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The Enhanced Activity of a Plant Mixture from the Brazilian Caatinga Biome against Venereal Trichomonads Confirms the Traditional Use

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Abstract: Women living in the semi-arid region of Caatinga in the northeast of Brazil report the use of plant mixtures to treat diseases in the genitourinary tract. Plant extracts were obtained from barks to simulate traditional use. The anti-trichomonads activity as well as the cytotoxic effect of plant extracts were tested. Herein, we confirmed this traditional knowledge by testing plants aqueous extracts against *Trichomonas vaginalis* and *Tritrichomonas foetus*, the etiologic agents of human and bovine trichomoniasis. All plant extracts were active individually against at least one trichomonads species except for *Prosopis juliflora* and *Amburana cearensis*. *Cedrela* sp. was the most active against both trichomonads species. Finally, a mixture of plants used in traditional medicine was evaluated for activity. A mixture containing extracts of the plants *Ximenia americana*, *Anadenanthera colubrina* var. *cebil*, *Myracrodruon urundeuva*, *Sideroxylon obtusifolium*, and *Amburana cearensis* was active against the two trichomonads. This finding confirms the traditional practice by women living in the Caatinga region of using a mixture of plants during sitz baths to treat vaginal infections. Altogether, these results highlight the ethnopharmacological use of *Cedrela* sp. and of the plant mixture for the treatment of venereal diseases by Caatinga residents.

Keywords: anti-*Tritrichomonas foetus*; anti-*Trichomonas vaginalis*; bovine trichomoniasis; Caatinga biome; human trichomoniasis; plant extracts; traditional medicine; Southern America

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1. Introduction

Trichomonas vaginalis causes human trichomoniasis, the most common non-viral sexually transmitted infection (STI) in the world [1], associated with complications and the transmission facilitation of HIV. Metronidazole and tinidazole are drugs approved by the FDA (USA) for the treatment; however, they may cause adverse effects and increasing drug resistance has leaded to therapeutic failures [2]. Bovine trichomoniasis is caused by *Tritrichomonas foetus* transmitted by coitus. The parasite survives in raw and processed bull semen, which allows its transmission via artificial insemination, causing significant economic losses. There is no FDA-approved drug to treat bovine trichomoniasis and the vaccines available are still under optimization [3].

The Caatinga, a semi-arid biome in the northeast of Brazil, retains diversity of plants used as popular medicine. Elevated temperatures and seasonally dry forests due to the irregular rainfall regime and shrubby, spiny vegetation characterize this biome [4]. This region is known as an area of low economic development; as a consequence, the population has low access to medicines and, therefore, use medicinal plants in the treatment of illnesses. Regional women report a large use of these native medicinal plants for diseases of the genitourinary system and, importantly, use a mixture of plants during sitz baths to treat vaginal infections. In addition to these valuable reports (unprecedented in the formal literature), studies have shown the traditional use and have confirmed the in vitro activity of plants including *Anadenanthera colubrina* (Vell.) Brenan, *Commiphora leptophloeos*, and *Myracrodruon urundeuva* to treat vaginal candidiasis, gonorrhea, and HIV infection [5–7]. The use of the plant *Ximenia americana* by healers to treat STIs was also described [8,9]. Considering this traditional knowledge, this study aimed to determine the anti-*Trichomonas vaginalis* and anti-*Tritrichomonas foetus* activities of extracts from *Ximenia americana*, *Anadenanthera colubrina* var. Cebil, *Myracrodruon urundeuva*, *Schinopsis brasiliensis*, *Cedrela* sp., *Commiphora leptophloeos*, *Hymenaea courbaril*, *Sideroxylon obtusifolium*, and *Amburana cearensis*. Moreover, we showed that a mixture of plant extracts following the traditional medicine methods enhanced the anti-trichomonads activity.

2. Materials and Methods

2.1. Plant Extracts

The plants *X. americana*, *A. colubrina* var. Cebil, *M. urundeuva*, *S. brasiliensis*, *Cedrela* sp., *C. leptophloeos*, *H. courbaril*, *S. obtusifolium*, and *A. cearensis* were collected at Parque Nacional do Catimbau (PARNA do Catimbau), Pernambuco, Brazil (8°37′ S 37°8′ W) in February 2017 under SISGEN authorization A08E18B. The authors confirm that the authority designated Chico Mendes Institute for Biodiversity Conservation (ICMbio) granted permission through the System of Authorization and Information on Biodiversity (SISBIO) with the authentication code n∘ 26743-1. Exsiccates were prepared and the specimen was incorporated into the Dárdano de Andrade Lima herbarium from the Instituto Agronômico de Pernambuco, Recife, Brazil (IPA-PE): *A. cearenses* voucher number 95185, *H. courbaril* voucher number 84888, *X. americana* voucher number 96261, *S. obtusifolium* voucher number 84076, *C. leptophloeos* voucher number 84037, *S. brasiliensis* voucher number 95154, *A. colubrina* var. Cebil voucher number 80351, *Cedrela* sp. voucher number 84110, and *M. urundeuva* voucher number 90471. The crude extracts were obtained from barks using aqueous maceration for 24 h at room temperature based on the traditional methods.

2.2. Screening of Anti-Trichomonads Activity and Determination of IC_{50} Values

The *T. vaginalis* ATCC 30236 isolate and *T. foetus* TFK isolate obtained by Dr. H. Guida (Embrapa, Rio de Janeiro, Brazil) from the urogenital tract of a bull were used in this study. Parasites were cultured in TYM medium (trypticase-yeast extract-maltose) with a pH of 6.0 and 7.2, respectively, and were supplemented with 10% inactivated bovine serum (purchased from Cripion Biotechnology, São Paulo, Brazil). The screening was performed in 96-well microplates. The plant extract concentrations used were 1.0 mg/mL and the trophozoites were added at a final density of 2.0×10^5/mL, maintained at 37 °C for 24 h in 5% CO_2. Two controls were conducted: parasites only and metronidazole (100 μM). The activity was determined by assessing the motility and morphology of parasites compared with the negative control by counting with a hemocytometer using trypan blue dye exclusion (0.2%, *v*/*v*). Viability was determined as the percentage of viable trophozoites compared to the negative control (100% viability). The active extracts in the screening assay had the half-maximal inhibitory concentration (IC_{50}) value determined with concentrations ranging from 1.0 to 0.0078 mg/mL via serial dilution. In addition, the activity of a mixture of extracts from the plants *X. americana*, *A. colubrine* var. *cebil*, *M. urundeuva*, *S. obtusifolium*, and *A. cearensis* (1:1:1:1:1) at 1.0 mg/mL was tested as described.

2.3. Effect of Plant Extracts on Trichomonads Kinetics Growth Assays

Parasite suspensions, at a final density of 2.0×10^5 trophozoites/mL, were incubated with the extracts at their IC_{50} value. The parasites were counted with a hemocytometer using trypan blue (0.2%) after 2, 4, 6, 12, 24, 48, 72, 96, and 120 h of incubation. Results were expressed as the number of viable trophozoites per milliliter.

2.4. Cytotoxicity Assay by MTT Assay

Human vaginal epithelial cells (HMVII) purchased from the European Collection of Authenticated Cell Cultures (ECACC, Porton Down, Wiltshire, England) were cultured in RPMI-1640 medium, supplemented with 10% fetal bovine serum and 25 µg/mL penicillin at 37 °C and 5% CO_2. Briefly, 1.5×10^4 cells per well at the fifteenth passage were seeded in 96-well microplates for 48 h; the medium was replaced with fresh medium containing (or not, in the case of the control condition) active extracts in the IC_{50} range (1.0–0.3 mg/mL). Triton X-100 0.2% was used as a positive control. The plates were incubated for 48 h. After this time, a solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylte-trazolium bromide (MTT) (0.5 mg/mL) was added and incubated for 1 h at 37 °C. MTT was removed and the insoluble purple formazan was dissolved in dimethyl sulfoxide (DMSO). The amount of reduced MTT was measured as 570 nm [10].

2.5. Thin Layer Chromatography (TLC)

The extracts were applied to TLC plates (Silica gel 60 F_{254}, Merck, Darmstadt, Germany) and developed using butanol, acetic acid, and water (5:1:4) as mobile phase. The plates were visualized under UV light (254 and 365 nm, Handheld UV Lamp Model 9403E, BioAmerica Inc., Miami, FL, USA) and revealed with different chemical sprays: natural reagent followed by polyethylene glycol was used to detect flavonoids; ninhydrin for amines and amino acids; anisaldehyde sulfuric for steroids, terpenoids, and saponins; and iodine vapor for alkaloids [11].

2.6. Statistical Analysis

All experiments were performed, at least, at three independent times (three different cultures, $n = 3$), in triplicate. The IC_{50} and half maximal cytotoxic concentration (CC_{50}) values were determined using GraphPadPrism6 software version 8.0.2 (263) through a non-linear regression model. Results were expressed as means ± SD. Statistical analysis was conducted using Student's *t*-test for comparison between two groups, test and control (only parasites). Statistical significance was considered at $p < 0.05$.

3. Results

3.1. Plants X. americana, M. urundeuva, S. brasiliensis, C. leptophloeos, and H. courbaril Aqueous Extracts Were Active against T. vaginalis and T. foetus

Based on ethnopharmacological data from residents of Caatinga, as well as the literature information, the plants investigated in this study were chosen to reproduce the form of use in traditional medicine, by testing the plants aqueous extract (Table 1).

Table 1. Traditional use of plants from Caatinga biome and determination of the IC_{50}, CC_{50}, and SI values of the plant extracts with anti-trichomonads activity.

Plant Scientific Name and Family	Plant Popular Name	Voucher	Popular Use (Reference)	IC_{50} (mg/mL) *T. vaginalis*	IC_{50} (mg/mL) *T. foetus*	CC_{50} (mg/mL) HMVII	SI
Cedrela sp. P. Browne—Meliaceae	Cedar	IPA 95.539	Bark infusion used against cold and flu (PC). Used to treat liver diseases, diarrhea, fever, chronic infantile dysentery, intestinal helminths, and inflammation [12]	0.68	0.74	0.75	1.10 [a]; 1.01 [b]
Commiphora leptophloeos (Mart.) J.B.Gillett—Burseraceae	Imburana or Imburana-de-cambão *	IPA 95.547	Bark infusion used against cold and flu and for wound washing (PC). Used to treat inflammation and infections [13]	N.D.	0.77	0.61	0.80
Hymenaea courbaril L.—Fabaceae	Jatobá *	IPA 95.536	Bark infusion used against cold and flu (PC). Used to treat diarrhea, cystitis, prostatitis, malaria, and leishmaniasis [14]	N.D.	0.71	1.01	1.25
Myracrodruon urundeuva Allemao—Anacardiaceae	Aroeira *	IPA 95.511	Bark infusion used against cold and flu and for wound washing (PC). Used to treat vaginal infections [5]	N.D.	0.84	0.72	0.86
Schinopsis brasiliensis Engl.—Anacardiaceae	Brauna or Barauna *	IPA 95.542	Bark infusion used for digestive problems (PC). Used to treat inflammation, diarrhea, and as an antiseptic [15]	N.D.	0.87	0.79	0.91
Ximenia americana var. *microphylla* Welw.—Olacaceae	Ameixa recanto *	IPA 95.524	Bark infusion used for inflammation and wound washing (PC) [16]	N.D.	0.83	0.50	0.61
Sideroxylon obtusifolium (Roem. and Schult.)—Sapotaceae	Quixabeira *	IPA 95.523	Bark infusion used for inflammation and wound washing (PC). Used for wounds, pain, chronic inflammation, genital problems, ovarian, colon, and kidney problems, heart disease, diabetes, fever, and as an expectorant (PC)	Used in the mixture			
Amburana cearensis (Allemao) A.C.Sm.—Fabaceae	Umburana *	IPA 95.537	Bark infusion used against cold and flu (PC). Used to treat inflammatory diseases [17]	Used in the mixture			
Anadenanthera colubrina var. *cebil*—Fabaceae	Angico	IPA 95.503	Bark infusion used against cold and flu (PC). Used for inflammation, diarrhea, cough, bronchitis, influenza, and toothache [18]	Used in the mixture			

PC—personal communication. N.D.—not determined; [a]—selectivity index (SI) value for the crude extract of barks of *Cedrela* sp. plant for *T. vaginalis*; [b]—SI value for the crude extract of barks of *Cedrela* sp. plant for *T. foetus*. * No English name found.

Among 10 plants collected, seven of them presented activity against the parasites, corroborating their popular use to treat ovarian or vaginal infection. Figure 1 shows the screening of ten aqueous extracts against *T. vaginalis* and *T. foetus*. Considering the plant *Cedrela* sp., the extract presented high anti-parasitic activity with 99.6% and 100% of the reduction in *T. vaginalis* and *T. foetus* viability, respectively. The plants *X. americana*, *M. urundeuva*, *S. brasiliensis*, *C. leptophloeos*, and *H. courbaril* showed activity against *T. foetus*, strongly reducing the trophozoite viability by 96% (Figure 1).

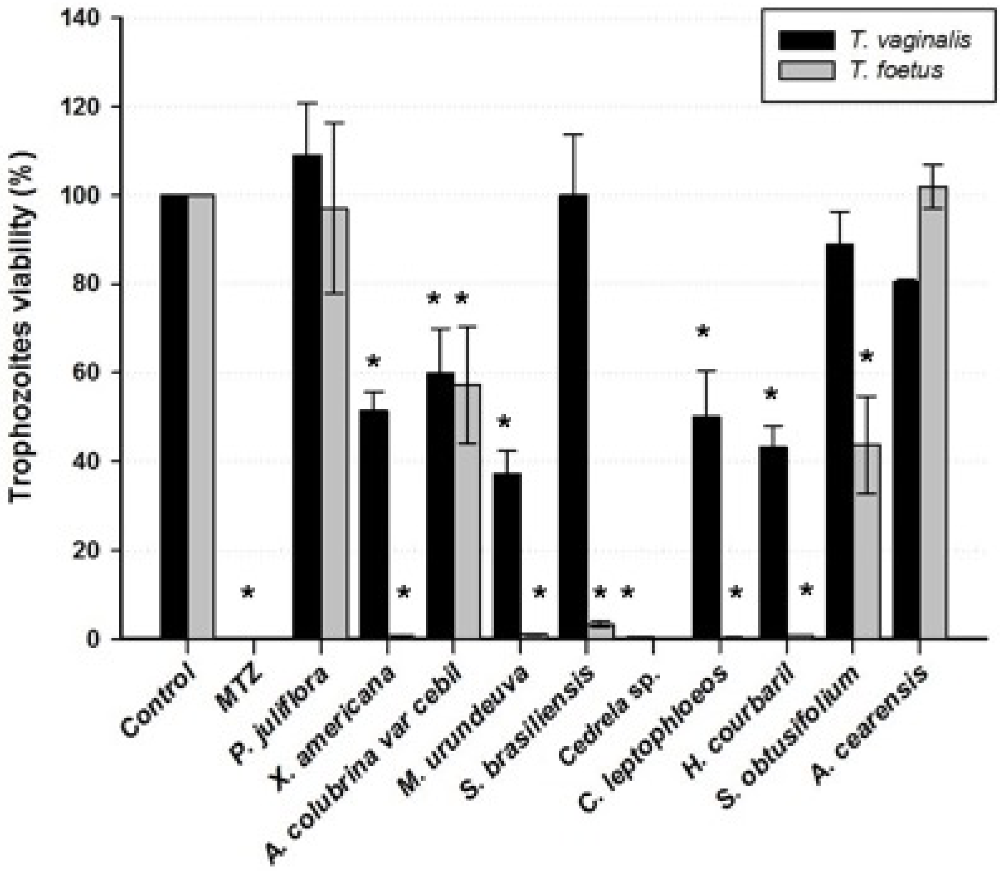

Figure 1. Effect of extracts from the barks of plants in trichomonads viability. MTZ: metronidazole as positive control (100 µM or 0.0171 mg/mL). Data are presented as mean ± standard deviation compared to control (considering the trophozoite viability as 100%). Results are representative of three independent experiments performed in triplicate assays. * means statistical significance in comparison with controls ($p < 0.05$).

3.2. Cedrela sp. Extract Was the Most Active against T. vaginalis and T. foetus

Based on the results of the screening, six plants that were active were chosen for the determination of the IC_{50}: *Cedrela* sp., *X. americana*, *M. urundeuva*, *S. brasiliensis*, *C. leptophloeos*, and *H. courbaril*. Corroborating the result of the screening, *Cedrela* sp. presented the highest anti-trichomonads activity (Table 1). Moreover, a decrease in parasite growth after 4 h of incubation with *Cedrela* sp. extract could be observed (Figure 2). All other plant extracts also reduced the *T. foetus* proliferation by 50% in 24 h. As expected, after 24 h of incubation, the untreated trophozoites (control) exhibited the classic growth peak (Figure 2).

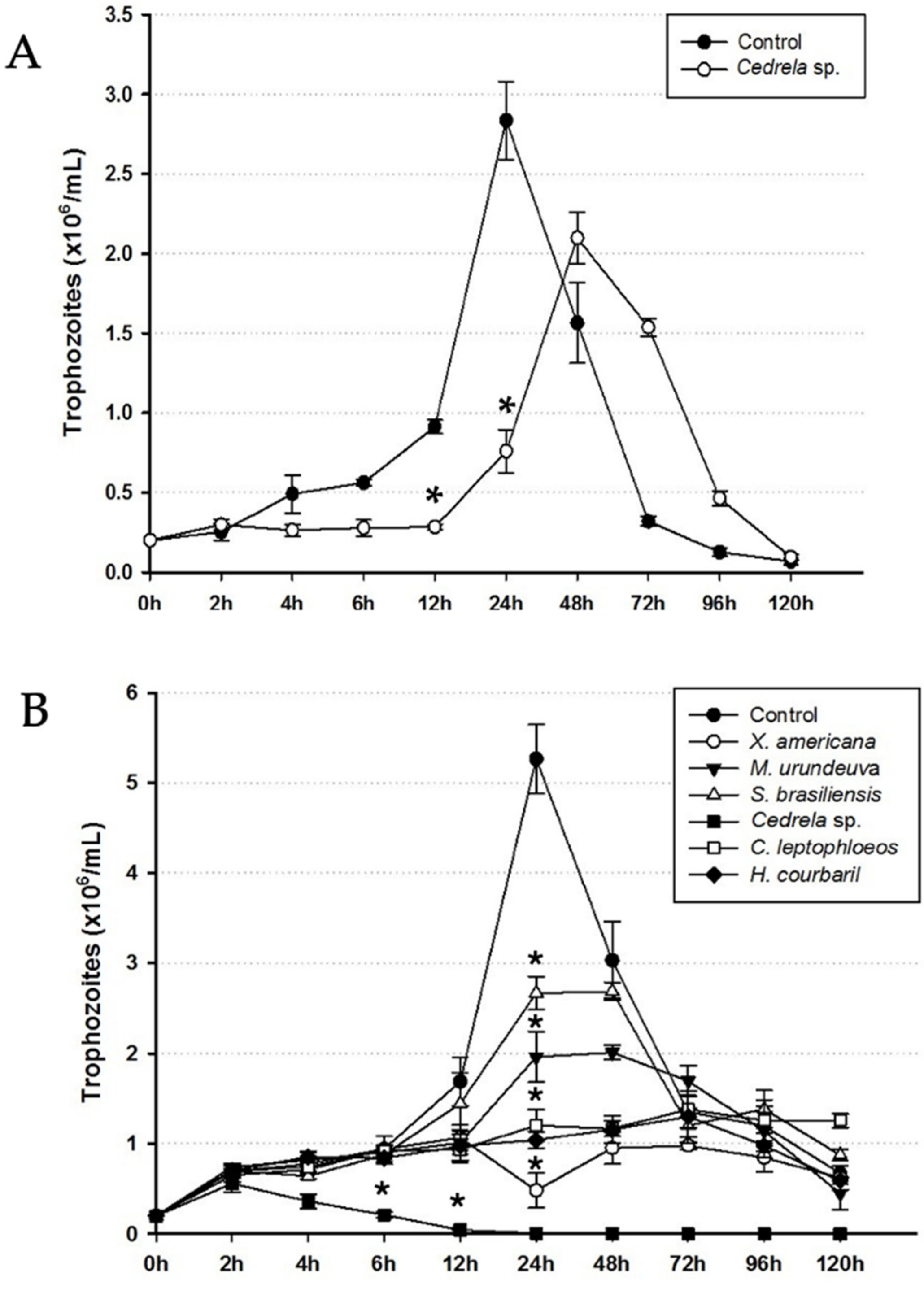

Figure 2. Effect of extracts from the barks of plants in the kinetic growth curve of (**A**) *T. vaginalis* and (**B**) *T. foetus.* Trophozoites treated with extracts of plants, at IC_{50} values, were counted in comparison to untreated parasites (control). The initial inoculum was 2.0×10^5 trophozoites/mL. Results are presented as mean ± standard deviation of three independent experiments in triplicate. * Satistically different from control ($p < 0.05$).

3.3. Active Plant Extracts Showed Low Selectivity

Cytotoxicity results of the most active extracts against the vaginal epithelial cell line (HMVII), *Cedrela* sp., *Commiphora leptophloeos*, *Hymenaea courbaril*, *Myracrodruon urundeuva*, *Schinopsis brasiliensis*, and *Ximenia americana*, are shown in Table 1 (Supplementary Materials, Figure S1). The selectivity index (SI) values obtained were below 1.5, indicating that the plant extracts were nonselective to the parasites.

3.4. The Mixture of Plants Was Effective against Both Trichomonads Species

The mixture of extracts from the barks of plants *X. americana*, *A. colubrina*, *M. urundeuva*, *S. obtusifolium*, and *A. cearensis* (1:1:1:1:1) reduced the viability of the trophozoites by 79.2% and 66.9% for *T. vaginalis* and *T. foetus*, respectively (Figure 3).

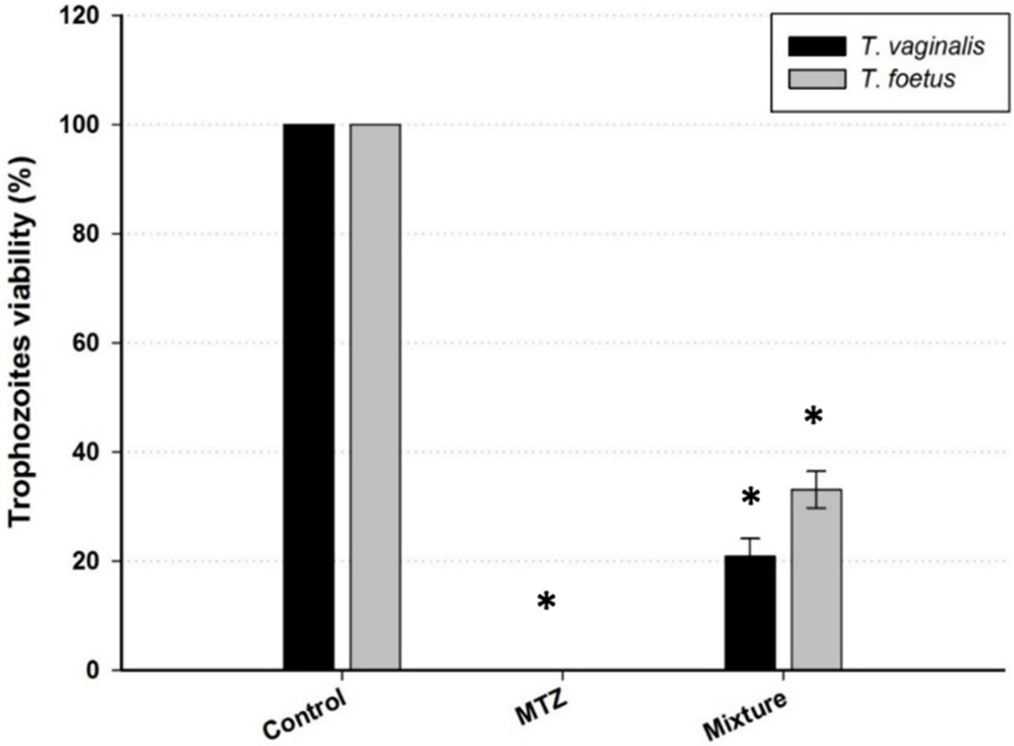

Figure 3. Effect of mixture of extracts from the barks of plants *X. americana*, *A. colubrina*, *M. urundeuva*, *S. obtusifolium*, and *A. cearensis* (1:1:1:1:1) in trichomonads viability. MTZ: metronidazole as control (100 µM). Data are presented as mean ± standard deviation compared to control (considering the trophozoite viability as 100%). Results are representative of three independent experiments performed in triplicate assays. * means statistical significance in comparison with controls ($p < 0.05$).

3.5. Qualitative Phytochemical Screening

The preliminary qualitative phytochemical screening of the plant extracts indicated the presence of flavonoids and tannins in the extracts of *P. juliflora*, *X. americana*, *A. colubrina* var *cebil*, *M. urundeuva*, *S. brasiliensis*, and *H. courbaril* (Figure 4A), while alkaloids were only detected in *P. juliflora* (Figure 4B). As it can be observed, no amines, amino acids, terpenoids, or saponins were detected (Figure 4C,D). However, more studies are needed to evaluate and characterize the constituents of these extracts, since the technique used, TLC, is a preliminary approach.

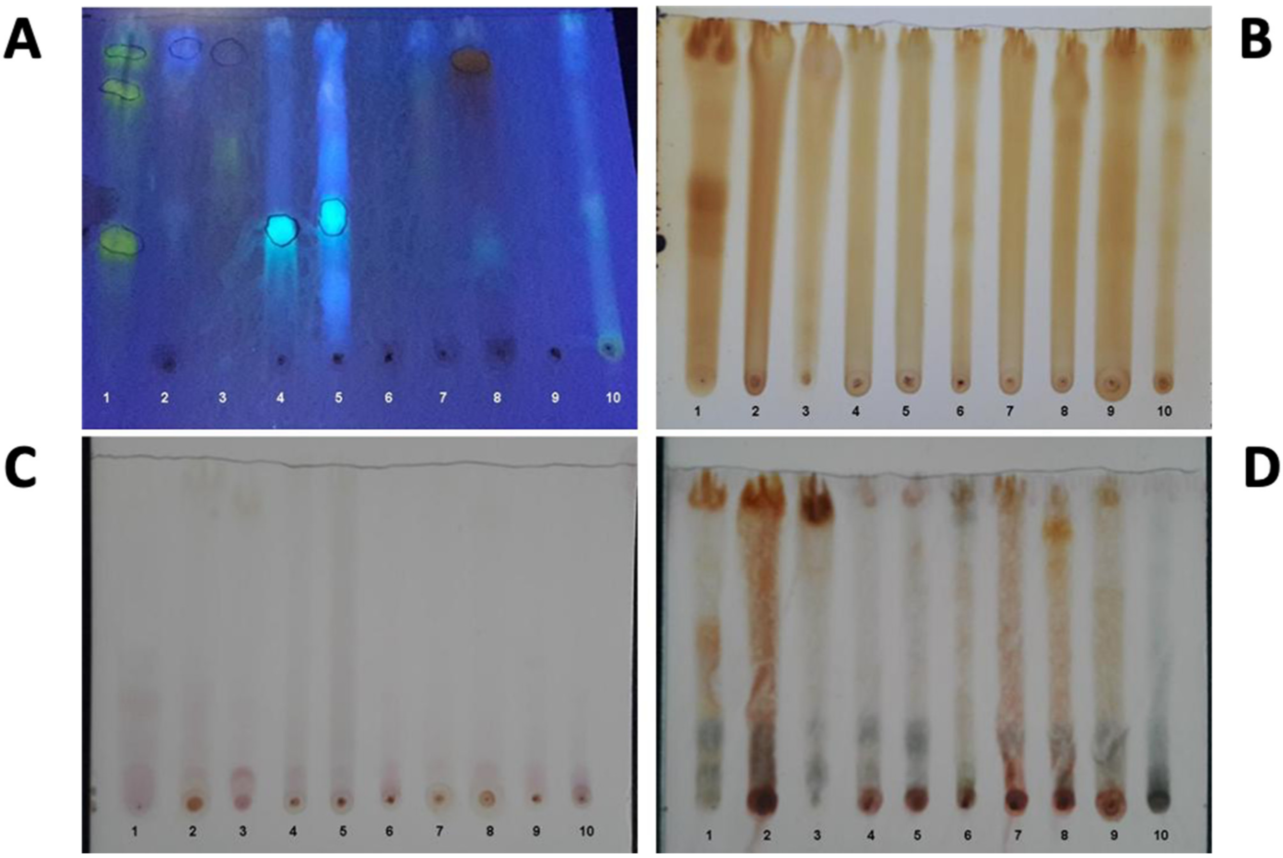

Figure 4. Revelation of the thin layer chromatography of the extracts with different developers. (**A**)—Natural reagent; (**B**)—Iodine vapor; (**C**)—Ninhydrin; (**D**)—Anisaldehyde. 1—crude extract of barks of *Prosopis juliflora* plant; 2—crude extract of barks of *Ximenia americana* plant; 3—crude extract of barks of *Anadenanthera colubrina* var. *cebil* plant; 4—crude extract of barks of *Myracrodruon urundeuva* plant; 5—crude extract of barks of *Schinopsis brasiliensis* plant; 6—crude extract of barks of *Cedrella* sp. plant; 7—crude extract of barks of *Commiphora leptophloeos* plant; 8—crude extract of barks of *Hymenaea courbaril* plant; 9—crude extract of barks of *Syderoxylum obtusifolium* plant; 10—crude extract of barks of *Amburana cearensis* plant.

4. Discussion

Ethnopharmacological usage rescues the traditional knowledge of medicinal plants and contributes to preventing it from disappearing or being restricted only to the population of origin. In local communities, such as in the Caatinga region, with poor economic development and limited access to pharmaceutical drugs, medicinal plants are the only alternative to the treatment of illness [19]. In this sense, the ethnopharmacological data from the residents of Caatinga as well as the literature information pointed to the plants investigated in this study to reproduce the form used in traditional medicine, by testing the plants aqueous extract (as detailed in Table 1). Indeed, among 10 plants tested, seven of them presented activity against *T. vaginalis* and *T. foetus*, corroborating their popular use to treat ovarian or vaginal infection. While the anti-trichomonads activities were demonstrated, the plant extracts were not selective since they presented cytotoxicity against human vaginal epithelial cells with a SI = 1.0 or lower. The SI is a value obtained by the ratio of CC_{50}/IC_{50} that defines the cytotoxic effect of a compound and, although there is no consensus in the literature, it is expected to be higher than 1.0 [10]. Therefore, the higher the SI, the more selective the compound. This selectivity was not found in the present study, but it is important to point out that the SI was calculated for a crude extract with complex composition and the SI values should be used as a general guideline and not as an exclusion factor for study of a particular compound. The in vitro cytotoxicity should not be the unique criterion to decide whether a compound should be rejected or forwarded to an animal model to continue the search for a new bioactive molecule. Moreover, previous studies showed anticancer activity and low toxicity of the plants used in this study in mouse and *Drosophila melanogaster* in vivo models [12,17,18,20,21].

Regarding the chemical composition of the extracts, the results found here are in agreement with other studies that identified the presence of polyphenols, terpenes, limonoids, and tannins in *X. americana*, *M. urundeuva*, *S. brasiliensis*, *Cedrela* sp., *C. leptophloeos*, and *H. courbaril* [22–28], and these classes of compounds have already demonstrated anti-trichomonads activities [29].

Women living in the Caatinga region use a mixture of plants during sitz baths to treat vaginal infections. Women's reports showed that plant species with anti-trichomonads activity are used in the treatment of candidiasis, discharge, urinary tract infection, pelvic inflammation, pelvic hemorrhage, hormone replacement, menopause, menstrual cramps, and uterine wounds. These dialogues also showed that popular knowledge and the practice of traditional medicine are still very present in an isolated area with difficult access to basic health care. An ethnobotanical study in these communities is interesting, being an important tool in the rescue and enhancement of traditional knowledge, the cultural diversification of these societies, and the preservation of natural resources, especially in areas with remnants of Caatinga (data from the Bioprospecting and Conservation Nucleus of Caatinga-NBioCaat). Taking into account the popular usage, the findings in this study are relevant, since the plant extracts mixture presented high anti-*T. vaginalis* activity. The limitation of this study is the lack of chemical composition of plant extracts, which does not compromise the contribution since the aim was to reinforce the popular use of these plants, and especially the plant mixture.

5. Conclusions

Overall, the anti-*T. vaginalis* and anti-*T. foetus* activities demonstrated in this study reaffirm the importance of the traditional knowledge for the treatment of venereal diseases. The anti-trichomonads activity of the mixture containing extracts of the plants *Ximenia americana*, *Anadenanthera colubrina* var. *cebil*, *Myracrodruon urundeuva*, *Sideroxylon obtusifolium*, and *Amburana cearensis* is highlighted, thus confirming the traditional use by women living in the Caatinga region of a mixture of plants during sitz baths to treat vaginal infections. The preliminary qualitative phytochemical screening of the plant extracts indicated mainly the presence of flavonoids and tannins. In addition, this study reinforces the impact of natural products as a source of new active molecules, demonstrating the significant pharmacological potential of the plant species from the Caatinga biome.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/venereology3010002/s1. Figure S1. Determination of IC_{50} values for anti-*Tritrichomonas foetus* activity (graphs B, D, F, H, J, L), except for *Cedrela* spp., which had IC_{50} values determined for anti-*T. vaginalis* and anti-*T. foetus* activities (graphs A and B, respectively). Cytotoxicity of plant extracts tested against human vaginal epithelial cells (HMVII lineage) is represented in graphs C, E, G, I, K, M. Graphs showing CC_{50} estimate using GraphPadPrism6 software version 8.0.2 (263) through a non-linear regression model. Bars represent cell viability as mean ± standard deviation obtained by MTT assay as described in Material and Methods.

Author Contributions: Conceptualization, N.L.F.S. and T.T.; methodology, N.L.F.S., P.d.B.V. and M.V.d.S.; resources, M.V.d.S.; data curation, M.V.d.S.; writing—original draft preparation, N.L.F.S. and P.d.B.V.; writing—review and editing, A.J.M. and T.T.; supervision, T.T.; project administration, A.J.M. and T.T.; funding acquisition, A.J.M. and T.T. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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