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Antidepressant activity of rohitukine in rats

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ABSTRACT

Depression is a serious and burden some psychiatric illness associated with high rates of chronicity, relapse and that is characterized generally, by pervasive low mood, anxiety, cognitive impairment, loss of interest or pleasure in normally enjoyable activities and suicidal behaviors.

Although a number of synthetic drugs are being used as the standard treatment for clinically depressed patients, they have adverse effects that can compromise the therapeutic treatment. These common adverse effects include dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety agitation, drowsiness, and cardiac arrhythmias. These conditions create an opportunity for alternative treatment of depression by use of medicinal plants. *Dysoxylum binacteriferum* is found to be highly effective against ovarian and breast cancer. Few previous studies showed that the anticancer activity of this plant is due to the rohitukine present in this plant. Rohitukine was also found to show antiestrogenic effect in adult female rats. Despite so many biological activities reported in this plant. No systematic work on antidepressant activity was done so far. Thus, *D.binecteriferum* was subjected to preliminary antidepressant screening studies. In the present investigation, stem bark of the plant was extracted with 95% ethanol and the ethanol extract and rohitukine was isolated as a major compound. Rohitukine exhibited significant antidepressant activity at a dose of 100 mg/kg body weight in mice with respect to control as well as standard (Imipramine, 60 mg/kg).

KEYWORDS

Dysoxylum binectariferum;
Rohitukine;
Antidepressant activity in rats.

INTRODUCTION

Depression is a serious and burdensome psychiatric illness associated with high rates of chronicity, relapse and that is characterized generally, by pervasive low mood, anxiety, cognitive impairment, loss of interest or pleasure in normally enjoyable activities and suicidal behaviours[1,2]. The high prevalence of suicide in depressed patients (up to 15%) coupled with complications arising from stress and its effect on the cardiovascular system have suggested that it will become the second leading cause of premature death or disability worldwide by the year 2020[3].

Although a number of synthetic drugs are being used as the standard treatment for clinically depressed patients, they have adverse effects that can compromise the therapeutic treatment. These common adverse effects include dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety agitation, drowsiness, and cardiac arrhythmias. These conditions create an op-

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portunity for alternative treatment of depression by use of medicinal plants. Despite a broad range of antidepressants available today, a significant proportion of these patients will not respond to treatment, or will show only partial response[4]. Clinical limitations and adverse effects of currently used antidepressants necessitate continuous development of novel, efficient and safe drugs for treatment of depression. In the present investigation we have selected rohitukine a major compound from *Dysoxylum binacteriferum* for bioassay of antidepressant activity. *Dysoxylum binacteriferum* is found in the Western Ghats of India. Crude extracts of this plant were found to be highly effective against ovarian and breast cancer[5], Few previous studies showed that the anticancer activity of this plant. Since rohitukine[6] was recently established to possess antiestrogenic effect in adult female rats[7]. In the present study we have screened the crude ethanol extract as well as its different fraction and the major compound rohitukine.

MATERIAL AND METHODS

Collection of the plant material

The stem bark of this plant was collected and identified by the Botany Division of the Institute from the Andaman coast of India. The voucher specimen (No. 8091) has been kept in the herbarium of the Institute.

Preparation of extract/ compound

Air-dried powdered plant material (1.0 kg) was extracted with distilled ethanol, concentrated under reduced pressure and fractionated into four fractions. From the chloroform fraction, major compound which is a known alkaloid rohitukine[6]{5,7-dihydroxy-2-methyl-8- [4-(3-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one)} was isolated and characterized by comparison of physicochemical data with those given in literature.

Bioassays

Animals

Albino male Swiss mice (22-25g) obtained from National Animal Laboratory Centre of Central Drug Research Institute, Lucknow were used in the study. The mice were kept at constant temperature (22±2°C) and 12 h light/12 h dark. Mice were fed standard laboratory food (Hind Lever diet pellets) and water was given *ad libitum*. Each animal was used once in the behavior tests. The experimental protocols for this study were approved by the Institutional Ethical Committee following the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) which complies with International norms of Indian National Science Academy (INSA).

Drugs and treatment schedule

Imipramine, IMP (60mg/kg) was used as the standard drug for depression (Sigma, USA). The compound was dissolved in 0.9% physiological saline and freshly prepared. Compound was administered per orally at a rate of 0.1 ml/10 g.

Depression model tail suspension test (TST)

The tail suspension test (TST) was performed according to the method described by Stern *et al*[8]. The mice were individually suspended 60 cm above the surface of table with an adhesive tape placed 1 cm away from the tip of the tail. Immobility duration was recorded for the last 5 minutes during 6 minutes by observers blind to the treatment conditions. Mice were considered immobile only when they hung passively and were completely motionless. Single administration (p.o.) of the rohitukine (25, 50 and 100 mg/kg) and IMP (60mg/kg p.o.) was given one hour prior to test.

Depression model forced swim test

The forced swim test (FST) is the most widely used pharmacological *in vivo* model for assessing antidepressant activity and was performed according to the method of Porsolt *et* al[9]. The apparatus consists of a clear plexi glass cylinder (20cmhigh by 12cm diameter) filled to a 15cm depth with water (24 ± 1°C). Animals were divided into groups of six animals each. One of the groups received only saline treatment. In the pretest session, every animal was placed individually into the cylinder for 15 mins, 24 hrs prior to the 6 mins swimming test, in which the duration of immobility was recorded for the last 5mins. Oral administration of the graded dose of rohitukine (25,50 and100 mg/kg) and IMP (60mg/kg p. o.) was administered one hour prior to final swimming test session. The period between when the mouse was immersed and when no further attempt to escape was made (apart from the move-

ments necessary to keep its head above the water) was recorded as the immobility time.

Statistical analysis

The results were expressed as mean ±S.E.M. The statistical significance was determined by One-Way Analysis of Variance (ANOVA) followed by Newman–Keul's multiple comparisons test. $P < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Antidepressant activity of rohitukine on the tail sususpension test (TST)

The effects of the rohitukine and imipramine (IMP) on active behaviors in the TST of mice are shown in TABLE 1. Oral administration of various doses of rohitukine (25, 50 and 100 mg/kg) were used to assess the extent of immobility in mice exposed to tail suspension test (TST). rohitukine and IMP induced significant diminution of immobility time [Vehicle, 190.3±16.1; rohitukine at 25, 50 and 100 mg/kg 133.5±23.4 ($p< 0.01$); 114.7±5.3**($p<0.01$) and 102 ±21.6**($p<0.01$) respectively and imipramine, 60mg/kg, 31.2±6.2*** ($p<0.001$)] as compared with the control. There was no significant difference between the effect of the various doses of the rohitukine and that observed with imipramine on the immobility time group when the mice were exposed to the TST.

TABLE 1 : Effect of rohitukine and imipramine on tail suspension model in mice

Group	Dose (mg/kg)	Duration of immobility (sec)
Control	-	190.3±16.1
Rohitukine	25	133.5±23.4
Rohitukine	50	114.7±5.3**
Rohitukine	100	102 ±21.6**
Imipramine	60	31.2±6.2***

Data represent means ± S.E.M. of 8 mice during the 5-min test session. Comparisons were made by using a one-way; ANOVA followed by post hoc Newman–Keuls's test: *p<0.05, **p< 0.01, ***p < 0.001 compared with control group

Effects of rohitukine on the forced swim test (FST)

The effect of the rohitukine and imipramine (IMP) on active behaviors in the FST of mice are shown in TABLE 2. Out the four doses of rohitukine (25, 50 and 100 mg/kg) administerd, only 100mg/kg significantly reduced the immobility time [Vehicle, 156.8±18.2 rohitukine 100mg/kg, 53. 6±3.6** ($p< 0.01$)] compared to negative control values. Also, imipramine significantly decreased the immobility time [imipamine, 60mg/kg, 11.8±5.3*** ($p< 0.001$)] during the 5 minute test session. There was no significant difference between the effects of the rohitukine (100mg/kg) and that observed with imipramine on the immobility time when the mice were exposed to the FST.

TABLE 2 : Effect of rohitukine and imipramine on forced swim model in mice

Group	Dose (mg/kg)	Duration of immobility (sec)
Control	-	156.8±18.2
Rohitukine	25	113.7±10.5
Rohitukine	50	103.0±20.5
Rohitukine	100	53. 6±3.6**
Imipramine	60	11.8±5.3***

Data represent means ± S.E.M. of 8 mice during the 5minute test session. Comparisons were made by using a one-way; ANOVA followed by post hoc Newman–Keuls's test: **p<0.01, ***p < 0.001 compared with control group

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