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Original Research Article

The protective effect of *L. siceraria* against depression using behavioural despair animal models

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ABSTRACT

Background: In recent years, the search for novel pharmacotherapy from medicinal plants for psychiatric illness was significantly progressed. The present study was performed to evaluate the antidepressant activity of ethanolic extract of *Lagenaria siceraria* in animal models.
Methods: The antidepressant activity of ethanolic extract of the fruit of *L. siceraria* in rats was assessed using forced swim test and tail suspension test. Imipramine at 15 mg/kg was used as standard antidepressant drug.
Results: The ethanolic extract of *L. siceraria* fruit (EELS) was significantly and dose-dependently reduced the duration of immobility after repeated treatment for 7 days in Forced swim test and Tail suspension Test. But combination of *L. siceraria* (200mg/kg) with Imipramine gave a highly significant result ($p<0.001$) in reduction of immobility duration and the effect of high dose (400mg/kg) with imipramine (15mg/kg) did not decrease the duration of immobility period in both animal models at end of the study. In this work the dose of 400mg/kg afforded more protection than the imipramine.
Conclusions: The results obtained from this study was indicate that the antidepressant activity of *L. siseraria*.

Keywords: Antidepressant activity, Behavioural despair, Forced swim test, Imipramine, *Lagenaria siceraria*, Tail suspension test

INTRODUCTION

Depression can be defined as a high common disorder with increasing lifetime rates.[1] World health organization reported that about 450 million people suffer from behavioral disorder and this percentage represent 12.3% of the global load of disease and prophesied to rise up to 15% by 2020.[2,3] Mental depression is a chronic illness that affects a person's mood, thoughts, physical health and behaviour. 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.[4] Patients with major depression have symptoms that reflect changes in brain monoamine neurotransmitters, specifically norepinephrine, serotonin and dopamine.[5] However, most of the anti depressant drugs exhibit serious side effects. Hence, there is a need for drugs that are equally efficacious but have lesser side effects. Several herbal medicines (e.g. St. John's wort) have shown promising results in treating clinical depression and appear to be quite safe.[6] Commonly used fruit and vegetables are labelled as 'super foods' because they contain high concentrations of some phytonutrients, particularly antioxidants, which appear to be beneficial to health.

Lagenaria siceraria (LS) has been used since ancient times in Indian folklore medicine for its many medicinal properties.[7] *Lagenaria siceraria* (Family: Cucurbitaceae) is commonly known as Bottle gourd (English) and lauki (Hindi), is reported to possess several medicinal properties such as, anti-oxidant activity, anti-hyperlipidemic activity, cardio protective activity, analgesic activity, anti-inflammatory activity and immunomodulatory activity. Lauki contains several pharmacologically active photochemical such as amino acids, vitamins, Fucosterol, campesterol and flavone-C glycosides.[8] Furthermore, bottle gourd contains high number of neurotransmitters such as serotonin, dopamine, adrenaline and noradrenaline.[9] Further, there is paucity of information regarding antidepressant activity of *L. siceraria*. Hence, the present study was designed to investigate the antidepressant activity of *L. siceraria* using behavioural despair animal models.

METHODS

Plant materials and extraction

Lagenaria siceraria fruits were obtained from a local vegetable market in Udaipur and scientifically authenticated by Botanist. Voucher specimens were deposited for future reference. The preparation of the extract of the fruit of *Lagenaria siceraria* was done in the Department of Pharmacology, Geetanjali Medical College, Udaipur using Soxhlet apparatus with 70% ethanol at 60°C for 24 hrs.

Preliminary Phytochemical screening

The EELS was subjected to phytochemical screening (Farnsworth, 1996) for the detection of major chemical constituents.[10]

Experimental animals

Adult healthy Albino rats of Wistar strain of either sex weighing between 180-250gm were used for the study. All the animals were procured from Animal House of Geetanjali Medical College, Udaipur. The animals were given free accesses to food and water. The protocol was approved by the IAEC, GMCH, Udaipur.

Acute toxicity study

An acute toxicity of test compound was carried out on normal healthy rats by fixed dose (OECD-420 Guidelines) method.

Experimental design

Forced swimming test (FST)[11]

Healthy adult albino rats of Wistar strain weighing 180-250gm were used for forced swim endurance stress. Animals were weighed, and appropriate dose of drug was administered per orally to different groups for 7 days. The experiment was conducted 1 hour after administrating the drug. A total of 48 animals were used. They were divided into 8 groups of 6 animals each (n=6).

- Group 1: Received 5ml/kg of normal saline orally (Control)
- Group 2: Received 15mg/kg imipramine orally
- Group 3: Received 100mg/kg EELS orally
- Group 4: Received 200mg/kg EELS orally
- Group 5: Received 400mg/kg EELS orally
- Group 6: Received 100mg/kg EELS + Imipramine (15mg/kg) orally
- Group 7: Received 200mg/kg EELS + Imipramine (15mg/kg) orally
- Group 8: Received 400mg/kg EELS + Imipramine (15mg/kg) orally

The rats were subjected to swimming stress for 7 days. On 8th day the rats were allowed to swim till complete exhaustion and the endpoint was taken when the animal started drowning. The mean swimming time for each group was calculated.

Tail suspension test (TST)[12]

Total of 48 rats were taken and divided into eight groups of 6 in each. The study of test compound and standard drugs were dissolved in normal saline and administered orally for 7 days with the help of gastric oral tube.

- Group 1: Received 5ml/kg of normal saline orally (Control)
- Group 2: Received 15mg/kg imipramine orally
- Group 3: Received 100mg/kg EELS orally
- Group 4: Received 200mg/kg EELS orally
- Group 5: Received 400mg/kg EELS orally
- Group 6: Received 100mg/kg EELS + Imipramine (15mg/kg) orally
- Group 7: Received 200mg/kg EELS + Imipramine (15mg/kg) orally

- Group 8: Received 400mg/kg EELS + Imipramine (15 mg/kg) orally

After an hour of the drug administration, TST was carried out as explained below and duration of immobility (in seconds) was recorded.

Statistical analysis

The results were expressed as Mean±SD. The intergroup variation was measured by using One-way analysis of variance (ANOVA) followed by Bonferroni t-test.

RESULTS

Effect of L. siceraria on behavioural despair animal models

Effect of L. siceraria on Forced swim test

In the present study, all the animals of different groups were treated for 7 days. The changes in immobility duration were studied after administrating drugs in separate groups of animals. The immobility parameter was recorded after 24 hours of preliminary rat forced swim test.

Table 1: Comparative effect of EELS and combination therapy on duration of immobility period of rats subjected to Forced Swimming Test (FST).

Gr. No.	Group	Duration of immobility period (Sec.)	
		0' Day	7th day
1	Control (FST)	172.33±6.59	194.16±5.49
2	Imipramine (15 mg/kg)	165.50±5.12	84.00±3.60***
3	EELS (100mg/kg)	170.16±10.22	106.66±4.76**
4	EELS (200mg/kg)	158.16±7.72	91.16±3.80***
5	EELS (400mg/kg)	160.33±10.86	81.66±4.97***
6	Imipramine + EELS (100mg/kg)	155.16±8.19	92.50±2.56***
7	Imipramine + EELS (200mg/kg)	152.16±6.99	72.33±6.02***
8	Imipramine + EELS (400mg/kg)	168.16±7.61	191.66±10.06

Values are expressed as Mean±SEM, (n=6). One-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons test as post hoc test. * P<0.05, **P<0.01, ***P<0.001 when compared with control group

In EELS (100, 200 and 400mg/kg) and imipramine treated animals, there was significant (P <0.05) decrease in duration of immobility compared to vehicle treated group. The effect was dose dependent.

The effect of high dose (400mg/kg) was statistically (P<0.001) shown superior effect to imipramine (15mg/kg) treated animals and effect of high dose (400mg/kg) with imipramine (15mg/kg) did not decrease the duration of immobility at end of the study period. Hence, in other words the effect of 400mg/kg can be considered good antidepressant dose of formulation. The results were depicted in Table 1.

Effect of L. siceraria on Tail suspension test

The immobility time in the TST using rats were markedly shortened after treatment with EELS (100, 200 and 400mg/kg) and imipramine (15 mg/kg), there was significant (P <0.05) reduction in immobility time compared to vehicle treated group. Whereas treatment to animals with EELS (100 and 200mg/kg), with imipramine (15mg/kg) were also significantly (P <0.01) decrease the immobility time. The observations are shown in Table 2.

Table 2: Comparative effect of EELS and combination therapy on duration of immobility period of rats subjected to Tail suspension test (TST).

Gr. No.	Group	Duration of immobility period (Sec.)	
		0' Day	7th day
1	Control (TST)	131.7±5.59	148.2±5.98
2	Imipramine (15mg/kg)	120.5±4.93	76.67±5.57***
3	EELS (100mg/kg)	130.2±4.94	96.67±4.83**
4	EELS (200mg/kg)	117.2±4.65	81±4.16***
5	EELS (400mg/kg)	128.8±4.21	73.17±2.91***
6	Imipramine + EELS (100mg/kg)	121.3±3.34	82.17±2.82**
7	Imipramine + EELS (200mg/kg)	113.3±2.95	68.17±1.51***
8	Imipramine + EELS (400mg/kg)	125.3±3.07	136.2±1.93

Values are expressed as Mean±SEM, (n=6). One way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons test as post hoc test. * P<0.05, **P<0.01, ***P<0.001 when compared with control group

However, the effect of high dose (400mg/kg) was superior to imipramine (15mg/kg) treated animals and combination with imipramine (15mg/kg) did not shown significant decrease in the immobility time at end of the study period.

Preliminary phytochemical study is revealed that EELS showed the presence of flavonoids, saponins, steroids and polyphenolic compounds.

DISCUSSION

Depression is a common, debilitating, life-threatening illness with a high incidence associated with lot of morbidity. Hence, it is very important to address this problem and find effective remedies. Even though several drugs are available, they associated with side effects including tricyclics, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants.

Therefore, there is an urgent need for alternative medications for the control of depression-related disorders. The present work was subjected to investigation for the evaluation of the anti-depressant activity of ethanolic extract of the fruit of *L. siceraria* in behavioural despair animal models.

On the basis of the clinical association of depressive episodes and stressful life events, many of the animal models for the evaluation of antidepressant drug activity assess stress-precipitated behaviours.

In the present study forced swimming test (FST) and tail suspension test (TST) were carried out which are widely used, accepted and simple models for screening the antidepressant activity. The immobility is noted as a measure of antidepressant action also swimming behaviour corresponds to the behavioural despair as seen in human depression.[13] It was reported that the major depressive disorder involves disturbances of life style, emotional changes, autonomic and endocrine functions affecting about 20% of population.[14]

In phytochemical study authors observed the presence of flavonoids (flavonol glycosides) in *L. siceraria* fruit extract. Recently several studies have suggested the antidepressant effect of flavonol glycosides.[15] Therefore one of the antidepressant mechanisms of *L. siceraria* fruits extract is thought to involve flavonoids, which exerts an antidepressant effect.

The effect of 100, 200 and 400mg/kg (EELS) was statistically significant when compared to vehicle treated animals. Effect of 400 mg/kg (EELS) was nearly equal to 15 mg/kg imipramine and 100mg/kg (EELS) shown minimum effect compared to imipramine (15mg/kg). This indicates that the effect of high dose was better than low dose of EELS test formulations in animal models.

While EELS treated animals, effect at dosage 400mg/kg with imipramine (combination therapy) was insignificant when compared with vehicle treated group. This indicates that EELS at high dose (400mg/kg) along with imipramine (combined) formulations did not reduce duration of immobility in rats of both models. Hence, this test formulation may not have antidepressant effect and probably showing window effect. In both models such as FST and TST, at dosage 200mg/kg along with imipramine has shown superior effect to the reference standard imipramine alone.

In mouse tail suspension test it has been argued that the TST is less stressful than FST and has greater pharmacological sensitivity.[16] In this study, rats are suspended by their tail for defined period of time (usually 6min.) and duration of their immobility is assessed. Typically, animal's immediately engaged in escape oriented behaviour followed by progressive increasing period of immobility. We observed that following acute administration of test formulations demonstrated significant (compare to vehicle treated animals) a dose dependent reduction in duration of immobility, furthermore the effect of *L. siceraria* extract in TST was similar to the effect produced by the oral administration of imipramine.

Imipramine exhibited the characteristic behavioral effects by noradrenaline and serotonin reuptake inhibition in the modified forced swim test, i.e. a decrease in immobility coupled with an increase in swimming behaviour. Since antidepressant effects have been observed in several flavonoids from Hypericum perforatum, it is possible that these polyphenolic substances might be responsible, at least in part, for the antidepressant activity in study. Thus, the flavonoids may be responsible for the said antidepressant activity of *Lagenaria siceraria*.[13,17]

Remarkably, these models detect the anti-immobility effects of wide array of antidepressants, including tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI) and even atypical antidepressants. Thus, the activity of ethanolic extract of the fruit of *Lagenaria siceraria* could involve one of mechanism of established agents as described above and further scientific research should be under taken towards this dimension.

CONCLUSION

The obtained results revealed that *L. siceraria* extract has got significant antidepressant activity. Therefore, *L. siceraria* may be served as a potential resource for natural psychotherapeutic agent against depression. However, further studies are needed to characterize the mechanism of the antidepressant effect of *L. siceraria* and extend these results before the safe application in humans.

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