

# Montanoa tomentosa. A review of the new scientific evidence on pharmacological properties

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## Abstract

*Montanoa tomentosa* is a shrub, belonging to the Asteraceae family, originally from Mexico and Central America, and it is known for its medicinal properties. The origins of its use in the field of herbal medicine can be traced back to the Mexican tradition. It was used for sexual dysfunctions. The extract of leaves was used in women to induce menstruation, abortion and labor, and also to reduce postpartum bleeding. The leaves are also used for their diuretic properties and the ground roots are used in the treatment of dysentery. Over time, studies have been conducted to identify the compounds responsible for the therapeutic activity and their mechanism of action. Two studies conducted in rats demonstrated the aphrodisiac properties of *Montanoa tomentosa*. This activity has been attributed to the presence of components that act as oxytocic agents. Furthermore, other studies have shown that *Montanoa* has anxiolytic

properties. The mechanism underlying this action lies in the interaction with the GABA<sub>A</sub> receptor. However, it has been shown that the anxiolytic effect is influenced by the individual endocrine status: in conditions of low hormone levels the anxiolytic effect is more pronounced; in conditions of high hormonal levels, a state like anxiety is observed. Despite the multiple properties of *Montanoa*, today's research is geared towards strengthening its clinical relevance as a natural antidepressant agent.

## Introduction

*Montanoa* is a genus of the Asteraceae family that includes about 25 species of shrubs, lianas, and trees widespread in Central America, from north-central Mexico to central Colombia. These are woody plants, characterized by bunches of flower heads like daisies, with white ligulate flosculi and usually yellow, but also green or brown to black disk flosculi.<sup>1</sup> Most of the species are shrubs, although often large, while four species are lianas and five real trees. According to the most recent studies, the arboreal habit is the result of an adaptation (which has occurred several times, given that the tree species do not all belong to the same evolutionary line) to the environmental conditions in which these species live, the cloud forest. The genus is very distinct within the family, while the boundaries between the species are difficult to establish, often characterized by an accentuated polymorphism. For example, the species *Montanoa tomentosa* (*M. tomentosa*), which is also the most widespread, is usually a shrub of about 1.5 meters in height, but it can exceed three and under certain conditions it becomes a climber; moreover, the size and shape of the leaves is extremely variable, and changes occur over the course of the year, in connection with the season and the humidity.<sup>1</sup> Many species have been used for centuries in indigenous medicine and have medicinal properties confirmed by biochemical research.<sup>2</sup> The inflorescences are corymbs composed of very numerous small flower heads with from 0 to 6 flosculi of the radius from cream to white and from 8 to 17 flosculi of the disk from light yellow to dark yellow.

Despite their great ornamental value, they are less widespread than they deserve, probably due to their ecological requirements; in fact, almost all require not only a mild climate, but also a high level of atmospheric humidity throughout the year. Where these conditions are available, at the time of flowering they offer an unforgettable sight. That's why they occupy a privileged space in the San Francisco Botanical Garden (whose bay is famous for its persistent fog banks); in 1984 a corner of cloud forest, the extraordinary ecosystem characteristic of the mountain ranges from Mexico to Peru between 1500 and 3000m of altitude, with mild temperatures, low temperature

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range and abundant humidity all year round, was reconstructed. Here, among dahlias, passion fruit, Mexican pines, and other wonders, four species of *Montanoa* also thrive: *M. guatemalensis*, *G. leucantha* var. *arborescens*, *M. tomentosa*, *M. pteropoda*.

In traditional Mexican medicine it is used to accelerate the contractions of childbirth and for having an anxiolytic-like effect; these properties have been confirmed by research, which has also highlighted its toxicity, which suggests a cautious use.<sup>1</sup>

### Pharmacological properties

*M. tomentosa* is a valued plant due to its medicinal properties: the leaves are diuretic, oxytocic and stomachic. Because it speeds up uterine contractions, the leaves are commonly used in Mexico as an aid to childbirth,<sup>2</sup> and as a menstruation inducer. This use, however, is also said to be dangerous. The ground uproots, mixed with lukewarm water, is used in the treatment of dysentery.<sup>2,3</sup>

The volatile constituents of the aerial parts (leaves and flowers) of this medicinal plant were analyzed by SPME-GC-MS.<sup>3</sup> The major constituents of the volatile fraction were monoterpenes, such as sabinene,  $\alpha$ -pinene and  $\alpha$ -thujene, which accounted for 65% of the total fraction.<sup>4-7</sup> Other identified compounds were sesquiterpenes, like  $\alpha$ -gurjunene, caryophyllene and germacrene D, but in minor amount.<sup>8-13</sup> The total proportion of identified compounds was 86.7% (17 volatiles) and 82.1% (14 volatiles) for leaves and flowers, respectively. Some of the most abundant terpenes found in this plant are well known for their relevant roles in the environment and in many industrial applications. The characterization of volatiles from *M. tomentosa* was established in that study for the first time, therefore their utility in different aspects opens an interesting area to carry out further investigation of the plant.<sup>3,4</sup>

In a recent study, the pro-sexual effect of the aqueous crude extracts from *M. tomentosa* (cihuapatli) and its possible pro-ejaculatory properties in spinal male rats were examined.<sup>14</sup> Systemic administration of the aqueous crude extracts of *Montanoa tomentosa* exerted a pro-ejaculatory effect and produced an increase in the number of discharges in the ejaculatory motor patterns in the spinal rats. The cihuapatli-induced ejaculatory responses included the expression of penile erections and penile movements, the potent expulsion of urethral contents, and in some cases the expulsion of seminal plugs. The cihuapatli-induced ejaculatory motor patterns were like that obtained after systemic oxytocin injections. Cihuapatli- and oxytocin-induced ejaculatory motor responses and the penile erections and movements were abolished by the pre-treatment with hexamethonium, a selective oxytocin antagonist. The data show that the cihuapatli extract acts directly at the spinal system in charge of the expression of the ejaculatory motor patterns and suggest that the aqueous crude extract exerts its aphrodisiac properties by increasing sexual potency acting as an oxytocic agent.<sup>3</sup> 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 non-copulating male rats. 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.<sup>15-19</sup>

An important study was conducted in 2015 by the Pharmacological Department in Mexico, with the purpose to evaluate the effect of *M. tomentosa* lyophilisate on rat's anxiety-like behavior and to analyze its mechanism of action.<sup>16</sup>

The anxiolytic-like action of *M. tomentosa* (1.5, 3.0, 6.0 and 12.0 mg/kg) was investigated in male Wistar rats tested in three

animal models of anxiety: the burying behavior, the elevated plus maze and the hole-board tests.<sup>3</sup> As a positive control, the anti-anxiety effects of different doses of the selective GABA<sub>A</sub> receptor agonist muscimol were also analyzed. Muscimol's doses were selected according to previous studies describing their anxiolytic-like effects in different animal models of anxiety. To evaluate the participation of the GABA<sub>A</sub> and oxytocin receptors in the anxiolytic-like actions of *M. tomentosa*, the GABA<sub>A</sub> chloride ion channel blockers picrotoxin (0.25 and 0.50 mg/kg), bicuculline (2.0 mg/kg-selective blocker of the GABA receptor) and flumazenil (5.00 and 10.0 mg/kg-competitive antagonist of benzodiazepines on the GABA receptor), the neurosteroid inhibitor finasteride (50.0 and 100 mg/kg) and the oxytocin receptor antagonist atosiban (0.25  $\mu$ g) were used. Finally, to evaluate general activity and motor coordination, the open field and rota-rod tests were used.

*M. tomentosa* at 3.0 mg/kg showed anxiolytic-like effects in the three anxiety paradigms without affecting reactivity, general motor activity or motor coordination; however, at higher doses sedative effects were observed. Picrotoxin (0.25 and 0.50 mg/kg), flumazenil (10.0 mg/kg) and finasteride (100 mg/kg) antagonized the anxiolytic-like actions of *M. tomentosa* in the burying behavior test. In the plus maze and hole-board tests, bicuculline (2.0 mg/kg) blocked the effects of the plant as well. Atosiban (0.25  $\mu$ g) did not antagonize the anxiolytic-like actions of *M. tomentosa*.

The results corroborate the anxiolytic-like actions of *M. tomentosa* and suggest that this effect is mediated through GABA<sub>A</sub> receptors but not oxytocin receptors.<sup>16-19</sup>

It has been scientifically shown that the endocrine state could modify the anti-anxiety-like actions of anxiolytic compounds. A study was conducted to evaluate the effect of the aqueous extract of *M. tomentosa* in rats with long-term absence of ovarian hormones induced by ovariectomy. Three concentration of *M. tomentosa* extract (12.5, 25 and 50 mg/kg) were evaluated in rats subjected to elevated plus maze and open field tests and comparisons against a control group and diazepam as reference of an anxiolytic drug were described. In the elevated plus maze only 50 mg/kg of *M. tomentosa* extract, alike to diazepam, increased the time spent and the number of entries into the open arms, respect to control group. Like diazepam, in the open field test none of the evaluated treatments produced significant changes in crossing and rearing, but 50 mg/kg of *M. tomentosa* extract increased the time spent in grooming behavior as compared with control group. In conclusion, *M. tomentosa* extract produces an anxiolytic-like effect in rats with long-term absence of ovarian hormones. The findings partially support the traditional use of this plant in the traditional Mexican medicine to solve women's emotional alterations.<sup>20</sup> We have already said that women are the primary user of *M. tomentosa*, but a very recent study (2019) by the same Department at the University of Mexico evaluated the potential impact of the endocrine milieu on its anti-anxiety actions.<sup>17</sup>

The aim of the study was to ascertain the anti-anxiety effects of *M. tomentosa* in rats with different hormonal conditions, and to analyze the participation of the GABA<sub>A</sub> receptor in ovariectomized rats treated with *M. tomentosa*. The animal model of anxiety used was the Elevated Plus-Maze (EPM). Rats' endocrine conditions were: i) low hormone levels (rats in diestrus I and II phases); ii) high hormone levels (proestrus/estrus phases); iii) no hormones (ovariectomized rats); and d) rats under Progesterone Withdrawal (PW). To evaluate the participation of the GABA<sub>A</sub> receptor in the anxiolytic-like action of *M. tomentosa* the antagonist picrotoxin was used. Results showed that *M. tomentosa* induced dose-dependent anxiolytic-like actions in rats with low hormone level conditions. Also, *M. tomentosa* reduced anxiety-like behavior in female rats

under PW, in contrast to diazepam, which was ineffective. *M. tomentosa*'s anxiolytic-like effect was blocked by picrotoxin, suggesting the participation of the GABA<sub>A</sub> receptor complex. However, increased anxiety-like behavior was observed in rats with a high hormone level condition and low doses of *M. tomentosa*. In conclusion, beneficial anxiolytic-like actions of *M. tomentosa* are observed under low hormone conditions, particularly in the PW challenge (a condition that can be related to a premenstrual period). Furthermore, the participation of the GABA<sub>A</sub> receptor is evidenced. However, hormonal variations could induce the opposite effects, hence women should be cautious.<sup>17-19</sup>

In 2019 the Instituto de Neuroetología (Universidad Veracruzana, Xalapa, Mexico) focused on the acute effect of an infusion of *M. tomentosa* on despair-like behavior and activation of oxytocin hypothalamic cells in Wistar rats. In pre-clinical research, both the extract and some of its active metabolites have produced oxytocinergic-like effects on female reproductive organs;<sup>18</sup> however, there are no detailed studies of its effects on mood state and brain structures. The aim of that study<sup>18</sup> was to analyze the behavioral effects of acute administration of a *M. tomentosa* infusion on male rats, during the Open Field (OFT) and Forced Swim (FST) Tests, and their association with the activation of Oxytocin (OXT) cells, indicated by Fos protein (Fos/OXT) in the Paraventricular (PVN) and Supraoptic Nuclei (SON).

The experimental procedure was based on the analysis of 52 adult male Wistar rats, which were assigned to two conditions: with (n=8) or without (n=5) FST. Each integrated condition included four groups [Control, Vehicle, Fluoxetine (Flx; 10 mg/kg), and *M. tomentosa* (50 mg/kg), p.o.]. The result showed that *M. tomentosa* and Flx treatment produced an anti-despair-like effect on the FST. Also, the *M. tomentosa* infusion—but not Flx—significantly increased the number of Fos/OXT cells in the PVN and SON, regardless of the condition, compared to the control and vehicle groups. These results show that *M. tomentosa*, but not Flx, produces an anti-despair-like effect that could be associated with the activation of OXT cells in PVN and SON. While an antidepressant effect was observed in the FST, in the Flx group, Fluoxetine did not exert any significant influence on the activation of oxytocin cells as did the *M. tomentosa* infusion. This is likely because fluoxetine activates the serotonergic system directly and may subsequently activate the release of oxytocin; whereas *M. tomentosa* seems to act primarily on the oxytocinergic system.<sup>18</sup>

Although the main objective of this study was not to identify the bioactive components of the *M. tomentosa* infusion that are involved in its behavioral and neurochemical action, they may offer a possible explanation for its partial antidepressant-like effects.<sup>19</sup> *M. tomentosa* infusion contains several bioactive compounds (e.g., flavonoids) that exert beneficial effects against some central nervous system disorders, related to stress, for example, isoquercitrin had a partial anti-despair effect associated with the activation of hypothalamic OXT neurons. Besides, some flavonoids also modulate GABAergic neurotransmission increasing the firing of OXT neurons and GABA<sub>A</sub> receptors are the main target for anxiolytic and anti-stress agents, including benzodiazepines.<sup>19</sup> Therefore, the anti-depressant-like effect and activation of OXT neurons produced by the *M. tomentosa* infusion could be related to the flavonoids contained in the extract, though this possibility requires additional research.<sup>19</sup>

Based on the above information we hypothesize that the behavioral and neuronal effects of *M. tomentosa* could be related to the flavonoids previously identified in the extract of this plant, though further pharmacological studies are necessary to test this hypothesis. The results of several studies have shown that the effect

of extract cannot be reproduced by only one of these compounds, thus suggesting that synergism between compounds may occur.

This study thus contributes to our knowledge of the pharmacological activity of *M. tomentosa* infusions, which could be a natural antidepressant agent with future clinical relevance.<sup>3-18</sup>

## Conclusions

In this review we reported the main studies conducted in recent years on *M. tomentosa* and the relevant pharmacological effects of this plant. In the light of what emerged from this review, *M. tomentosa* is not only important in reproductive medicine, but its relevance has been extended to other areas of experimental biology (such as cancer, immunological, pathological, and biotechnological research). Instead, there are reports indicating that this plant was also consumed by Mexican ancient people for its relaxing properties. So, recent important studies corroborate/confirm the anxiolytic-like actions of *M. tomentosa* and suggest that this effect is mediated through GABA<sub>A</sub> receptors. In addition, the present data support the hypothesis that *M. tomentosa* possesses some properties that modulate mood states, possibly associated with OXT-like properties, but distinct from the common antidepressant, fluoxetine. However, there are still many other research areas to be developed.

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