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MANAGEMENT OF DRUG INDUCED SEXUAL DYSFUNCTION IN MALE RATS BY ETHYL ACETATE FRACTION OF ONION

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Abstract: The present study aimed to investigate the effect of ethyl acetate fraction of *A. cepa* bulb on mating behavior in paroxetine-induced sexually dysfunction male rats. Sexual dysfunctions such as decreased libido, delayed orgasm, difficulties in maintaining an erection, and inhibition of ejaculation are common side effects of paroxetine. *A. cepa* bulb ethyl acetate fraction (200 mg/kg) was administered orally in paroxetine-induced sexually impaired male rats for 7 days. At the end of 7th day, mount frequency (MF), intromission frequency (IF), ejaculatory frequency (EF), mount latency (ML), intromission latency (IL), ejaculatory latency (EL) and post-ejaculatory interval (PEI) were the parameters observed. Results showed that in relation to the paroxetine treated group, ethyl acetate fraction, significantly restored the normal sexual behavior as evident from increased MF, IF, EF and reduced ML, IL, EL and PEI.

Keywords: *A. cepa,* mating behavior, paroxetine, sexual dysfunction

Paroxetine, a selective serotonin reuptake inhibitor antidepressant drug, on chronic administration delays or abolishes orgasm, inhibits nitric oxide synthase (NOS) activity, increases the ejaculation latencies and reduces the total number of ejaculations in rats (1-3). *Allium cepa* L. (Liliaceae), commonly known as onion, is one of the most widely used medicinal plants in Indian system of medicine and traditionally used as diuretic, expectorant, antibacterial and in treatment of jaundice, hemorrhoids, dysentery, epilepsy, tumor and as an aphrodisiac (4-6). It has been reported to have antithrombotic (7-10) hypolipidemic (11, 12), hypotensive (13), androgenic (14), antidiabetic (15, 16), and anticancer properties (17). In Indian system of medicine juice of *Allium cepa* L. is recommended as a traditional remedy for the management and treatment of male sexual dysfunction, however, this claim is based largely on subjective opinion rather than scientific observation. Therefore, in the present study, we investigated the effect of ethyl acetate fraction of *Allium cepa* bulb on mating behavior in paroxetine-induced sexual dysfunction male rats.

MATERIALS AND METHODS

Plant material

The bulb of *A. cepa* L. was collected from local market of Indore district (M.P.), India and authenticated by Dr. Sanjay Vyas, Prof. Department of Botany, Government Holkar Science College Indore, M.P., and a voucher specimen of the same has been deposited for future reference.

Preparation of ethyl acetate fraction

The bulbs of *A. cepa* were air dried, chopped into small pieces and pulverized. The dried powder (50 g) was extracted with 200 mL of ethanol at room temperature for 48 h in a Soxhlet extractor. The resulting solution was filtered and freeze dried. The dried extract was suspended in water and fractionated with ethyl acetate (3 × 150 mL) using separating funnel. Separated ethyl acetate fraction was freeze dried and subjected to pharmacological screening.

Animals

Healthy adult Wistar albino male rats (150-200 g) were used. The animals were housed individual-

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ly, maintained under standard conditions (12 h light and 12 h dark cycle, 25-30°C, 35-60% relative humidity), the animals were fed with standard rat pellet diet (Hindustan Lever Ltd., Mumbai, India) and water *ad libitum*. The institutional animal ethics committee approved the experimental design.

Induction of sexual dysfunction in male rats

Sexually experienced male rats were divided into two groups, group A served as control and received vehicle only (normal saline) and group B served as paroxetine treated group and received oral dose of 10 mg/kg paroxetine suspension (suspension was prepared daily in Tween 80, suspended in 0.9% saline solution) (18, 19). Dosing was done for 3 weeks once in a day. At the end of 3 weeks, after 30 min of last dosing, estrus female was introduced into respective cages and observed for mating performance and results were recorded and compared with control group. Mating performance analyses were conducted in the dark phase of the light-dark cycle under dim light condition. Assessment of MF, IF, EF, ML, IL, EL and PEI were monitored for 30 min after pairing (20). Animals which showed minimum 25% reduction in sexual behavior were considered as sexually impaired and they were incorporated for subsequent study.

Induction of estrus phase in female rats

Female rats were brought to estrus by sequential administration of suspension of ethinyl estradiol orally (100 µg/rat) 48 h prior to the pairing and progesterone (1 mg/rat), through subcutaneous route, 6 h before the experiment (21). Estrus phase in rats was confirmed by vaginal smears examination according to OECD-106 guideline (22).

Effects of *A. cepa* L. ethyl acetate fraction on mating behavior in paroxetine-induced sexual dysfunction male rats

Normal sexually experienced male rats and sexually impaired male rats were employed for this investigation. Three groups of animals were formed, group I served as normal control (sexually experienced normal male rats) and received vehicle only, group II served as negative control (sexually impaired male rats, obtained from above study) and received paroxetine suspension orally (10 mg/kg), group III (sexually impaired male rats obtained from above study), received 200 mg/kg of ethyl acetate fraction suspension orally (suspension was prepared daily in Tween 80, suspended in 0.9% saline solution) besides paroxetine suspension (10 mg/kg). Dosing frequency was once in a day for 7 days. At the end of 7th day, after 30 min of last dosing, estrus female was introduced into respective cages and observed for mating performance and results were recorded and statistically analyzed (18, 19).

Statistical analysis

Data were presented as the mean ± SEM. The data were subjected to analysis of variance (ANOVA) followed by Tukey's test. $p < 0.05$ was taken as significant.

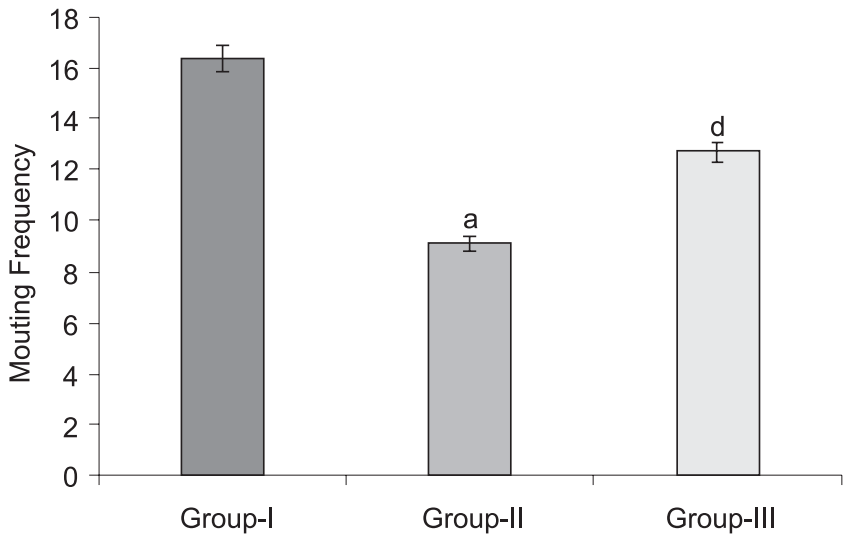

Figure 1. Effect of ethyl acetate fraction of *A. cepa* on mounting frequency in paroxetine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: paroxetine treated; Group-III: ethyl acetate fraction treated. Values are the mean ± SEM, n = 6; [a] $p < 0.05$ and [d] $p < 0.01$, [a]: compared to normal control; [d]: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test

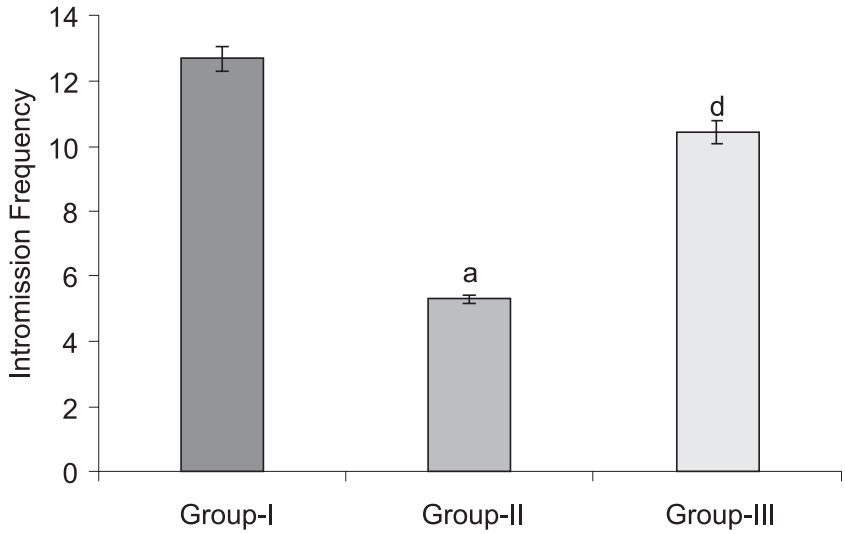

Figure 2. Effect of ethyl acetate fraction of *A. cepa* on intromission frequency in paroxetine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: paroxetine treated; Group-III: ethyl acetate fraction treated. Values are the mean ± SEM, n = 6; [a] $p < 0.05$ and [d] $p < 0.01$, [a]: compared to normal control; [d]: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test

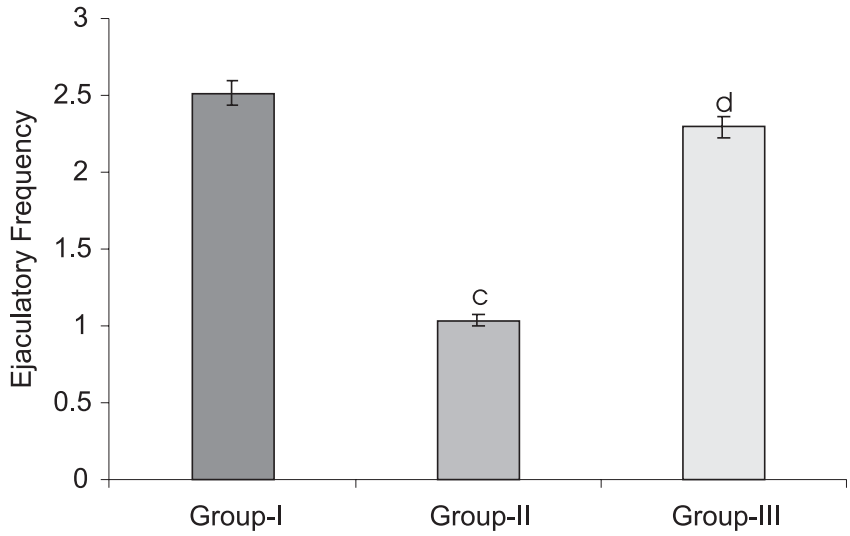

Figure 3. Effect of ethyl acetate fraction of *A. cepa* on ejaculatory frequency in paroxetine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: paroxetine treated; Group-III: ethyl acetate fraction treated. Values are the mean ± SEM, n = 6; [c, d] $p < 0.01$, [c]: compared to normal control; [d]: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test

RESULTS

The results of mating behavior analysis showed that in group I, normal rats exhibited usual sexual behavior, evident by MF (16.34 ± 2.78), IF (12.67 ± 1.37), EF (2.51 ± 1.52), ML (98.01 ± 1.48), IL (127.89 ± 1.77), EL (149.2 ± 1.03), and PEI (176.24 ± 1.43). In paroxetine treated group (group II), males demonstrated diminished sexual behavior as reflected by decreased MF (9.12 ± 2.41 [a]), IF (5.31 ± 2.49 [a]), EF (1.03 ± 1.42 [c]) and increased ML (151.78 ± 1.1 [a]), IL (201.33 ± 2.11 [a]), EL (194.16 ± 2.05 [a]), and PEI (243.71 ± 2.49 [a]) in comparison to normal control. On the other hand, animals of ethyl

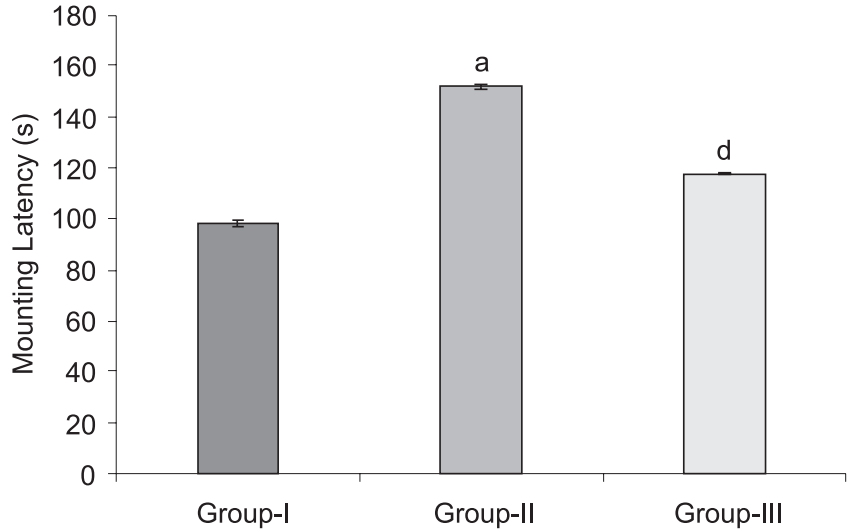

Figure 4. Effect of ethyl acetate fraction of *A. cepa* on mount latency in paroxetine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: paroxetine treated; Group-III: ethyl acetate fraction treated. Values are the mean ± SEM, n = 6; [a] $p < 0.05$ and [d] $p < 0.01$, [a]: compared to normal control; [d]: compared to negative control. Data were analyzed by ANOVA followed by Tukey's tes

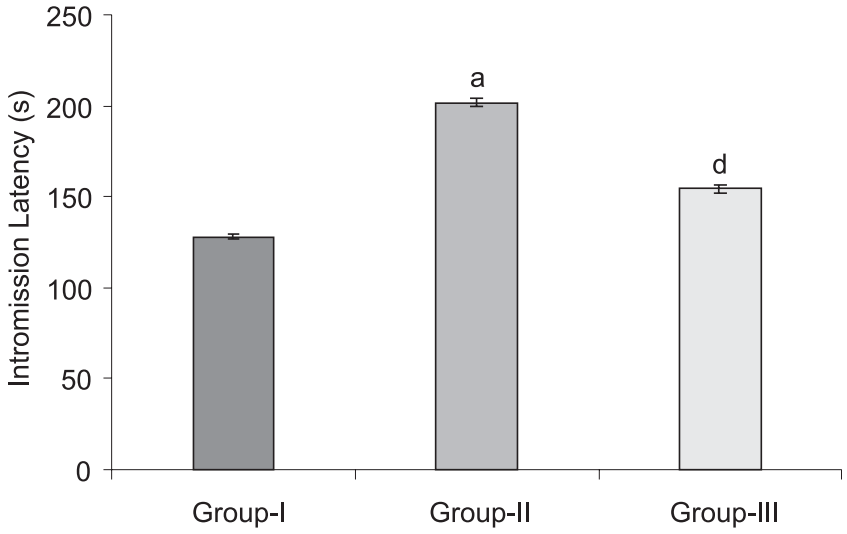

Figure 5. Effect of ethyl acetate fraction of *A. cepa* on intromission latency in paroxetine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: paroxetine treated; Group-III: ethyl acetate fraction treated. Values are the mean ± SEM, n = 6; [a] $p < 0.05$ and [d] $p < 0.01$, [a]: compared to normal control; [d]: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test

acetate fraction treated group (group III), restored sexual performance significantly compared to paroxetine treated group (group II). The males of group III showed significant increase in the frequencies MF (12.71 ±1.27 [d]), IF (10.43 ±2.06 [d]), EF (2.29 ±2.17 [d]) and decrease in latencies ML (117.31 ± 0.32 [d]), IL (153.77 ±1.88 [d]), EL (176.19 ±1.13 [d]), PEI (214.23 ±0.56 [d]) in relation with normal control.

DISCUSSION AND CONCLUSION

Sexual activity is a multifaceted activity, involving complex interactions between the nervous system, the endocrine system, the vascular system and a variety of structures that are instrumental in sexual excitement, intercourse and satisfaction. Normal male sexual response cycle can be functionally divided into

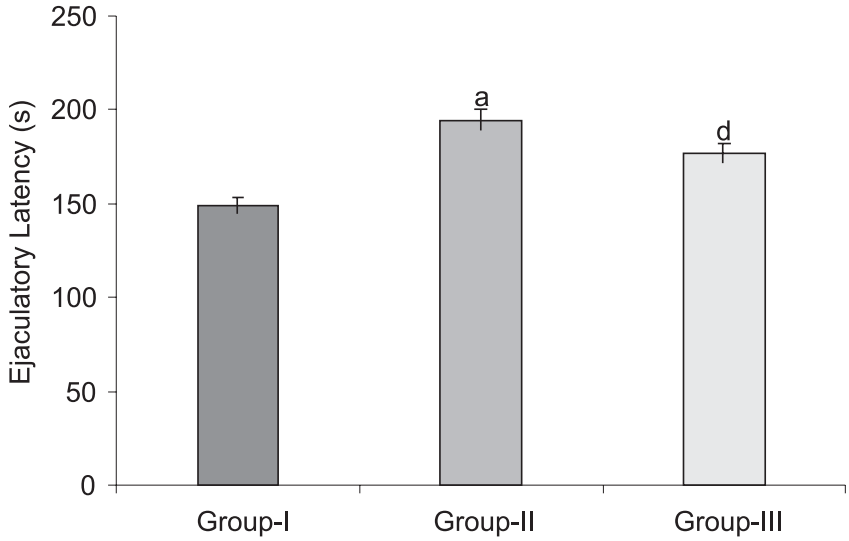

Figure 6. Effect of ethyl acetate fraction of *A. cepa* on ejaculatory latency in paroxetine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: paroxetine treated; Group-III: ethyl acetate fraction treated. Values are the mean ± SEM, n = 6; [a] $p < 0.05$ and [d] $p < 0.01$, [a]: compared to normal control; [d]: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test

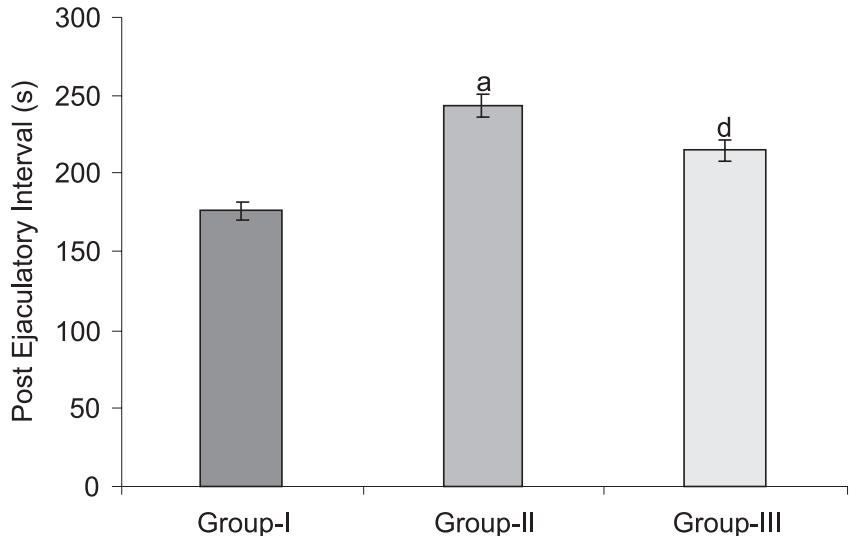

Figure 7. Effect of ethyl acetate fraction of *A. cepa* on post-ejaculatory interval in paroxetine induced sexual dysfunction male rats. Group-I: vehicle treated; Group-II: paroxetine treated; Group-III: ethyl acetate fraction treated. Values are the mean ± SEM, n = 6; [a] $p < 0.05$ and [d] $p < 0.01$, [a]: compared to normal control; [d]: compared to negative control. Data were analyzed by ANOVA followed by Tukey's test.

five interrelated sequence that occur in a defined sequence: libido, erection, ejaculation, orgasm, and detumescence. Problem anywhere in the entire sequence may lead to sexual dysfunction. Sexual dysfunction is a common side effect of psychoactive medications as well as a number of other frequently prescribed medications. Considerable attention has been recently focused on antidepressants, perhaps because of their widespread use and because they are often taken for long periods of time (e.g., months or years). Paroxetine (selective serotonin reuptake inhibitor) became the most frequently prescribed drug for the treatment of depression. Sexual dysfunctions such as decreased libido, delayed orgasm, difficulties in maintaining an erection, and inhibition of ejaculation are common side effects of paroxetine.

MF, IF and EF are useful indices of vigor, libido and potency (23). An increase in MF (Fig. 1) reflects sexual motivation and increase in the number of IF (Fig. 2), and EF (Fig. 3) shows the efficiency of erection, penile orientation and the ease by which ejaculatory reflexes are activated (23). Therefore, the increase in MF and IF suggests enhanced mating behavior of male rats. Results of mating performance analysis showed that ethyl acetate fraction remarkably increases the MF, IF, and EF, whereas in paroxetine-induced experimental rats MF, IF, and EF decreases remarkably.

Mount latency, intromission latency and ejaculatory latency are indicators of sexual motivation. ML, IL and EL are inversely proportional to sexual motivation (23). According to biological theory, serotonin reuptake inhibitors increase the accumulation of serotonin in the synapse, which lead to delayed or inhibited ejaculation and ejaculatory inhibiting effects of serotonin in the brain are enhanced (24). Therefore, the decrease in the ML (Fig. 4), IL (Fig. 5) and EL (Fig. 6) observed in ethyl acetate fraction treated animals might imply stimulation of sexual motivation and arousability as compared to paroxetine treated group. It may also be an indication of enhanced sexual appetitive behavior in the male rats. All these facts further support the sexual function improving effect of the ethyl acetate fraction of *A. cepa*. The PEI is considered an index of potency, libido and the rate of recovery from exhaustion after mating (23). Therefore, the significantly decreased PEI (Fig. 7) in ethyl acetate fraction treated male rats may be attributed to libido as compared to paroxetine treated group. In conclusion, the present study has demonstrated that *A. cepa* bulb ethyl acetate fraction has potential to restore the normal sexual behavior in experimental animal.

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