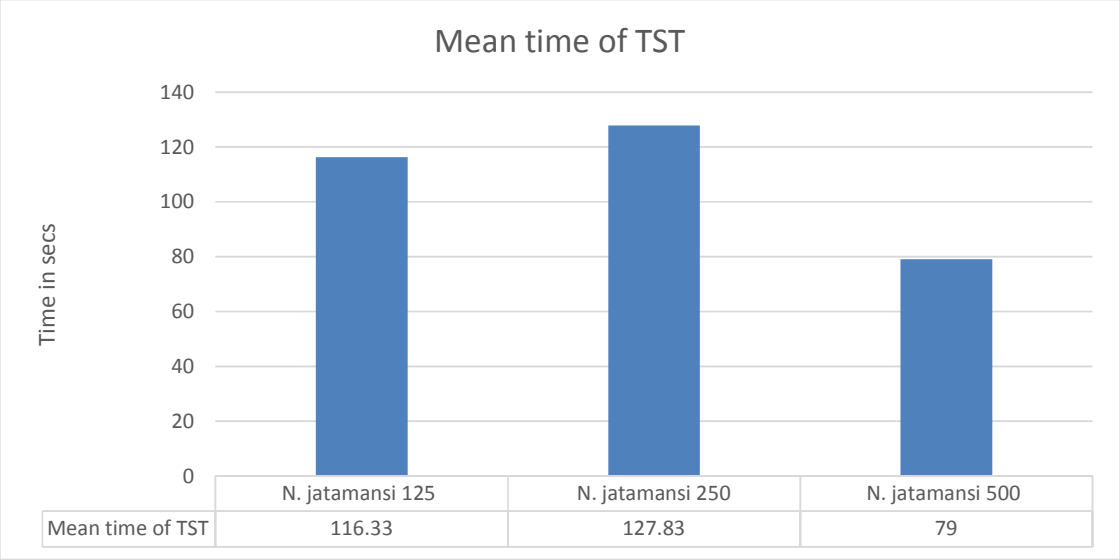

Fig. 4. Intra group comparison of *Nardostachys jatamansi* at different doses after TST

Table 3. Locomotor counts PRE and POST treatment

NaCl counts	*N. jatamansi* 500 counts	p-value
221.40 ± 54.058	219.10 ± 55.677	0.365

Table 4. Percentage mortality after yohimbine potentiation test

Treatment	Group	Total no. of animals	Dose (mg/kg)	No. of deaths after 24 hours	% Mortality
Normal saline (0.9% NaCl)	12	10	0.9%	1	10%
Fluoxetine	13	10	0.5	3	30%
N. jatamansi	14	10	500	5	50%

4. DISCUSSION

In the present study different doses of *Nardostachys jatamansi* extract were compared selective serotonin reuptake inhibitor fluoxetine. Antidepressant properties were scientifically validated by conducting behavioral studies i.e. FST, TST, LT and YPT [27,28]. Animal models of psychopathology serve as a central tool for psychopharmacologists in their attempts to develop new, more efficient medications for psychiatric disorders and also to explore the mechanism(s) of novel drugs [29].

FST and TST are behavioral animal models, which have a strong predictive validity and are used to explore the efficacy of antidepressant drugs [30,31]. Immobility is reduced by variety of agents, which are therapeutically active in depression [32]. In our study fluoxetine caused reduction in immobility time in mice after FST, which was statistically significant and these findings are similar with the previous findings of Porsolt et al. in 1977 who created and validated the FST model by other antidepressants such as tricyclic antidepressants, monoamine oxidase inhibitors and atypical antidepressants [33,34]. Fluoxetine caused significant reduction in immobility time of mice in FST and TST at 0.5 mg /kg, i.p. administration with mean difference of 43 and 57 seconds in FST and TST respectively. These results are similar with previous studies reported by Ismail et al in 2009, 2010 [27,28]. Almeida et al in 2015 conducted a study by using rats in FST and administered fluoxetine 10 mg/kg, i.p. and the results seemed to be similar with our findings [35].

Ethanolic extract of *N. jatamansi* (125, 250 and 500 mg/kg) showed reduction in immobility time which was 120.67 ± 12.863, 120.67 ± 27.792 and 74.67 ± 29.351 respectively using FST. The same extract showed reduction of immobility time, 116.33 ± 21.584, 127.83 ± 29.329 and 79 ± 30.080 respectively using TST. *N. jatamansi* at the dose of 250 and 500 mg/kg was effective as antidepressant in our study by using FST and showed significant reduction in immobility time of mice as compared to controls while 125 mg/kg dose of *N. jatamansi* showed reduction in immobility time that was not significant statistically. In TST all three doses of *N. jatamansi* (125, 250 and 500 mg/kg) showed significant reduction in immobility time as compared to controls. A study conducted in India in year 2008 reported significant reduction in immobility time as compared to controls using ethanolic extract of *N. jatamansi* (100, 200 and 400 mg/kg, per oral) for 14 successive days to mice using FST and TST [36]. Another study on poly herbal formulation containing *N.jatamansi* using FST and anti-reserpine test stated significant reduction in immobility time as compared to controls [37]. A study from India used *N. jatamansi* (200 mg/kg and 500 mg/kg) orally with rats in chronic fatigue induced by forced swimming test showed similar results [38]. When fluoxetine was compared to the different doses of *N. jatamansi,* only 500 mg/kg dose showed significant result. The important finding at this dose reflects that *N. jatamansi* has dose dependent antidepressant activity and can also be used in patients suffering from depression [15,39]. One of the possible explanations for the above is that perhaps the highest concentration of active constituent(s) or their combination is present at this dose. A study explored the effect of poly herbal formulation containing *N. jatamansi*_to be statistically significant when compared to fluoxetine [40]. Methanolic extract of *N. jatamansi* (200 and 400 mg/kg) was compared with imipramine using animal models of depression and it also showed significant reduction in immobility time [39]. Same doses as our study were used to evaluate the anxiolytic effect of ethanolic extract of *N. jatamansi and this study reported* significant results when compared to diazepam [41]. Ethanolic extract of *N. jatamansi* extract administered orally to evaluate anti-anxiety effect and compared with diazepam and it was found to be effective as an anxiolytic drug [42].

In order to prove that the reduction in immobility time in FST and TST is not caused by the possible central nervous stimulating effect, the most effective dose of *N. jatamansi* was investigated in the open field test / locomotor test [43].

The ethanolic extract of *N. jatamansi* did not cause any significant change in motor counts at the dose at which it produced statistically significant reduction in immobility time of animals by using FST and TST. These findings are similar with other antidepressants [28]. Similar results as our study findings were observed in locomotor activity in control and drug treated animals by Rahman et al in 2010 when 200 and 400 mg/kg of methanolic extract of *N. jatamansi* was used [39]. Razack et al. observed increase in locomotor counts after the treatment of 70%

ethanol extract of *N. jatamansi* concluded it to be an anxiolytic plant [42]. Another study showed non-significant findings similar to our results when ethanolic extract of *N. jatamansi* administered for 14 successive days [36]. A study with 70% ethanolic extract of *N. jatamansi* also significantly increased the locomotor activity as observed in the open field test confirming the anxiolytic effects in mice [41]. In a recent study ethanolic extract of *N. jatamansi* showed increase in locomotor activity in open field test concluded it to be an anxiolytic [44].

No statistically significant change in the locomotor activity was observed, indicating that the reduction in immobility time were not based on any stimulation of locomotor activity and it also favors the antidepressant effect of this herb.

Yohimbine is an alpha-2 adrenergic antagonist that blocks adrenergic receptors due to which release of norepinephrine increases at the neuronal levels, results in increased central epinephrine and norepinephrine turn over [45]. Thereby causing cardiovascular excitation in animals, referred as yohimbine lethality. Potentiation of yohimbine lethality in mice is also considered as a classical screen [46] and is widely used for the assessment of antidepressant drugs [26]. In our study pretreated animals with SSRI i.e. fluoxetine potentiated yohimbine induced lethality, indicating that it may have occurred due to increase in norepinephrine in the brain and peripheral tissues. The ethanolic extract of *N. jatamansi* caused 50% mortality at 500 mg/kg. This result of ethanolic extract of *N. jatamansi* in yohimbine potentiation test are consistent with the reference drug, favoring that reduction in immobility time of mice by these two extracts in behavioral models i.e. FST and TST is due to their antidepressant activity.

5. CONCLUSION

On the basis of our study observations it may be concluded that extract of *Nardostachys jatamansi* possess antidepressant like actions in animal models of depression that are comparable to fluoxetine. The best antidepressant like activity was observed by *Nardostachys jatamansi* at the dose of 500 mg/kg. Feedback mediated by Alpha-2 adrenoceptors tends to be an underlying cause for these behaviors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Study was approved by AEC of Ziauddin University. Protocol number 2019-001 was issued.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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