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Full Length Research Paper

Role of the methanolic extracts of *Boswellia serrata* and *Lavandula angustifolia* on apomorphine induced ejaculation in male Wistar rats

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Ejaculation is a complex physiological and psychological process which cholinergic and dopaminergic mechanisms might be involved in regulation of it. Rapid ejaculation is the most frequently encountered sexual complaint of men and different method of treatments were recommended. The aim of this study was to investigate possible role of the methanolic extracts of the *Boswellia serrata* and *Lavandula angustifolia* on ejaculatory responses induced by apomorphine in male Wistar rats. Ejaculation was induced by subcutaneous injection of apomorphine dissolved in saline and was counted by direct observation after drug injection. The effects of methanolic extracts of *B. serrata* and *L. angustifolia* on apomorphine induced ejaculation were examined. The results showed dose related decrease of semen drop numbers due to extracts administration. During monotherapy the effective doses of both extracts were 100 mg/kg. Combination therapy with both *B. serrate* and *L. angustifolia* extracts (50,100 mg/kg) significantly decreased semen drop numbers. It was concluded that, mono/combination therapy with *B. serrate* and *L. angustifolia* extracts decreased apomorphine - induced ejaculation and may have a beneficial role in the treatment of rapid ejaculation.

Key words: Ejaculation, apomorphine, sexual behavior, herbal.

INTRODUCTION

One of components of male sexual behaviors is ejaculation. Ejaculation in males is a complex physiological process and some central neurotransmitters such as cholinergic, serotonergic and dopaminergic (DA) deserve further investigation (Andersen and Tufik, 2005). Rapid ejaculation, marked lowering ejaculation threshold, is the most frequently encountered sexual complaint of men (Allen et al., 2000). It is well established that, DA mechanisms might be involved in the regulation of ejaculation (Bitran et al., 1987; Hyun et al., 2002). In laboratory animals, DA agonists decrease the ejaculatory threshold, whereas destruction of DA neurons is associated with prolonged ejaculatory latencies (Bitran et al., 1987). Major role of DA system for induction of yawing and ejaculation was described previously (Stief et al., 1989). According to these, Sexual medicine has evolved greatly in the past several years. Conversely, despite some substantial progress in medical and scientific knowledge in areas of sexual medicine including ejaculation disorders (Giuliano and Clément, 2006), the high cost of acquiring synthetic drugs, their inadequate supplies, the side effects associated with their uses, and the belief that plants hold cure to many disease conditions have led to a reawakening of interest in the utilization of plants and plant products in recent years (Phillipson et al., 1989). A variety of plants have been used as sex stimulants and ejaculation modulators in the traditional medicine (Islam et al., 1991). *Lavandula angustifolia* Mill., is one of the commonly used and well

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known to have various physiological effects including relaxation, sedation (Cavanagh and Wilkinson, 2002), anti-conflict (Umezu, 2006), and altered sexual activity (Linck et al., 2009). Linalool, a major component of lavandula extract, is reported to indicate not only glutamatergic and GABAergic effects (Silva Brum et al., 2001; Elisabetsky et al., 1995), but also acts on dopaminergic receptors (Kim et al., 2009). According to psychological and physiological potential of this plant and different mechanisms which involved in ejaculation behavior, it seems that *L. angustifolia* metabolites can be effective on ejaculation. On the other hand *Boswellia* species (Burseraceae), which are trees native to Ethiopia, Somalia and India, produce a gum resin that is known as olibanum (frankincense). Ayurvedic medicine illustrates the use of the gummy exudates from *B. serrata*, which are collectively referred to as guggals, are used for a variety of conditions including arthritis, diarrhea, sexual behaviors and pulmonary disorders (Gayathri et al., 2007; Krieglstein et al., 2001). The resin *B. serrate* (guggals) contains a mixture of terpenoids made up of four pentacyclic triterpene acids: ß-boswellic acid (the most abundant), 3-O-acetyl ß (ABA), 11-keto-ß-boswellic acid, and 3-O-acetyl-11- keto-ß-boswellic acid. The triterpenoids are the active constituents and are collectively called boswellic acids (Dermarderosian, 2002). Traditionally *B. serrate* gum resin has been used to increase energy and as an aphrodisiac for both men and women (Cicero et al., 2001). In western countries, the advent of synthetic drugs has obscured the pharmaceutics use of *Boswellia*, until it was reported that an ethanolic extract exerts anti-inflammatory and anti-arthritic effects (Anthoni et al., 2006; Kiela et al., 2005). However, these claims are largely based on subjective opinion rather than on scientific observation. Apomorphine is a mixed DA receptor agonist, which induced marked lowering of ejaculation threshold in the male rats (Napoli-Farris et al., 1984), which can be considered as a good model to assess the effect of different drugs on ejaculation procedure (Zarrindast et al., 1994). Due to the limitation and side effects of synthetic drugs, there is a continuing search for new ejaculation modulator drugs. In view of this and on account of the alleged usefulness of those plants in the traditional treatment of some sexual behaviors which has not yet been scientifically verified, this current study was aimed to investigating possible role of the methanolic extracts of the *B. serrata* and *L. angustifolia* on ejaculatory responses induced by apomorphine in male Wistar rats.

MATERIALS AND METHODS

Plant material

The flowering aerial parts of *L. angustifolia* including stems and leaves and *the gum of B. serrate* have been collected, identified in Herbarium of Medicinal plants (ACECR), Iran (Research Institute of Forest and Rangelands, Tehran). A voucher sample under have been deposited in the herbarium (Ajani 322 (ACECR) and Ajani 323 (ACECR) respectively). The aerial parts of *L. angustifolia* were cleaned, air dried and chopped into small pieces, powdered and stored. The *gum of B. serrate* has been cleaned and powdered for extraction.

Phytochemical analyses

The lavender sample (100 g powder) was submitted to hydrodistillation for five hours, using a Clevenger-type apparatus (Dorsa, Iran), according to the method of USP XVIII Pharmacopoeia. The volatile distillate was collected over n-pentane and refrigerated about one week till time of analysis and pharmacological tests. The yield of the oil was 1.0% (v/w) based on dry plant weight. The chemical compositions of the oil sample were analyzed by means of chromatographic–spectrometric methods. The analytical gas chromatography was carried out using a Thermoquest 2000 GC chromatograph with capillary column DB-1 (30 m x 0.25 mm x 0.25 µm); carrier gas, helium (He); split ratio 1:25, and a flame ionization detector. The column temperature was programmed at 50°C for 1 min and then heated to 265°C with a 2.5°C/min rate and then kept constant at 265°C for 20 min. GC-MS was performed on a Thermoquest 2000 with a quadrupole detector, on capillary column DB-1 (see GC); Carrier gas, He; flow rate, 1.5 ml/min and oven temperature as above. The MS was operated at 70 eV ionization energy. Retention indices were calculated by using retention times of n-alkans that were injected after the oil at the same chromatographic conditions. The compounds were identified by comparison of retention indices (RI) with those reported in the literature and by comparison of their mass spectra with the Wiley library (Adams et al., 1995) or with the published mass spectra (Vallejo et al., 1989). For analysis of Boswellic acids (α and β) in Boswellia gum, we used previousely reported method with some modifications (Buchele et al., 2005); ODS column (250mm×4.0mm I.D., particle size 5 µm), guard columns were not required. For the elution of the compounds, the following mobile phase and gradient program were used. Mobile phase A: methanol–water–acetic acid (80:20:0.2, v/v/v); mobile phase B: methanol–acetic acid (100:0.2, v/v). Initial conditions were 100% A at a flow rate of 1 ml/min. Isocratic elution at 100% A over 10 min, then linear gradient to 5% A until 12 min, 5% A until 17 min, 100% A until 19 min. At the end of this program, all remaining matrix compounds were eluted from the column. In order to stabilize the chromatographic system, the column was maintained at 28°C. UV detector was adjusted to 210 nm.

Extract preparation

The following extraction procedure was done on both *L. angustifolia* and the gum of *B. serrate*. Two hundred grams of powdered plants were subjected to maceration with methanol (99.9%) for 72 h. Methanolic extracts were filtered. Evaporation of extracts was done *in vacu* using a rotary evaporator at temperature about 35 - 40°C to powder. Both powdered extracts subjected to extraction with Petroleum Ether (35 - 45°C) in order to remove unwanted fatty materials. The yields extracts were 15.5% w/w and 28.7% w/w respectively. The dried extracts were kept at 4°C until used.

Formulations

The dried extracts were dissolved in non pyrogene sterile water containing 0.9% (w/v) of sodium chloride using Tween 80 as solubilizing agent and passed through a weighed paper filter. The filtered solutions were used for intraperitonealy (I.P.) injection. Following the filtration the filters were dried and weighed again, and

to obtain the real concentration of the extracts, the unfiltered particles were calculated. Plant extracts (50, 100 and 200 mg/kg) were administered via I.P. in a volume lower than 1 ml. Apomorphine HCL (Sigma, St Louis, MO, USA) freshly dissolved in bidistilled water containing 0.2 mg/ml ascorbic acid and administered subcutaneously. Animals were allowed to habituate for 30 min before drug injection.

Laboratory animals

Male Wistar rats aged approximately 100 days and weighing 200 - 250 g were used in these experiments. The animals were housed at 24°C, 60% humidity, under 12/12 h light- dark cycle. Standard laboratory food and water were freely available except during the time of the experiments. The study protocol was approved by the local ethics committee for the use of animals in research and we followed the guidelines of ethical standards for investigation of experimental pain in animals were followed (Zimmermann, 1983).

Behavioral observation

Rats were placed in Plexiglas boxes (25 cm wide, 25 cm high) for 10 - 15 min before testing in order to habituate to test environment and a mirror was arranged in a oblique position under the cylinder to make observation. Ejaculation was counted by direct observation after drug injection. The results were recorded and expressed as number of semen drops in 60 min period (Zarrindast et al., 1994).

Experimental procedures

In order to determine the effects of *L. angustifolia* and *B. serrate* extracts on ejaculation process and if a dose - response relationship exists, a series of experiments were performed (n = 6/group). Ejaculation was induced by subcutaneous injection of apomorphine dissolved in saline with vitamin C in all experimental groups as positive control group. The effective dose of apomorphine was selected on the basis of preceding experience with the behavioral effects of apomorphine on male rat ejaculation (Olivier et al., 2007). *L. angustifolia* and *B. serrate* extracts injected separately or combined together in doses 50, 100 and 200 mg/kg 30 min before ejaculation induced by apomorphine. The effect of the CMC, vehicle of the extracts, also was assessed on ejaculation induced by apomorphine. The drugs were prepared immediately before use, and the volume of the apomorphine and extracts were not more than 0.5 and 1 ml respectively.

Statistical analysis

Data were presented as the mean ± standard error of mean (SEM). The statistical significance of the results was evaluated by using the one way analysis of variance (ANOVA) followed by post hoc Turkey's multiple comparison test (Statistica, 6.0), and unpaired student *t*-test. Statistical significance was accepted at $P < 0.05$.

RESULTS

Phytochemical analyses

Chemical composition of the Lavander oil is presented in Table 2, which the components are listed in order of their abundance. About 17 constituents were found in the HD extract representing 87.9% of the oil; 2. j. pinene (35.9%) and lavandulyl acetate (14.1%) were the main components.

Total boswellic acid amount (comprising both α and β forms) in boswellia gum was 3.27 % (w/w) in which α-boswellic acid was predominant (2.43%).

Ejaculation induced by apomorphine

Subcutaneous injection of low doses of apomorphine caused ejaculation in all experimental groups compared to control rats. Findings indicated significant increase in semen numbers with 0.4 mg/kg dose of apomorphine during 60 min of study compared to other doses (16.9 ± 0.1) ($P < 0.001$). There was no significant difference between 0.4 and 0.5 mg/kg doses of apomorphine in numbers of seminal ejaculation (16.3 ± 0.5, 16.9 ± 0.1 respectively). Administration of bidistilled water with ascorbic acid, vehicle of apomorphine, did not stimulate the ejaculation (Figure 1 and Table 1). According to these results, 0.4 mg/kg of apomorphine was selected as the effective dose to investigating the effects of different extracts on ejaculation in experimental groups of this study.

Effect of the *L. angustifolia* methanolic extract on ejaculation induced by apomorphine

L. angustifolia extract-treated groups indicated dose-dependent decrease in the numbers of semen compared to only apomorphine-treated group. Rats which received 100 and 200 mg/kg doses of this extract indicated significant decrease in semen drops (6.1 ± 0.4, 14.1 ± 0.3 respectively) compared to 50 mg/kg (15.9 ± 0.5) and control groups (16.9 ± 0.1) ($P < 0.001$, $P < 0.05$ respectively). Experimental group which treated by 100 mg/kg doses of *L. angustifolia* indicated significant decrease in semen drops compared to 200 mg/kg ($P < 0.01$). There was no significant difference between 50 mg/kg extract treated and control group (Figure 2). Table 1 demonstrates the variation of semen numbers in animals which received apomorphine effective doses (0.4 mg/kg) and different doses of *L. angustifolia* and *B. serrate* extract.

Effect of the *B. serrate* methanolic extract on ejaculation induced by apomorphine

Pretreatment with methanolic extract of *B. serrate* decreased the number of semen dose-dependently in apomorphine induced ejaculation group. There was significant decrease in semen number during 60 min study when extract injected in 100 and 200 mg/kg (11.2 ± 0.4, 14.1 ± 0.4 respectively) compared to 50 mg/kg doses

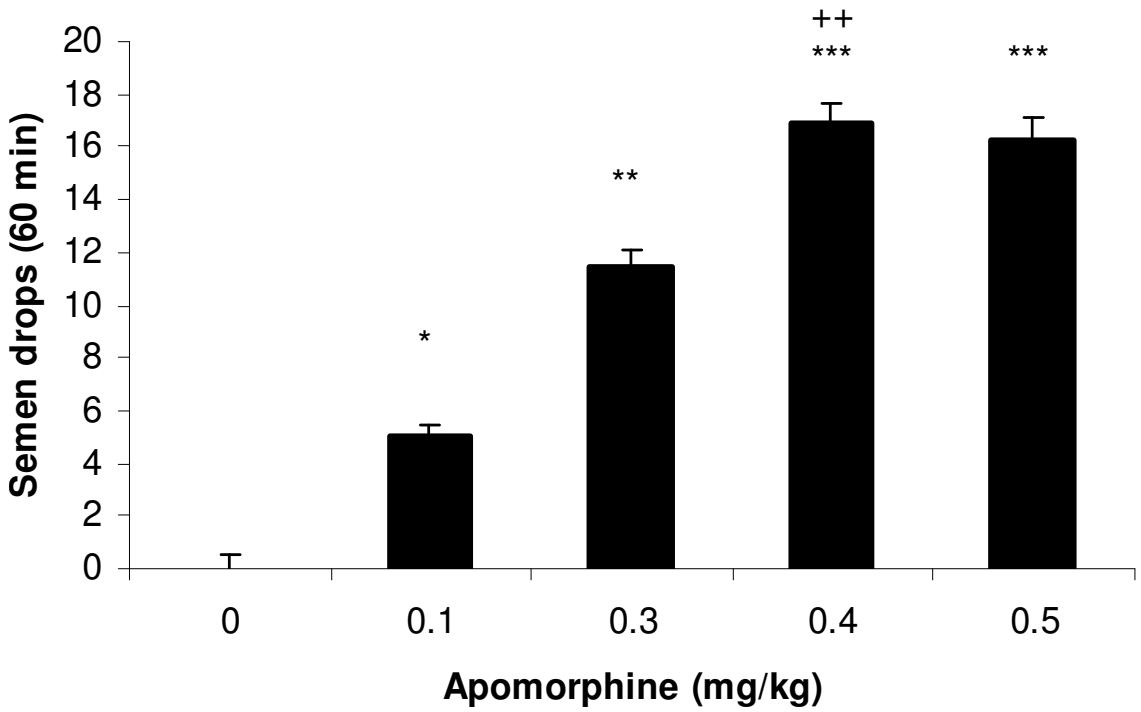

Figure 1. Ejaculation induced by apomorphine. There was significant increase in semen numbers with 0.4 mg/kg dose of apomorphine during 60 min of study compared to other doses. Data are shown as mean ± SEM (n = 6/group). *P< 0.05, ** P < 0.01, *** P < 0.001: for comparing semen drops variation between apomorphine and control groups. ++ P < 0.001: indicated significant difference in semen drop numbers between 0.3 and 0.4 mg/kg doses of apomorphine.

Table 1. Effect of different doses of methanolic extracts on apomorphine induced ejaculation.

Drugs	(mg /kg)	Semen drops (60 min) Mean ± SE
Vehicle (bidistilled water + ascorbic acid)		0
	0.1	5 ± 0.2*
	0.3	11.4 ± 0.4**
	0.4	16.9 ± 0.1***
	0.5	16.3 ± 0.5***
	0.4 + *L. angustifolia* 50	15.9 ± 0.5
	0.4 + *L. angustifolia* 100	6.1 ± 0.4***
	0.4 + *L. angustifolia* 200	14.1 ± 0.3*
Apomorphine	0.4 + *B. serrate* 50	16.3 ± 0.3
	0.4 + *B. serrate* 100	11.2 ± 0.4**
	0.4 + *B. serrate* 200	14.1 ± 0.4*
	0.4 + Combined extracts 50	12.5 ± 0.4**
	0.4 + Combined extracts 100	11.7 ± 0.3**
	0.4 + Combined extracts 200	16.2 ± 0.3
	0.4 + Vehicle of extracts	16 ± 0.3

Ejaculation was induced by subcutaneous injection of apomorphine dissolved in saline with vitamin C. *L. angustifolia* and *B. serrate* extracts injected separately or combined together in doses 50,100 and 200 mg/kg 30 min before ejaculation induced by apomorphine. * P < 0.05, ** P < 0.01, *** P < 0.001: significant semen drop difference in groups.

Table 2. Composition of the essential oil of *Lavandula angustifolia* extracted by hydrodistilation.

No	Compound	RI	%	KI
1	j-Pinene	35.72	35.91	1009.2
2	Lavandulyl acetate	45.32	14.14	1306.8
3	Geranyl acetate	48.52	7.39	1380.0
4	Trans-caryophyllene	52.10	6.69	1466.0
5	Trans-ocimen	30.98	4.8	1021.0
6	Neryl acetate	47.92	3.89	1366.3
7	j-Farnesene	53.57	3.44	1502.0
8	j-Myreene	28.78	2.22	985.4
9	Linalyl acetate	44.31	2.21	1284.8
10	β-Pinenoxide	40.35	2.18	1200.4
11	t-Cadinene	54.62	1.42	1529.5
12	Sabinaketon	35.01	1.30	1095.6
13	Limonen	29.61	1.12	997.9
14	Cis-Ocimen	30.44	0.95	1012.8
15	α-Terpinolene	31.87	0.79	1037.1
16	Linalool	39.41	0.71	1081.8
17	j-Chamigren	51.62	0.53	1454.3

(16.3 ± 0.3) of extract and control groups (16.9 ± 0.1) ($P < 0.01$, $P < 0.05$ respectively) (Figure 3). 100 mg/kg dose of *B. serrate* extract significantly decreased semen drops compared to 200 mg/kg ($P < 0.05$). Rats which pretreated by 50 mg/kg of extract indicated no significant difference with control group (Table 1).

Effect of the combination therapy with both *B. serrate* and *L. angustifolia* methanolic extract on ejaculation induced by apomorphine

Pretreatment with both *B. serrate* and *L. angustifolia* methanolic extracts (50, 100 and 200 mg/kg of each extracts) caused a potent and dose-related reduction in semen number compared to only apomorphine-treated group. Results indicated that, combination therapy with 50 and 100 mg/kg doses of extracts significantly decreased the semen number (12.5 ± 0.4, 11.7 ± 0.3 respectively) compared to and 200 mg/kg dose (16.2 ± 0.3) ($P < 0.01$) (Figure 4). There was no significant difference between the semen number reduction with 50 and 100 mg/kg doses of combined extracts.

Administration of vehicle of the extracts in apomorphine treated group did not cause significant variation in semen numbers (Table 1).

DISCUSSION

Natural product research can often be guided by ethnopharmacological data and it can give substantial contribution to drug innovation by providing novel chemical substances and/or mechanisms of actions (Harvey, 1999). In the present study the influence of *B. serrate* and *L. angustifolia* extracts on ejaculation induced by apomorphine was examined. Rats were used as subjects because there are several homologies between human sexual behaviors and that of rat such as the ejaculation (Pfaus, 1996). Apomorphine has been indicated to possess dopaminergic properties on D-1 and D-2 (dopamine) receptors (Seeman, 1980). Dose of apomorphine which was used in this study induced significant ejaculatory response which was supported by previous reports (Ahlenious and Larsson 1990; Zarrindast et al., 1994). Pretreatment with *L. angustifolia* extract (100 mg/kg) significantly decreased apomorphine-induced ejaculation during this study. The main constituent of *L. angustifolia* extract, linalool possesses anticonvulsant properties in glutamate-related seizure models and affects on NMDA (N-methyl d-aspartate) receptors (Silva Brum et al., 2001; Abuhamdah et al., 2008). It also inhibited potassium-stimulated glutamate release and modified the kinetics of the nicotinic receptor ion channels in the mouse neuromuscular junction (Barocci et al., 2000). However, *L. angustifolia* could be attributed to anxiolytic activity (De Moura Linck et al., 2009), some studies defined its role on sexual behavior (Jannini et al., 2005). Furthermore, some studies stated linalool not only modulates release of dopamine from rat brain striatum slices (Okuyama et al., 2004), but also alters plasma dopamine levels in ovariectomized female rats (Yamada et al., 2005). *L. angustifolia* extract also had apparent dual cholinergic activity (Adams et al., 2007). It was known that dopaminergic and cholinergic neurotransmitters involved in ejaculation behaviors (Zarrindast et al., 1994). These observations may suggest that *L. angustifolia* can exert its physiological effects on ejaculation at least in part by disturbing dopaminergic and cholinergic neurotransmission.

On the other hand, *B. serrate* extract administration during this study (100 mg/kg) reduced apomorphine-induced ejaculation. Traditionally *B. serrate* has been used to increase energy and endurance to physical efforts, promote mental clarity and as an aphrodisiac for men (Cicero et al., 2001). This plant also suggested for treatment of inflammatory and psychological disorders (Shah et al., 2007). *B. serrate* is reported to contain monoterpenes, diterpenes and triterpenes (Gayathri et al., 2007). Boswellic acids are considered to be the ingredients responsible of the plant anti-inflammatory activity, since these compounds inhibit leukotriene biosynthesis by impairing the lipoxygenase activity (Wildfeuer et al., 1998; Safayhi et al., 2000). Moreover, 12- ursene 2-diketone which was isolated from this crude extract can block specific cellular targets that are responsible for dopaminergic and cholinergic effects (Gayathri et al., 2007; Shah et al., 2007). *B. serrate* is shown to modulate dopaminergic and cholinergic responses in the brain (Burlando et al., 2008; Banno et al., 2006), and this mechanism could also play a role in *B. serrate*-induced

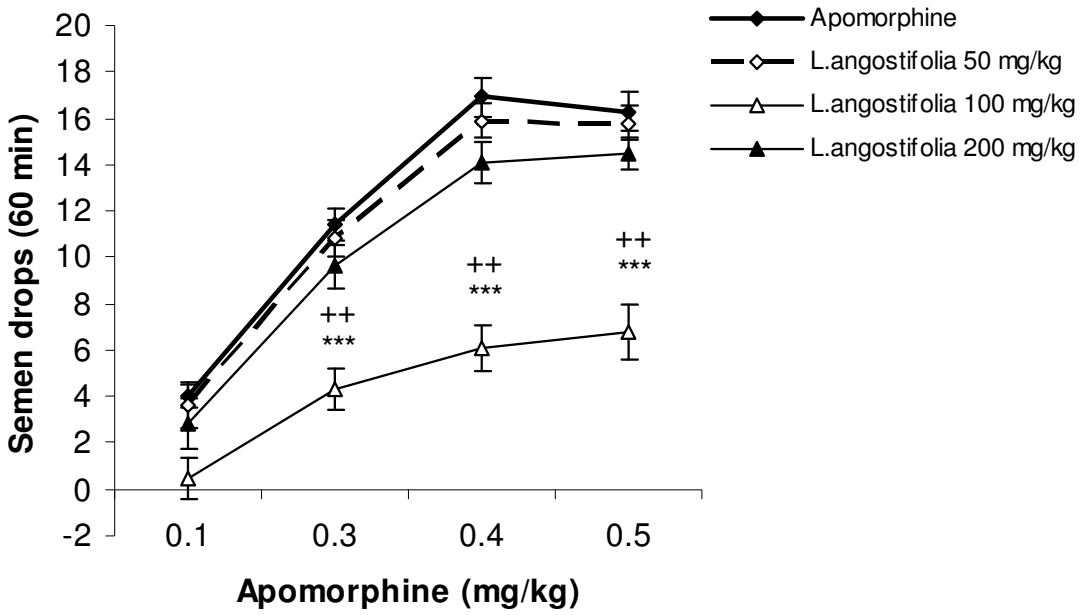

Figure 2. The effect of different doses of methanolic extract of *L. angustifolia* (50, 100, 200 mg/kg) on apomorphine induced ejaculation. Rats which received 100 mg/kg dose of this extract indicated significant decrease in semen drops compared to 50, 200 mg/kg doses of extracts and control groups. Data are shown as mean ± SEM (n=6/group). *** P< 0.001: for comparing semen drop numbers variation in *L. angustifolia* 100 mg/kg treated group with control (apomorphine-treated) and 50 mg/kg extract-treated groups. ++ P< 0.01: demonstrated significant difference in semen drop numbers between 100 and 200 mg/kg doses of *L. angustifolia* extract.

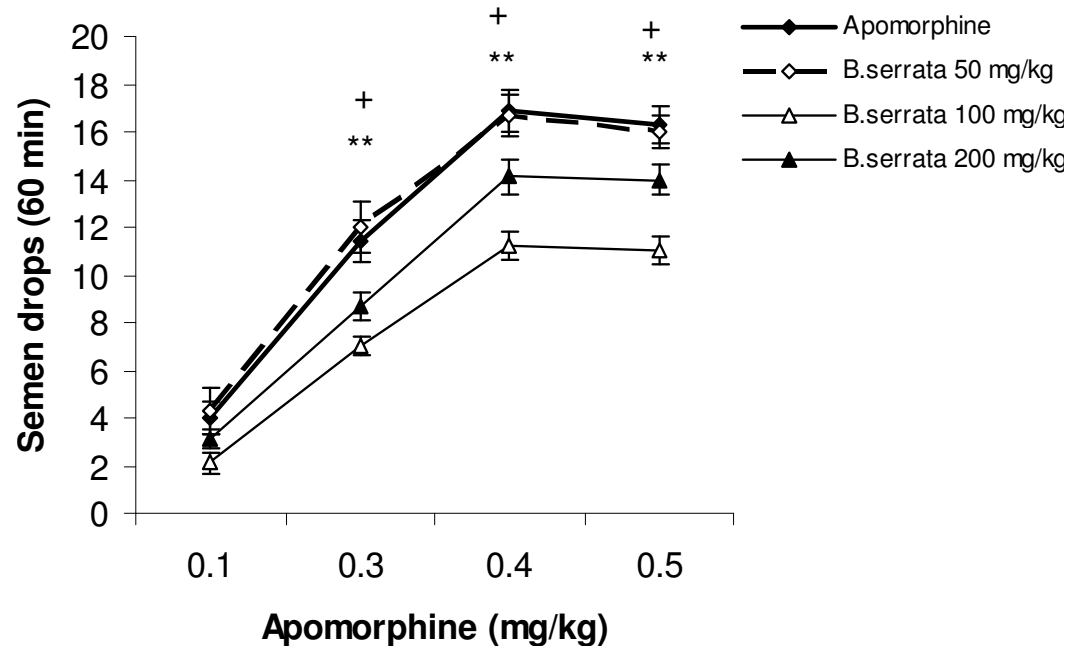

Figure 3. The effect of different doses of methanolic extract of *B. serrate* (50, 100, 200 mg/kg) on apomorphine induced ejaculation. Rats which received 100 mg/kg dose of this extract indicated significant decrease in semen drops compared to 50, 200 mg/kg doses of extracts and control groups. Data are shown as mean ± SEM (n = 6/group). **P < 0.01: for comparing semen drop numbers variation in *B. serrate* 100 mg/kg treated group with control (apomorphine-treated) and 50 mg/kg extract-treated groups. + P < 0.01: for comparing semen numbers variation between 100 and 200 mg/kg doses of *B. serrate* extract.

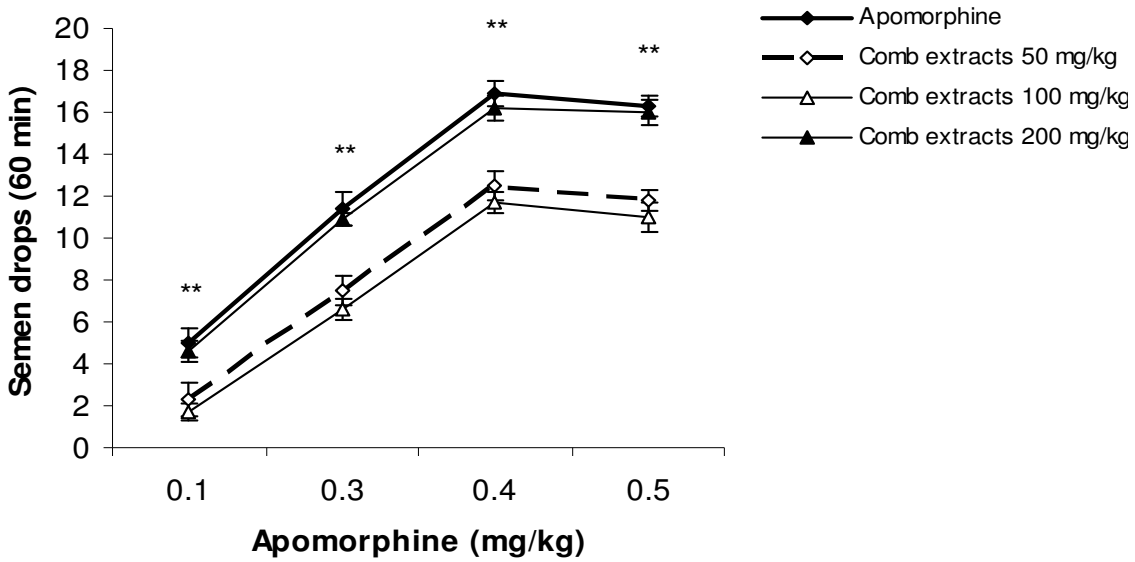

Figure 4. The effect of different doses of combined methanolic extracts of *B. serrate* and *L. angustifolia* (50, 100, 200 mg/kg) on apomorphine induced ejaculation. Combination therapy with 50 and 100 mg/kg doses of both extracts significantly decreased the semen number compared to control and 200 mg/kg and control groups. Data are shown as mean ± SEM (n = 6/group). **P < 0.01: indicated significant difference between combined extracts-treated groups (50 and 100 mg/kg) with 200 mg/kg extract-treated and control groups.

variation of ejaculation (Ratnasooriya and Fernando 2008; Napoli-Farris et al., 1984). Combination therapy with both *B. serrate* and *L. angustifolia* indicated significant reduction in ejaculation-induced by apomorphine compared to monotherapy.

Furthermore, when extracts administered together the effective dose (50 mg/kg) was lower than when we used them separately (100 mg/kg). This may be as a result of possible synergistic interactions between constituents of extracts sample (Vongtau et al., 2004). On the other hand, high doses (200 mg/kg) of extracts mono/ combination therapy indicated less or no significant decrease in semen numbers compared to other effective doses of extracts in this study. It may be due to their antagonizing effects in higher doses, which can decrease the inhibitory effect of extracts on ejaculation. The most plausible explanation for the present study is that, mono/combination therapy with *B. serrate* and *L. angustifolia* extracts decreased the apomorphine induced ejaculation and may have a beneficial role in the treatment of rapid ejaculation. However, further studies are needed to determine the precise mechanism of action of these two extracts potency on sexual behaviors such as ejaculation.

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