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Short Communication

Spasmolytic Effects of *Ageratum conyzoides* in Vas Deferens

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ABSTRACT

Premature ejaculation is a disorder that affects many men. This pathology may be the result of uncoordinated contraction of the vas deferens. *Ageratum conyzoides* is a plant used for the treatment of several pathologies in many regions in Brazil. Both in vitro and in vivo studies have shown that the *A. conyzoides* has many pharmacological properties, including a beneficial effect on benign prostatic hyperplasia, antitumoral effect and relaxation of gastrointestinal and genitourinary organs. The aim of the present study was to evaluate the effect of the *A. conyzoides* essential oil in the contractility of the vas deferens. 60-day old male Swiss mice were used in the experiment. Vas deferens were stimulated with potassium chlroride (KCl 80 mM), which induced a biphasic contractile response (phasic and tonic). The treated group had previous growing doses of the essential oil. The *A. conyzoides* induced the relaxation both of the phasic and tonic components, although the effect on the tonic component was statistically significant when compared to phasic. This inhibitory effect of the contractility may be potentially explored in order to guide clinical studies to treat premature ejaculation.

Keywords: *Ageratum conyzoides*; Premature ejaculation; Vas deferens; Contractility

INTRODUCTION

Among the sexual pathologies that affect men, Premature Ejaculation (PE) and Erectile Dysfunction (ED) can be mentioned. They are underdiagnosed pathologies, as they involve psychosocial aspects of the patient, which hinder or delay the search for health services [1]. The World Health Organization's ICD-10 definition of PE includes both an inability to control ejaculation, as well as a cut-off of ejaculation within 15s of beginning intercourse [1]. The coordinated contraction of the vas deferens, among other mechanisms, is necessary for male ejaculation to happen. This contraction is responsible for the transport of sperm from the epididymis to the urethra. Thus, substances that decrease the contraction of the vas deferens might be promising for the treatment of PE.

There are several treatment options for PE, including Selective Serotonin Reuptake Inhibitors (SSRIs) in off-label, long term or on demand use, Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) and tricyclic antidepressants, tramadol, phosphodiesterase inhibitors, alpha blockers and local anesthetics, and behavioral therapy [1].

Ageratum conyzoides is a plant which has been widely used in folk medicine. It comprises many phytochemicals, such as flavonoids, vitamins, terpenes, alkaloids and chromenes, Precocene I being the most prevalent, accounting for over 70% of the essential oil composition [2,3].The extract contains substances with anti-

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inflammatory, antipyretic, analgesic and spasmolytic properties [4]. For this reason, the aim of the present study was to evaluate the effect of the *A. conyzoides* on KCl induced contractility of the vas deferens, as these mechanisms are involved in the process of ejaculation.

MATERIALS AND METHODS

The experiments were carried out on vas deferens mounted in a bath chamber. Twenty male mice were used and were euthanized with an association of Ketamine (135 mg/Kg PV, Vetanarcol, König, Brazil) and Xylazine (6 mg/Kg PV, Dopaser, Calier, Spain). Vas deferens were maintained in laboratory solutions [5,6] and the contractions by KCl were recorded (software LabChart). The experimental groups were the ones which received increasing doses of *Ageratum* extract (1×10^{-6} mg/mL, 2×10^{-6} mg/mL, 4×10^{-6} mg/mL, 8×10^{-6} mg/mL and 16×10^{-6} mg/mL.) while to the control group nothing was administered. The effect of *Ageratum conyzoides* was evaluated through the analysis of negative logarithm of the concentration that produces 50% of the maximum inhibitory effect (pIC_{50}). Unpaired Student's t-test was used for analyzing data, and significance was accepted at $P<0.05$. All data are in the form mean ± error.

RESULTS AND DISCUSSION

Figure 1 shows the inhibitory effect of the *A. conyzoides* essential oil on the KCl induced contractility. It was observed that both the phasic and the tonic components are susceptible to its action. While analyzing the pIC_{50}, it was observed that the inhibition on the tonic component was statistically different from the phasic component, which shows that the tonic component is more sensitive to the effect of the *Ageratum* (Table 1).

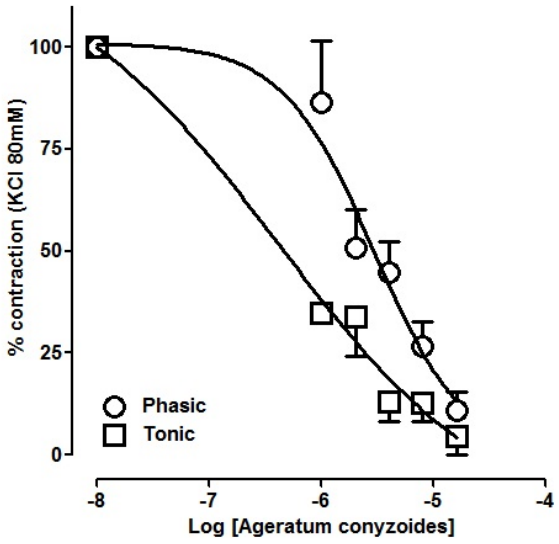

Figure 1: Effect of pre-incubation of *Ageratum conyzoides* on phasic component (open circle) and tonic component (open square) to KCl (80 mM) contraction in vas deferens. Each point is the mean ± error of at least 6 experiments.

It is well-known in literature that the KCl induces a biphasic contraction, formed by the phasic and tonic components [7-9]. Also, that the contraction of these components is caused by the participation of two types of voltage-dependent calcium channels: the fast opening one, which is responsible for the phasic component of the contraction, and the slow opening ones, responsible for the tonic component [10,11]. The results obtained showed different responses from the phasic and tonic components to the action of the *A. conyzoides* essential oil, thus suggesting that it may have acted mainly upon the channels in the tonic component.

Table 1: Log IC_{50} of *Ageratum conyzoides* on phasic and tonic component to KCl (80 mM) contraction in vas deferens.

Component	pIC_{50} (mg/mL)
Phasic	-5.447
Tonic	-6.228*

*Significantly different from the phasic component. $P<0.05$.

Only a few studies suggest this mechanism of action of the *Ageratum* Silva et al. [4] verified, similarly to the present study, that derivatives of *A. conyzoides* cause inhibition of organ contraction in both the gastrointestinal and genital systems. However, in their study, they evaluated the female genital system. The authors suggest that this inhibition effect may be caused by the inhibition of cyclic AMP phosphodiesterase and/or influx of calcium ions. Achola and Munenge [12] demonstrated that *Ageratum conyzoides* plant extract was able to inhibited uterine contractions induced by 5-hydroxytryptamine, this results suggested an antiserotonergic effect, whereas Yamamoto et al. [13] verified that the water extract of *Ageratum* has a partial agonist action when compared to the action of histamine and acetylcholine.

Amongst male disorders, PE can be mentioned. Ejaculation depends on the contraction of the vas deferens [14]. Our results showed that *A. conyzoides* essential oil inhibits contraction of the vas deferens, which might indicate its potential to treat PE. Amongst the different treatments for PE, there is the use of antidepressants, opioid analgesics and alpha receptor antagonists. The use of antidepressants is based on the hypothesis that PE occurs due to a dysfunction of serotonergic receptors. It has already been demonstrated that their over-stimulation has an inhibitory action on ejaculation [1]. On the other hand, it has been shown that tramadol, which is an agonist for mu receptors, also acts as antagonist for 5-HT2C receptors, being a strong candidate for the treatment [1]. As previously mentioned the *Ageratum conyzoides* may have an anti-serotonergic effect [12]. The therapeutic use of local anesthetics occurs due to their ability to decrease the penile hyper stimulation effects and, consequently, delaying PE. Alpha blockers inhibit the contraction of the seminal vesicle thus inhibiting the PE emission phase [1].

BOTANICAL ASPECTS

Ageratum conyzoides L. is a plant that belongs to the Asteraceae family. A voucher specimen of *Ageratum* was deposited in the Herbarium of the Federal University of São João de Rei (code HUFSJ 10293, collector: Monteforte PT).

CONCLUSION

So, it's the first study that demonstrated the effect of *Ageratum conyzoides* on vas deferens. Our results, suggests the use of *A. conyzoides* as a new treatment option, acting directly on the vas deferens, may be to delay ejaculation through the inhibition of muscle contraction.

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