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Anti-Anxiety and Antidepressant Activity of Ethanolic Extract of *Dalbergia Sissoo* for Anxiety and Depression in Ovariectomized Rats

Vaidya Mrunal*, Kolhe Swati, Tembhurne Sachin

All India Shri Shivaji Memorial Society's College of Pharmacy, Kennedy Road, Near R.T.O., Pune, Maharashtra, India-411001

ABSTRACT

There are studies showing the effects of long-term ovarian hormones withdrawal and post-menopause on animal behavior. Ovarian hormones play a critical role is modulating anxiety and depressive symptoms in female. Thus, this current study evaluated the anxiety and depression of long-term ovariectomy (OVX) in adult rats subjected to the light and dark chamber and forced swimming tests. In this study, we tested the effect of hydroalcoholic extract of *Dalbergia sissoo* on female anxiety and depression in long-term postsurgical bilateral ovariectomized female rats. 6-month old female Wistar rats were used and distributed in 5 groups; diestrus rats, ovariectomized (OVX) groups with 60 days, OVX treated with standard β Estradiol (0.1mg/kg/s.c), OVX treated hydroalcoholic extract of *Dalbergia sissoo* (200 & 400 mg/kg). All treatments were given for further 28 days after post-surgical period (60 days) in ovariectomized female rats. They were evaluated on the 28th day in the light and dark chamber and forced swim test apparatus. The treatment of the hydroalcoholic extract of *Dalbergia sissoo* (200 and 400 mg/kg) in the OVX rats shows significant increase in the time spent in the light chamber and the immobility time was significantly decrease in the extracted treated groups as compared to the OVX group. Anxiety-like and depressive-like behaviors were observed in rats which were influenced by post-menopause or ovarian hormone withdrawal. Results suggested that 28 days of treatment with hydroalcoholic extract of *Dalbergia sissoo* is able to lower the anxiety levels and depression in estrogen deficient females.

Keywords: *Dalbergia sissoo*, Post menopause, Anxiety, Depression, Light dark box, Forced swim test.

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***Address for Correspondence:**

Mrunal M. Vaidya, All India Shri Shivaji Memorial Society's College of Pharmacy, Kennedy Road, Near R.T.O., Pune, Maharashtra, India-411001

INTRODUCTION

Depression and anxiety are among the most cited psychological symptoms related to the absence of ovarian hormones that are observed in postmenopausal women [1, 2]. In human, menopause causes depletion of estrogens, whereas in experimental animals OVX is a common method to deplete animals of their gonadal hormones. In females the absence of the ovaries induces a drastic decrease of circulating estrogens [1]. Women carry a greater burden of affective and anxiety disorders than do men, with the lifetime prevalence of depression in women at about 21% compared with 13% in men [4]. During the perimenopausal/ menopausal period, which occurs at approximately 45-55 years of age, women often suffer from mood disorders such as depression, altered emotionality, and malaise [5, 6, 7]. Depressive symptoms develop during natural and surgical menopause, and estrogen replacement therapy has been used as a beneficial treatment for many years [8]. Relatively high levels of depression and anxiety have been reported in women post physiological or after surgical induction of menopause in comparison with premenopausal intact women [1, 9].

Okada et al. (1997) demonstrated that ovariectomized rats showed significantly prolonged immobility as compared to sham-operated rats 14 days after ovariectomy [10]. Therefore, it is conceivable that the prolongation of immobility following ovariectomy might be a useful tool for experimentally investigating menopausal depression and for evaluating the efficacy of potential treatments [11].

Studies have demonstrated that 17β-estradiol, a primary estrogen produced by the ovaries, decrease anxiety- related behavior and produce antidepressant-like effects in animal models. In fact, proestrus rats, which have high physiological 17β-estradiol levels, have decreased anxiety-like behavior across a variety of tasks and decreased mobility time in the forced swim test compared to female rats in diestrus phases, which have lowering 17β-estradiol levels [12, 13, 14]. Furthermore, the administration of 17β-estradiol regimen in

OVX rats produces anti-anxiety and antidepressant-like effects compared to non-treated animals [15, 16]. Behavioral and neurochemical studies employ OVX rats 1-4 weeks after surgery as an animal model of menopause. This time frame is generally adopted as a consequence of lower plasma concentrations of estrogens and progestins in OVX compared to intact animals [17].

The actions of phytoestrogens are principally established by interactions with ERα and ERβ, which are differentially distributed in the brain and other organs [18]. Diverse natural or synthetic compounds can be recognized by estrogen receptors, thus regulating most of the physiological processes that depend on estrogens. The activation of ERβ produces anxiolytic and antidepressant-like effects [19].

Dalbergia sissoo, popularly known as shisham in India, is an erect deciduous tree. *D. sissoo* is widely available throughout the Indian subcontinent. Phytopharmacological evaluation program aimed at finding an effective alternative therapy for postmenopausal osteoporosis, we recently reported that several phytoestrogens, particularly methoxy isoflavones, were present in the crude extract made from the leaves of D. *sissoo* and exhibited in vitro bone-forming activity [20]. Comprehensive investigation of D. *sissoo* reported to contain estrogenic flavonoids and some sterols with estrogenic activity. The reported results of phytochemical analysis indicated to the presence of flavonoids in *Dalbergia sissoo* [21]. Thus, the objective of the present study was to evaluate the anxiolytic and antidepressant effect of hydro alcoholic extract of *Dalbergia sissoo* on bilateral ovariectomized induced post-menopausal female rats.

MATERIALS AND METHODS

Collection and Identification of Plant Material:

D. sissoo leaves were collected from the surrounding area of rural Pune during September 2018. The plant was identified and authenticated by M/s. Shamantak Enterprises, Dr. Gautam, Botanist, Pune, India.

Preparation of Plant Extract:

A weighed quantity (50g) of the air-dried powdered leaves of *D. sissoo* was drawn and then it was extracted with 90% ethanol in a Soxhlet extractor. The hydroalcoholic extract was concentrated in a rotary flash evaporator at a temperature not exceeding 50° C to get a solid residue. Different concentration (200mg/kg and 400mg/kg p.o.) of hydroalcoholic extract of leaves of *D. sissoo* was given according to body weight of animals [22].

Animals:

The study was undertaken at the AISSMS College of Pharmacy, Pune. The Institutional Animal Ethical Committee approved the protocol (CPCSEA/IAEC/PC-08/01-2K18) for the study. Wistar female rats (200-250g) of about 6 months were used. They were maintained at 25±2º C and relative humidity of 45 to 55% and under light dark cycle (12 h light: 12 h dark cycle). The animals had free access to food and water ad libitum throughout study. All experiments were carried out between 9:00 – 16:00 hours.

Surgical Procedure of bilateral Ovariectomy (OVX):

The acclimatized rats were ovariectomized using the dorsal midline skin incision. The rats underwent surgical procedure after being anesthetized with ketamine (80 mg/kg). Rat was put on its ventral surface and ovariectomy was preceded by a single 2 cm long longitudinal skin incision on the dorsal midline (the hump) and the base of tail. After deep incision the bilateral ovaries were found, surrounded by a variable amount of fat. Ligation of blood vessels was necessary. Both ovaries were identified and then silk thread was tightly tied around the oviduct, including the ovarian blood vessels. The oviduct was cut and ovary was removed, taking good care in leaving the knot intact. The uterine horn was returned into the abdominal cavity. The muscle incision was required suturing with 0 size chromic absorbable catguts. The skin was sutured with non-absorbable silk thread. Broad spectrum antibiotic Neosporin antibiotic powder was used topically after surgery for 15 consecutive days [23].

Animal Grouping and Treatment Protocol:

After 1 month, ovariectomized rats were categorized into 5 groups. Group 1 – Diestrus group, Group 2 – OVX rats, Group 3 – Ovx treated with Estradiol benzoate (0.1 mg/kg/s.c), Group 4 and 5 – Ovx treated with hydroalcoholic extract of *Dalbergia sissoo* (200 and 400 mg/kg/p.o respectively). Treatments i.e. standard Estradiol (0.1 mg/kg/s.c), *D. sissoo* (200 & 400 mg/kg/p.o), respectively were given for a period of 28 days.

Vaginal cytology:

To evaluate the animals for anxiety and depression in the diestrus phase, estrous cycle phases were determined by vaginal lavage [24] every morning between 8:00 to 9:00 a.m. and female rats with at least two regular 4-day cycles were used.

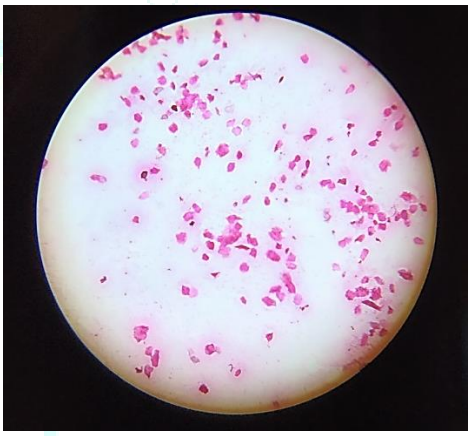

Fig 1. Vaginal cytology – Diestrus Phase

Forced Swimming test:

The forced swimming test by VJ Instruments, consisted of placing rats, individually, in Plexiglas cylinders (46 cm high, 20 cm in diameter) containing water (24-26 ˚C, 30 cm deep), for two swimming sessions: an initial 15-min training session, which was followed, 24 h later, by a 5-min test session [25]. At the end of each swimming session, the animal was removed from the cylinder, dried with paper towels, placed in an individual cage to rest and recover for 15 min and then returned to its collective home cage. Three behavioral parameters were scored cumulatively in the second swimming session test only: (i) immobility time (i.e. the time spent floating in the water without struggling, making only those movements necessary to keep the head above the water), (ii) swimming time (i.e. the time spent making active swimming motions to move around in the cylinder) and (iii) climbing time (i.e. the time spent making active movements with its forepaws in and out of the water, directed specifically to the cylinder wall) [17].

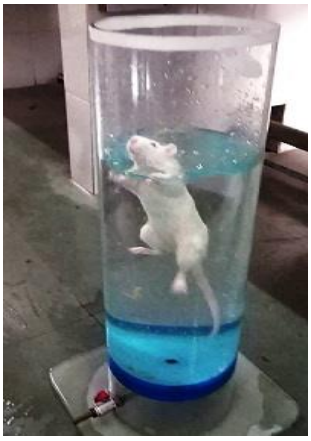

Fig 2. Forced Swim Test Apparatus

Light – dark box testing:

The apparatus used for the Light/Dark Box test by VJ Instruments, consist of a cage divided into two chambers divided by a partition with a door. One chamber is brightly illuminated with a lamp, whereas the other chamber is dark. It was made of Plexiglas (20×30×30 cm light chamber and dark chamber each).

Fig 3. Light/Dark Box Test Apparatus

The chambers were connected by a 10×10 cm door in the middle of the wall separating the two chambers. Animals were habituated to the experimental room for at least 30 min before the beginning of the test. After habituation, the animal was placed in the middle of the light chamber facing a side away from the door and then released. They were allowed to move freely between the two chambers with the door open for 10 min. the latency to first enter the light chamber, the locomotor activity in each chamber, the total number of transitions between chambers, and the time spent in each chamber can be recorded. Transitions between the light and dark chambers and total locomotor activity, as an indication of exploratory activity, were measured for 10 min [26].

Statistical Analysis:

Statistical analysis was carried out using GraphPad Instat 3. All of the data is shown as the mean ± standard error of the mean (S.E.M) and were analyzed using one-way analysis of variance (ANOVA). Significant differences between the estrous control and experimental groups were determined using Tukey-Kramer test all comparison test, P<0.001 was considered significant.

RESULTS AND DISCUSSION

Forced Swimming Test:

The forced swimming test was used to evaluate behavioral despair. Depressive-like behavior was defined as an increase in the time (in seconds) spent immobile. At the 8th week of OVX, rats showed significant increase in immobility time and decrease in swimming time as compared to diestrus control group. Following Estradiol benzoate treated (0.1 mg/kg s.c. for 28 days from 4th week after OVX), rats showed a decreased immobility and increased swimming time on the 28th day as compared to diestrus group and OVX group. There were significant differences in swimming behavior and swimming time was increased and immobility time was decreased in the *D. sissoo* 400 mg/kg after the 28 days of treatment. There was no significant interaction between the treatment group and diestrus group for struggling (P<0.05). Results are shown in **Table 1**.

Table 1: Effect of *D. sissoo* in the 5 min forced swimming test apparatus in rats

Groups	Immobility (s)	Swimming (s)	Struggling (s)
Diestrus Control	32±1.39	176.83±6.17	91.16±6.84
OVX	82±3.10	115.5±9.07**	102.5±10.19
Standard Estradiol 0.1 mg/kg/s.c	30.83±5.51	191.66±8.38	77.5±5.30
***D. sissoo* 200 mg/kg p.o.**	43±14.44	164.17±16.28	92.83±2.63
***D. sissoo* 400 mg/kg p.o.**	24.5±3.69	190.16±12.28*	85.33±9.26

Results are expressed as mean ± SEM. (n=6) Data was analyzed by one-way analysis of variance (ANOVA) followed by Tukey-Kramer's test. *p<0.05, **p<0.001.

Light-Dark Box Test:

The time spent in the light box was significantly increased in the *D. sissoo* 200 and 400 mg/kg (P<0.05, P<0.001 respectively) compared with the diestrus control group. The time spent by the OVX animals in the light box was less than that of the diestrus group and was not significant (P>0.05). Latency to enter dark was more significant in the *D. sissoo* 400 mg/kg (P<0.001). number of crossings showed no significant interactions between the groups (P>0.05). Locomotor activity in the light box was significant in the standard estradiol group and also *D. sissoo* 400 mg/ kg group (P<0.001). There was significant increase in the locomotor activity of the OVX group in the dark box (P<0.05) and no significant interactions with other treatment groups were observed (P>0.05). Results shown in Table **2**.

Table 2: Effect of *D. sissoo* in 10 min light/dark transition test in rats

Groups	Time in light box (s)	Latency to enter dark (s)	Number of crossings	Locomotor activity in light box	Locomotor activity in dark box
Diestrus Control	35.16±7.24	12.83±1.88	25±1.39	45.83±7. 05	211.66±19.49
OVX	25.66±3.38	5±0.51	21.5±2.77	88.5±17.96	528.66±51.59*
Standard Estradiol 0.1 mg/kg/s.c	47±4.82	8.33±0.55*	27.5±2.20	125.83±16.55**	442.33±99.81
***D. sissoo* 200 mg/kg**	45.16±9.32*	8.16±1.07*	19.66±1.89	62±11.20	291.33±52.08
***D. sissoo* 400 mg/kg**	61.5±8.31**	6.5±0.76**	23.16±1.74	120.83±10.90**	294.16±27.74

Results are expressed as mean ± SEM. (n=6) Data was analyzed by one-way analysis of variance (ANOVA) followed by Tukey-Kramer's test. *p<0.05, **p<0.001.

Studies have shown that experimental anxiety levels can vary during hormonal fluctuations period in female rats [12, 27, 28, 29]. Likewise, it has been observed that higher anxiety levels match with lower plasmatic concentrations of ovarian hormones in distinct animal models [12, 30, 31]. It should be noted that in menopausal women, ovarian hormones biosynthesis reduces gradually, whereas after surgical removal of ovarian glands estrogen and other steroid hormones reduces abruptly in the blood [32]. In this context, it is known that hormone therapy in perimenopause women promoted potential cognitive benefits, but these positive effects disappear when initiating the administration in late post menopause [33]; preclinical findings also support these observations [34]. Therefore, it suggests that a rapid and consistent reduction of gonadal circulating hormones may be related to decreased responsiveness to ovarian steroids, such as estradiol, which could contribute to synaptic alterations in estradiol brain targets [17].

Literature data have shown that in the forced swimming test, ovariectomized rats display significantly prolonged immobility time in comparison with intact or diestrus animals [10, 11, 35]. Chronic treatment with estradiol after ovariectomy significantly shortened the duration of immobility in a dose-dependent manner. The recovery of the duration of immobility after chronic treatment with estrogen concurs with the results of a previous study of OVX rats [10]. Therefore, it is conceivable that the depletion of estrogen correlates closely with the manifestation of depressive-like behavior. Although numerous clinical studies have indicated that estrogen plays an essential role in the manifestation of mood disorders in peri- and postmenopausal women [36], information concerning the possible role of estrogen on depressive-like behavioral states in laboratory animals is limited. In female rats, estrogen produced an antidepressant-like effect during forced swimming test [37, 38, 15]. Furthermore, estrogen has been shown to modulate neurotransmission in the brain [39, 40] especially through serotonin in receptors [41]. Because it is clear that behavioral changes during the forced swimming test following ovariectomy depend upon estrogen concentrations, the experimental protocol that we used in this study may provide clues as to whether there are interactions among these variables [11].

The data obtained from the Light/Dark box test is generally visualized by graphing the time the animal spends either in the dark or in the light chamber. The time spent in the light chamber can be easily graphed and compared. The latency to first enter the light chamber, the distance traveled in each chamber, and the total number of transitions between chambers can also be presented. However, since the time spent in the bright chamber is regarded as the most consistent and useful measurement in dose-effect pharmacological evaluations [42]. In this study, the time spent in light area latency to enter dark chamber and tunnel crossing is an index of anxiety. The *Dalbergia sissoo* extract (400 mg/kg) had significantly increased the time spent in light area, latency to enter dark chamber and tunnel crossing, similar to standard drug, suggesting that anxiolytic activity of *D. sissoo* leaves extract as compare to diestrus control group.

Taken together, this information contributes to understand the effect of ovarian hormone withdrawal in modulating the anxiety and depressive behaviors in female rats. The present study provides evidence that the ethanolic extract of *Dalbergia sissoo* is a shown to have anxiolytic and anti-depressant like effects in ovariectomized rats. Therefore, further comparative studies, including neurobiological tests, are needed to establish an animal model of psychopathological depression and anxiety.

CONCLUSION

The main findings of the present study can be summarized as follows: (a) OVX rats displayed an anxiogenic-like behavior compared to diestrus control group, (b) OVX animals showed increase in the immobility time compared to diestrus group, (c) Standard estradiol benzoate (0.1 mg/kg s.c.) showed anxiolytic and antidepressant-like behavior after the treatment, (d) *D. sissoo* 400 mg/kg showed significant effect of anxiolytic and antidepressant-like behavior as that of the standard estradiol group.

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