ejpmr, 2016,3(12), 335-341

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ANTIDEPRESSANT-LIKE ACTIVITY OF *SMILAX ZEYLANICA* LINN IN BEHAVIORAL DESPAIR TESTS IN MICE

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Article Received on 30/09/2016 **Article Revised on 21/10/2016** **Article Accepted on 11/11/2016**

ABSTRACT

Background: The present study was undertaken to evaluate the anti-depressive activity of *Smilax zeylanica* Linn after two weeks administration by using a mouse forced swimming test (FST) and tail suspension test (TST). **Methods:** Animals were divided into 5 groups (n = 6 /group): control (0.9% saline), the three doses of *Smilax zeylanica* (125, 250, 500 mg/kg) and Imipramine 10mg/kg for two weeks treatment. To assess the antidepressant effect of *Smilax zeylanica* Linn Forced swimming test (FST) and Tail suspension test (TST) were used to take as a measure of antidepressant activity. The probable mechanism of action of the anti-depressive effect of *Smilax zeylanica* Linn was also investigated by measuring the levels of monoamines in the cortex, striatum, hippocampus and hypothalamus of the mice and MAO-A inhibition activity. **Results:** *Smilax zeylanica* significantly reduced the immobility time of mice in both the FST and TST; it increased the levels of 5-HT in cortex, striatum, hippocampus, and hypothalamus, the level of NE in striatum and hippocampus, the level of DOPAC in hypothalamus, the level of 5-HIAA in striatum, and the level of DA in striatum, hippocampus, and hypothalamus. **Conclusions:** After two weeks administration, *Smilax zeylanica* produced antidepressant-like effect. The mechanism of action of anti-depressive effect of *Smilax zeylanica* seemed to involve an increase of the monoamines levels.

KEYWORDS: *Smilax zeylanica*, Forced swimming test, Tail suspension test, Antidepressant, Monoamines, MAO-A.

INTRODUCTION

Mood disorders are recurrent, life threatening (due to the risk for suicide), and a major cause of morbidity worldwide (Nestler EJ et al. 2002). Depression is a major clinical illness affecting 9.5% of population(Mishra et al. 2013) and is ranked by the World Health Organization as among the most burdensome diseases of society(Dang et al.2009). Mental depression is a chronic illness that affects a person's mood, thoughts, physical health and behavior. Symptoms of depression include biological and emotional components. Biological symptoms include retardation of thought, action and appetite. Emotional symptoms include mystery, apathy and pessimism, low self- esteem consisting of feeling of guilt, inadequacy and ugliness, indecisiveness and loss of motivation(Rang et al. 2000). The life time risk of depression varies from 5% to 12% in men and 10% to 25% in women(Gupta et al. 206). According to the most accepted hypothesis of depression, the monoamine theory, patients with major depression have symptoms that are reflected changes in brain monoamine neurotransmitters, specifically norepinephrine (NE) and serotonin (5-HT) (Hindmarchm, 2002). Clinical data suggests that dopamine (DA) is also involved in the pathophysiology and treatment of depression (Kulkarni et al. 2008). Enzyme levels also get altered in serum and brain of depressed patients when compared to normal people (Caisong et al.1994). Numerous antidepressant compounds are now available, presumably acting via different mechanisms including serotonergic, noradrenergic and/or dopaminergic systems (Elhwuegi, 2004). At present, there are several types of antidepressants used in clinical practice, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective reversible inhibitors of monoamine oxidase A (RIMAs), and specific serotonin–norepinephrine reuptake inhibitors (SNRIs)(Fava, 2003), however, these drugs can produce many side-effects, Insomnia and loss of libido with selective serotonin (5 HT) reuptake inhibitors and tolerance and physical dependence with tricyclic antidepressants are very common; several drug-drug interactions may occur(Kothari et al.2010). This necessitates the development of newer and more

effective antidepressants from traditional medicinal plants whose psychotherapeutic potential has been assessed in a variety of animal models (Zhang,2004).

Smilax zeylanica Linn. is an evergreen woody climber endemic to Western Ghats of Southern India. It is a slow growing riparian species distributed up to 1200 m altitude. In the folkloric system of medicine, the plant was used in veneral diseases, to promote healing of wounds, swellings, abscesses, in rheumatism and pain in lower extremities, skin diseases, leucorrhoea, colic, dysentery, dysuria and fever (Anisuzzaman et al.2007, Arunvijayan et al.2007). Chopachinee is an important drug used in ayurveda for the treatment of several diseases like diseases of the nervous system, epilepsy, psychosis(Sharma et al. 2005, Yoganarasimhan, 2002), urinary disorders, polyuria, hemiplegia, Parkinson's disease, congenital diseases, leprosy, rejuvenator, blood purifier(Varro et al. 1988), while *Smilax zeylanica* may be a potential alternate source of Chopachinee (Madhavan et al.2010). The antiepileptic and anticataleptic activities, in *Smilax zeylanica* were established(Rasheed et al. 2012, Porsolt et al. 1977). The roots of *Smilax zeylanica* have a steroidal saponin glycoside diosgenin (Yoganarasimhan2002). However no scientific study on antidepressant activity of the plant has been reported. The present investigation was undertaken to study the antidepressant activity of *Smilax zeylanica* Linn in behavioral despair tests in mice.

MATERIALS AND METHODS

Experimental animals

Male albino mice, weighing 25–30gm were obtained from the animal house of the Nizam Institute of Pharmacy, Deshmukhi, Ramoji Film City, Hyderabad. They were maintained at 22 ± 1°C and humidity (30%–40%). with free access to water and food, under a 12:12 h light/dark cycle (lights on at 08:00 h). All manipulations were carried out between 9:00 and 15:00 h, with each animal used only once. They were fed with a standard pellet diet obtained from Gold Moher, Lipton India Ltd, Hyderabad and water *ad libitum* throughout the experimental period. All animal experiments were carried out in accordance with the guidelines of CPCSEA and study was approved by the IAEC (Institutional animal ethical committee) with registration number. (1330/AC/10/CPCSEA).

Plant materials

Dried roots of *Smilax zeylanica* were purchased from a herbal Market (Hyderabad, Andhra Pradesh, India.) and authenticated by Dr. K. Madhava Chetty, Assistant Professor, Department of Botany, S.V University, Tirupati. A specimen voucher was deposited at the Department of Pharmacology, Nizam Institute of Pharmacy, India.

Preparation of ethanol extract of *Smilax zeylanica*

The dried roots were coarsely powdered and weighed quantity of powder was subjected to continuous hot percolation in soxh let apparatus with ethanol at 65-70^{0}C. The extract was evaporated under reduced pressure using Rota flash evaporator until all the solvent had been removed. The yield of the extract was 10% w/w. when compared to the dried starting material. The extract obtained was suspended in 0.9% saline for oral administration.

Chemicals and reagents

Imipramine hydrochloride10mg/kg (Sun Pharmaceutical Industries Ltd., Mumbai, India) and the monoamine standards: norepinephrine (NE), dopamine (DA), 5-hydroxytryptamine (5-HT), 3, 4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindole-3-acetic acid (5-HIAA) were purchased from Sigma-Aldrich (Steinheim, Germany). Ethylenediamine tetraacetic acid (EDTA), Sodium dihydrogenphosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), Sodium 1-octane sulfonate, Methanol and ethanol were purchased from Hychem Laboratories Ltd. (Hyderabad., India). All other chemicals were of reagent grade or better.

Behavior despair study

For FST and TST, animals were divided into five groups (n = 6 /group): control (0.9% saline), Imipramine 10 mg/kg and three doses of *Smilax zeylanica* (125, 250, 500 mg/kg) for two weeks treatment.

Forced swimming test (FST)

The method was carried out on mice according to the method of Porsolt et al.(1977). Mice were placed in an open cylindrical container (diameter 10 cm, height 25 cm), containing 15 cm of water at 25±1◦C. The duration of observed immobility was recorded during the last 4min of the 6-minute testing period(Zomkowski et al. 2004, Zomkowski et al. 2005). Mice are forced to swim in a restricted space from which they cannot escape and are induced to a characteristic behavior of immobility. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. Decrease in the duration of immobility during the FST was taken as a measure of antidepressant activity.

Tail suspension test (TST)

The total duration of immobility induced by tail suspension was measured according to the method of Steru et al. 1985. Mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. The time during which mice remained immobile was quantified during a test period of 6 min. Mice were considered immobile only when they hung passively and completely motionless.

Determination of Monoamines and Their Metabolites Levels in the Mice Frontal Cortex, Striatum, Hippocampus, and Hypothalamus.

Animals were divided into six groups (n = 6/group): control (0.9% saline), control versus FST, the three experiment groups (125, 250, 500g/kg, for two weeks' administration) and IMI (10mg/kg for two weeks' administration). Monoamines were measured according to the method of Renard et al. 2003. Briefly, mice were killed by cervical dislocation without anesthesia just after the FST. The brain was removed after a rapid dissection of frontal cortex; striatum, hippocampus, and hypothalamus were isolated. The four brain tissues were weighed and placed separately in 5mL of ice-cold homogenizing solution (8.8mg of ascorbic acid and 122mg of EDTA in 1000mL of perchloric acid 0.1M). After homogenization, the solution was centrifuged at 10,000×g for 10min at 4◦C. Twenty microliters of the resultant supernatant was injected in the high-performance liquid chromatography (HPLC) system. The levels of monoamines (NE, DA and 5-HT) and their metabolites (DOPAC, 5-HIAA) were measured by HPLC (Waters 610) with electrochemical detection in the three brain tissues. The mobile phase [4.2g/L] citric acid monohydrate, 6.8g/L sodium acetate trihydrate, 0.8g/L octanesulfonic acid sodium salt, 0.05g/L tetrasodium ethylenediamine tetraacetate, 0.02% (v/v) dibutyl amine and 7% (v/v) methyl alcohol) was delivered at1.0mL/min. The reverse-phase column used was a Merk Lichrospher 100RP-18 endcapped column with a length of 12.5cm and an internal diameter of 4.0mm (E. Merk 50734). The compounds were measured at +0.75V using a Bio analytical Systems LC-4C electrochemical detector.

Measurements of monoamine oxidase (MAO) activity
Animals were divided into five groups (n = 6/group): control (0.9% saline), and three doses of *Smilax zeylanica* (125, 250, 500 mg/kg, for two weeks' administration). The mice were killed after the FST which was performed 1 hr. after the last administration.

Mouse brain fraction was prepared following the procedure described previously(Schurr et al. 1976). Briefly, the fraction suspended in 10 volume of cold sodium phosphate buffer (10 mM, pH 7.4, containing 320 mM sucrose), was mingled at 48°C for 20 min. The mixture was centrifuged at 15,000 g for 30 min at 8°C and the pellets were re-suspended in the same buffer. The protein concentration was adjusted to 1 mg/ml. Protein concentration was measured by the Lowry method et al. (1951**)** using bovine serum albumin as the standard. The MAO activity was assessed spectrophotometrically as described previously (Yu et al. 2002). The assay mixtures contained 4 mM 5-HT as specific substrates for MAO-A, 250 ml solution of the fraction, and 100 mM sodium phosphate buffer (pH 7.4) up to a final volume of 1 ml. The reaction was allowed to proceed at 37°C for 20 min and stopped by adding 1 M HCl(200 ml), the reaction product was extracted with 5 ml of butyl acetate (for MAO-A assay). The organic phase was measured at wavelength of 280 nm for MAO-A assay with spectrophotometer, respectively. Blank samples were prepared by adding 1 M HCl (200 ml) prior to reaction, and worked up subsequently in the same manner.

Statistical Analysis.
All results are expressed as mean± SEM. Data were analyzed by one-way ANOVA followed by Bonferroni,s multiple range test. The criterion for statistical significance was $P<0.05$. All statistical analyses were carried out by using SPSS for Windows (SPSS Inc.).

RESULTS
Effect of Repeated Treatment with *Smilax zeylanica* on the Immobility Time Both in the FST and TST.
In order to investigate whether *Smilax zeylanica* can produce chronic changes in depression related behavior in FST and TST, we treated mice with different dosages to mice via continuous oral administration for 14 days. *Smilax zeylanica* decreased significantly the immobility time in FST (dose range: 125mg–500g/kg, p.o.; Table 1) and *Smilax zeylanica* also caused a reduction in the immobility time in TST (dose range: 125mg–500g/kg, p.o.; Table 2).

Determination of Monoamines and Their Metabolites Levels in the mice Frontal Cortex, Striatum, Hippocampus, and Hypothalamus.
The concentrations of NE, DA, 5-HT, and its metabolites in the frontal cortex, striatum, hippocampus and hypothalamus are presented in Tables 3, 4, 5 and 4. *Smilax zeylanica* (125mg/kg, p.o.) increased the level of NE in hypothalamus, and the level of DOPAC in striatum. *Smilax zeylanica* (250mg/kg, p.o.) increased the level of 5-HT in cortex and striatum, the level of 5-HIAA in striatum, hippocampus, and hypothalamus, and the level of NE in cortex, hippocampus, and the level of DOPAC in striatum. Smilax zeylanica (500mg/kg, p.o.) increased the levels of 5-HT and 5-HIAA in cortex, striatum, hippocampus, and hypothalamus, the levels of NE in cortex and hippocampus, the level of NE in striatum, and level of DOPAC in striatum.

Measurement of Monoamine Oxidase Activity
Table 7 summarizes the effect of Smilax zeylanica on the activities of type A monoamine oxidase in mouse brain. Smilax zeylanica (250, 500 mg/kg,) inhibited the activity of type A monoamine oxidase in the mouse brain.

Table: 1 Effect of EESZ on immobility period of rat using forced swim test

Group	Treatment	Dose	Immobility Duration (sec)
1.	Vehicle control	10ml/kg	182.4 ± 16.46
2.	Imipramine	10mg/kg , p.o	65.32 ± 5.892***
3.	EESZ	125mg/kg, p.o	121.2 ± 4.684**
5.	EESZ	250mg/kg, p.o	97.9 ± 6.324***
6.	EESZ	500mg/kg, p.o	85.8 ± 5.463***

The values are mean ± SEM for each group (n = 6). **P<0.01, ***P<0.001 as compared with control group (one-way ANOVA followed by Bonferroni's multiple range test).

Table: 2 Effect of EESZ on immobility period (sec) of mice using tail suspension test

Group	Treatment	Dose	Immobility Duration (sec)
1.	Vehicle control	10ml/kg	160.7 ± 20.88
2.	Imipramine	10mg/kg , p.o	55.83 ± 6.327***
3.	EESZ	125mg/kg, p.o	118.7 ± 4.944**
4.	EESZ	250mg/kg, p.o	98.4 ± 6.009***
5.	EESZ	500mg/kg, p.o	89.2 ± 5.862***

The values are mean ± SEM for each group (n = 6). **P<0.01, ***P<0.001 as compared with control group (one-way ANOVA followed by Bonferroni's multiple range test).

Table: 3 Effect of EESZ on the concentration (ng/g tissue) of monoamines and their metabolites in the cortex of mice brain

GROUPS	NE	DA	DOPAC	5-HT	5-HIAA
Normal	465.96±23.71	685.36±33.4	598.26±53.78	430.75±26.89	352.32±10.22
Control vs FST	156.49±17.15###	550.01±27.13	480.69±49.32	210.67±25.11##	134.76±31.54###
Imipramine10mg/kg	490.92±28.9***	650.97±56.63	400.47±49.71	685.42±63.27***	322.13±18.26**
EESZ 125mg/kg	150.39±10.11	710.17±55.66	375.71±26.67	335.30±8.91	160.40±31.30
EESZ 250mg/kg	300.78±26.93*	640.69±29.25	423.10±16.43	480.49±19.78***	145.02±46.22
EESZ 500mg/kg	350.69±20.16**	575.98±67.15	557.92±88.01	619.27±49.86***	301.63±23.23**

Value were the mean± SEM (n = 6). #P<0.05 as compared with the normal group. *P<0.05, **P<0.01, ***P<0.001 as compared with the control group (one-way ANOVA following by Bonferroni's test).

Table 4: Effect of EESZ on the concentration (ng/g tissue) of monoamines and their metabolites in the striatum of mice brain

GROUPS	NE	DA	DOPAC	5-HT	5-HIAA
Normal	422.22±74.25	985.35±74.58	1198.23±160.42	328.60±65.88	236.45±21.90
Control vs FST	348.74±33.07	651.62±69.78	915.96±198.73	95.09±44.16#	145.02±50.36
Imipramine10mg/kg	680.74±83.8**	958.93±58.4	1050.17±160.68	400.01±60.75*	360.37±87.32
EESZ 125mg/kg	446.40±33.77	785.30±92.92	1820.85±272.97*	218.71±29.87	274.62±36.12
EESZ 250mg/kg	460.62±24.12	735.40±61.14	1833.61±189.68*	336.64±73.28*	515.37±43.27***
EESZ 500mg/kg	780.02±67.30***	750.81±86.79	1795.19±182.61*	390.20±94.71*	730.38±34.33***

Value were the mean± SEM (n = 6). #P<0.05 as compared with the normal group. *P<0.05, **P<0.01, ***P<0.001 as compared with the control group (one-way ANOVA following by Bonferroni's test).

Table 5: Effect of EESZ on the concentration (ng/g tissue) of monoamines and their metabolites in the hippocampus of mice brain

GROUPS	NE	DA	DOPAC	5-HT	5-HIAA
Normal	561.57±25.89	723.98±27.06	619.43±49.15	618.07±31.74	598.67±78.51
Control vs FST	185.67±24.01#	265.21±34.86##	248.46±26.14	117.72±25.71###	186.77±15.70##
Imipramine 10mg/kg	785.76±96.22***	650.56±63.63	450.35±94.67	875.71±35.47***	989.46±75.43***
EESZ 125mg/kg	411.38±52.01	455.43±63.16	370.87±107.15	198.48±73.29	374.73±91.78
EESZ 250mg/kg	490.95±52.67**	550.59±72.49	452.42±67.79	210.74±55.82	540.97±44.55*
EESZ 500mg/kg	724.21±71.69***	632.29±84.59	546.09±42.28	386.89±10.25**	685.73±42.55**

Value were the mean ±SEM (n=6). #P<0.05, ##P<0.01, ###P<0.001 as compared with the normal group. *P<0.05,**P<0.01,***P<0.001 as compared with the control group (one-way ANOVA following by Bonferroni's test).

Table: 6: Effect of EESZ on the concentration (ng/g tissue) of monoamines and their metabolites in the hypothalamus of mice brain

GROUPS	NE	DA	DOPAC	5-HT	5-HIAA
Normal	156.87±18.84	683.24±39.45	622.91±31.21	86.70±1.59	590.04±52.00
Control vs FST	78.12±10.34#	381.95±24.42##	339.99±20.43	35.61±4.24###	230.69±51.46##
Imipramine 10mg/kg	486.34±17.78**	480.00±49.59	488.45±12.95	78.86±5.06***	750.53±78.00***
EESZ 125mg/kg	95.59±20.24	340.62±49.34	354.75±46.98	39.00±6.16	592.67±65.72**
EESZ 250mg/kg	150.51±11.41	430.61±23.02	572.04±42.35	48.99±3.46	623.35±65.61**
EESZ 500mg/kg	138.62±13.21	460.88±51.01	585.68±26.87	80.84±11.23***	867.39±75.70***

Value were the means±SEM (n=6). #P<0.05, ##P<0.01, ###P<0.001 as compared with the Normal group. **P<0.01, ***P<0.001 as compared with the control group (one-way ANOVA following by Bonferroni's test).

Table: 7 Efects of EESZ on MAO-A activity in in different regions of the mouse brain.

Group	MAO-A activity (U·h-1·mg-1)			
	Cortex	Striatum	Hippocampus	Hypothalamus
Control	13.3±1.1	24.8±3.0	35.6±1.0	43.0±1.9
EESZ 125mg/kg	12.4± 0.7	24.2 ± 1.2	32.4±1.8	39.2±1.6
EESZ 250mg/kg	10.1 ±0.8**	24.4 ±0.6	29.6±1.2	37.6±1.7
EESZ 500mg/kg	8.9±0.3**	22.6±0.6	23.5±0.9*	38.2±4.3

Value were the mean± SEM (n = 6). * p < 0.05,**P<0.01 as compared with the control group (one-way ANOVA following by Bonferroni's test).

DISCUSSION

The forced swimming and tail suspension tests are behavioral despair tests useful for probing the pathological mechanism of depression and for the evaluation of antidepressant drugs (Porsolt et al 1978). FST and TST were widely used to screen the chemicals for their antidepressant activity. All the major class of antidepressants including TCAs, SSRIs, MAO inhibitors and atypical antidepressants were evaluated by using these models (Zomkowski et al.2004). Characteristic behavior scored in both tests is termed immobility, reflecting behavioral despair as seen in human depression (Steru et al.1985).

In this model, when rodents are forced to swim in a confined space, they tend to become immobile after vigorous activity (struggling). This inescapable stressful situation leads to depression (Porsolt et al. 1978).

In the present study we investigate whether *Smilax zeylanica* can produce chronic changes in depression-related behavior in FST and TST, we treated mice for two-weeks with different dosages via daily oral administration. *Smilax zeylanica* caused a reduction in the immobility time in FST and TST (Table 1). The results presented here show, to our knowledge, that *Smilax zeylanica* given orally is effective in producing significant antidepressant-like activity, when assessed in the FST and TST.

Neurochemical research has revealed that the monoamines (5-HT, NA and dopamine) have a crucial role in the development of the depression syndrome (Naughton et al.2000).

Antidepressant activity of selective monoamine reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors is by potentiating monoaminergic neurotransmission (Tripati, 2013). It has been previously suggested by RÈnÈric and Lucki that an increase in both swimming and climbing behaviors in the FST occurs when the animal is treated by a drug which increases serotonin, norepinephrine and dopamine levels in the nerve terminals. An increase in all the three neurotransmitters could be by inhibition of monoamine oxidase (MAO) activity in the brain (Reneric et al.1998).

Intensive research into the neurobiology of depression suggests that an increase in the monoamine levels at the synapse is believed to be the first step in a complex cascade of events that results in antidepressant activity (Xu et al. 2010).

There is abundant evidence from anatomical, electrophysiological and pharmacological studies that the interactions between neurotransmitter systems are important (Borsini et al.1998). Four brain regions were studied: the frontal cortex, the striatum, the hippocampus, and the hypothalamus, which are involved in important behavioral functions, such as emotion, motivation and learning and memory (Xu et al.2010, Shiflett et al.2011). Abnormal monoamine levels in the four brain regions may be relevant to the depressed state. Our results show that *Smilax zeylanica* increased the levels of 5-HT and 5-HIAA in cortex, striatum, hippocampus, and hypothalamus, the levels of NE in cortex and hippocampus, the level of NE in striatum, and the level of DOPAC in striatum. These results indicated that the effect of *Smilax zeylanica* on depression may be mediated via the increase in monoamines levels in the hippocampus, cortex, striatum, and hypothalamus of mice. we inferred that the anti-depression mechanism of *Smilax zeylanica* might be partly due to its influence on the function of 5HT, NE systems through the regulation

of serotonergic and adrenergic receptors and/or the metabolism of 5-HTand NE.

MAO is an important enzyme in the metabolism of a wide range of monoamine neurotransmitters, including NE, DA, and 5-HT. MAO-A inhibitors are efficacious for treating depression while the inhibitors of MAO-B appear to be effective in preventing and treating Parkinson's disease. Furthermore, a positive correlation between oxidative stress and depression is reported in some studies (Herken et al.2007). *Smilax zeylanica* (250, 500 mg/kg) decreased the activity of MAO-A in the frontal cortex and hippocampus of mouse brain.

Phytochemical analysis showed the presence of Flavonoids and phenolic compounds have been reported to have multiple biological effects such as Central nervous system disorders, antioxidant activity, and neurodegenerative diseases (Priyanka et al.2012, Bors et al.1987, Amresh et al.2007). It has been reported that flavonoids isolated from plant species such as Hypericum perforatum showed antidepressant activity (Butt et al.2000). Thus, it is likely that flavonoids present in Smilax zeylanica **(**Rasheed et al. 2012**)** may be responsible for the observed antidepressant effect.

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