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Aphrodisiac properties of *Montanoa tomentosa* aqueous crude extract in male rats

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Abstract

Cihuapatli, the Mexican zoapatle (*Montanoa tomentosa*) has an extensive ethnomedical history of use as a traditional remedy for reproductive impairments. During the study of the ejaculatory function in rats and by testing a set of Mexican plants with medicinal properties, we observed that crude extracts of *M. tomentosa* facilitated ejaculation. Thus, we decided to analyze the possibility that this plant possessed sexual stimulant properties. To that aim, copulatory behavior of sexually active male rats receiving doses of 38, 75 and 150 mg/kg of the aqueous crude extract of *M. tomentosa*, as it is prepared in traditional medicine, was assessed. In addition, we evaluated the effect of the 75-mg/kg dose of the extract on males with anesthetization of the genital area and on sexual behavior of sexually inactive male rats (noncopulators). Results showed that acute oral administration of crude extracts of *M. tomentosa* facilitates expression of sexual behavior in sexually active male rats, significantly increases mounting behavior in genitally anesthetized animals and induces the expression of sexual behavior in noncopulating males. Altogether, these data reveal a facilitatory action of this extract on sexual activity and particularly on sexual arousal. Present findings provide experimental evidence that the crude extract preparation of *M. tomentosa*, used as a traditional remedy, possesses aphrodisiac properties.

Keywords: Sexual stimulant; Male rat sexual behavior; Mexican plant; Traditional remedy; Sexual arousal; Noncopulators

1. Introduction

Cihuapatli, the Mexican zoapatle (*Montanoa tomentosa)* and its close relatives have an extensive ethnomedical history of use as a traditional remedy for reproductive impairments. *M. tomentosa* aqueous crude extract has been used for the last five centuries for the induction of labor, regulation of fertility, treatment of postpartum bleeding problems and to induce menses (Gallegos, 1983, 1985; Southam et al., 1983). This plant has been described to possess antipregnancy activity in women when the aqueous extract of the leaves is administered orally during early stages of pregnancy (Hahn et al., 1981; Gallegos, 1983, 1985; Levine et al., 1981; Ponce-Monter et al., 1983). Experimental studies in rats and mice confirm popular observations showing that the antipregnancy effects of *M. tomentosa* crude extract are provoked by inhibition of implantation, cervical dilatation and uterine bleeding (Hahn et al., 1981). This extract does not modify the hematological, blood lipid, protein and electrolytic status or the function of the liver, kidney and thyroid gland (Hahn et al., 1981). The abovementioned physiological events lack influence upon the general endocrine status (Bejar et al., 1984; Hahn et al., 1981; Pedrón et al., 1985, 1988), other than its unique antipregnancy, oxytocic-like effects on the female reproductive tract (González-Angulo et al., 1985; Perusquía et al., 1985; Smith et al., 1981). Likewise, effects on female reproductive function are obtained with the administration of more purified fractions derived from this plant (Bejar et al., 1984; Gallegos, 1985; Guzmán-Durán et al., 1988; Wani et al., 1983). In contrast, acute administration of *M. tomentosa* crude extracts to males does not significantly affect

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fertility. Thus, human and rabbit sperm motility or viability is not affected by the administration of *M. tomentosa* aqueous crude extract in a wide range of concentrations (Wens et al., 1985). Purer fractions derived from *M. tomentosa* extracts display only a weak to negligible capacity for killing human sperms (Valencia et al., 1986).

During the study of the ejaculatory function in male rats and by testing a set of Mexican plants with medicinal properties, we observed that acute oral application of aqueous extracts of *M. tomentosa* facilitated the expression of sexual behavior as reflected by a diminution of the ejaculatory threshold. On this basis, it was proposed that this plant could possess sexual stimulant properties. Although different Mexican plants have been found to possess aphrodisiac properties (Arletti et al., 1999), there are no reports on *M. tomentosa* ascribing prosexual effects to this plant. Aphrodisiacs can be categorized according to their mode of action into three groups: substances that increase libido (i.e., sexual desire, arousal), substances that increase sexual potency (i.e., effectiveness of erection) and substances that increase sexual pleasure (Sandroni, 2001).

In the present study, we examined the effect of the acute administration of *M. tomentosa* aqueous crude extract upon the expression of male rat sexual behavior in sexually experienced animals. In addition, its effect on sexually inactive rats, i.e., so-called noncopulators, and on animals with local anesthetization of the glans penis was established in order to evaluate the possibility that this plant extract might possess aphrodisiac properties. Analysis of sexual behavior performance in animals with anesthetization of the glans penis is a model commonly used to specifically evaluate sexual arousal (Clark et al., 1984). The use of sexually inactive rats in the present study serves the same purpose. Finally, evaluation of the sexual performance of sexually active males allows the assessment of the sexual behavior components, i.e., motivation and performance, which are modified by a given treatment.

2. Methods

2.1. Animals

Sexually vigorous and sexually inactive male Wistar rats (300–350 g body weight) were used. Animals were housed in groups (four rats per cage) under an inverted 12:12 h LD cycle at 22 °C and with free access to food and water. Before experimental testing all animals received five sexual behavior tests; sexually active males, those showing ejaculation latency shorter than 15 min in at least the last three sessions, were selected and considered sexually experienced. Sexually inactive animals that failed to show sexual activity in five consecutive experimental tests were classified as noncopulators. The Local Committee of Ethics on Animal Experimentation approved all experimental procedures, which followed the regulations established in the Mexican Official Norm for the use and care of laboratory animals NOM-062-ZOO-1999.

2.2. Preparation of zoapatle solutions

M. tomentosa was collected near Tlaxcala City in its natural habitat and was authenticated by the Jardín Botánico Universitario from the Universidad Autónoma de Tlaxcala, where voucher specimens are preserved and cultured. The voucher number is *Montanoa* variety *tomentosa* 101. Leaves and flowers were collected and dried during a period of 20 days. Once dried, the material was ground into a fine powder, 200 g of which were mixed with 1 l of distilled water. This mixture was then heated for approximately 10 min, just to avoid boiling. The obtained infusion was filtered and corresponded to a 200-mg/ml concentration (200 g powder/1000 ml of distilled water). Dilutions were prepared from this initial extract to obtain the different concentrations used (12.5, 25 and 50 mg/2 ml). Infusions were prepared 40 min before administration.

2.3. Treatments

Sexually vigorous male rats were randomly assigned to one of the following groups ($n = 9$, each): Group 1 received the vehicle (distilled water) orally (2 ml) and served as control. Groups 2 to 4 received a single oral treatment with 12.5, 25 or 50 mg/2 ml of the aqueous crude extract of *M. tomentosa* (doses of 38, 75 and 150 mg/kg, respectively). Once prepared, the different concentrations of the tea were administered orally to animals via a catheter 1 h after the onset of darkness. After 30 min of the application of each dose, animals were tested for male rat sexual behavior. Animals in Group 5 ($n = 8$) received a single oral dose of 75 mg/kg of the *M. tomentosa* crude extract and were anaesthetized in the genital area with tetracaine hydrochloride (4-[butylamino]benzoic acid 2-[dimethylamino]ethyl ester; Sigma, St. Louis, MO). Sexual behavior tests were conducted in these rats 30 min after treatment administration and 10 min after application of local anesthesia. Group 6 included noncopulating males ($n = 8$) that received a single oral dose of 75 mg/kg of *M. tomentosa* crude extract and after 30 min copulation, if present, was monitored for 15 min. Groups 7 to 10 ($n = 8$ each) were selected to test motor activity and included animals receiving either vehicle solution orally (2 ml) or a single acute dose of 38, 75 or 150 mg/kg of *M. tomentosa*.

2.4. Sexual behavior testing protocol

All sexual behavior tests were conducted 2 h after the onset of darkness. Males were introduced into a cylindrical observation cage and a 5-min adaptation period was allowed. Thereafter, a stimulus-receptive female was introduced and sexual behavior was recorded along 15

min. Female receptivity was induced by the sequential subcutaneous administration of estradiol valerianate (4 μg/rat) followed 44 h later by progesterone (2 mg/animal). Behavioral observations were conducted 4 h after progesterone administration. The sexual behavior parameters analyzed were mount latency, time from introduction of the female until the first mount with pelvic thrusting; intromission latency, time from introduction of the female until the first mount with pelvic thrusting and vaginal penetration (intromission); ejaculation latency, time from the first intromission until ejaculation and postejaculatory interval, time from ejaculation until the next intromission. In addition, the number of mounts and intromissions displayed in an ejaculatory series was recorded. Latency data were expressed in minutes as mean ± S.E.M. and the number of mounts and intromissions as median numbers.

2.5. Open-field test

In order to discard a possible plant-extract-induced motor impairment that could influence the sexual behavior recordings, the effect of the different doses of *M. tomentosa* crude extract was tested in the open-field test. In brief, the apparatus consisted of an opaque Plexiglas box (40 × 30 × 20 cm) with the floor divided into 12 equal squares (10 × 10 cm^2). The animals were placed in a corner of the apparatus, and an observer blind to the treatments registered the number of times that the animal crossed squares during a 5-min session (Estrada-Camarena et al., 2003).

2.6. Data analysis

To determine statistical significant differences among treatments, the sexual behavior data were analyzed by means of a one-way ANOVA followed by the Dunnett *t* test. Paired comparisons were conducted by using the Mann–Whitney *U* test. The percentage of animals showing sexual behavior was analyzed with the Fisher exact test. The Sigma Stat program (version 2.03) was employed for all statistical analyses. Motor activity data were expressed as mean ± S.E.M. of crosses and statistically evaluated by means of the Mann–Whitney *U* test.

3. Results

In the first part of the present study, copulatory behavior was examined in sexually experienced male rats that were acutely treated with vehicle or with 38, 75 or 150 mg/kg of the crude extract of *M. tomentosa.* In Fig. 1 the specific sexual behavior parameters registered after the different doses of *M. tomentosa* show statistically significant reductions in the number of intromissions, the ejaculation latency and the postejaculatory interval. The reduction in the number of intromissions was a constant, independent of the dose of the extract administered (Fig. 1, lower left panel), the dose of 75 mg/kg of the aqueous extract being the most effective in reducing this parameter ($P < .001$, Mann Whitney *U* test). As to the ejaculation latency, the 38 and 75 mg/kg doses of *M. tomentosa* extract significantly

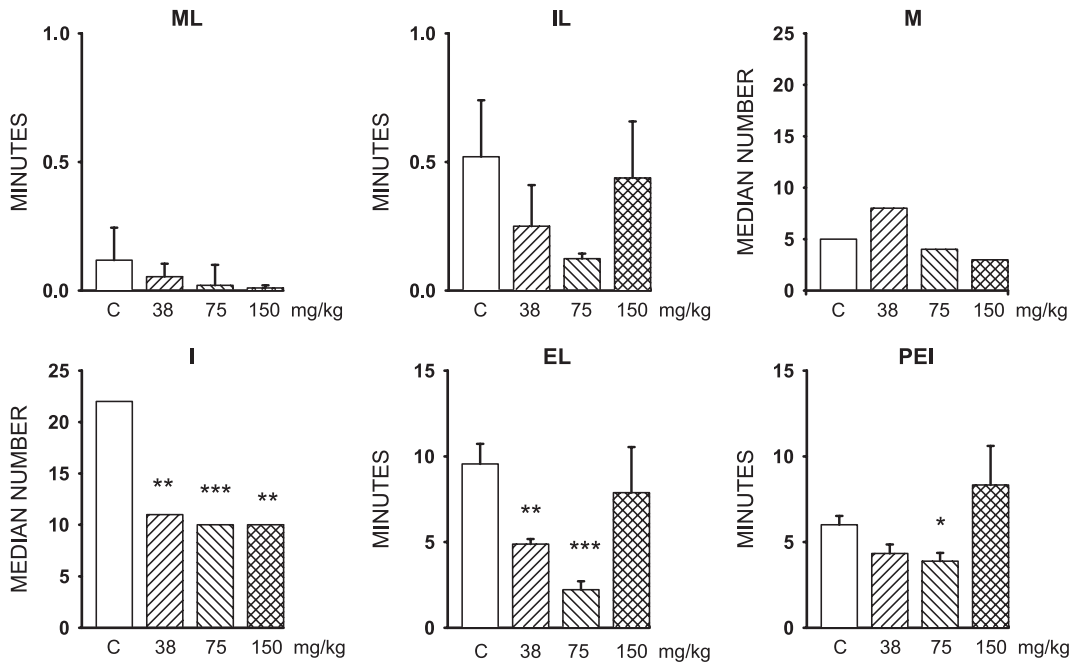

Fig. 1. Specific sexual behavior parameters of sexually active male rats treated with 0 (C), 38, 75 and 150 mg/kg *M. tomentosa* aqueous extract. ML = mount latency, IL = intromission latency, M = number of mounts, I = number of intromissions, EL = ejaculation latency, PEI = postejaculatory interval. Latencies are expressed as mean ± S.E.M. and numbers as medians. One-way ANOVA followed by Mann–Whitney *U* test, *** $P < .001$; ** $P < .01$; * $P < .02$.

and dose dependently reduced its duration, while the dose of 150 mg/kg returned the values of this parameter towards control levels (Fig. 1, lower middle panel). A trend toward a reduction in the postejaculatory interval was observed at the 38-mg/kg dose, which reached statistical significance after 75 mg/kg (Fig. 1, lower right panel). Again, the highest dose of the extract (150 mg/kg) returned the duration of the PEI towards control values. No statistically significant changes were observed in mount and intromission latencies, although a trend toward a reduction can be observed in both parameters, the intromission latency showing a biphasic trend. As a whole, a U-shaped dose–response curve was obtained after treatment with this extract, with the lower concentrations showing facilitatory effects that shifted towards control values at the highest dose tested. The clearest facilitatory effects of the *M. tomentosa* extract upon male rat sexual behavior were obtained with the dose of 75 mg/kg; therefore this dose was selected for the experiments involving animals with genital anesthesia and noncopulating males.

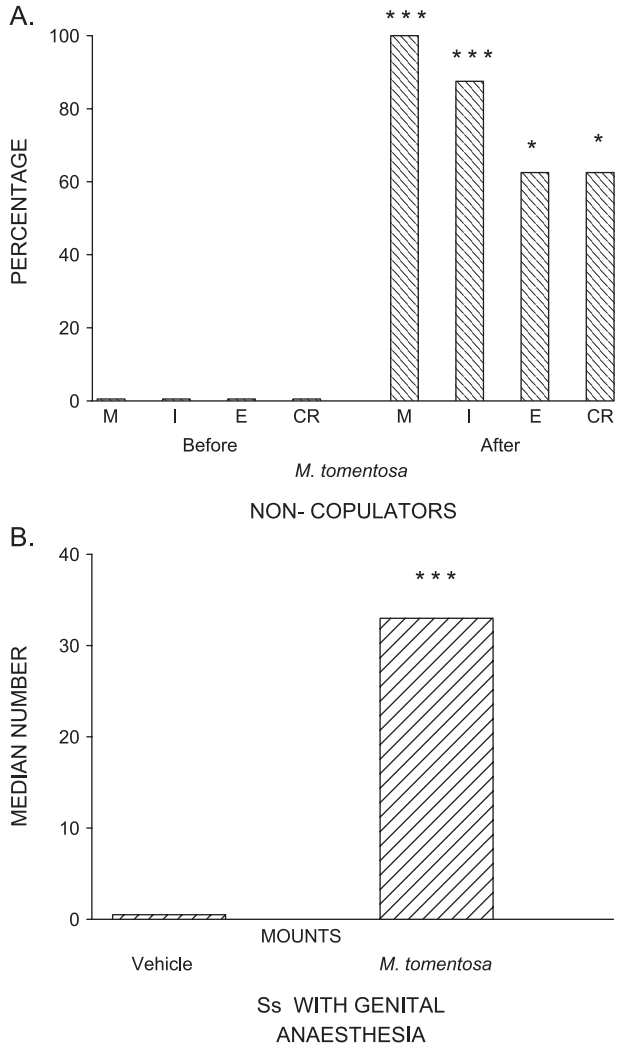

Fig. 2. (A) Percentages of noncopulating rats that exhibit mounts (M), intromissions (I), ejaculation (E) or copulation resumption after ejaculation (CR) in response to 75 mg/kg *M. tomentosa* aqueous extract (Fisher exact probability test, * * * $P<.001$, * $P<.05$). (B) Effect of 75 mg/kg *M. tomentosa* on mounting behavior of sexually active males with anesthetization of the glans penis. Mann–Whitney *U* test, * * * $P<.001$.

Table 1
Effect of oral administration of *M. tomentosa* aqueous crude extract on the open-field test in male rats

Treatment	Number of crossed squares in 5 min
Saline solution	54.13 ± 3.32
M. tomentosa	
38 mg/kg	53.50 ± 2.92
75 mg/kg	56.00 ± 1.38
150 mg/kg	48.75 ± 2.46

In the second part of this study, the data obtained after acute administration of *M. tomentosa* extract to genitally anesthetized animals showed an important facilitation of mounting behavior. Thus, a statistically significant increase in the number of mounts was observed in animals treated with 75 mg/kg *M. tomentosa* as compared to vehicle-treated control animals (Mann–Whitney *U* test, $P<.001$, see Fig. 2, panel B), with no differences in the mount latency (data not shown). Neither control vehicle- nor *M. tomentosa*-treated rats displayed intromissive or ejaculatory behaviors and there was no evidence of seminal deposition.

Administration of a dose of 75 mg/kg of *M. tomentosa* aqueous extract to noncopulating animals promoted the display of copulatory behavior. Thus, mounting behavior was observed in all tested males, intromissive behavior was exhibited by 87.5%, and 62.5% of the previously sexually inactive animals displayed ejaculatory behavior (see Fig. 2, panel A). The specific sexual behavior parameters recorded from the previously noncopulating animals that achieved ejaculation after *M. tomentosa* treatment were not different from those exhibited by sexually experienced vehicle-treated rats (data not shown).

Finally, none of the three doses of the extract tested had an effect on the locomotor activity of male rats (see Table 1).

4. Discussion

The present study provides evidence for the ability of the crude extract of the Mexican plant zoapatle, *M. tomentosa*, to enhance male sexual behavior expression in sexually active rats and to promote sexual activity in sexually inactive male animals. The data obtained reveal that when orally administered the aqueous crude extract of *M. tomentosa* effectively facilitates several aspects of copulatory behavior. In the experimental analysis of male sexual activity, the concept of the existence of two different physiological mechanisms responsible for sexual behavior expression was introduced in the early 50s by Frank Beach. This notion holds that one of these mechanisms is respon-

sible for sexual arousal and the other for sexual performance (Beach, 1956). This concept has been central for the neurobiology of sexual behavior.

In the present study, we were interested in establishing whether *M. tomentosa* extracts exhibited prosexual effects and, if this were the case, upon which of the physiological mechanisms the facilitatory actions were exerted. As mentioned in the Introduction, prosexual effects of so-called aphrodisiacs might be exerted at different levels, i.e., sexual arousal or performance. The data obtained in the present study with sexually active animals reveal that the facilitatory actions of the *M. tomentosa* extract are exerted on both mechanisms, sexual arousal and performance. Thus, the main facilitatory effect of the extract was a reduction in the number of intromissions and the ejaculation latency, which together reflect a lowering of the ejaculatory threshold. However, the fact that the aqueous extract of this plant had a clear facilitatory effect on a model specifically designed to test sexual arousal, i.e., mounting behavior in animals with the glans penis anesthetized, shows that it specifically facilitates sexual motivation. Actually, this experimental manipulation was designed to eliminate the expression of the genital reflexes involved in intromissive and ejaculatory behaviors, allowing the measurement of sexual motivation, as reflected by the number of mounts, uninfluenced by the other sexual behavior components (Clark et al., 1984). In further support of a facilitatory effect of the extract of zoapatle on sexual arousal is the fact that 100% of the previously sexually inactive male rats engaged in copulation after extract administration, 65% of them achieving ejaculation. It is well documented that these so-called "noncopulators" are otherwise normal rats that fail to initiate copulation despite repeated exposure to receptive females (Stefanick and Davidson, 1987). Failure to mate in this population has been attributed to deficits in sexual arousal (Crowley et al., 1973), since neither erectile nor ejaculatory function is impaired (Stefanick and Davidson, 1987). Hence, the prosexual effects of the zoapatle extract influence sexual behavior expression in a broad manner.

Among the biologically active principles isolated from *M. tomentosa* extracts are a diterpene named grandiflorenic acid, which is present in the "tea" traditionally used by native women (Enríquez et al., 1983), and a triplet of oxepane diterpenoids including zoapatanol, montanol and an unidentified compound overlapping with montanol (Guzmán-Durán et al., 1988). None of these compounds have been tested on male rat sexual activity. The data obtained in the present series of experiments do not allow one to propose the mechanism through which the extract might exert the prosexual effects reported here. As to the mechanisms involved in other biological actions of *M. tomentosa*, they appear to be similar to those produced by oxytocin (Levine et al., 1981; Gallegos, 1985), and β-adrenoceptors have been found to participate in some of the extract actions (Gallegos, 1985; Perusquía et al., 1985). It is well known that both oxytocin and noradrenaline, certainly among other neurotransmitter systems, play a role in the expression of male rat sexual behavior (Gimpl and Fahrenholz, 2001; Hughes et al., 1987; Ivell et al., 1997). Thus, administration of oxytocin agonists to male rats facilitates copulation by mainly reducing the ejaculation latency and the postejaculatory interval (see Gimpl and Fahrenholz, 2001, for a review). Stimulation of β-adrenoceptors reduces the number of mounts and intromissions to ejaculation and increases the postejaculatory interval of sexually experienced male rats (see Meisel and Sachs, 1994, for a review). Interestingly, β-adrenoceptor agonists promote copulation in noncopulators (see Meisel and Sachs, 1994, for a review). Based on these facts, both mechanisms are candidates to participate in the prosexual effects of *M. tomentosa*. Endogenous opioid systems might be also be a target of the extract of *M. tomentosa* for the facilitation of sexual activity, since these systems have been found to be involved in the maintenance of sexual inactivity in noncopulators. Thus, opioid antagonists such as naloxone induce copulatory behavior in previously sexually inactive male rats (Gessa and Paglietti, 1979), and an increased enkephalinergic content in the hypothalamus of noncopulators has been demonstrated (Rodríguez-Manzo et al., 2002).

As to the possibility that a steroid-like effect of the aqueous crude extract of *M. tomentosa* might be responsible for the prosexual effects here reported, there are data showing the absence of estrogenic and androgenic activity as well as a lack of effect of this extract on progesterone and estradiol plasma levels (Bejar, 1988 Landgren et al., 1979; Pedrón et al., 1988; Wens et al., 1985). Nevertheless, specific experiments are necessary to establish the mechanisms involved in the prosexual effects of the crude extract of *M. tomentosa*.

There is considerable evidence that the extract of *M. tomentosa* and some of its more purified fractions affect reproductive function. Earlier in vivo and in vitro physiological studies have demonstrated that *M. tomentosa* increases spontaneous uterotonic activity and induces cervical dilatation and uterine bleeding (Gallegos, 1983, 1985; Hahn et al., 1984; Levine et al., 1981; Lozoya et al., 1983; Smith et al., 1981; Southam et al., 1983). The main hypotheses of those studies suggest that the potential target of *M. tomentosa* aqueous crude extract or its derivatives is the female reproductive tract. However, whether *M. tomentosa* compounds had other targets such as neural tissue was not explored. The fact that *M. tomentosa* aqueous crude extract as traditionally prepared promoted a facilitation in male rat sexual arousal suggests the possibility that the compounds included in the "tea" crossed the blood–brain barrier to exert some of its effects. In all probability the prosexual effects of this extract involves both peripheral and central actions. Again, specific experimentation is necessary to determine the site(s) and mechanism(s) of action involved in the effects of *M. tomentosa* on masculine sexual behavior.

In summary, the present study provides evidence that the aqueous crude extract of *M. tomentosa* is a potent stimulator of sexual behavior, particularly of sexual arousal in male rats, and that it promotes the expression of masculine sexual behavior in previously sexually inactive animals. On these bases, this extract can be considered to possess aphrodisiac properties.

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