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## EFFECTS OF VALERIANA OFFICINALIS AND PASSIFLORA SP ON THE BEHAVIOR OF WISTAR RATS

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### ABSTRACT

Anxiety affects millions of adults worldwide. *Valeriana officinalis* (VO) contains several active compounds that may work as anxiolytic as well as *Passiflora sp* (PA). Due to this reason, the aim of this study is to evaluate the acute and chronic effects of *Valeriana officinalis* and *Passiflora sp* in the behavioral test of Wistar rats. Wistar rats were divided into seven groups (n= 5): G1: a control group that received saline solution; G2, G3, and G4 were treated respectively with 11, 22 and 44mg/kg of VO extract and G5, G6 and G7 with PA in the same doses used with VO. Our results for the behavioral test showed that the use of VO and PA significantly modify the behavior of the rats. We verified that the acute treatment with doses of 22mg/kg for VO and 11 and 22mg/kg for PA resulted in a suggestive anxiolytic effect. For the chronic uses, doses of 44mg/kg (VO) and 22mg/kg (PA) resulted in a suggestive anxiolytic effect. Our results show that both VO and PA may exhibit anxiolytic effects in Wistar rats. In acute use of the plants, we may observe stronger effects of VO when comparing with PA. The opposite was seen in the chronic use of the plants.

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## INTRODUCTION

Anxiety affects millions of adults worldwide, and complementary health approaches reached almost 35% in 2012. This may be observed as a growing tendency worldwide due to the low costs and low risk of side effects and addiction (Dantas et al., 2017; Thomas et al., 2016; NHIS, 2012). *Valeriana officinalis* (VO) is widely known to produce sedative effects and is commonly used in popular medicine. This plant, also known as cat grass, belongs to the family *Valerianaceae* and contains several active compounds such as valproate, isovalproate, didovalproate and the valerenal and valernik acids. It also may work as anticonvulsant, anti-stress and anti-anxiety and may induce relaxation in the central nervous system.

These effects may help in enhancing sleep. Thus it is also used to treat insomnia (Anheyer et al., 2017; Behboodi Moghadam et al., 2016; Dietz et al., 2016; Gharib et al., 2015). *Passiflora sp* (PA) is popularly known as passion fruit or passion flower and belongs to the family *Passifloraceae*. This plant is widely distributed in tropical and warm areas and is commonly used as producing mild sedative, anxiolytic effects, in the treatment of insomnia, convulsion, in relieving neuropathic conditions and improving attention deficit hyperactivity disorder (Dantas et al., 2017; Giovannini P, Howes et al., 2017; Aman et al., 2016; Villet et al., 2016). VO and PA are commonly used for the treatment of anxiety (Giovannini P, Howes, 2017; Dantas et al., 2017; Becker et al., 2014). Mild anxiety and sleep problems are often treated with psychotropic drugs that may bring serious side effects such as chronic dependency or

withdrawal syndrome. The use of alternative therapeutic approaches such as medicinal plants may play an important role as adjuvant or as the main therapy for anxiety. Due to this reason, the aim of this study is to evaluate the acute and chronic effects of *Valeriana officinalis* and *Passiflora sp* in the behavioral test of Wistar rats.

## METHODS

### Ethical principles

This study was approved by the Animal Research Ethics Committee of the Medical School of Marília, Marília - SP, Brazil. Animals were fed and watered *ad libitum* during the experimental period and were cared for according to the recommendations of the Canadian Council's "Guide for the care and use of experimental animals".

### Plant material and aqueous extract (EA)

VO and PA powder were purchased from local market in the city of Marília / São Paulo were used in the preparation of the aqueous extract by infusion. After the process, the material was filtered, and the resulting aqueous extracts were aliquoted, stored in vials (9-10 mL each) of amber glass and frozen at  $-4^{\circ}\text{C}$ . Each aliquot was withdrawn one hour before the assay to reach room temperature.

### Open field model (OFM)

The open field model is performed with wooden boxes (1m x 1m x 20cm), with the white background divided into quadrilaterals with  $10\text{cm}^2$  where the exploratory behavior of each animal was observed for 10 minutes. The parameters evaluated were the time of locomotion (in seconds) and the number of quadrilaterals the animals visited. The movement time was considered from the moment the animal moved on the ground (excluding movements when they stayed in the same place). The displacement was considered only from the moment when the animal completely or partially surpassed the limits of the other quadrilateral.

### Administration of extract of VO and PA

Thirty-five male Wistar rats with 200g-220g were housed in collective cages under a dark/light cycle of 12 hours, room temperature of  $22 \pm 2^{\circ}\text{C}$ , and relative air humidity of  $60 \pm 5\%$  at the University of Marília, Marília – São Paulo, Brazil. After seven days of acclimation to the laboratory conditions, the animals were divided randomly into seven groups (n= five each group) as follows:

- G1: control group that received 500 $\mu\text{l}$  of saline solution by intraperitoneal route;
- G2: treated with 11mg/kg of VO extract by intraperitoneal route;
- G3: treated with 22mg/kg of VO extract by intraperitoneal route;
- G4: treated with 44 mg/kg of VO extract by intraperitoneal route;
- G5: treated with 11 mg/kg of PA extract by intraperitoneal route;
- G6: treated with 22 mg/kg of PA extract by intraperitoneal route;
- G7: treated with 44 mg/kg of PA extract by intraperitoneal route.

All groups were fed water and rat food *ad libitum* and were treated for 21 days, and weight gain was evaluated each three days to adjust the administered dose. At the end of the treatment, the locomotor behavior of the animals was assessed using the Open Field Test (OFT). The locomotor activity was evaluated on the first day of administration of the plants (acute effect) and the twenty-first day (chronic effect).

### Statistical analysis

The variables: time of movement (in seconds) and displacement of the animals (number of quadrilaterals) were adjusted in Quadratic Regression models, and the estimated values were submitted to Analysis of Variance and complemented with the Bonferroni test, which compared the means two by two.

## RESULTS

Results for the behavioral test show that the acute and chronic use of VO and PA significantly modify the behavior of the rats. Table 1 and figure 1 express the acute effect of EA of *Valeriana officinalis* and *Passiflora sp* on the activity of rats.

Table 1. Mean of movement time, standard deviation (sd) and the result of the statistical analysis of the acute effects of *Valeriana officinalis* (G2-G4) e *Passiflora spp* (G5-G7) in different concentrations.

Groups	G1	G2	G3	G4	G5	G6	G7
Mean	13.4 $\pm$	19.2 $\pm$	33.7 $\pm$	19.5 $\pm$	17.8	17.8 $\pm$	12.4 $\pm$
and Sd	1.0	0.2	0.8	0.7	$\pm 0.4$	1.8	0.8
	B	D	E	D	C	C	A <sup>1</sup>

<sup>1</sup>Different letters indicate a significant difference between the treatments at a level of 5%.

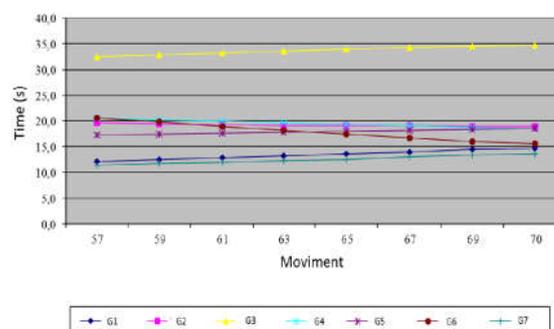


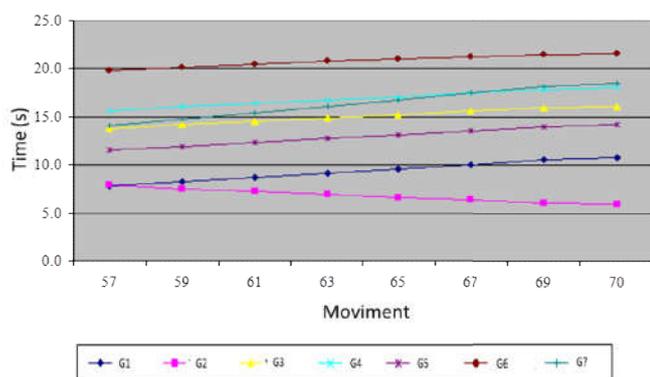
Figure 1. Mean time of the groups submitted to the acute effects of *Valeriana officinalis* e *Passiflora sp* in the movement of 57 to 70 units

In Table 2 and figure 2 we may see the results for the chronic effects of *Valeriana officinalis* and *Passiflora sp* on the activity of rats. Significant differences were found between the groups.

Table 2. Mean of movement time, standard deviation and result of the statistical analysis of the chronic effects of *Valeriana officinalis* (G2-G4) e *Passiflora spp* (G5-G7) in different concentrations

Groups	G1	G2	G3	G4	G5	G6	G7
Mean	9.4 $\pm$	6.8 $\pm$	15.0 $\pm$	16.9 $\pm$	12.9 $\pm$	20.8 $\pm$	16.4
and Sd	1.1	0.7	0.9	0.9	1.0	0.6	$\pm$
	B	A	D	E	C	F	1.6
							E

<sup>1</sup>Different letters indicate a significant difference between the treatments at a level of 5%.



**Figure 2. Mean time of the groups submitted to the chronic effects of *Valeriana officinalis* e *Passiflora* spp in the movement of 57 to 70 units**

## DISCUSSION

Anxiety problems affect 40 million American adults, and millions of dollars are spent in its treatment. In addition to the high cost of conventional drugs, numerous side effects are also disadvantageous as they are used (Thomas *et al.*, 2016). The OFT was originally described as a circular arena to test the effects of unfamiliar environments on the emotionality of rats. The measure of emotional state usually had as parameters the rates of ambulation (number of sectors drawn on the floor of the apparatus that are transpassed by the animals) and defecation of the animal during its performance in the test. From these two parameters, an emotional animal exhibits a lower rate of ambulation (less locomotion) and a higher rate of defecation. The statement in the test is that an unfamiliar environment much distinct from its constant infer fear and anxiety in the rat. Fear would produce reactions in the central nervous system leading to defecation and freezing. Because it is historically related to research on emotionality, the OPT has been performed to evaluate the anxiolytic drug potential (Weinstock, 2016; Frilde, Weinstock, 1988; Handley, Mithani, 1984). In our study, we obtained the results by the number of squares traversed and the time of displacement of the rats observed in 10 minutes. We verified that the acute treatment with doses of 22mg/kg for VO and 11 and 22mg/kg for PA resulted in a suggestive anxiolytic effect (VO seems to produce stronger effects than PA). For the chronic use, doses of 44mg/kg (VO) and 22mg/kg (PA) also resulted in a suggestive anxiolytic effect. PA seems to produce stronger effects than VO in the chronic use of the plants.

VO is commonly used to treat insomnia and generalized anxiety disorder possibly due to the modulation of GABA receptors and increase in GABA levels, leading to decrease of vagus nerve stimulation. Thus, the extract of this plant may be a drug target. Some authors point that the use of 1600 mg dose, commonly used to reduce insomnia, does not impair driving simulator performance after acute ingestion of this plant (Thomas *et al.*, 2016; Kessler *et al.*, 2012; Kessler *et al.*, 2005; Yuan *et al.*, 2004). Valeric acid and valepotriates present in the roots of VO reduces anxiety and improve the quality of sleep possibly due to relation to Valium-like receptors in the brain. Furthermore, there are no side effects related to the use of this plant, and it has been allowed to be used in food products by FDA in the USA (Gharib *et al.*, 2015; Agwn, Okoye, 2005). You *et al.* (2012) studied the effects of different doses of *Valeriana jatamansi* in mice performing the Elevated Plus Maze (EPM) and found significant differences

in the time spent in the open arms and the percentage of open-arm entries. Higher concentrations significantly increased the percentage of time spent in the open arms and the number of entries into the open arm, when compared to control group. Becker *et al.* (2014) found similar effects and showed that VO extract might a significant anxiolytic effect. Murphy *et al.* (2014) studied the effects of VO extract in rats as well as a solution of valeric acid and exogenous GABA and evaluated the number of entries and time spent on the open arms of the EPM. These authors found a significant decrease in anxious behavior supporting the evidence that this plant may play an important role as a potential alternative to treat anxiety.

Many *Passiflora* species have been popularly used as promoting sedative and tranquillizer activities such as *Passiflora incarnata*, *Passiflora quadrangularis*, *Passiflora edulis*, *Passiflora actinia*, and *Passiflora alata* (Otify *et al.*, 2015; Braga *et al.*, 2014; Barbosa *et al.*, 2008). Grundmman *et al.* (2009) investigated the anxiolytic effect of *Passiflora incarnata* L. in mice performing the EPM. Animals in this study were treated with three different concentrations of the plant and exhibited a significant increase in a number of entries in the open arm at a concentration of 375 mg/kg. However, no activity was seen in 150 and 600 mg/kg, indicating a U-shaped dose response curve. We found similar results in the acute use of VO. Authors have concluded that this plant may display putative anxiolytic effects in these animals. Barbosa *et al.* (2008) investigated the acute effects of *Passiflora alata* and *Passiflora edulis* on anxiety and memory process of male Wistar rats performing the EPM and OFT and found anxiolytic results similar to diazepam that is a drug commonly used in the clinical practice. Memory was not affected by the treatment with *Passiflora* sp but was disrupted with the use of the drug. Authors have shown that anxiolytic-like activity of PA is linked with lower doses and sedative effects have been associated to higher doses of plant extracts. Aman *et al.* (2015) found an anxiolytic-like effect when performing the OPT, where the use of PA extract decreased the number of lines crossed at doses of 400 and 600 mg/kg what is comparable to diazepam. Sedative and anxiolytic effects of PA have been linked to benzodiazepine and GABA receptor leading to biochemical mechanisms promoted by the binding to GABA<sub>A/B</sub> sites and inhibition of GABA uptake (Aman *et al.*, 2015; Appel *et al.*, 2011; Sampath *et al.*, 2011; Grundmann *et al.*, 2009; Grundmann *et al.*, 2008; Dhawan *et al.*, 2001; Soulimani *et al.*, 1997).

## Conclusion

Our results show that both *Valeriana officinalis* and *Passiflora* sp may exhibit anxiolytic effects in Wistar rats. In acute use of this plant, we may observe stronger effects of VO when comparing with PA. The opposite was seen in the chronic use of the plants.

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