Antifungal activity of yacon (*Smallanthus sonchifolius*) extract against candida spp.

Atividade antifúngica do extrato de yacon (*Smallanthus sonchifolius*) contra candida spp.

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ABSTRACT
Introduction: Yacon (*Smallanthus sonchifolius*) is a functional food, rich in fructooligosaccharides, and has been widely used in scientific research, showing effects in reducing lipid and glycemic levels, in addition to having antibacterial, antioxidant and neuroprotective properties. The objective was to evaluate the hydroalcoholic extract of yacon leaf in Candida species. Methods: Thirty-three samples of different species of the genus Candida treated with yacon leaf extract at concentrations of 25 to 400ug/ml were analyzed using the Minimum Inhibitory Concentration method described by the M27-A3 protocol of the Clinical and Laboratory Standards Institute. Results: Among the species of C. albicans, 16

samples showed sensitivity to the extract at the concentrations used. Conclusion: Yeasts of the Candida genus are able to adapt to different environments due to their high degree of resistance to antifungal agents, making it increasingly necessary to use natural substances as alternatives for the treatment of diseases caused by fungi. The antifungal activity of yacon leaf extract against fungi of the genus Candida is being reported for the first time in this study, making yacon a new therapeutic alternative.

Keywords: antifungal activity, *Candida* spp, yacon, plant extracts activity.

RESUMO
Introdução: Yacon (Smallanthus sonchifolius) é um alimento funcional, rico em fructo-oligossacarídeos, e tem sido amplamente utilizado em pesquisas científicas, mostrando efeitos na redução dos níveis lipídicos e glicêmicos, além de ter propriedades antibacterianas, antioxidantes e neuroprotetoras. O objetivo era avaliar o extrato hidroalcoólico da folha de yacon na espécie Candida. Métodos: Trinta e três amostras de diferentes espécies do gênero Candida tratadas com extrato de folha de yacon em concentrações de 25 a 400ug/ml foram analisadas usando o método de concentração mínima inibitória descrito pelo protocolo M27-A3 do Clinical and Laboratory Standards Institute. Resultados: Dentre as espécies de C. albicans, 16 amostras mostraram sensibilidade ao extrato nas concentrações utilizadas. Conclusão: As leveduras do gênero Candida são capazes de se adaptar a diferentes ambientes devido a seu alto grau de resistência aos agentes antifúngicos, tornando cada vez mais necessário o uso de substâncias naturais como alternativas para o tratamento de doenças causadas por fungos. A atividade antifúngica do extrato de folhas de yacon contra fungos do gênero Candida está sendo relatada pela primeira vez neste estudo, tornando o yacon uma nova alternativa terapêutica.

Palavras-chave: atividade antifúngica, *Candida* spp, yacon, atividade de extratos de plantas.

1 INTRODUCTION

Yeasts are microorganisms found on the skin, in the genitourinary tract and in the gastrointestinal tract. Among them, the genus *Candida* is considered one of the most important from a clinical and epidemiological point of view (Nucci *et al.*, 2010; Vallabhaneni *et al.*, 2016). This microorganism has a commensal relationship with the host, and to the extent that there is an imbalance in the microbiota, it becomes pathogenic (Lewis e Williams, 2017).

The pathogenic potential of yeasts varies significantly, with *Candida albicans* being the species responsible for more than 80% of oral cavity infections, capable of generating deadly diseases (Laurent *et al.*, 2011). However, the incidence of infections caused by non-*albicans Candida* has been increasing in recent years, such as *C. parapsilosis*, *C. krusei*, *C. tropicalis*, *C. glabrata e C. dubliniensis* (Barchiesi *et al.*, 2016; Patil *et al.*, 2015, Souza *et al.*, 2022), may cause systemic infections in immunocompromised patients (Terças *et al.*, 2017) in addition to having a low sensitivity to antifungals (Pfaller *et al.*, 2013).

The indiscriminate use of antifungals has grown each year, causing resistance and public health concerns (Berman e Krysan, 2020). In immunocompromised patients, fungal infections by the genus *Candida* are the main cause of resistance, often leading to therapeutic failure. (Ebrahimi-Shaghaghi *et al.*, 2021).

Yacon [*Smallanthus sonchifolius* (Poepp. et Endl.) H. Robinson] belongs to the family *Asteraceae* – also called *Compositae* – Some bibliographies also use *Polymnia sonchifolia* Poepp. & Endl. e *Polymnia edulis* Wedd. This plant is rich in compounds such as fructooligosaccharides (FOS) (Santana e Cardoso, 2008; Simanca-Sotelo *et al.*, 2021) has demonstrated efficacy in reducing blood lipid and blood glucose levels, in addition to its antioxidant properties and prebiotic effects in chickens infected with *Salmonella* spp. (Oliveira, M. G. X. *et al.*, 2017; Oliveira, P. M. *et al.*, 2017, Da Silva. *et al*., 2019). A study carried out in 2018(Martinez-Oliveira *et al.*, 2018) used yacon leaf extracts and observed a neuroprotective effect against memory deficit related to β-amyloid-induced neurotoxicity, demonstrating that it is a functional food with a wide variety of applications. The objective of this work was to evaluate the antifungal activity of the hydroalcoholic extract of yacon leaves against isolates of the genus *Candida*.

2 MATERIALS AND METHODS

2.1 STRAINS

33 samples of *Candida spp* were used, of which 8 strains were ATCC (*American Type Culture Collection*). 23 samples of *C. albicans* (10A, 14A, 15A, 26A, 55A, 66A, 69A, 91B, 14C, 36C, 6E, 55E, 76E, 8F, 49F, 69F, 10G, 3H, 3Q, 55Q, ATCC 28804, ATCC 10231, ATCC 28367); four sample of *C. krusei* (85A, 15B, 91A, ATCC 6258); 2 sample of *C. tropicalis* (57A, ATCC 750); 2 sample of *C. glabrata* (61B, ATCC 2001); 1 sample of *C. dubliniensis* (ATCC 7987) e 1 sample of *C. parapsilosis* (ATCC 22019) from the Microbiology Laboratory of the Federal University of Pampa, RS, Brazil.

2.2 PLANT

The yacon leaves were supplied by Emater (Company of Technical Assistance Rural Extension) of Alegrete, Rio Grande do Sul, Brazil, harvested fresh, and transported to the Federal University of Pampa, UNIPAMPA, in the municipality of Uruguaiana, Rio Grande do Sul, Brazil, where they were processed.

2.3 EXTRACT PREPARATION

The leaves were washed and dried in an oven for five hours at 37°C and then immersed for seven days in 70% ethanol (v/v), without the presence of light. The extract was filtered and concentrated under reduced pressure using a rotary evaporator at 40°C and the remaining fraction was lyophilized. The lyophilized powder was stored in a freezer at -18º C in a closed amber bottle until use.

2.4 PHYTOCHEMICAL ANALYSIS

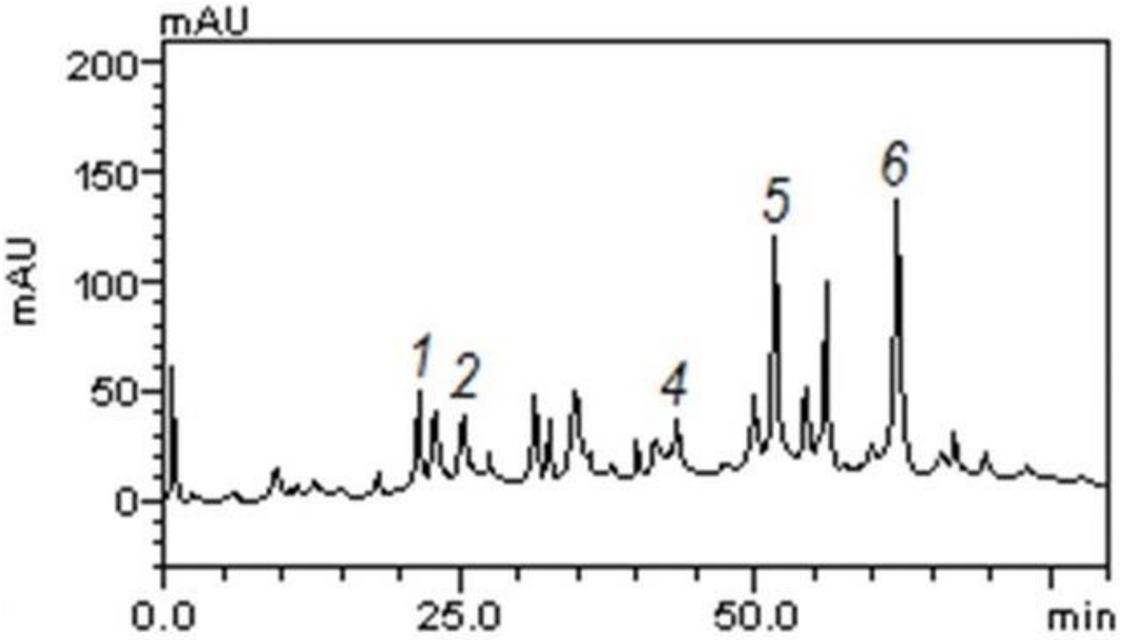
High-performance liquid chromatography with diode array (HPLC-DAD) was performed with Shimadzu Prominence AutoSampler (SIL-20A) HPLC system (Shimadzu, Kyoto, Japan), equipped with Shimadzu LC-20AT reciprocating pumps connected to DGU 20A5 degasser with a CBM 20A integrator, SPD-M20A diode array detector, and LC solution 1.22 SP1 software. The reference substances used in this study were caffeic acid, chlorogenic acid, ellagic acid, apigenin, quercetin and rutin. All chromatographic procedures were performed at room temperature and in triplicate. The major compounds found in the yacon leaf extract were the flavonoids apigenin and quercetin. The extract composition is shown in Table 1 and Figure 1(Martinez-Oliveira *et al.*, 2018).

Table 1- Composition of Yacon Leaf Extract.

	Yacon (mg/g)	**LOD (µg/mL)**	**LOQ (µg/mL)**	**Standart Curve**	**Correlation coefficient (r)**
Chlorogenic acid	2.81 ± 0.02 a	0.008	0.026	y = 12158x + 1174.9	0.9996
Caffeic acid	2.49 ± 0.01 b	0.017	0.057	y = 20367x – 1162400	0.9890
Ellagic acid	_	0.023	0.075	y = 13485x + 1195.9	0.9993
Rutin	2.35 ± 0.03 b	0.028	0.093	y = 19217x – 16913	0.9998
Quercetin	7.08 ± 0.04 c	0.011	0.035	y = 32214x – 259717	0.9968
Apigenin	7.25 ± 0.01 d	0.015	0.049	y = 12,873x + 1325.6	0.9998

Results are expressed as mean • } standard deviations (SD) of three determinations. Averages followed by different letters differ by Tukey test at $p < 0.05$. LOD:limit of detection and LOQ: limit of quantification.

Figure 1. Representative reversed-phase HPLC analysis of Yacon extracts. Chlorogenic acid (peak 1), caffeic acid (peak 2), ellagic acid (peak 3), rutin (peak 4), quercetin (peak 5) and apigenin (peak 6) Using standard and spectral analysis, peaks 1, 2, 4 , 5 and 6 were identified as chlorogenic acid, caffeic acid, rutin, quercetin and apigenin respectively.



2.5 ANTIFUNGAL SUSCEPTIBILITY TESTING

Minimum inhibitory concentrations (MIC) were determined by the broth microdilution technique, as described by the Clinical and Laboratory Standards Institute (CLSI) protocol M27-A3. Candida samples were subcultured on Sabouraud Dextrose Agar at 35°C for 24h. After this period, the inoculum was prepared in saline solution (0.9%) and standardized in a spectrophotometer with absorbance between 0.08 and 0.13. The suspensions were diluted in RPMI 1640 broth (Gibco-BRL, USA) buffered with morpholinopropanesulfonic acid (MOPS) (Sigma-Aldrich, Spain) at pH 7.0. After homogenization, aliquots of the fungal suspensions were added to each microdilution well containing serial dilutions of the hydroalcoholic extract of yacon, in the final concentration range of 400 to 0.78 µg/ml. Fluconazole was used as a standard antifungal at concentrations of 0.06 - 64 ug/ml. Afterwards, the plates were incubated in an oven with controlled temperature at 35º C for 24 hours and the MICs were visually determined, as the lowest concentration capable of totally inhibiting fungal growth (100% inhibition). Assays were performed in triplicate and growth control (without extract) was included.

3 RESULTS

In this study, the antifungal activity of the hydroalcoholic extract of yacon leaf was evaluated in 33 clinical isolates of Candida spp. According to Table 2, the species of *C. albicans* (10A, 14A, 15A, 26A, 55A, 66A, 69A, 91B, 14C, 36C, 6E, 55E, 76E, 8F, 49F, 69F, 10G, 3H, 3Q, 55Q, ATCC 28804, ATCC 10231, ATCC 28367) showed the highest MIC range, ranging from 25 to >400 ug/mL, but did not show the lowest geometric mean when compared to other species. Among the species of *C. albicans*, 16 samples showed sensitivity to the extract at concentrations from 25 to 400 ug/mL, both resistant to the antifungal fluconazole. the isolate of *C. dubliniensis* it was not inhibited at the concentrations used of the extract (0.78 to 400 ug/ml). The isolates of *C. parapsilosis e C. tropicalis* showed the lowest MIC values, being 400 to >400 ug/ml, both with a geometric mean of 400 ug/mL, while the isolates of *C. krusei (*85A, 15B, 91A, ATCC 6258) *e C. glabrata (*61B, ATCC 2001) had MIC from 50 to >400 ug/ml, and 200 to >400 ug/ml, respectively. The lowest geometric mean among the species was for the isolates of *C. krusei*, being 100 ug/mL, followed by *C. glabrata* with a mean of 200 ug/mL. Of the 17 isolated (*C. albicans* 14A, 69F, 66A, 14C, 10A, 10G, 6E, 3H, 3Q, ATCC 28804, ATCC 16231, ATCC 28367; C krusei 85A, ATCC 6258; *C. tropicalis* ATCC 6258; *C. glabrata* ATCC 2001; C. *dubliniensis* ATCC 7987) resistant to yacon extract, 10 were resistant to the standard antifungal Fluconazole (*C. albicans* 14A, 69 F, 66A, 10A, 10G, 6E, 3H, 3Q, ATCC 28367; *C. krusei* 85A), with MIC greater than 64 ug/L, while the others had MIC between 8 to 32 ug/mL.

Table 2. Candida spp. isolates. against the hydroalcoholic extract of the yacon leaf, and the antifungal Fluconazole, based on the minimum inhibitory concentration (MIC).

	MIC	
	Yacon Extract (ug/mL)	**FCZ** (ug/mL)
***Candida Albicans* (n=23)**		
8F	200 (S)	>64 (R)
14A	>400 (R)	>64 (R)
15 A	25 (S)	>64 (R)
55 E	200 (S)	>64 (R)
69 F	>400 (R)	>64 (R)
49 F	200 (S)	>64 (R)
66 A	>400 (R)	>64 (R)
14 C	>400 (R)	16 (S)
91 B	400 (S)	>64 (R)
55 Q	200 (S)	>64 (R)
55 A	100 (S)	>64 (R)
10 A	>400 (R)	>64 (R)
10 G	>400 (R)	>64 (R)
26 A	400 (S)	>64 (R)
6 E	>400 (R)	>64 (R)
36 C	400 (S)	>64 (R)
69 A	200 (S)	>64 (R)
76 E	50 (S)	>64 (R)

3H	>400 (R)	>64 (R)
3Q	>400 (R)	>64 (R)
ATCC 28804	>400 (R)	8 (S)
ATCC 16231	>400 (R)	8 (S)
ATCC 28367	>400 (R)	>64 (R)
Break	25 - >400	8 - >64
Geometric mean	165,55	10,08
***Candida krusei* (n=4)**		
85 A	>400 (R)	>64 (R)
15 B	200 (S)	>64 (R)
91 A	50 (S)	>64 (R)
ATCC 6258	>400	32 (S)
Break	50 - >400	32 - >64
Geometric mean	100	32
***Candida tropicalis* (n=2)**		
57 A	400 (S)	>64 (R)
ATCC 6258	>400 (R)	32 (S)
Break	50 - >400	32 - >64
Geometric mean	400	32
***Candida glabrata* (n=2)**		
61 B	200 (S)	>64 (R)
ATCC 2001	>400 (R)	32 (S)
Break	200 - >400	32 - >64
Geometric mean	200	32
***Candida dubliniensis* (n=1)**		
ATCC 7987	>400 (R)	16 (S)
Break	>400 (R)	16
Geometric mean	400	16
***Candida parapsilosis* (n=1)**		
ATCC 22019	400 (S)	>64 (R)
Break	400	>64
Geometric mean	400	64
***Candida spp.* (n=33)**		
Break	25 - >400	8 - >64
Total geometric mean	166,25	17,07

4 DISCUSSION

Polyphenols or phenolic compounds are products of the secondary metabolism of plants and are the most abundant antioxidants in the diet, having several bioactivities, such as antimicrobial, antiviral, antiallergic and anti-inflammatory due to their antioxidant potential. (Mocan *et al.*, 2017). Such substances possess an aromatic ring having one or more hydroxyl substituents. They are divided into several different classes, with flavonoids and phenolic acids being the most frequent phenolic compounds in nature. (Geleijnse e Hollman, 2008; Scalbert *et al.*, 2005). Flavonoids can be categorized as flavonols, flavones, flavanones, catechins, anthocyanidins and chalcones, these compounds have powerful antioxidant activities in vitro, being able to inhibit a wide variety of reactive species (Chua, 2013; Halliwell, 2008; Heleno *et al.*, 2015). The major compounds found in yacon leaf extract, quercetin (3,3,4,5,7-pentahydroxyflavone) and apigenin (4,5,7-trihydroxyflavone) are natural flavonoids found in fruits, vegetables and teas. , and known to have multiple bioactive properties (Venigalla, Gyengesi e Munch, 2015; Zhao *et al.*, 2013).

Yacon is a perennial plant native to the Andean region of South America, cultivated mainly in Colombia, Ecuador, Peru, Bolivia and northwest Argentina, but its cultivation has also expanded to other parts of the world (United States, New Zealand, Japan, between others). In the Andes its cultivation is very old since the ancient Inca civilization, being consumed as food and for medicinal purposes by the local population. (Borges *et al.*, 2012; Moura, de *et al.*, 2012). Yacon is a tuber rich in FOS compounds (unconventional sugars), which are not metabolized in the human gastrointestinal tract due to the lack of enzymes capable of hydrolyzing them. (Passos e Park, 2003). Studies with leaf and fruit extracts report the effectiveness of yacon as a functional food with multiple health benefits (Valentova *et al.*, 2003). FOS is a substrate used by host microorganisms, capable of generating health benefits. In addition, the leaves of this plant are rich in antioxidants and in popular use these leaves are dehydrated and consumed in the form of tea (Valentová *et al.*, 2006). The use of yacon already has different pharmacological activities, making it an important food for patients with chronic conditions, (Aybar *et al.*, 2001; Gibson *et al.*, 2017; Ojansivu, Ferreira e Salminen, 2011) but, so far, its antifungal activity has not been described in the literature.

Candida yeasts are a frequent cause of morbidity and mortality in immunosuppressed patients and are the most common manifestation in healthy individuals. (Raman *et al.*, 2013). Among the species, *Candida albicans* has the ability to adapt to different environments due to its high degree of resistance to antifungal agents. (Ghannoum e Rice, 1999; Paramythiotou *et al.*, 2014).

Fluconazole is an azole antifungal agent capable of inhibiting the cell multiplication of *Candida* yeasts, and the indiscriminate use of this drug is capable of originating new pathogenic species. (Li *et al.*, 2014; Patil *et al.*, 2015; Prasad, Shah e Rawal, 2016). Currently, it is possible to verify four different mechanisms related to the antifungal resistance of azoles in *Candida* species. (Pfaller, 2012). In our study, of the 33 isolates of *Candida* spp., 26 showed resistance to the antifungal fluconazole, with MIC ≥ 64 ug/mL

With the lack of data on the antifungal activity of Yacon, the hydroalcoholic extract of the leaf was tested, which showed moderate inhibitory activity in different samples of *Candida*. However, we found that *C. dubliniensis* was resistant to the concentrations of the extract used. Until then, there are no data regarding the sensitivity profile for natural extracts of *C. dubliniensis.*

The antifungal potential of some vegetables may be related to the type of phenolic compounds present (Ejechi, Nwafor e Okoko, 1999) due to damage to the microorganism's enzymatic system, which is involved in the synthesis of structural components and energy production (Porte e Godoy, 2001). In the study by Oliveira and his collaborators in 2007 (Oliveira *et al.*, 2007) it was observed that different plant extracts with phenolic properties showed inhibition on fungal growth. However, in the study by Santos, and his collaborators in 2019 (Santos, Dos *et al.*, 2020) the antifungal activity of caffeic acid in yeasts of the genus *Candida* was not significant.

Conclusion

With the increase in resistance due to the inappropriate use of antifungals, it is increasingly necessary to use natural substances as alternatives for the treatment of diseases caused by fungi. In our study, we can conclude that the hydroalcoholic extract of yacon showed antifungal activity *in vitro* on isolates of *Candida* spp., considering yacon an alternative method in the treatment of diseases of the genus *Candida* in the near future.

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CONFLICT OF INTEREST

The authors declare no competing interests.

ETHICAL APPROVAL

This is article does not contain any studies with human participants or animals performed by any of the authors.

CONSENT FOR PUBLICATION

The authors consented to the publication.

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