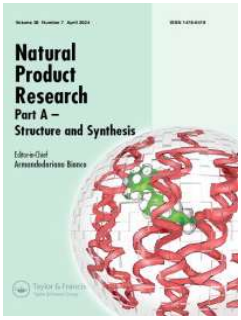

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# Phytochemical study of *'tajy'* (*Handroanthus impetiginosus* (Mart.) Mattos) and *'ka'a ovetĩ'* (*Luehea divaricata* Mart.) extracts

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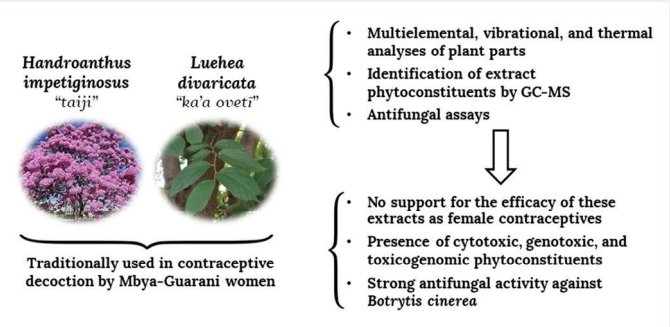
**ABSTRACT**

This study explores the phytochemical composition of leaf extracts from *Handroanthus impetiginosus* (Mart.) Mattos and *Luehea divaricata* Mart., used in a contraceptive decoction by Mbya-Guarani women. The phytocompounds were identified by gas chromatography-mass spectrometry, while Fourier-transform infrared spectroscopy, multi-elemental, and thermal analyses were used to characterise plant biomass. Notably, no phytoconstituent supporting the efficacy of these extracts as female contraceptives was found, except for a small amount (0.3%) of sitosterol. Conversely, *L. divaricata* leaves contained compounds like 1,3-dihydroxyacetone dimer, N-methyl-N-nitroso-2-propanamine, 2-methoxy-N-(2-methoxyethyl)-N-methyl-ethanamine, and 1,3,5-triazine-2,4,6-triamine, potentially exerting cytotoxic, genotoxic, and toxicogenomic effects. Due to the absence of scientific support for the claimed contraceptive efficacy and the presence of safety concerns, we propose an alternative valorisation pathway centred on the presence of phytochemicals exhibiting antimicrobial activity. This proposition is substantiated by their considerable *in vitro* efficacy against *Botrytis cinerea*.

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## 1. Introduction

*Handroanthus impetiginosus* (Mart.) Mattos is a tree from the *Bignoniaceae* family, predominantly found in the Amazon rainforest and other Central and South American tropical areas. Zhang J et al. (2020) recently conducted a thorough review of its traditional applications and phytochemical composition. *Luehea divaricata* Mart. is another species of deciduous tree native to South America, belonging to the *Malvaceae-Tiliceae* family, whose pharmacological and chemical properties have been reviewed by Calixto-Júnior et al. (2016). Additional information on the traditional uses and previous phytochemical profiling of various plant organs from both species is presented in the supplementary material.

Although *H. impetiginosus* and *L. divaricata* were not included in the review by Kujawska and Schmeda-Hirschmann (2022) concerning the medicinal plant usage among the people of Paraguay, according to an ethnographic study carried out with funding from the National Council of Science and Technology of Paraguay (Fogel Pedroso et al. 2016), women in six Mbya Guaraní indigenous communities use a mixture of these two plants as contraceptives. Martínez et al. (2006) indicated that the way of administration of *H. impetiginosus* was as an infusion, obtained by 'concoction in combination with other elements'. Martínez Crovetto (2012) indicated that the bark of *H. impetiginosus* with the fern *Blechnum australe* L. subsp. *auriculatum* (Cav.) de la Sota was taken in the water for mate and consumed monthly. Therefore, the mixture of *H. impetiginosus* and *L. divaricata* could be considered an alternative recipe. This use of mixtures differs from the one reported by Yazbek et al. (2016), who only referred to *H. impetiginosus* in a comprehensive investigation into the utilisation of plants in Brazilian cultures for menstrual cycle, maternity, and various women's health issues.

Since no phytochemical study has been conducted on these two plants' leaf aqueous extracts to date, the aim of this study was to investigate the constituents present in these extracts and to determine whether the presumed contraceptive activity is backed up by scientific evidence.

## 2. Results and discussion

The results of plant biomass characterisation through multi-elemental, thermal, and Fourier-transform infrared spectroscopy analyses are presented in the supplementary information.

Regarding the gas chromatography-mass spectrometry (GC-MS) characterisation results, the analysis of the *H. impetiginosus* leaf extract (Table S2, Figure S4) revealed the presence of terpenic constituents, including megastigmatrienone (3,5,5-trimethyl-4-(1,3-butadienyl)-2-cyclohexene-1-one, also known as tabanone); megastigm-4-ene-3,9-dione (or 3,5,5-trimethyl-4-(3-oxobutyl)-2-cyclohexen-1-one); 9-hydroxymegastigma-4-en-3-one (4-(3-hydroxybutyl)-3,5,5-trimethyl-2-cyclohexen-1-one); phytol (Figure S5); and $\gamma$-sitosterol. The percentage of megastigmatrienone was found to be 2.8%. Other phytochemicals were also identified, including linolenic acid (or 9,12,15-octadecatrienoic acid) and its methyl ester; phenol; *n*-hexadecanoic acid and its esters; 1-methylpyrrolidine-2-carboxylic acid; 1,2,3,4-butanetetrol; and 1-ethylideneoctahydro-7a-methyl-1*H*-indene.

(7*E*)-4,7,9-megastigmatrien-3-one is a product found in *Aptenia cordifolia* (L.fil.) Schwantes (DellaGreca et al. 2007) and *Chenopodium album* L. (DellaGreca et al. 2004) without any known reproductive toxicity. Phytol is an acyclic diterpene alcohol that is part of chlorophyll. *γ*-Sitosterol was found to possess anti-fertility and contraceptive effects in rodents, exhibiting *in vitro* inhibitory properties on cultured decidual stromal cells (Zhang X et al. 2007), which are important for female fertility, as they are involved in the preparation of the uterus for implantation of the embryo. Nonetheless, the content in the extract would be small (0.3%). Concerning other phytoconstituents of *H. impetiginosus* leaf extract, *α*-linolenic acid methyl ester is antiandrogenic (Duke 1992; Abdel Aziz et al. 2020); 1-methylpyrrolidine-2-carboxylic acid (also known as N-methyl-L-proline) was located in the placenta in spontaneous preterm birth (Elshenawy et al. 2020), but its reproductive toxicity is unknown; and 1,2,3,4-butanetetrol is suspected of causing infertility (Halpern et al. 2016).

As for the main phytochemicals detected in the *L. divaricata* leaf extract (Table S3, Figure S6), they include 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one, also known as DDMP (Olaniyan et al. 2018); N-methyl-N-nitroso-2-propanamine (NMIPA); a dimer of 1,3-dihydroxyacetone (DHA); 2-methoxy-N-(2-methoxyethyl)-N-methyl-ethanamine; 2-hydroxy-2-cyclopenten-1-one (2-HCP); 2-methoxy-4-vinylphenol (2M4VP); L-arabinitol; phytol; 1,3,5-triazine-2,4,6-triamine; 1-(3,6,6-trimethyl-1,6,7,7a-tetrahydrocyclopenta[c]pyran-1-yl)ethanone; 4-(3-hydroxybutyl)-3,5,5-trimethyl-2-cyclohexen−1-one; 2,4-dimethylanisol; and coniferyl alcohol (Figure S7).

DDMP has antioxidant activity (Imad et al. 2015); NMIPA exhibits antibacterial and genotoxic properties; and DHA dimer exhibits cytotoxic, genotoxic, and toxicogenomic effects (Striz et al. 2021). 2-methoxy-N-(2-methoxyethyl)-N-methyl-ethanamine causes acute toxicity according to the European Chemical Agency. Finally, 1,3,5-triazine-2,4,6-triamine is genotoxic (Scognamiglio et al. 2012). The analgesic and anti-inflammatory activities reported for *L. divaricata* (Agra et al. 2007) can be associated with the presence of 2-HCP (Kala and Ammani 2017) and 2,3-dihydrobenzofuran (Diaz et al. 2009).

While acknowledging potential individual, genotype-dependent variations, location-related intra-varietal differences, seasonal fluctuations, and the presence of distinct chemotypes resulting from minor genetic and epigenetic changes—factors that could notably impact phytochemical composition and bioactivity (Chander et al. 2022)—the phytochemicals identified in the examined plant samples do not lend support to the efficacy of the plant extracts as a female oral contraceptive. The phytochemical profile of the *H. impetiginosus* leaf extract does not appear to have any component that could produce the abortifacient properties preconised for the stem bark extract in the literature (Martínez et al. 2006; Agra et al. 2007). However, the *L. divaricata* leaf extract contains phytochemicals that display cytotoxic, genotoxic, and toxicogenomic effects. This is consistent with the findings of Nunes (2015), who warned about the acute and subacute toxicity of extracts of *L. divaricata* in Wistar rats, and of Mendes Arrúa et al. (2020), who investigated their toxicity on *Daphnia magna* neonates. This raises concerns about the application of *L. divaricata* as a medicinal remedy.

Concerning other possible valorisation pathways, as an alternative to contraceptive use, the extracts have potential for other applications. *H. impetiginosus* leaf extract,

due to the identified phytochemicals, could be a valuable source of antimicrobial agents. For example, linolenic acid has shown antibacterial activity against *Xylophilus ampelinus* and *Erwinia amylovora* (Sánchez-Hernández et al. 2021). *n*-Hexadecanoic acid and its esters have been found to have antifungal activity against various fungi, including *Alternaria solani*, *Aspergillus erythrocephalus* (Abubacker and Deepalakshmi 2013), *Fusarium equiseti*, *Fusarium oxysporum* f. sp. *niveum*, *Neocosmospora falciformis*, *Neocosmospora keratoplastica*, *Macrophomina phaseolina*, and *Sclerotinia sclerotiorum* (Sánchez-Hernández, Martín-Ramos, et al. 2023).

Figure S8 displays the outcomes of the *in vitro* tests assessing mycelial growth inhibition conducted using leaf extracts of *H. impetiginosus* and *L. divaricata*. The extract of *H. impetiginosus* completely halted the growth of *B. cinerea* at 375 µg/mL, while *L. divaricata*'s extract exhibited higher activity, with a minimum inhibitory concentration (MIC) value of 250 µg/mL.

While conducting individual antimicrobial tests for each identified compound would be essential to conclusively determine the specific chemical species responsible for the observed antifungal activity, existing literature allows for a tentative attribution of this activity to several phytoconstituents: 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one has demonstrated activity against plant pathogens, such as *Phytophthora megasperma*, *Verticillium dahliae*, and *Diaporthe amygdali* (Sánchez-Hernández et al. 2023). Catechol has been reported to inhibit bacterial phytopathogens, such as *Clavibacter michiganensis*, several *Pseudomonas syringae* pathovars, *Pseudomonas cichorii*, and *Xanthomonas vesicatoria* (Sánchez-Hernández, González-García Vicente, et al. 2023). Additionally, 2-hydroxy-2-cyclopenten-1-one exhibits antimicrobial properties (Kala and Ammani 2017), while 2-methoxy-4-vinylphenol shows strong antibacterial activity and it can act as a food bio-preservative (Rubab et al. 2020). Methyl stearate also demonstrates high antibacterial and antioxidant ability (Hagr et al. 2019). These findings may explain the antimicrobial activity observed against *Candida albicans*, *Salmonella typhimurium*, and *Trichomonas vaginalis* (Mendes Arrúa et al. 2020).

This pathway of valorisation of the extracts as sources of biorationals for crop protection was successfully demonstrated against *B. cinerea*, a phytopathogen that holds the second position on the rank of fungal pathogens, both in terms of economic impact and scientific significance (Dean et al. 2012). The MIC values obtained for *H. impetiginosus* and *L. divaricata* aqueous extracts (375 and 250 µg/mL, respectively) are very promising, being comparable to those reported for *Uncaria tomentosa* L. (375 µg/mL) (Sánchez-Hernández et al. 2022), which is among the most active plant extracts reported to date. Moreover, they would be lower than those of traditional synthetic fungicides such as azoxystrobin, metalaxyl, and fosetyl-Al, with MIC values of 625, 21, and 2 mg/mL, respectively (Sánchez-Hernández et al. 2022).

## 3. Conclusions

No phytochemicals detected by gas chromatography-mass spectroscopy support the purported activity of the two leaf extracts (separately or mixed) as female oral contraceptives. The content of compounds with anti-fertility activity (sitosterol and 1,2,3,4-butanetetrol) in *H. impetiginosus* extract was very low (0.3, and 2.8%, respectively). In turn, several constituents of *L. divaricata* leaf extract

(N-methyl-N-nitroso-2-propanamine, 1,3-dihydroxyacetone dimer, 2-methoxy-N-(2-methoxyethyl)-N-methyl-ethanamine, and 1,3,5-triazine-2,4,6-triamine) suggest toxicity, as they are genotoxic. In contrast, the finding of noticeable amounts of linolenic acid and *n*-hexadecanoic acid and its esters in *H. impetiginosus* extract; and of 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one, catechol, 2-hydroxy-2-cyclopenten-1-one, 2-methoxy-4-vinylphenol, and methyl stearate in *L. divaricata* extract suggests an alternative pathway for valorisation, as sources of biorationals. To test this hypothesis, the extracts were assayed *in vitro* against *B. cinerea*, showing strong antifungal activity with mycelial growth inhibition values of 375 and 250 µg/mL for *H. impetiginosus* and *L. divaricata* leaf extracts, respectively. These values rank among the lowest documented in the literature for plant extracts and are lower than those of several synthetic fungicides. Further studies are needed to determine their suitability as crop protection products against other phytopathogens.

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## Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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