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ANTIDEPRESSANT LIKE EFFECTS OF JASMINUM SAMBAC – INVESTIGATION OF INVOLVEMENT OF MONOAMINERGIC SYSTEM

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ABSTRACT

Jasminum sambac (JS), an evergreen plant belongs to the family of Oleaceae, extensively used in traditional Malay medicine for the treatment of depressive disorders. The present study investigates the antidepressant activity of JS and also to evaluate possible mechanisms involved in its antidepressant action. JS at a dose of 250mg/kg and 500mg/kg were administered to mice for 7days. Imipramine (25 mg/kg) was used as standard. Tail Suspension Test (TST) and Forced Swim Test (FST) were used to evaluate the antidepressant activity of JS. Malondialdehyde, Reduced glutathione and Vitamin C were evaluated to assess the antioxidant activity of JS against depression induced oxidative stress. The mechanisms were probed by measuring brain neurotransmitters and monoamine oxidase enzyme activities. After one week of treatment, JS showed decreased immobility time in TST and FST, increased climbing time in FST significantly, but with no change in swimming time. JS showed increased brain dopamine levels dose dependently and increased brain serotonin levels at 500 mg/kg significantly, but showed no significant effect on brain norepinephrine, monoamine oxidase-A and monoamine oxidase-B levels. These findings demonstrated that JS produces antidepressant activity and the mechanism involves serotonergic and dopaminergic systems there by causing generalized increase in the monoamine turnover.

KEY WORDS: Depression, Jasminum sambac, Tail Suspension Test, Forced Swim Test, Dopaminergic system, Serotonergic system.

INTRODUCTION

Depression is the most prevalent, chronic, recurrent and potentially life threatening psychiatric illness with impact on quality of life of the patients and most significant risk factor for suicide in adolescents, young adults and elderly people[1]. It is one of the leading causes of mortality and morbidity; and according to World Health Organization, by the year 2020, depression will be in the second place as largest contributor to the global burden of diseases[2,3]. The pathophsysiology of depression is hypothesized due to decrease in monoamine neurotransmitter turnover viz. noradrenaline, dopamine and serotonin [4]. An increase in the monoamine neurotransmitter turnover results in antidepressant activity[5,6]. Although a number of antidepressants are available acting through various mechanisms like serotonergic, dopaminergic or adrenergic systems, each therapy has its own undesirable effects, and also unresponsiveness to the therapy by certain patients. From past few years, investigation on herbal medicines for psychiatric disorders is growing at a faster pace with the aim to search newer phytochemical alternatives for the treatment of depression as effective antidepressant agents.

Jasminum sambac (English: Jasmine), an evergreen plant belongs to the family of Oleaceae and has been extensively used in traditional medicine. It possesses immense therapeutic applications like curing mouth infections, weakness of sight, insanity, ulcers, leprosy and skin diseases[7], as analgesic, anti-inflammatory, antidepressant, antiseptic, aphrodisiac, sedative, antimicrobial[8], cytotoxic and expectorant. JS has been used since ages in Malay medicine as antidepressant. The plant contains sambacin, Jasminum, sambacoside A, sambacolignoside, quercitin, isoquercitin, rutin, kaempferol, ursolic acid, linalool, phenyl methanol and glucoside-sambacoside A-G along with oleoside 11-methylester [7].The present study was designed to investigate the antidepressant like activity of Jasminum sambac in experimental mice, using behavioral models of screening of antidepressants i.e., locomotor activity, alertness, TST and FST and also analyzing the monoamine neurotransmitter turnover by HPLC- EC Detector to establish the mechanism involved in the antidepressant like effect of JS.

MATERIALS AND METHODS

Preparation and Standardization of JS extract

Jasminum sambac leaves were collected from Sri Padmavati Mahila Visvavidyalam campus, Chittoor, Tirupati, Andhra Pradesh. The plant was authenticated by Dr. Madhava Shetty, Department of Botany, Sri Venkateswara University, Tirupati and the voucher specimen was deposited in the department with Voucher No. 1528. The leaves were cleaned thoroughly, sun dried to remove moisture and ground into coarse powder and was soaked in 1300ml of 80% alcohol for seven days with occasional stirring and shaking, filtered and concentrated to get crude extract. The percentage yield was found to be 3.22 %w/w and subjected to determine the total phenolic[9], flavonoid [10] and tannin content[11].

Chemical characterization of JS extract

For HPTLC analysis, JS was dissolved in HPLC grade methanol (1 mg/ml) and subjected to analysis. Elution was initiated with mobile phase of n-butanol : acetic acid : water [4:1:1]. The eluted spots were identified by Spraying vanillin –sulphuric acid, heated at 105° for 5 minutes and detected at 254nm, 366nm in Densiometry TLC Scanner III, The chromatographic peaks of the analytes were identified and confirmed by comparing their retention time and UV spectra with those of the reference standards. Results (mg/g dry weight) were obtained from the peak areas (254 nm) of JS and reference standards (purity >97%).

Column chromatography of hydroalcoholic extract of JS

The hydroalcoholic extract of JS were subjected to column chromatography using silica gel 60-120 mesh as adsorbent by gradient dilution to isolate the phytoconstituents. The bottom of the column (45 cm length, 12 cm diameter) was packed with adsorbent cotton, above which silica gel (60 g) was filled as a slurry in ethyl acetate. Care was taken to prevent entrapment of air bubbles into the column. About 3 g of the hydroalcoholic extract of JS was dissolved in 25 ml of alcohol, dispersed uniformly in 20 g of silica gel and loaded over the filled column. The top portion of the column was covered with a piece of Whattman No.1 filter paper, above which mobile phase level was maintained. The column was prepared in ethyl acetate and left overnight. Next morning, the column contents were eluted with gradient elution starting with pet ether: to luene followed by chloroform, ethyl acetate, methanol and water (90:10, 70:30, 50:50, 30:70 and 10:90). Each time, 100 ml of elute was collected. Elution of different components was monitored by TLC on silica gel-G to know the nature of compounds in the

fractions and homogeneity of the compounds. Chloroform :Ethyl acetate (80:20) and ethyl acetate : Methanol (20:80) elutes produced a single spot on TLC with silica gel–G respectively. The fractions were combined and concentrated under reduced pressure, yielded a white substance, which was recrystallized from acetone.It was found to be homogenous by TLC studies and was designated as JS - 1 and JS - 2. The isolated compound was subjected to UV, IR, ^{1}H NMR,^{13}C NMR Mass Spectral studies.

Acute toxicity studies

The acute toxicity studies were conducted as per the OECD guidelines 420 where the limit test dose of 2000 mg/kg used[12,13]. Observations were made and recorded systemically 1, 2, 4 and 24 h after dose administration for skin changes, morbidity, aggressivity, sensitivity of the sound and pain, as well as respiratory movements.

Animals

Male Swiss Albino mice weighing 18–20 g were used. The animals were housed 10 per cage (440 mm × 270 mm ×178 mm) under controlled conditions of light (12h light/dark cycle, lights on at 7:00 AM), temperature (22 ± 2 ^{0}C) and humidity 50–60% with free access to food and water. The animals were acclimatized to the laboratory for at least 3 days before they were tested. All the experiments were carried out between 9:00 AM and 3:00 PM after prior approval from Institutional Animal Ethical Committee No.1677/PO/a/12/CPCSEA.

Drug administration

The animals were divided into six groups (n = 6/group). Animals in group 1 were administered with distilled water. Animals in group 2, 3 and 4 were administered with Imipramine at a dose of 25 mg/kg, JS extract at the doses of 250 and 500 mg/kg suspended in 1% tween 80respectively, as the dose was calculated from the 1/10th& 1/20th of LD_{50} dose (5000 mg/kg) which was determined from acute toxicity studies. All drugs were orally administered short-term (7 days).The behavioral tests were conducted 1 h after the short-term. At the end of experimental period (7days of treatment) the animals were fasted overnight and sacrificed by cervical decapitation. The brains were excised immediately and the brain tissue was homogenized and used for further analysis.

Effect of JS on Spontaneous motor activity

Locomotor activity was recorded with a photocell activity meter for 15 min beginning 60 and 120 min after p.o. administration of each test extract.

Tail suspension test (TST)

TST was performed according to the method of Steru et al., [14] and Cunha et al., [15].

Forced swimming test (FST)

The immobility time was scored in FST[16]. The total duration of swimming time and climbing time was also scored in order to investigate the mechanism of antidepressant activity of JS.

Neurotransmitter estimations

The content of NE, DA and 5-HT in brain were measured as described previously[17,18].

Measurement of monoamine oxidase (MAO) activity

MAO activity was measured according to the method described previously[19,20]. Protein concentration was determined using bovine serum albumin as the standard[21].

Antioxidant studies

The homogenates were subjected for the estimation MDA[22], reduced glutathione [23] and vitamin C [24].

Statistical analysis

All the data were expressed as Mean ± SEM. Difference in mean values between groups were analyzed by one – way analysis of variance (ANOVA) followed by Dunnett 'T'test in order to detect inter-group differences using Graphpad Prism Version 5.0. A value of $P < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Preliminary phytochemical analysis of JS revealed the presence of tannins, phenolic compounds, flavonoids, sterols, triterpenoids, sugars and coumarins. The total phenolic content in JS extract was found to be 1.5 mg/g of GAE (gallic acid equivalent), flavonoid content was found to be 0.14 mg/g of QE (quercetin equivalent) and the tannin content was found to be 7.8% mg / g of TAE (tannic acid equivalent). TLC characterization of JS revealed the presence of flavonoids, coumarins and alkaloids. Compounds like JS-1 and JS-2 are isolated from column chromatography of JS. JS-1 was identified as Cholorocoumarin and

JS-2 as Kaempferol from spectral studies. Acute toxicity was studied by OECD guidelines 423 (limit test) at a dose of 2000mg/kg p.o in female albino mice. No mortality was observed at this dose. Hence 5000mg/kg was considered as LD_{50} cut off value. The dose selected was 250 and 500 mg/kg. Clinically used antidepressant agents have varying therapeutic responses, many undesirable effects and have high cost of treatment. Moreover, some of the patients are unresponsive to the therapy and complete remission occurs in 70% of treated patients[25]. During last few decades, interest has grown on the investigation of herbs for their neuroprotective actions and cure of many psychiatric illnesses. Therefore, effective alternative medical therapies with plants may be developed for the treatment of depressive disorders with less undesirable effects and more efficacious therapeutic outcomes.

The present study was the first case to demonstrate that acute administration of JS (250 and 500 mg/kg, p.o.) had a specific antidepressant-like effect in both the FST and TST in mice, since the significant reduction of immobility time elicited by JS cannot be attributable to any psychostimulant effect in the Spontaneous motor activity. Moreover, it was noteworthy that the anti-immobility effect produced by JS was comparable to that produced by the classical antidepressant Imipramine. In order to determine whether JS has an antidepressant-like action, we had to find whether it has excitatory or inhibitory actions on the central nervous system. JS at dose of 250 and 500 mg/kg had no effect on spontaneous motor activity in mice as shown in Figure 1, indicating that JS had no excitatory or inhibitory action on the central nervous system at least at the doses of 250 and 500 mg/kg.

Figure 1

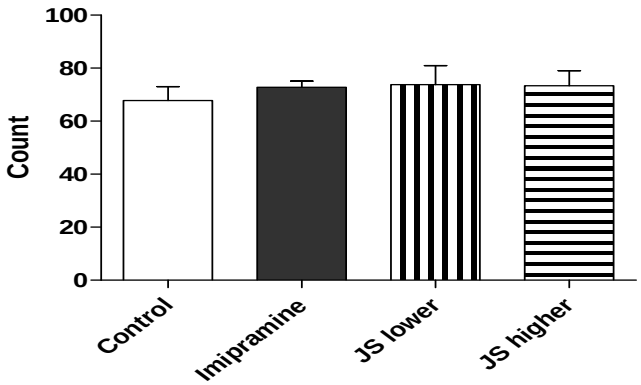
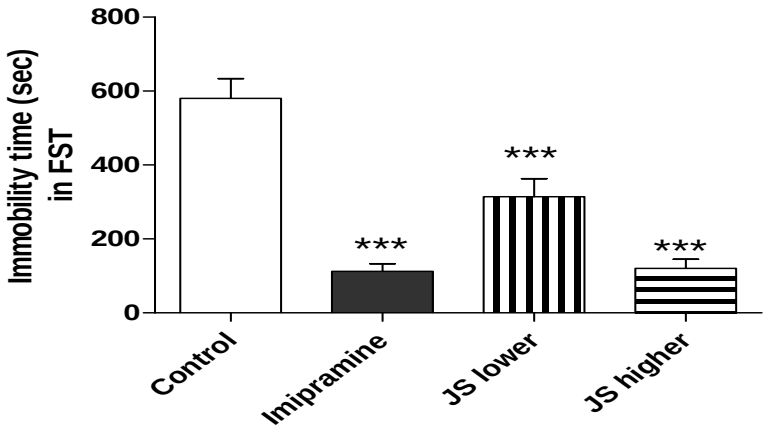


Figure. 1 Showed the effect of JS extract and Imipramine on Spontaneous Locomotor activity. Values are expressed as Mean ± SEM [n = 6]

The FST and TST are widely accepted stress models of depression used to screen new antidepressant drugs, as they are sensitive to all major classes of antidepressant drugs

including tricyclics, serotonin-selective reuptake inhibitors, monoamine oxidase inhibitors. However, these tests do not have an identical neurochemical basis[26]. Considering that the TST is commonly used to detect and characterize the efficacy of antidepressant drugs and possesses greater sensitivity than the FST[27], and depression is known to be associated with dysfunction in monoaminergic systems such as serotonergic, noradrenergic or dopaminergic systems[28], the study also analyzes some of the possible neuropharmacological mechanisms related to the antidepressant - like effect of JS observed in the TST. Since 5-HT is the main neurotransmitter involved in the cognitive functions, it has been proposed that an increase in serotonergic neurotransmission might counteract the cognitive impairment including in memory and learning which is considered a core feature of major depressive disorder[39,30]. Modulation of 5-HT at synapses is thought to be a major action of several classes of pharmacological antidepressants. The acute effects of JS and Imipramine on the immobility time in the mouse FST and TST are shown in Figure2A and 2B. After 7 days treatment, JS at the doses of 250 and 500 mg/kg and Imipramine 25 mg/kg showed significant decrease in the immobility time in the FST [$P < 0.001$] and TST[$P < 0.001$]. Imipramine and JS at 250 and 500 mg / kg showed no effect on swimming time in TST, but induced a significant increase in climbing time [$P < 0.001$] as compared with vehicle treated group which was shown in Figure 3A and 3B.

Figure 2A



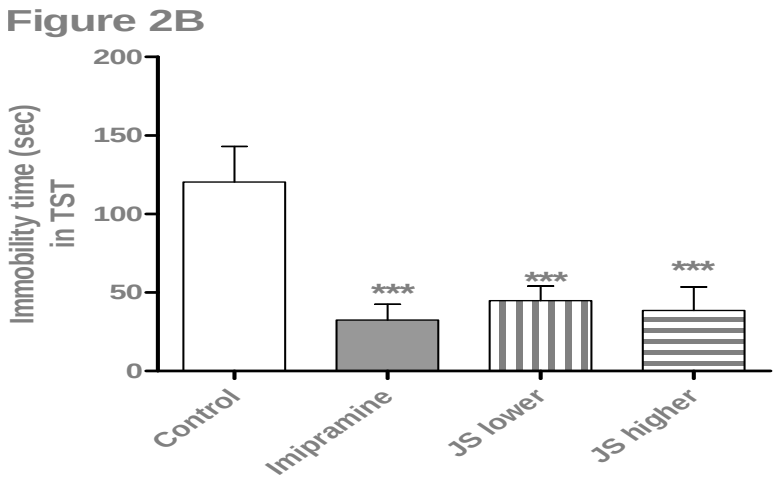
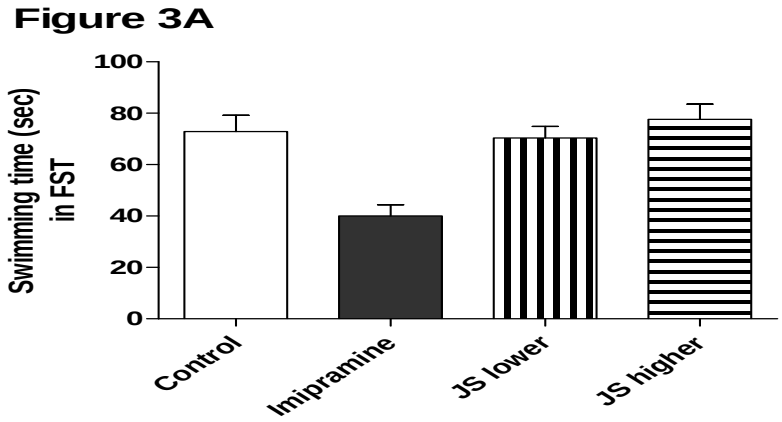


Figure 2A and 2B showed the effect of JS extract and Imipramine on immobility time in the mouse FST (panel A) and TST (panel B). Values are expressed as mean ± S.E.M [n=6]. ***P < 0.001 vs FST or TST with control group.



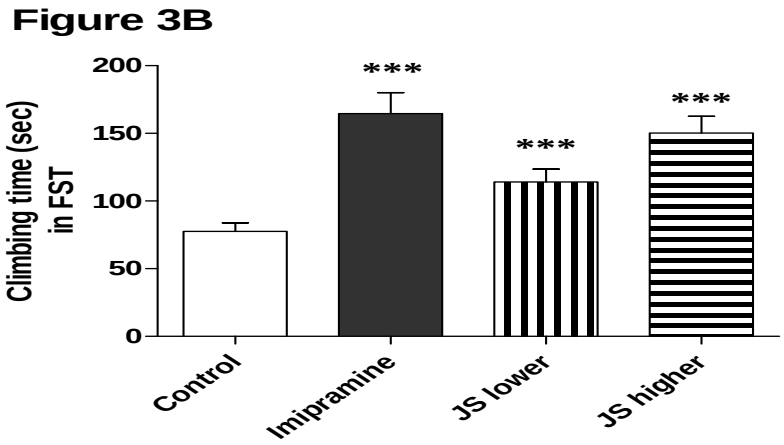


Figure 3A and 3B showed the effect of JS extract and Imipramine on swimming time and climbing time in FST. Values are expressed as mean ± S.E.M [n=6]. ***P <0.001 vs control group.

Increase in the levels of monoamine neurotransmitters in the brain is the effective way for the treatment of depression [31,32]. Monoamine hypothesis states that dysregulation of the central nervous system involving the monoamine neurotransmitters norepinephrine, dopamine and serotonin play role in the pathogenesis of depression [33,34]. Norepinephrine and serotonin system dysfunction is the most widely accepted hypothesis for the development of depression. Therefore, in our study we detected the brain monoamine neurotransmitter levels by a sensitive HPLC method. Our results showed that JS caused increase in the brain 5-HT levels, but only at higher dose ($p<0.01$). However, our results indicated that tricyclic antidepressant Imipramine caused reduction in the brain serotonin turnover as supported by the finding that chronic administration of Imipramine results in reduction in the brain serotonin turn over [35]. The antidepressant activity results from the involvement of not only serotonergic system, but also the might be due to adrenergic system. Clinical studies showed that combine serotonin and norepinephrine uptake inhibitors are more effective clinically than serotonin reuptake inhibitors alone [36]. To rule out the involvement of adrenergic system, we have detected the levels of norepinephrine in brains. Results showed a significant increase in the levels of brain norepinephrine levels in the treated groups. Hence the antidepressant activity of JS may result from involvement of both serotonergic and norepinephrine systems. Several studies proved the augmentation of dopaminergic neurotransmission in the antidepressant activity[37,38]. So we investigated for the involvement of dopaminergic system and results showed a significant increase in the dopamine levels in the brains of treated groups. DA is a precursor for the synthesis of NE; this suggests that the antidepressant like effects may be due to increased availability of precursor increased NE synthesis is responsible for the antidepressant activity of JS. Figure 5A and 5Bshows the effects of JS extract treatment on brainMAO-A and MAO-B activities. After 7-day JS extract treatment at dose of 250 and 500 mg/kg showed no effect on MAO-A and MAO-B levels when compared with the vehicle-treated mice. Imipramine showed no significant effect on MAO-A, but showed significant effect on MAO-B levels [$P< 0.05$].

Figure 4A

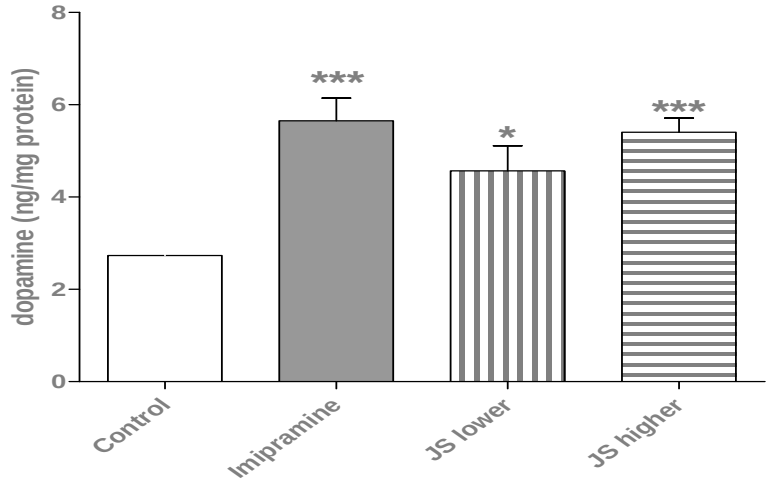


Figure 4B

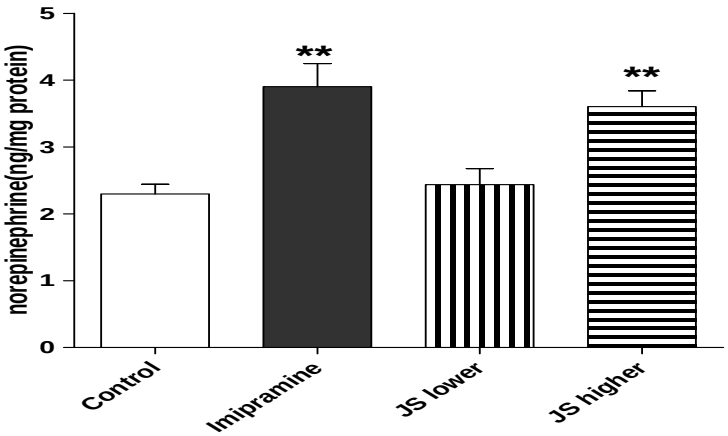


Figure 4C

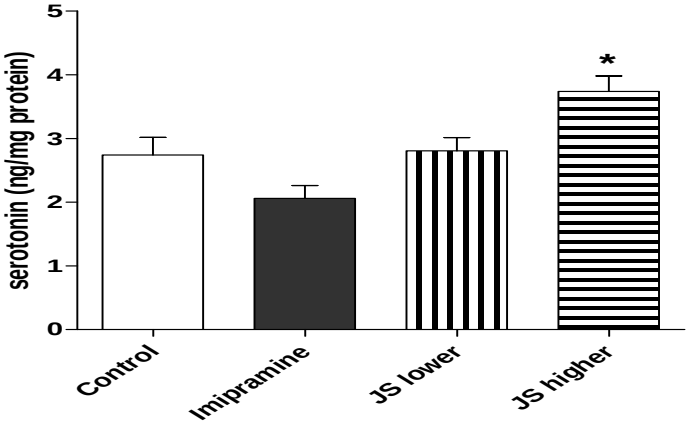


Figure 4A, 4B, 4C. Effect of JS on brain dopamine levels, norepinephrine and serotonin levels. Values are expressed as Mean ± SEM [n=6], *(P<0.05) Vs Control group

Figure 5A

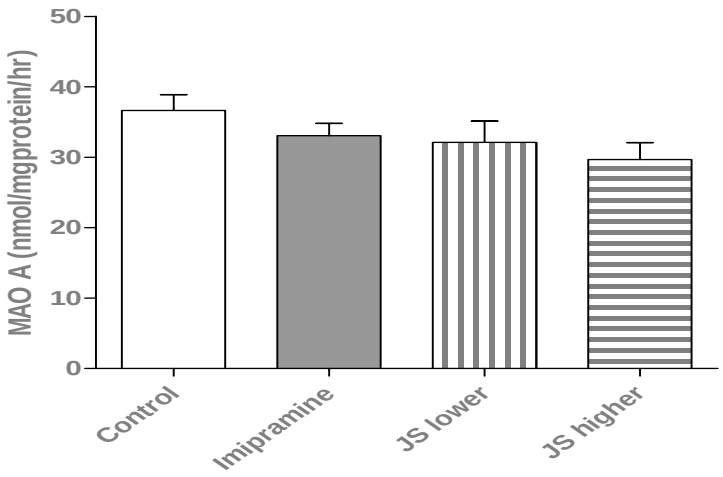


Figure 5B

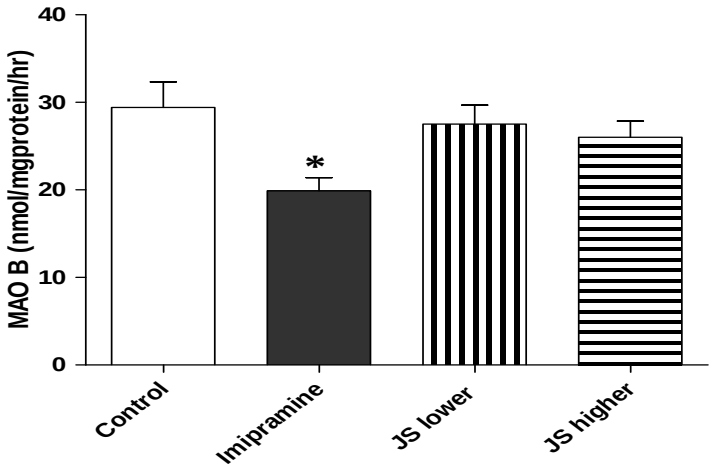


Figure 5A, 5B. Effect of JS extract and Imipramine on brain MAO –A levels and MAO – B levels. Values are expressed as Mean ± SEM [n=6], *[p < 0.05] Vs Control group

MAO is the catalytic enzyme that metabolizes the monoamines. Compounds with MAO A inhibitory activity have antidepressant activity and compounds with MAO B inhibitory activity can be used in the treatment of Parkinson's disease. So to rule out the involvement of MAO inhibitory activity in the mechanism of antidepressant activity of JS, we have estimated the levels of MAO A and MAO B in brains. Results showed very slight increase in MAO A but not to statistically significant level. So synthesis enhancement or reuptake inhibition may be the major mechanism involved in the antidepressant activity of JS and played an important role than MAO inhibition. It is important to note that there exists no direct relation between reduced monoamine levels and depression although the adrenergic and serotonergic drugs are

successfully used in depression treatment. It was clinically proven that depletion of monoamines in normal individual did not lead to depression and further depletion of monoamines in depressed patient did not further worsen the depression behavioral symptoms[39]. Furthermore, it was clinically reported that monoamines may not have role in the development of depressive symptoms but are important for the response of antidepressant drugs. Hence while investigating the other factors that might be involved in the pathogenesis of depression it came across that oxidative free radicals increase in chronic stress and play role in pathogenesis of depression. Moreover, reversal of oxidative damage might be one of the reasons for their antidepressant activity. So in our present study we investigated the antioxidant potential of JS. The plant extract significantly reduced the amount of free radicals produced in the brains of mice subjected to FST and TST as it decreased the amounts of MDA in the treated groups. The antioxidant activity of the JS may be due to the augmentation of the antioxidants reduced glutathione and vitamin C in the brain which were decreased during FST and TST. Imipramine and JS higher dose treated rats showed significant [P< 0.01, P< 0.05 respectively] decrease in the levels of MDA and significant increase in GSH [P < 0.001, P< 0.001 respectively] and Vitamin C [P < 0.05, P< 0.001 respectively] levels when compared to the control group. JS at lower dose did not show any effect in the brain MDA, GSH and Vitamin C levels (Figure 6A, 6B and 6C).

Figure 6A

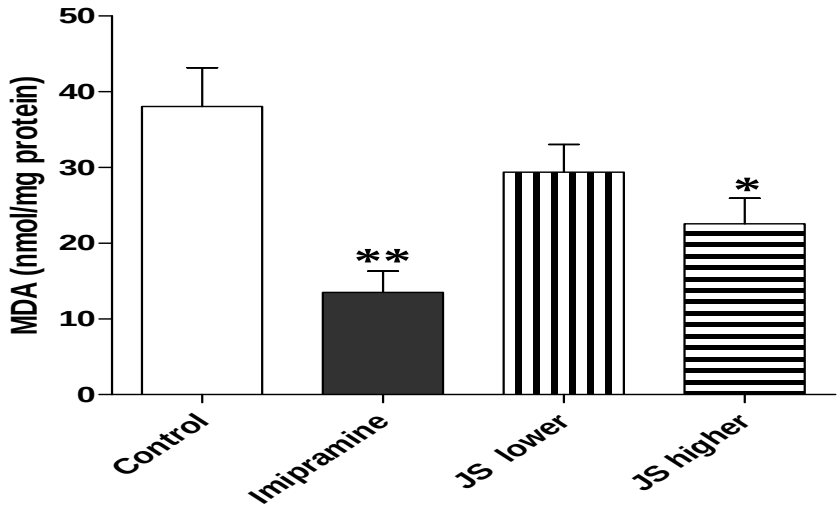


Figure 6B

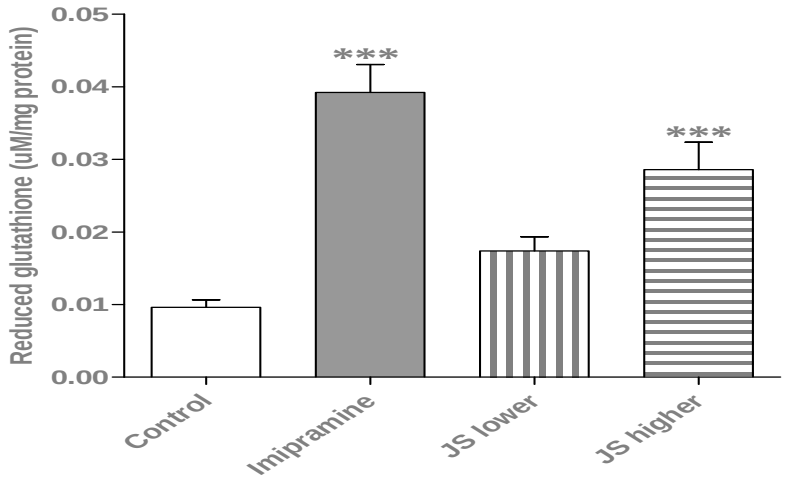


Figure 6C

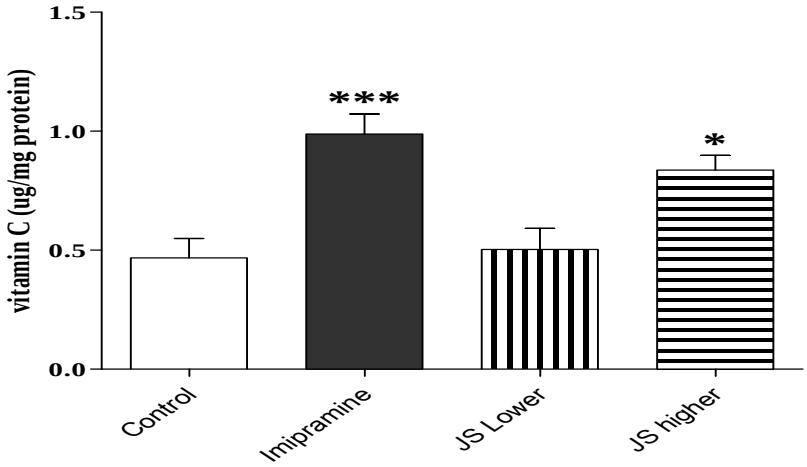


Figure 6A, 6B, 6C. Effect of JS extract and imipramine on brain MDA, reduced glutathione and Vitamin C levels. Values are expressed as Mean ± SEM [n=6], *(P<0.05), ** (P<0.01), * (P<0.001) Vs Control group**

From our results it can be concluded that the antidepressant activity of JS might be due to its action on both serotonergic and adrenergic and/or dopaminergic systems, apart from the antioxidant effects, resulting in the enhanced monoamine neurotransmitter turnover in the brain.

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