E-ISSN:2454-9894 P-ISSN: 2454-9886
International Archives of
BioMedical and Clinical Research
(An Official Publication of "Ibn Sina Academy of Medieval Medicine & Sciences")
WWW.IABCR.ORG

Original Article

A Comparative Study of Antidepressant Activity of Aqueous Extract of *Berberis Aristata* with Fluoxetine in Albino Rats

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ABSTRACT

Introduction: *Depression belongs to the heterogeneous group of mental disorders characterized by extreme exaggerations and disturbance of mood, which adversely affect cognition and psychomotor functions. It results from abnormal brain mechanisms functionally deficient monoaminergic (noradrenaline and/or 5-hydroxytryptamine) transmission in the central nervous system.*

Aims and Objectives: *To evaluate comparatively the Anti- depressant activity of Berberis aristata (Daru haridra) in albino rats after inducing experimental depression using different methods.*

Materials and methods*: The antidepressant activity of aqueous extract of berberis aristata was screened by tail suspension method and the forced swimming test and compared with the control and standard drug (fluoxetine) for two weeks. Group1- were kept as control. Group 2- were treated with fluoxetine in a dose of 14mg/kg/day as standard drug for one week. Group 3, 4 and 5- were given aqueous extract of berberis aristata intraperitoneally in three graded doses 400,800 and 1600mg/kg/day respectively for two weeks.*

Results: *berberis aristata exhibits antidepressant activity depicted by reduction in the immobility time when compared to the control group. The onset of action was after few days according to the dose of the test drugs following their administration. The effect is comparable with that of standard drug fluoxetine which may be attributed to the phytoconstituents like berberine, berbamine and palmitine, among them most probably with berberine alkaloid. The berberine alkaloid is known to inhibit the monoamine oxidase enzyme particularly monoamine oxidase- A isoform. berberine influenced either dopaminergic system by monoamine oxidase-B inhibiting property or by blocking the reuptake of dopamine by inhibiting its transporter.*

Conclusion*: Berberis aristata has significant antidepressant activity demonstrated by tail suspension and forced swimming test compared to the test drug.*

Key words: *Berberis aristata; Antidepressant activity; Immobility; Monoamine oxidase.*

INTRODUCTION

Mood disturbance is characterized by a disturbance in the regulation of mood, behaviour and affect. Mood disorder is subdivided into Depressive disorders, Bipolar disorders and and substance abuse [1]. Depression belongs to the heterogeneous group of mental disorders characterized by extreme exaggerations and disturbance of mood, which adversely affect cognition and psychomotor functions. It results from abnormal brain mechanisms functionally deficient monoaminergic (noradrenaline and/or 5-hydroxytryptamine) transmission in the central nervous system.[2]

Approximately 15% of the population experiences a major depressive episode at some point in life. Depression in general remains associated with high disability and societal cost; in the Global Burden of disease study conducted by the World Health Organization, unipolar major depression is ranked fourth in percentage of disability-adjusted life years and was projected to rank second in the year 2020.[3]

Numerous treatment modalities are used currently to combat the mood disorders. At present, there are several types of antidepressants used in clinical practice, including tricyclic antidepressants (TCAs), selective serotonin

Access this article online	
Website: www.iabcr.org	Quick Response code
DOI: 10.21276/iabcr.2016.2.3.28	

Received:02.09.16| **Revised**:05.09.16| **Accepted**:07.09.16

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reuptake inhibitors (SSRIs), selective reversible inhibitors of monoamine oxidase A (RIMAs), and specific serotonin–norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants. Inspite of the introduction of these drugs depression continues to be a major problem, therefore, considerable efforts are being invested in the discovery of better drugs for the treatment of depression.[4]

There are numerous traditional medicinal plants which possess antidepressant activity.[5,6,7] Berberis aristata is commonly used indigineous plant which possess antidepressant activity.[8,9] So the present study has been designed to compare the antidepressant activity of aqueous extract of berberis aristata with the standard drug fluoxetine in experimental animals (albino rats) by various methods.

MATERIALS AND METHODS

The present study was conducted on adult albino rats weighing 150-200 gm after taking approval from the Institutional Animal Ethical Committee (IAEC) according to the guidelines for the purpose of control and supervision of experiments on animals (CPCSEA) in Muzaffarnagar Medical College and hospital. The animals were housed individually in standard polypropylene cages and kept under controlled room temperature (24± 2˚C) in a 12 h light and dark cycle, given standard laboratory diet and water ad libitum and acclimatized to the laboratory conditions at least one day prior to the behavioral experiments. All the experiments were carried out between 12:00 to 16:00 h. The food was withdrawn 12 h before the experiments. Each animal was used only once. The animal handling was performed according to the Good Laboratory Practice (GLP) guidelines. The animals were equally divided into 5 groups (6 animals in each group).

Group1- were kept as control.

Group 2- were treated with fluoxetine in a dose of 14mg/kg/day as standard drug for one week.

Group 3, 4 and 5- were given aqueous extract of berberis aristata intraperitoneally 400, 800 and 1600mg/kg/day respectively for two weeks.

The antidepressant like activity of berberis aristata and fluoxetine was evaluated by forced swimming test (FST)[10] and tail suspension test (TST)(11).

The results were statistically analyzed using unpaired Student's t test and presented as mean ± SEM. P values were calculated referring to appropriate tables.

Preparation of extracts

Dried stem powder of berberis aristata was obtained from Bhartiya ayurvedic pharmacy, Delhi. 100g powder of Berberis Aristata was boiled separately with 2 litre of water for decoction till ¼ th of the original solution and then this final solution was preserved in refrigerator. A fresh solution will be prepared from time to time according to the requirement.

Effects of the aqueous extract Of berberis aristata and fluoxetine solution on the duration of immobility in the rat tail suspension test were shown in Table 1.

RESULTS

Table 1: Effects of the aqueous extract of berberis aristata and fluoxetine on the duration of immobility in the rat tail suspension test (mean ± S.E.M.) (n=6)

Drugs	Dose	Immobility time in seconds(mean ± SEM)		
		Days 1	Days 7	Days14
Control (normal saline)	1ml/200g	*45.3±0.29*	43.34±0.80	44.10±0.53
Standard drug(fluoxetine)	14mg/200g	41.22±0.56***###	25.40±0.22***###	11.30±0.26***###
Berberis Aristata	400 mg/kg	44.30±0.48	39.33±0.37**	34.21±0.21***
	800 mg/kg	43.20±0.60**	35.43±0.48***	25.40±0.37***
	1600 mg/kg	42.12±0.50***	30.65±0.22***	15.43±0.22***

*/# P<0.05(not significant); **/##P<0.01(significant); ***/###P<0.001(highly significant.* - For comparison of berberis aristata with the control group.# - For comparison of berberis aristata with the standard drug

The extract showed no any change after 1 day treatment, and had the tendency to reduce the immobility time after 7-day treatment. After a 14-day treatment, the extracts at the doses of400, 800 and 1600 mg/kg significantly decreased the duration of immobility in a dose-dependent manner. However, the reference antidepressant fluoxetine at the dose of 14 mg/200g resulted in significant reduction. The effects of berberis aristata at the dose of 1600 mg/kg appeared to be equipotent with that of fluoxetine on 14-day treatment in the study.

Table 2: Comparative effects of the aqueous extract of Berberis Aristata with the standard drug (fluoxetine) on the duration of immobility in the rat forced swimming test (mean S.E.M.)(n=6)

Drugs	Dose	Immobility time in seconds(mean ± SEM)		
		Days 1	Days 7	Days14
Control (normal saline)	1ml/200g	42.76± 0.34	39.65± 0.55	40.43± 0.22
Standard drug(fluoxetine)	14mg/200g	41± 0.11	23.45± 0.13###	10.65± 0.11###
Berberis Aristata	400 mg/kg	41.3± 0.31*	36.43± 0.56**	29.4± 0.17***
	800 mg/kg	38.55± 0.31***	36.47± 0.22**	26.4± 0.43***
	1600 mg/kg	42.12± 0.26	30.65± 0.17***	15.43± 0.21***

*/# P<0.05(not significant); **/##P<0.01(significant); ***/###P<0.001(highly significant.* - For comparison of berberis aristata with the control group.# - For comparison of berberis aristata with the standard drug.

Effects of the aqueous extract of berberis aristata and fluoxetine solution on the duration of immobility in the rat forced swimming test were shown in Table-2.

The extract showed no any change after 1 day treatment. The extract at the dose of 800 mg/kg exhibited to show significant immobility reduction after 7-day treatment. Fluoxetine at the dose of 14 mg/kg significantly produced a time-dependent immobility reduction. The effect of berberis aristata at the dose of 400mg/kg appeared to be equipotent with that of fluoxetine after 14-day treatment.

DISCUSSION

The present study demonstrated the antidepressant-like effect of berberine, an alkaloid obtained from berberis aristata, in the forced swim and tail-suspension tests in experimental animals. Berberis aristata has a long history of medicinal usage in both the Ayurveda and Siddha systems of medicine. It has been reported to possess multiple pharmacological effects. Recent reports have elucidated its role in various central nervous system related disorders.[9] In this study, berberis aristata decreased the immobility period in both the forced swim and tail-suspension tests. However, the effect was dose-dependent. The antidepressant effect of the aqueous extract of Berberis aristata has been seen in albino rats which may be attributed to the phytoconstituents like berberine, berbamine and palmitine, among them most probably with berberine alkaloid. Berberine is an isoquinoline alkaloid with a long history of medicinal usage in India and China. It is an acetylcholinesterase inhibitor having enzyme inhibiting property similar to galantamine (Ingkaninan et al., 2006) and can block transient outward potassium current and delayed rectifier potassium current in a concentration-dependent manner in acutely 1998)(isolated CA1 pyramidal neurons of rat hippocampus,[12] thus it improves the memory process. The berberine alkaloid is known to inhibit the monoamine oxidase enzyme particularly monoamine oxidase-A isoform.[13] Monoamine oxidase inhibitors are known to enhance the availability of biogenic amines (norepinephrine, serotonin or dopamine) in the synapse, and are indicated in mental depression.[14] Previous studies has also demonstrated reversal of the reserpine-induced immobility period in mouse forced swim test with berberine probably by inhibiting vesicular uptake of catecholamines. Another study reports that pretreatment with berberine enhanced the anti-immobility effect of subeffective doses of imipramine (dual reuptake inhibitor of norepinephrine and serotonin), tranylcypromine (monoamine oxidase inhibitor), fluoxetine (selective serotonin reuptake inhibitor), venlafaxine (dual reuptake inhibitors of serotonin and norepinephrine)[13]. However, berberine did not affect the anti-immobility effect of mianserine, trazodone, and two atypical antidepressants. The lack of interaction between berberine and trazodone or mianserine signifies that berberine probably doesnot act through serotonin 5HT2 receptors. The fact that there are reports of enhancement of anti-immobility effect of tranylcypromine by berberine that may be due to its monoamine oxidase A enzyme inhibiting property. Besides causing significant increase in the levels of norepinephrine and serotonin, berberine also produced a significant rise in the levels of dopamine following its acute administration. Therefore, it can be said that berberine influenced either dopaminergic system by monoamine oxidase-B inhibiting property or by blocking the reuptake of dopamine by inhibiting its transporter. However, the exact mechanism has to be further explored.[13] Antidepressant activity of berberis aristata may be associated with reduced synthesis of nitric oxide as in previous studies, it has been demonstrated that inhibition of nitric oxide synthesis may underlie the reduction in the immobility period in the forced swim test elicited by berberine. Nitric oxide plays a significant neuromodulatory role in the central nervous system.[13] ya 14? Any pharmacological manipulation of nitric oxide pathway may be considered as a novel therapeutic approach for the management of central nervous system disorders, more so for mental depression.[15,16] Several in vivo studies have shown a modulatory role of nitric oxide in the extracellular levels of serotonin reuptake mechanism in the central nervous system.[17] The nitric oxide synthase inhibitors have been reported to possess antidepressant-like behavioral properties at doses that are without any effect on locomotor activity.[13] The antidepressant effect of aqueous extract of berberis aristata may be due to modulation of sigma receptors as various studies have reported the involvement of sigma receptors in the action of various antidepressants. Sigma receptors, a non-opioid, non-phencyclidine receptor type are subgrouped into two subtypes: sigma1 and sigma2 receptors. Sigma1 receptors are expressed in specific regions of the brain such as layers of the cortex, hippocampus, hypothalamic nuclei, substantia nigra and purkinje cells in the cerebellum[18] and have recently been the target of drug development related to psychiatric disorders including)(schizophrenia and depression)(162). Sigma1 receptors modulate the release of various neurotransmitters[19] like serotonin,[20] dopamine[21] or glutamate (Yagasaki et al., 2006) and known to alleviate the symptoms of depression. Sigma1 agonists have been then tested in various behavioral tests classically used to predict an antidepressant activity. Various sigma1 receptor agonists such as [1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine (SA 4503), (+)-pentazocine, 1, 3-di-o-tolylguanidine (DTG), N-cyclopropylmethyl-N-methyl-1,4-diphenyl-1-ethyl-but-3-en-1-ylamine(JO-1784),and N-allylnormetazocine (SKF-10,047) dose dependently decrease immobility in the forced swim test.[22] These effects were blocked by the sigma1 receptor antagonist NE-100 or BD1047. Further, SA 4503 and (+)-pentazocine (both sigma1 receptor agonists) also decreased immo-bility period in the tail-suspension test, an effect also antagonized by NE-100.[23] As Mendelvo vic et al mentioned that major depression is associated with dysfunction of immunity[24] and there are reports of immunomodulatory effect of berberis aristata in animal models (Bhardawaj et al). So its antidepressant effect may be due to involvement of immune system. Sharma komal et al mentioned that the extract of Berberis aristata has strong potential to decrease oxidative stress and oxidative stress play an important role in the pathogenesis of depression. So its antidepressant effect may be due to its antioxidant property. Therefore, antidepressant effect of aqueous extract of berberis aristata may be due to the possible involvement of brain biogenic amines (norepinephrine, serotonin and dopamine) and/or role of L-arginine-nitric oxide-cyclic guanosine monophosphate and/or sigma receptors pathway and/or by

immunomodulation and/or due to its antioxidant property. In previous studies, it has been seen that pretreatment of berberine with subeffective doses of MAOIs, SSRIs, TCAs and SNRIs like imipramine, tranylcypromine, fluoxetine, venlaxafine, etc enhanced their antidepressant effect.[13] So herbal drugs like berberis aristata may be used as adjuvant drugs to conventional antidepressants to minimize the dose dependent adverse effects of established antidepressant drugs. Our study suggest that berberis aristata have good antidepressant effect which is comparable to standard drug (fluoxetine). Species variations can be present and further studies are required for their efficacy in human beings. However, the exact mechanism of action for the antidepressant effect cannot be ascertained and further studies are required.

CONCLUSION

From the analysis of generated data the aqueous extract of berberis aristata has significant antidepressant activity which was demonstrated by tail suspension test and forced swimming test and are dose dependent and significantly compared to the control group and the standard group.

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How to cite this article: Rehman S, Naim F. A Comparative Study of Antidepressant Activity of Aqueous Extract of Berberis Aistata with Fluoxetine in Albino Rats. Int Arch BioMed Clin Res. 2016;2(3):110-113. DOI: 10.21276/iabcr.2016.2.3.28

Source of Support: Nil, **Conflict of Interest:** None