Productos naturales

Antifungal and cytotoxicity effect of floral extracts of *Fridericia platyphylla* and *Fridericia florida*

Efecto antifúngico y citotóxico de extractos florales de *Fridericia platyphylla* y *Fridericia florida*

Antonio Carlos Pereira de Menezes Filho[1*] https://orcid.org/0000-0003-3443-4205

Matheus Vinicius Abadia Ventura[1] https://orcid.org/0000-0001-9114-121X

Hellen Regina Fernandes Batista-Ventura[1] https://orcid.org/0000-0003-4815-4159

Cinthia Alves Porfiro[2] https://orcid.org/0000-0002-4398-0323

Carlos Frederico de Souza Castro[1] https://orcid.org/0000-0002-9273-7266

[1]Goiano Federal Institute, Campus Rio Verde. Goiás State, Brazil.

[2]UniBras Faculty, Campus Rio Verde. Goiás State, Brazil.

*Corresponding author: astronomoamadorgoias@gmail.com

ABSTRACT

Introduction: *Fridericia platyphylla* and *Fridericia florida* are two species belonging to the Bignoniaceae family with potential biological activities such as antifungal and cytotoxic.
Objective: To evaluate the floral extracts of *Fridericia platyphylla and Fridericia florida* for antifungal activity on *Candida* sp. and cytotoxic activity on *Artemia salina*.
Methods: *F. platyphylla* and *F. florida* flowers, were collected and, the extract produced by static maceration using hydroethanolic solution (70%). The antifungal activity on *Candida* sp. was carried out using paper disk diffusion methodology, and the cytotoxic activity on *Artemia salina*, both assay in different concentrations of extract.
Results: The floral extract of *F. platyphylla* showed potential inhibitory activity on *C. guilliermondii* 13.8-9.7 mm and *C. albicans* 18.6-14.5 mm at the highest concentrations of 100-50 mg mL^{-1}, respectively. For the floral extract of *F.*

florida it showed potential inhibitory action on *C. albicans* 11.5-6.8 mm and *C. krusei* 14.3-11.1 mm at the highest concentrations between 100 and 50 mg mL^{-1}, respectively. The extracts proved to be toxic with LC_{50} of 237.81 and 301.20 µg mL^{-1}, respectively.
Conclusions: The floral extracts of *Fridericia platyphylla* and *Fridericia florida* demonstrated in this study, the first results of antifungal activity on *Candida* and cytotoxic action on *Artemia salina*. In view of these results, it is observed that the extracts of *Fridericia* species evaluated have potential for the development of new phytotherapic drugs.
Keywords: *Fridericia* genus, *Artemia salina*, Cytotoxic activity, *Candida albicans*, *Candida krusei*, *Candida tropicalis*.

RESUMEN

Introducción: *Fridericia platyphylla* y *F. florida* son dos especies que pertenecen a la familia Bignoniaceae con actividades biológicas antifúngica y citotóxica potenciales.
Objetivo: Evaluar los extractos florales de *Fridericia platyphylla and Fridericia florida* en cuanto a su actividad antifúngica sobre *Candida* sp. y actividad citotóxica sobre *Artemia salina*.
Métodos: Se recolectaron flores de *F. platyphylla* y *F. florida*, y el extracto se produjo por maceración estática con solución hidroetanólica (70%). La actividad antifúngica sobre *Candida sp.* se llevó a cabo mediante la metodología de difusión en disco de papel, y se estudió la actividad citotóxica sobre *Artemia salina*, en ambos casos se analizaron diferentes concentraciones del extracto.
Resultados: El extracto floral de *F. platyphylla* mostró actividad inhibidora potencial sobre *C. guilliermondii* 13,8-9,7 mm y para *C. albicans* 18,6-14,5 mm en las concentraciones más altas de 100-50 mg mL^{-1}, respectivamente. El extracto floral de *F. florida* mostró una potencial acción inhibidora sobre *C. albicans* 11,5-6,8 mm y para *C. krusei* 14,3-11,1 mm en las concentraciones más altas entre 100 y 50 mg mL^{-1}, respectivamente. Los extractos demostraron ser tóxicos con CL_{50} de 237,81 y 301,20 µg mL^{-1}, respectivamente.
Conclusiones: Se reportan en este estudio los primeros resultados de actividad antifúngica sobre *Candida* y acción citotóxica sobre *Artemia salina* para los extractos florales de *Fridericia platyphylla* y *Fridericia florida*. Según estos resultados, se observa que los extractos de especies de *Fridericia* evaluados, tienen potencial para el desarrollo de nuevos fármacos fitoterápicos.
Palabras clave: Género *Fridericia*, *Artemia salina;* actividad citotóxica; *Candida albicans*; *Candida krusei*; *Candida tropicalis*.

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Introduction

Fridericia platyphylla (Cham.) L. G. Lohmann and *Fridericia florida* (DC.) L. G. Lohmann is a species of the Bignoniaceae family, popularly known as "*pedra ume-caá*, *cipó-uma* or *tinteiro*", which has a wide geographic distribution, found in all Brazilian biomes and *Cerrado* domain.[1,2,3,4,5,6]

F. platyphylla presents several studies directed to pharmacology, in folk medicine, Brazilian people consume its roots to treat kidney stones, joint pains, and gastric ulcers.[4,5] In addition to these traditional uses presenting potential anti-inflammatory, analgesic, antibacterial, antitumor, gastroprotective and antifungal activity.[3,5,6,7,8,9,10]

F. florida, on the other hand, presents little data, and studies are focused on floristic knowledge and territorial distribution.[9,10] Although there are few phytochemical records of *F. florida* showing cytotoxic, anti-inflammatory and analgesic activity, it is still poorly studied.[2,11] According to *Castillo* and others.[12], *F. florida* is also used as a traditional dye in indigenous communities and artisans in some regions of Colombia. These species are easily found in clearings, forest edges and restricted *Cerrado* areas.[13]

Currently, numerous plant species with potential antifungal and cytotoxic activity are being studied, capable of inhibiting the growth of fungi, mainly of the genus *Candida*, which already has resistance to the main reference antifungals such as amphotericin B, fluconazole and caspofungin. This genus is formed by 163 species and 10 are intimately responsible for infections in humans, causing superficial or invasive mycoses in organs.[14,15]

The interesting thing about the use of vegetables is the potential for resistance and dosages, since there is no need for overdosing as observed in substances of synthetic origin.[16,17] In addition, extracts that have a high cytotoxic potential also have phytomedicinal use in preventing and assisting in the treatment of numerous diseases such as cancer.[17,18] Thus, the need to evaluate extracts that present a rich and varied amount of phytomolecules in different classes based on secondary metabolism becomes the duty of the scientific community.

The study aims to evaluate the floral extracts of *Fridericia platyphylla and Fridericia florida* for antifungal activity on *Candida* sp. and cytotoxic activity on *Artemia salina*.

Methods

Plant material: Flowers from both plants were collected in November 2019 and February 2020 at Rio Verde University (UniRV) (17°47'07.9''S 50°58'01.0''W) and permanent protection area of *Rio Verde* environmental police (17°46'01.8''S 50°55'36.7''W), Goiás, Brazil. The voucher specimens were obtained fresh

material and deposited in the Herbarium of the Vegetable Systematic laboratory of Goiano Federal Institute, Rio Verde Campus, with registration numbers: *F. platyphylla* (n. HRV 13.157) and *F. florida* (n. HRV 13.158) and identified by the Dr^{a}. Isa Lucia de Morais and, Ms^{o}. Antonio Carlos Pereira de Menezes Filho.

Extract production: The extract was produced with 500 g of flowers in 1 L of extracting solution. The *in natura* plant material was submitted to exhaustive extraction by maceration using as extracting solvent solution hydroethanolic (70%) (*v*/*v*) for 72 h at room temperature. The extracts were concentrate on a rotary evaporator under reduced pressure and subsequently taken to an oven with forced air circulation at 35 °C until complete drying.

Microorganisms: Were fungal acquired strains of the American Type Culture Collection (ATCC) used in this study: *Candida albicans* (ATCC 2115-1), *Candida krusei* (ATCC 2047-3), *Candida tropicalis* (ATCC 2591-4) and *Candida guilliermondii* (ATCC 2018-2).

Antifungal assays: Antifungal assay was performed as described by Menezes Filho et al.[19] adapted. The strains were resuspended in 25 mL of sterile Sabouraud Dextrose Broth (Kasvi-SDB) medium. The suspension was shaken on a shaking table with incubation (Solab, Mod. Shaker SL-222) for 24 h at 36 °C. Starting from this culture inoculum containing approximately 1x10^{6} CFU mL^{-1} were prepared according to the turbidity in a tube of 0.5 on the McFarland scale, in a UV-*Vis* spectrophotometer (Bel Photonics - Mod. UV-M51). The antifungal assay was carried out in a solid medium (SDB) using sterile filter paper discs with a diameter of 7 mm.

Four paper disks containing 50 µL in different concentrations of floral extract (100; 50; 25 and 12.5 mg mL^{-1}), diluted in hydroethanolic solution (70%), and were added to each *Petri* dish. As a negative control hydroethanolic solution (70%) was used, absence of interferents and, as a positive control, Ketoconazole (purity 98-102%, Purifarma) (50 µg mL^{-1}). Zones of inhibition were examined after 24-46 h, measured and recorded as the diameter (mm) of complete growth-inhibition, obtained with the aid of a digital caliper (Digimess, Mod. 100.174 BL) 150 mm, 0.01 mm/,0005'' resolution and, measurement error = 0.01 mm. The minimum inhibition zone considered was 5 mm.

Brine shrimp lethality bioassay Artemia salina Leach: The lethality assay in *A. salina* was performed as described by *Pereira* and others.[19] adapted. *A. salina* lethality bioassay, was carried out to investigate the cytotoxicity of extracts of *F. platyphylla* and *F. florida*. *A. salina* were hatched using brine shrimp eggs in a beaker 1 L, filled with sterile artificial seawater conc. sea salt 23 g L^{-1} and 0.7 g L^{-1} sodium bicarbonate (purity 99%, Uniphar), and adjusted to pH 8.5 using aqueous solution, conc. 1N of NaOH (purity 92-100%, Neon) at room temperature 27 °C and under constant aeration for 48 h. After hatching, active nauplii free were collected and used for the assay.

Ten nauplii were drawn through a *Pasteur* pipette and placed in each vial containing 5 mL of brine solution. In each experiment, 500 µL of the plant extract was added to 5 mL of brine solution and maintained at room temperature for 24 h under the light and surviving larvae were counted. Experiments were conducted along with control (seawater), different concentrations in hydroethanolic solution (35%) (1.000; 500; 100; 50; 25 and 1 µg mL^{-1}) of the test substances in a set of four tubes per concentration. The percentage lethality was determined by comparing the mean surviving larvae (*A. salina*) of the test and control tubes. Letal concentration (LC_{50}) values were obtained from the best-fit line plotted concentration verses percentage lethality. Potassium dichromate (purity 98-102%, Synth) and seawater was used as a positive control in the bioassay, and negative control containing only 100 µL de DMSO (purity 100%, Vetec) and 5 mL of seawater.

Statistical analysis: The results are presented as the mean values ± SD. In order to determine the reproducibility of the measurement, each antifungal assay was carried out in quadruplicate. Data were submitted to the analysis of variance (ANOVA) and the means of the treatments were evaluated by the *Scott-Knott* test at 5% significance level, and LC_{50} in lethality assay in *A. salina*, values were obtained by best-fit line method, by the Assistat Software Free.

Results

Both species of *Fridericia* have a flowering period between the rainy months in the *Cerrado* domain. These plants are lianas or rarely shrubs, with inflorescences in thyrses, terminal or axillary, flowers with green calyx, campanulate, tubular or urceolate, corolla usually magenta, pink (*F. platyphylla*) (Fig. A), red or rarely white (*F. florida*) (Fig. B), tubular or infundibular, and septicidal capsule, corroborating with *Vieira* and others.[20] The figure shows *F. platyphylla* and *F. florida* inflorescences.

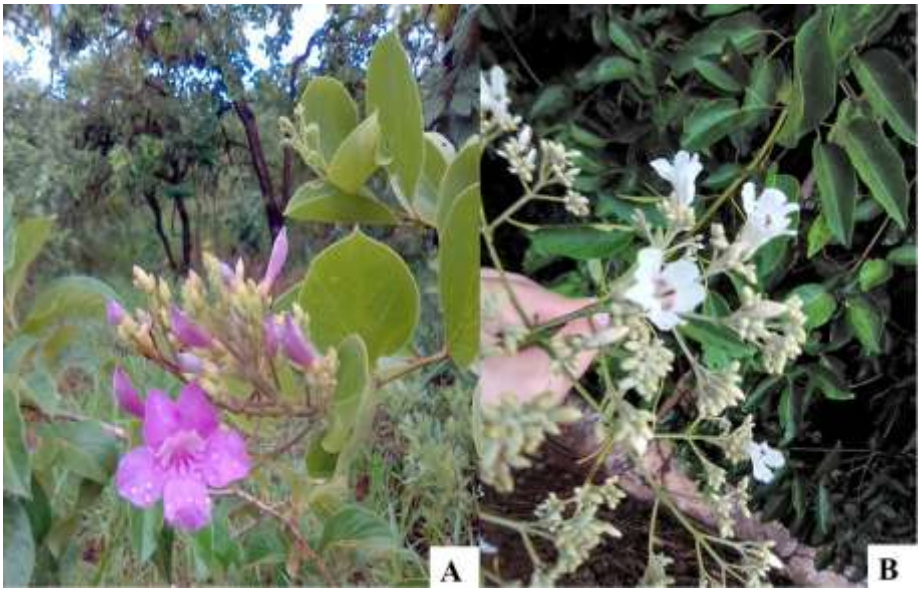

Fig. - A) Individuals of *Fridericia platyphylla* and B) *Fridericia florida* in the *Cerrado* domain area of *Goiás* State, Brazil.

The floral extract of *F. platyphylla* showed fungal inhibition activity, especially for *C. albicans* between 18-8 mm and for *C. guilliermondii* between 13-5 mm at concentrations 100-25 mg mL^{-1}. A statistically significant difference was observed by the *Scott-Knott* test at a 5% significance level between the dosage of the reference antifungal ketoconazole 50 µg mL^{-1}, with the concentrations of floral extract. The formation of two groups is observed for *C. tropicalis*, *C. guilliermondii* and *C. krusei*, and for *C. albicans* three groups. All concentrations of the extract showed discrete activity, except for *C. tropicalis*, which proved to be resistant. Even with inhibition activity, the extract showed low inhibition potency, with lower results than Ketoconazole (Table 1).

Table 1 - shows the results of growth inhibition in (mm) for *C. albicans*, *C. krusei*, *C. guilliermondii* and *C. tropicalis* in different concentrations of *F. platyphylla* floral extract

Microorganisms	Concentrations (mg mL^{-1}) (Inhibition zone mm)				Ketoconazole
	100	50	25	12.5	disc 50 µg
C. tropicalis	7.3 ± 0.06b	0.0 ± 0.0c	0.0 ± 0.0c	0.0 ± 0.0c	28.6 ± 0.08a
C. guilliermondii	13.8 ± 0.09b	9.7 ± 0.8b	5.3 ± 0.10cb	2.2 ± 0.09cb	30.1 ± 0.09a
C. albicans	18.6 ± 0.11b	14.5 ± 0.07b	8.8 ± 0.12c	2.6 ± 0.08d	27.5 ± 0.10a
C. krusei	7.4 ± 0.08b	2.4 ± 0.09c	0.0 ±0.0c	0.0 ± 0.0c	33.2 ± 0.07a

Equal letters on the same line show no statistical difference by the *Scott-Knott* test at 5% significance.

Compared with the results of Table 1, the floral extract of *F. florida* demonstrated greater antifungal activity on *C. krusei* with results of 14-6 mm, and less inhibition activity for *C. albicans* with results of 11-6 mm. Discreet inhibition was observed in *C. tropicalis* with a result of 7 mm only at the highest concentration 100 mg mL^{-1}. *C. guilliermondii*, on the other hand, proved to be resistant to all concentrations of the floral extract (Table 2). Although the extract showed inhibitory activity on most strains of *Candida*, the results were lower than those obtained by the reference antifungal. Statistically there is a difference between the antifungal ketoconazole forming the group (a), followed by two groups for *C. tropicalis* and *C. krusei* (b, c), one group for *C. guilliermondii* (b) and four groups for *C. albicans* (b, c, d, e) according to the *Scott-Knott* test with 5% significance.

Table 2 shows the results of growth inhibition in (mm) for *C. albicans*, *C. krusei*, *C. guilliermondii* and *C. tropicalis* in different concentrations of *F. florida* floral extract

Microorganisms	Concentrations (mg mL^{-1}) (Inhibition zone mm)				Ketoconazole
	100	50	25	12.5	disc 50 µg
C. tropicalis	7.2 ± 0.09b	4.6 ± 0.11b	0.0 ± 0.0c	0.0 ± 0.0c	28.6 ± 0.08a
C. guilliermondii	0.0 ± 0.00b	0.0 ± 0.0b	0.0 ± 0.0b	0.0 ± 0.00b	30.1 ± 0.09a
C. albicans	11.5 ± 0.13b	6.8 ± 0.09c	2.4 ± 0.08d	0.0 ± 0.00e	27.5 ± 0.10a
C. krusei	14.3 ± 0.05b	11.1 ± 0.12b	6.6 ±0.10c	3.2 ± 0.09c	33.2 ± 0.07a

Equal letters on the same line show no statistical difference by the *Scott-Knott* test at 5% significance.

In the toxicity test of the floral extract of *F. platyphylla* and *F. florida* with larvae of *A. salina* the lethal dose capable of killing 50% of the larvae LC_{50} = 237.81 and 301.20 µg mL^{-1}, respectively.

Discussion

The monotypic genus *Fridericia*[21] obtained 66 additional species including *Arrabidaea rego* (Vell.) DC. (the type of *Arrabidaea*).[22,23] The natural environments where both species live are heterogeneous, while *F. platyphylla* presents restricted areas, with a high vegetative rate, especially in the *Cerrado*, *F. florida* has a more widespread distribution including the Amazon Rainforest and Atlantic Rainforest, and also in *Cerrado* domain.[3,22,24,25]

A few studies about the species *F. platyphylla* and *F. florida*, were made and have pharmacological activities attributed to the species, particularly as antimicrobial and action against fungi.[2,4] This is verified using *Candida* strains in this study. However, both floral extracts showed growth inhibiting activity for most strains, except for *C. guilliermondii* in the extract of *F. florida*. Where resistance is observed even at a high concentration of 100 mg mL^{-1}.

Menezes Filho and others,[3] evaluated the essential oil of the flower of *F. platyphylla* where was observed potential antifungal activity for the genera *Sclerotinia*, *Colletotrichum* and *Aspergillus*. Especially for the genus *Candida* with inhibition between 12-21 mm *C. albicans*, 6-12 for *C. guilliermondii*, 11-20 mm for *C. krusei* and between 5-14 mm for *C. tropicalis* at concentrations (2%, 4%, 6% and 8% respectively).

Toxicity of plant materials (extracts, essential oils, fixed-oils and oil-resins) is a major concern was phytopharmacy and medicine practitioners and therefore cytotoxic assay was conducted in this study to determine the toxicity of the floral extracts through the brine shrimp lethality test.[26] Simple zoological organism *A. salina* is used as a convenient for cytotoxic screening low cost, and easy and fast experimental assay. The LC_{50} value of *F. platyphylla* and *F. florida* less than or equal to 1000 µg mL^{-1} indicates that it has biological activity considered significant.[19,27] According to the measured LC_{50} values of the floral extracts no one was found severely lethal. It can be used as a potential antitumor agent antitumor uses.[28,29,30,31,32,33,34,35,36,37]

The search for new antifungal agents on the resistance observed in the main reference antifungals on *Candida* control, inferred the continuity of research in the search for new phytochemicals with fungal inhibiting action, as well as potential cytotoxic activity that can be used in the control inhibition, prevention and treatment of different cancer cell lines. New studies should be carried out with a toxicological, and clinical nature providing safety support for this the floral extracts, should be analyzed by checking the classes of phytocomposites, identification of phytomolecules by isolation and, determination in different biological and human models due to the good results observed in this study.

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Conflict of interests

The authors declare that there are no conflicts of interest.

Authors' contributions

Conceptualization: Antonio Carlos Pereira de Menezes Filho.

Writing – original draft: Antonio Carlos Pereira de Menezes Filho; Matheus Vinicius Abadia Ventura.

Formal Analysis: Matheus Vinicius Abadia Ventura; Hellen Regina Fernandes Batista-Ventura.

Data curation: Hellen Regina Fernandes Batista-Ventura.

Project administration: Cinthia Alves Porfiro; Carlos Frederico de Souza Castro.

Translation: Cinthia Alves Porfiro.

Resources: Carlos Frederico de Souza Castro.

Writing – review & editing: Antonio Carlos Pereira de Menezes Filho.