ARTIGO ORIGINAL

Mutagenic evaluation of the aqueous extract of Jurema (*Mimosa tenuiflora*, Fabaceae) using the Somatic Mutation And Recombination Test (SMART) on the wings of *Drosophila melanogaster*

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ABSTRACT: The Jurema, *Mimosa tenuiflora*, is widely used in semi-arid regions of Brazil as a remedy for an ample variety of health problems. The extract is either applied as a salve or ingested and is used as an analgesic or anti-inflammatory medicine. While the use of plants in traditional medicine is common in some populations, this practice requires detailed studies of the components of the substances used, given that even differences in dosage may have harmful effects on a person's health. Phytochemical studies of the compounds found in some species of the genus *Mimosa* (*Mimosa pudica* and *Mimosa rubicaulis*) have indicated antioxidant, bactericidal, and toxicological activity, depending on the dosage, although the probable mutagenic effects are still unknown. In the present study, the possible mutagenic effects of three different concentrations of the aqueous extract of *M. tenuiflora* (3.91, 15.625, and 62.5 mg/ml) were evaluated using SMART (Somatic Mutation and Recombination Test) on the wings of two crosses (standard and high bio-activation) of three lineages of *Drosophila melanogaster – multiple wing hairs* (*mwh*), flare3 (*flr*^{3}), and Oregon R/ flr3 (ORR/*flr*^{3}). The results indicated clear mutagenic effects in all the concentrations tested, reflecting the complex phytochemical composition of the aqueous extract of *M. tenuiflora* including compounds that may act alone or synergistically, having direct or indirect effects on the mutagenic potential recorded in the study. A more detailed understanding of the constituents of this plant responsible for the reactions observed in this study will be necessary, however, before the therapeutic use of the extracts of this plant can be regulated more reliably.
Key words: *Mimosa tenuiflora*, mutagenesis, recombinogenesis, phytotherapy, *Drosophila melanogaster*.

RESUMO: Avaliação mutagênica do extrato aquoso de Jurema (*Mimosa tenuiflora*, Fabaceae) utilizando o Teste de Mutação e Recombinação Somática (SMART) nas asas de *Drosophila melanogaster*. A Jurema, *Mimosa tenuiflora*, é amplamente utilizada em regiões semi-áridas do Brasil como um remédio para uma ampla variedade de problemas de saúde. O extracto é aplicado, quer como uma pomada ou ingerida, e é utilizado como um analgésico ou medicamento anti-inflamatório. Enquanto o uso de plantas na medicina tradicional é comum em algumas populações, esta prática requer estudos detalhados sobre os componentes das substâncias utilizadas, uma vez que até mesmo as diferenças de dosagem podem ter efeitos nocivos sobre a saúde de uma pessoa. Estudos fitoquímicos dos compostos encontrados em algumas espécies do gênero *Mimosa* (*Mimosa pudica* e *Mimosa rubicaulis*) indicaram atividade antioxidante, bactericida, atividade toxicológica e, dependendo da dosagem, embora os prováveis efeitos mutagênicos ainda são desconhecidos. No presente estudo, os possíveis efeitos mutagênicos de três diferentes concentrações do extrato aquoso de *M. tenuiflora* (3,91, 15,625, e 62,5 mg/ml) foram avaliados usando o SMART (Somatic Mutation E Teste Recombinação) nas asas de duas cruzes (padrão e de alta bioativação) de três linhagens de *Drosophila melanogaster* - vários cabelos asa (MWh), flare3 (flr3) e Oregon R / flr3 (TRG / flr3).

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Os resultados indicaram efeitos mutagênicos em todas as concentrações testadas, o que reflete a composição fitoquímica complexa do extrato aquoso de *M. tenuiflora*, incluindo compostos que podem agir sozinhos ou em sinergia, com efeitos diretos ou indiretos sobre o potencial mutagênico registrados no estudo. Uma compreensão mais detalhada dos componentes desta planta responsável pelas reações observadas neste estudo irá ser necessário, no entanto, antes da utilização terapêutica dos extratos desta planta pode ser regulada de forma mais viável.
Palavras-chave: *Mimosa tenuiflora*, mutagênese, recombinogênese, fitoterapia, *Drosophila melanogaster.*

INTRODUCTION

The Jurema, *Mimosa tenuiflora* (Willd) Poir. (Fabaceae, Mimosoideae), is a common plant of the semi-arid environments of the New World and is found throughout most of the Brazilian Northeast (Oliveira et al. 1999). This tree is widely used by local populations for materials such as fence posts, the production of charcoal, and chemicals for tanning leather (Oliveira et al. 1999; Raetsch 2005; Souza et al. 2008; Martinez et al. 2009; Alves et al. 2018), as well as providing forage for ruminants during the low season (Alves et al. 2018; Camargo-Ricalde 2000). The plant is also widely used as a traditional remedy *for* health problems, such as burns, lesions, eczema, toothache, internal pain, ulcers, herpes, acne, and parasite-related disorders (Ohsaki et al. 2006; Souza et al. 2008). This ample spectrum of use has resulted in the jurema being known as the “miraculous drink” by some indigenous tribes of the Brazilian Northeast (Raetsch 2005; Souza et al. 2008; Martinez et al. 2009).

A number of constituents have been identified, including alkaloids (5-hydroxy-tryptamin and *N*,*N*-dimethyltriptamine), which are linked to the use of the plant as a hallucinogen, chalcones (cuculcanin A and cuculcanin BP), steroids, terpenoids, and triterpenoid saponins, considered to be responsible for the rupture of the erythrocyte membrane, as well as phenoxycromones, which are rare flavonoids (Oliveira et al. 2006). Experimental studies in pregnant Wistar rates have shown as association between the ingestion of *M. tenuiflora* seeds and the occurrence of malformations in the fetus, indicating that the plant may also have toxic, carcinogenic, and teratogenic properties (Akinboro and Bakare 2007; Medeiros et al. 2008; Bezerra et al. 2021), due to the presence of genotoxic substances which generate major genetic modifications that induce hereditary disorders, as well as triggering cancers (Guzmán-Rincón and Graf 1995).

Medicinal products can be evaluated through studies of safety and efficacy (Romero-Jiménez et al. 2005). A number of tests can be used to assess the mutagenic activity of certain substances, such as the SMART (Somatic Mutation and Recombination Test), which detects somatic mutation and recombination (Graf et al. 1994) using mutant linages of *Drosophila melanogaster* to monitor the expression of mutations and recombination in somatic cells. This test permits the detection of a wide range of mutations, as well as the activity of promutagens and/or carcinogens using lineages with a high capacity for the transformation of certain mutagens into active metabolites (Guzmán-Rincón and Graf 1995; Idaomar et al. 2002). This test represents a useful analytical tool that provides important insights into the administration of therapeutic substances in humans, as well as contributing to the discovery of new drugs for the treatment of specific types of disease.

The present study analyzes the mutagenic potential of *Mimosa tenuiflora* based on the results of SMART analyses, given the lack of data on the limitations of the therapeutic properties of this species, which impedes the systematic assessment of its uses and applications in traditional medicine. Specifically, the study tests the mutagenic potential of the plant extract at different concentrations. Jurema extract is widely used in traditional medicine the Brazilian Northeast, although there is an urgent need for effective proof of its properties, as well as its safety limits. The analysis of the extracts of *M. tenuiflora* based on the SMART technique will provide important input for the development of more reliable therapeutic procedures based on the extract of this plant.

MATERIAL AND METHODS

Collection and preparation of the *M. tenuiflora* extracts

Samples of the plant’s bast were collected at Lago de Xingó (09º37’25” S, 37º45’24” W) in Piranhas, a municipality in the state of Alagoas, Brazil. A voucher specimen was deposited in the herbarium of the Federal University of Sergipe under catalog number ASE 13166. The samples were dried in a stove at 37 °C with air circulation and renewal until their complete desiccation.

The dry bast (4.828 kg) was reduced to powder in a mincer. The aqueous extract of the Jurema (AEJ) was extracted by decoction from 70 g of the powder. For each 10 g of the plant material, 20 ml of distilled water was added. Following vacuum filtration, the material was evaporated on a hot plate,

concentrated, and lyophilized, for the production of the aqueous extract (18.75 g).

4.2 Treatment of the *D. melanogaster* larvae

Three *D. melanogaster* lineages (Lindsley and Zimm, 1992) were used in the present study: (1) multiple wing hairs (mwh): *mwh/mwh*; (2) flare-3 (*flr^3/In (3LR)TM3, rip^p sep l(3)89Aabx^{34e} and Bd^S*, and (3) ORR, flare-3 (*ORR/ORR; flr^3/In (3LR)TM3, rip^p sep l(3)89Aabx^{34e} and Bd^S*). The specimens were kept in 500 ml glass containers with *Drosophila* growth medium (820 ml of water, 25 g of yeast, 11 g of agar, 150 g of banana, and 1 g of ethylparaben as a fungicide).

For the experiments described here, two types of crosses were conducted. One was a standard (ST) cross between virgin flare-*3* females and mwh males, and the other, a high bio-activation (HB) cross between virgin ORR flare-*3* females and mwh males (Graf et al. 1996). The eggs produced by both crosses were collected over an 8-hour period in flasks containing a solid agar base (3% agar in water) and a layer of yeast supplemented with saccharose. After 72 ± 4 h, the third-stage larvae were washed under running tap water and distilled water using a thin-meshed sieve before being transferred to smaller recipients containing 1.5 g of alternative culture medium (Yoki® instantaneous mashed potato) and 5 ml of one of the concentrations of the aqueous extract of *M. tenuiflora* (3.91, 15.625, and 62.5 mg/ml). The 62.5 mg/ml concentration was defined based on parameters found in the literature on experimental trials of plant extracts using the SMART technique. The two other concentrations were determined as quarter fractions of the maximum value. The positive control for the experiment was prepared with urethane (ethyl carbamate, Sigma-Aldrich®) at 0.891 mg/ml, while the negative control consisted of ultrapure water (Ultrapure Water Systems – Sartorius® 611). The chronic treatment was run for a period of approximately 48 hours.

Preparation of the slides and analysis of the specimens

The adults produced by the two crosses (ST and HB) of the marked trans-heterozygotic genotypes – MH (*mwh + / + flr^3*) – and the balanced heterozygotes – BH (*mwh + / + TM3, BdS*) – were collected and conserved in 70% ethanol. The wings of the MH flies were extracted carefully using a stereomicroscope and entomological tweezers and fixed in Faure's solution (30 g gum arabic, 20 ml glycerol, 50 g chloral hydrate, and 50 ml water) on glass slides. The wings of five pairs of flies were mounted on each slide, with a total of six slides for each concentration. In addition to the positive and negative controls, slides were also mounted for the concentrations at which the BH descendants returned positive results. The wing hairs were analyzed and the number of mutant spots of different types (type of cell and the size of the spots, that is, the quantity of mutant cells in each spot) was quantified.

Statistical analysis of the data

A two-tailed χ^2 test with a significance level of $\alpha = \beta = 0.05$, following Frei and Würgler (1988), was used to compare the frequencies recorded in the experimental groups with those of the respective controls. The genetic recombination activity was evaluated from the frequency of induction of clones per 10^5 cells, where the frequency of mutation (F_M) = frequency of BH clones/frequency of MH clones; the frequency of recombination (F_R) = 1 - F_M, and the total frequency of spots (F_T) = total number of spot on MH flies (considering *mwh* and *flr^3* spots)/number of flies. Mutation = F_T x F_M, recombination = F_T x F_R (Santos et al. 1999; Sinigaglia et al. 2006).

RESULTS AND DISCUSSION

Tables 1 and 2 summarize the results for the standard (ST) and high bioactivation (HB) crosses, respectively, following the chronic treatment of the larvae with the different concentrations of the aqueous extract of *jurema*, or AEJ (3.91, 15.625, and 62.5 mg/ml), ultrapure water (negative control), and urethane (positive control). The positive and negative controls were tested simultaneously with the other treatments. The frequency of mutant spots (small simple, large simple, and double) and the total number of spots are presented for both lineages, i.e., the marked heterozygotes (MH), with smooth wings, and the balanced heterozygotes (BH), with serrated wings. The results were compared with the negative control.

Table 1 shows the frequency of mutant spots recorded in the analysis of the MH and BH progenies of the ST cross. In the MH individuals, a significant increase in the frequency of small simple spots and the overall number of spots were recorded at the 15.625 and 62.5 mg/ml concentrations in comparison with the negative control. The number of spots increased systematically with the concentration of the extract. For the descendants of the HB cross treated with AEJ (Table 2), an increase in the frequency of both types of spot can also be observed at the lower concentrations (3.91 and 15.625 mg/ml). This may reflect cytotoxic effects in the larvae, where the few surviving individuals were unaffected. This indicates that the AEJ has mutagenic effects which are dependent on metabolic activation.

In the case of treatment with URE, a

significant (P < 0.05) increase was found in the frequency of small simple spots and the total number of spots in the MH descendants of the ST cross, in comparison with the negative control (ultrapure water). A significant increase was also recorded in the frequency of spots of all types (large and small simple, and twin) and the total number of spots. In the case of the HB cross treated with URE, higher frequencies of mutant spots were recorded in comparison with the ST cross. This is due to the metabolic activation of the URE by the P450 enzymatic system (Frölich and Würgler 1990; Graf and Van Schaik 1992; Abraham and Graf 1996; Dogan et al. 2005). A similar pattern was recorded in the group treated with AEJ.

Graf et al. (1984; 1996; 1998), Spanó et al. (2001), recorded a systematic relationship between the timing of the induction of a given genetic mutation in somatic cells and the size of the resulting spot. In the late development phase, the cells of the imaginal discs of the wings of *D. melanogaster* may be affected by mutations that favor the development of small spots, as observed in the MH individuals in the present study.

The sum of the evidence indicates clearly that the AEJ has mutagenic effects. As this extract is made up of a complex set of components (Nascimento et al. 2013), it seems reasonable to

Table 1- Frequency of mutant spots recorded in the progeny of the standard (ST) crosses. subdivided into marked (MH - *mwh/flr*^{3}) and balanced (BH - *mwh/TM3*) heterozygotes, after different concentrations (0; 3.91; 15.625; 62.5 mg/ml) de *M. tenuiflora*.

***Genotypes* and Conc.**		Number of fly Indiv.	Spot for fly (number of spots) statistical diagnosis*								Total mwh[c] Clones	Recombination (%)
EAJ (mg/ml)	URE (mg/ml)	**(*N*)**	Small single spots **(1-2 céls)**[b] ***m* = 2**		Large spot cells **(>2 céls)**[b] ***m* = 5**		Twin Spots ***m* = 5**		Total Spots ***m* = 2**		**(*n*)**	
mwh/flr[3]												
0	0	60	0.27 (16)		0.00 (00)		0.00 (00)		0.27 (16)		14	
0	0.891	60	1.78 (107)	+	0.10 (06)	+	0.00 (00)	i	1.88 (113)	+	102	13.83%
3.91	0	60	0.37 (22)	i	0.03 (02)	i	0.02 (01)	i	0.42 (25)	i	18	
15.625	0	60	0.50 (30)	+	0.03 (02)	i	0.00 (00)	i	0.53 (32)	+	30	3.77%
62.5	0	60	0.50 (30)	+	0.02 (01)	i	0.00 (00)	i	0.52 (31)	+	26	19.23%
mwh/TM3												
0	0	60	0.28 (17)		0.00 (00)				0.28 (17)		17	
0	0.891	60	1.52 (91)	+	0.10 (06)	+	d		1.62 (97)	+	97	
15.625	0	60	0.52 (31)	+	0.03 (02)	i			0.55 (33)	+	33	
62.5	0	60	0.58 (35)	+	0.03 (02)	i			0.62 (37)	+	37	

[a]Statistical diagnosis based on Frei and Würgler (1988): +. positive; -. negative; i. inconclusive. *m* = multiplication factor for the evaluation of significantly negative results (significance level: a = b = 0.05). [b] Includes rare simple *flr3* spots. [c]Considering the mwh clones for the simple mwh spots and the double spots.

Table 2- Frequency of mutant spots found in the progeny of the high bio-activation (HB) crosses, subdivided into marked (MH - *mwh/flr*[3]) and balanced (BH - *mwh/TM3*) heterozygotes, after different concentrations (0; 3.91; 15.625; 62.5 mg/ml) de *M. tenuiflora.*

***Genotypes* and Conc.** EAJ (mg/ ml)	URE (mg/ ml)	Number of flies (*N*)	Spot for fly (number of spots) statistical diagnosis* MSP (1-2 céls)[b] *m* = 2			MSG (>2 céls)[b] *m* = 5			MG *m* = 5			TM *m* = 2			Total spot mwh[c] (*n*)	Recombination (%)
mwh/flr[3]																
0	0	60	0.58	(35)		0.05	(03)		0.00	(00)		0.63	(28)		26	
0	0.891	60	4.50	(270)	+	0.42	(25)	+	0.08	(05)	+	4.98	(299)	+	232	56.42%
3.91	0	60	1.28	(77)	+	0.07	(04)	i	0.02	(01)	i	1.37	(82)	+	77	2.91%
15.625	0	60	1.22	(73)	+	0.10	(06)	i	0.00	(00)	i	1.32	(79)	+	64	37.87%
62.5	0	60	0.42	(25)	-	0.07	(04)	i	0.03	(02)	i	0.52	(31)	-	27	
mwh/TM3																
0	0	60	0.55	(33)		0.05	(03)					0.60	(36)		36	
0	0.891	60	2.13	(128)	+	0.03	(02)	i	d			2.17	(130)	+	130	
3.91	0	60	1.30	(78)	+	0.03	(02)	i				1.33	(80)	+	80	
15.625	0	60	0.82	(49)	+	0.00	(00)	-				0.82	(49)	i	49	

[a]Statistical diagnosis based on Frei and Würgler (1988): +. positive; -. negative; i. inconclusive. *m* = multiplication factor for the evaluation of significantly negative results (significance level: a = b = 0.05). [b]Includes rare simple *flr3* spots. [c]Considering the mwh clones for the simple mwh spots and the double spots.

conclude that some of these constituents are more closely related to the mutagenic effects observed in the experimental trials than others.

Comparing the results obtained for the MH and BH descendants, differences were found in the frequency of mutant spots following the URE treatment in the ST and HB crosses. This difference is equivalent to the somatic rate of recombination, given that the development of cells that have suffered recombination is impeded in the BH descendants due to the presence of the balancing TM^3Bd^s chromosome, which contains multiple inversions. Tables 1 and 2 also show the recombination rates for the total number of spots in the two treatments.

The analysis of recombination is of considerable importance, because it reveals the strict correlation between carcinogenesis and genetic mutations and homologous recombination. Some of these genetic alterations may indicate a potential for carcinogenesis, although it seems more likely that that they are involved in secondary stages of the process in which recessive oncogenic mutations are revealed (Bishop and Schiestl 2002).

No reduction in the frequency of mutant spots was found in the MH and BH descendants equivalent to the recombination rate in the ST crosses treated with AEJ, which presented positive results. No analysis was necessary in the cases of the BH descendants of the ST cross treated with AEJ at 3.91 mg/ml, and those of the HB cross treated at 62.5 mg/ml, given the lack of positive results.

Extracts are complex mixtures of compounds with a wide range of chemical constituents (Chung et al. 2005). The qualitative assessment of plant chemistry is based on the identification of major classes of active chemical constituents (Rodrigues et al. 2009). This provides a preliminary understanding of the chemical behavior of the extracts and facilitates the selection of samples for research and the isolation and characterization of the pure

substances (Matos 1997).

A number of important groups of secondary metabolites were identified in the aqueous and ethanolic extracts, including its hexane, chloroform, ethyl acetate, and hydromethanol fractions (Table 3). Experiments in phytochemical prospection, and the analysis of antioxidant activity and the total phenol content of extracts are important strategies for the identification of their constituents and the analysis of their effects (Matos 1997; Nascimento et al 2013). In their analysis of the aqueous extract of *M. tenuiflora*, for example, Nascimento et al (2013) confirmed antioxidant activity, and the presence of phenols and their potential for the sequestration of free radicals.

In recent years, a number of studies have related mutagenic and carcinogenic effects in some alkaloids, such as the pyrrolizidines, which are common in many plant species and are responsible for the deleterious effects in both foods and medicinal herbs and dietary supplements used for humans and animals. Half of the molecules that have already been identified (clivarine, heliotrine, lasiocarpine, ligularidine, LX201, and sencircine) are mutagenic and many of them are tumorigenic. During metabolic activation, they produce adducts and breaks in the DNA, and chromosome exchange, both *in vivo* and *in vitro* (Chen et al. 2010).

Other components of the *M. tenuiflora* extracts, such as triterpenoids, saponins and sterols, have returned negative results for mutagenesis in other experiments (Chen et al. 2002; Zhang et al. 2004; Nascimento et al. 2013). Traditional medicine based on the use of plant extracts is often the only pharmaceutical resource available to rural communities and indigenous groups, but this does not mean that scientific research cannot provide essential guidelines on dosage, for example, which may help to not only optimize the therapeutic properties of the substances used, but also to minimize any potentially adverse effects. In this context, studies of mutagenesis and anti-mutagenesis may provide important insights into the effectiveness and safety of natural products.

CONCLUSION

The present study successfully confirmed the occurrence of mutagenic activity in the aqueous extract of the *Jurema*, *Mimosa tenuiflora*, including recombination at some concentrations, as well as metabolic activation by the P450 cytochrome system. Based on the results of the present study and the bio-prospection of the components of the aqueous extract of *M. tenuiflora*, it is possible to confirm that the observed mutagenic effects are related to the complex phytochemical constitution of the plant, and that some of these components may be intimately related to specific mutagenic effects or even act synergistically. It will, however, be essential to identify which components, alone or combined, are responsible for the findings of the present study, in order to decide whether to support or prohibit the use of the extract as a natural remedy. A better understanding of the plant and the activity of its active components will be vital for a safer and more reliable medicinal use.

The present study provides important guidelines for future research on *M. tenuiflora*, given the paucity of the published data. The findings of this study have nevertheless provided important new insights into the complexity of the components of this species. In addition to providing important data on the phytotherapeutic constituents of the plant, the findings of this study also reinforce the effectiveness of ethnopharmacological knowledge.

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CONFLICT OF INTERESTS

The author declares no competing interests.

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