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Original Article

Coriandrum sativum L. essential oil obtained from organic culture shows antifungal activity against planktonic and multi-biofilm *Candida*

Óleo essencial de *Coriandrum sativum* L. obtido de cultura orgânica apresenta atividade antifúngica contra *Candida* planctônica e multibiofilme

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Abstract

This study aimed to analyze the phytochemical profile of essential oil obtained from the leaves of *Coriandrum sativum* L., and its antifungal activity against *Candida* spp. The research consisted of an *in vitro* study including collecting the vegetable product, analysis of its macronutrients, extraction, and chemical analysis of the essential oil, and assaying antifungal activity through minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC), with growth inhibition kinetics, and the product's effects on multi-species *Candida* biofilm. Nitrogen (47.08 g Kg^{-1}), phosphorus (5.3 g Kg^{-1}) and potassium (50.46 g Kg^{-1}) levels were within the normal range. The major constituents were octanal, decanal, dec-(2E)-enal, and dodecanal. The MIC and MFC of the product evaluated against 11 tested *Candida* strains ranged from 31.25 to 250 µg/mL. There was inhibition of fungal growth during 24 hours of exposure at the 3 concentrations tested (250, 125, and 62.5 µg/mL). The concentration of 80 mg/mL promoted the greatest reduction in multispecies biofilm (70% reduction in biofilm). *Coriandrum sativum* L. essential oil extract is principally constituted of alcohols and aldehydes and presents fungicidal activity against *Candida* spp. in its in planktonic and biofilm forms.

Keywords: antifungals, candidiasis, essential oil, medicinal plants.

Resumo

Este trabalho teve como objetivo analisar o perfil fitoquímico do óleo essencial obtido das folhas de *Coriandrum sativum* L., e sua atividade antifúngica contra *Candida* spp. A pesquisa consistiu em um estudo *in vitro* incluindo a coleta do produto vegetal, análise de seus macronutrientes, extração e análise química do óleo essencial e ensaio da atividade antifúngica por meio da concentração inibitória mínima (CIM) e concentração fungicida mínima (MFC), com crescimento cinética de inibição e os efeitos do produto no biofilme de *Candida* multi-espécies. Os níveis de nitrogênio (47,08 g Kg^{-1}), fósforo (5,3 g Kg^{-1}) e potássio (50,46 g Kg^{-1}) estavam dentro da normalidade. Os principais constituintes foram octanal, decanal, dec-(2E)-enal e dodecanal. A CIM e CFM do produto avaliado contra 11 cepas de *Candida* testadas variaram de 31,25 a 250 µg/mL. Houve inibição do crescimento fúngico durante 24 horas de exposição nas 3 concentrações testadas (250, 125 e 62,5 µg/mL). A concentração de 80 mg/mL promoveu a maior redução no biofilme multiespécies (redução de 70% no biofilme). O extrato do óleo essencial de *Coriandrum sativum* L. é constituído principalmente por álcoois e aldeídos e apresenta atividade fungicida contra *Candida* spp. em suas formas planctônicas e biofilme.

Palavras-chave: antifúngicos, candidíase, óleo essencial, plantas medicinais.

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1. Introduction

Oral candidiasis is an infection caused by fungi of the genus *Candida* spp. which causes oral discomfort, pain, and loss of taste, among other symptoms. It usually affects patients with acquired immunodeficiency syndrome (HIV). *Candida albicans* is the main etiological factor, a yeast-like fungus that is commonly found in the oral cavity which can evolve to a pathogenic state under favorable conditions R (Dangi et al., 2010). However, in addition to this species, there are also other causative agents such as: *C. glabrata, C. tropicalis, C. parapsilosis, C. krusei, C. guilliermondii,* and *C. dubliniensis*, among others (Rodloff et al., 2011). It is important to consider that oral candidiasis is also associated with the use of dental prostheses that is sometimes related to the presence of systemic diseases, such as diabetes and hypertension, as demonstrated in some experimental studies with a sample of carriers. Furthermore, *Candida albicans*, *Candida krusei* and *Candida tropicalis* species are the most identified in this type of candidiasis (Dias et al., 2018).

The available antifungal therapeutic options are few (Lima et al., 2013), and include drugs such as azoles (fluconazole and miconazole), and polyenes (amphotericin B) which act on ergosterol, a constituent of the fungal cell's plasma membrane, and echinocandins (caspofungin) which act by inhibiting the synthesis of the 1,3-β-glucan synthase protein (Bhattacharya et al., 2020; Chandrasekar, 2011). The phylogenetic similarity between human and fungal cells makes access to new pharmacological targets difficult (Chandrasekar, 2011). In addition, the ability of the fungi to acquire resistance to the currently available antifungals (Spettel et al., 2019) is well noted. The situation demands investigation into new antifungal agents, including studies with medicinal plants that present potential antimicrobial activity, due to the increasing rates of resistance of Candida species to antifungal therapeutic (Gupta et al., 2018; Siddique et al., 2018; Singh et al., 2012; Vieira et al., 2019).

Thus, *in vitro* and *in vivo* studies have been carried out with *Coriandrum sativum* L. (de Almeida Freires et al., 2014; Galvão et al., 2012; Ibrahim et al., 2017; Kasmaei et al., 2016; Sousa et al., 2016; Yaghini et al., 2014), which is an aromatic plant, widely used as food in China, Mexico, India, South America and Iran. In addition to flavoring, *Coriandrum sativum* L. "coriander" is also used as an antiseptic (Zare-Shehneh et al., 2014). In northeastern Brazil, coriander is recognized in cooking and enjoys extensive production. Its therapeutic use is associated with hypoglycemic, anti-inflammatory, hypolipidemic, analgesic, sedative, anxiolytic, antimutagenic, antihypertensive, diuretic, antioxidant, antispasmodic, relaxant, and antimicrobial activities. In addition, *Coriandrum sativum* L. presents activity against different *Candida* species and both Gram-positive and Gram-negative bacteria (Begnami et al., 2010). However, the previous studies did not evaluate the effect of this natural product against multispecies biofilm of *Candida*. Besides that, the standardization of the collection and extraction of essential oil were not well described.

In this context, our study identified chemical constituents and evaluated the antifungal activity of *Coriandrum sativum* L. essential oil, obtained from organic culture, against planktonic and multispecies biofilm of *Candida*.

2. Materials and Methods

2.1. Collection of plant product

C. sativum L was collected in Northeastern Brazil, in the "*agreste*" region of Paraíba, at Sítio Pau Ferro, in Lagoa Seca, a Brazilian municipality located in the Metropolitan Region of Campina Grande, State of Paraíba, (7° 09'15.582" S, 35°54'12.538" W), early in the morning before the dew point, and then stored under refrigeration. The plant material was identified, and a sample was deposited at the Lauro Pires Xavier Herbarium (Registration: JPB 62346), and also registered in the Brazilian National System for the Management of Genetic Heritage and the Associated Traditional Knowledge (SisGen), under number A2D56B0. The vegetable species used was produced from Tabocas type seeds and cultivated using organic farming techniques, the producer being registered with the Brazilian Ministry of Agriculture.

2.2. Essential oil extraction

The essential oil was obtained from *C. sativum* L. leaves by means of hydro-distillation technique and using an essential oil distiller. The process of separating the organic layer started by extracting a 200 mL aqueous phase from the condensed substance (oil + water), using a separation funnel. For the drying process, 100 g of anhydrous sodium sulfate (Na_2SO_4) was used, and after the separation and drying process a pure essential oil resulted. The product was stored in a sealed glass bottle at a temperature of approximately 20°C (Gilardoni et al., 2020).

2.3. Macronutrient analysis

To investigate the composition of the leaves of the studied culture, samples of the botanical material were taken to determine accumulated nitrogen (N), phosphorus (P) and potassium (K) macronutrients. The process was carried out in a drying oven at 60°C, after which they were crushed and sent to the Plant Tissue Analysis Laboratory of the Agricultural Sciences Center at UFPB for determinations (Malmir et al., 2020).

2.4. Chemical analysis of the essential oil (EO)

To perform the EO chromatograms, a gas chromatograph coupled to a mass spectrometer (SHIMADZU GC-MS-QP5050A), with capillary column (J&W SCIENTIFIC®) and a stationary phase of 5% phenyl and 95% dimethylpolysiloxane, with 30 m of length, 0.25 mm internal diameter and 0.25 µm film thickness. The initial temperature programming was from 60ºC to 240ºC (3ºC/min). Helium was used as carrier gas (mobile phase) at a flow rate of 1.0 mL/min, with a split ratio of 1:20, and an injection volume of 1µL (McLafferty and Stauffer, 1989). The *C. sativum* L. essential oil was injected at a concentration of 2 ppm, with hexane as a solvent. Identification was carried out by comparing its

mass spectra with the spectra existing in the equipment's database.

2.5. Chemicals and microorganisms

In order to determine the Minimum Inhibitory Concentration (MIC) and Minimum Fungicide Concentration (MFC); and to evaluate potential mechanisms of action, reference strains of *Candida* spp. were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA) - *C. albicans* ATCC 60193, *C. albicans* ATCC 10231, *C. albicans* ATCC 90028, *C. tropicalis* ATCC 750, *C. glabrata* ATCC 2001, *C. krusei* ATCC 34135; and also strains form the Central Bureau voor Schimmelcultures (CBS) - *C. albicans* CBS 562, *C. tropicalis* CBS 94, *C. utilis* CBS 5609, *C. krusei* CBS 573; and from the Instituto Zimotécnico - (ESALQ/USP, Campinas, São Paulo, Brazil) *C guilliermondii* 207. The Nystatin and Tween 80% used during the tests were obtained from Sigma-Aldrich® Chemical Co. (St. Louis, MO, USA).

2.6. Analysis of activity against Candida spp.

Analysis of antifungal activity against *Candida* spp. was performed using microdilution to determine the Minimum Inhibitory Concentration (MIC) of the essential oil (EO). To perform this technique, the protocol of the Clinical and Laboratory Standards Institute (CLSI) was adopted using a 96-well plate (CLSI, 2002). A yeast suspension with turbidity adjustment was used for the fungal inoculum (2.5 x 10^3 CFU/mL, 530 nm, abs 0.08 - 0.1), being added to plates containing Sabouraud Dextrose Broth (SDB) (KASVI®, Kasv Imp and Dist de Prod p/Laboratorios LTDA, Curitiba, Brazil).

The *Coriandrum sativum* L. EO was tested in differing concentrations (1000 to 7.81 µg/mL); Nystatin (Sigma-Aldrich, São Paulo, SP) was used as a positive control in differing concentrations (120 to 1.875 µg/mL); and concomitantly with the tests, there were also sterility and strain viability controls. The Minimum Fungicide Concentration (MFC) was performed using the subculture in Sabouraud Dextrose Agar (SDA) (KASVI®, Kasv Imp and Dist de Prod p/Laboratorios LTDA, Curitiba, Brazil) from the wells referring to the MIC and the 2 higher concentrations. The ratio between MFC and MIC was calculated, classifying the substance as fungistatic when MFC/MIC ≥ 4, and fungicidal when MFC/MIC < 4 (Siddiqui et al., 2013). The tests were performed in triplicate and the results were expressed in µg/mL

2.7. Microbial growth inhibition kinetics

The growth curve assay was performed using *Candida albicans* strain ATCC 90028. The study aims to verify the time in which the EO presents inhibition of fungal growth. The microdilution technique as described for the MIC was used. The EO concentrations corresponding to MIC (62.5 µg/mL), MIC x 2 (125 µg/mL) and MIC x 4 (250 µg/mL) were used for this strain, and the inoculum adjusted to a concentration of 2.5 x 10^3 CFU/mL. The plates were incubated for 24 hours at 35 ± 2ºC in a microplate reader (BIOTEK-EON), and the absorbance values were read at 530 nm at selected time points (Zore et al., 2011).

2.8. Effects on multi-species Candida biofilm

In this assay, the effect of differing EO concentrations used to reduce multi-species biofilm (*C. albicans* ATCC 90028; *C. albicans* CBS 562; *C. tropicalis* CBS 94; *C. krusei* CBS 573) was determined. The inoculum, prepared with Sabouraud Dextrose Broth (SDB) (KASVI®, Kasv Imp and Dist de Prod p/Laboratorios LTDA, Curitiba, Brazil) enriched with sucrose (2%) in the concentration of 2.5 x 10^6 CFU/mL, was added, and after 48h, the essential oil was applied in concentrations which varied from 10 to 100 mg/mL. The biofilm was quantified using a 0.4% (w/v) aqueous crystal violet solution, followed by dissolution in 95% ethanol at 48h after application of the test product. The tests included the sterility controls for the culture and growth medium (Furletti et al., 2011).

2.9. Statistical analysis

All tests were performed in triplicate in three independent experiments. Through an exploratory analysis of the data it was possible to choose the specific statistical approach. It is worth mentioning that the analysis was descriptive with modal measurement. Statistical analysis considered type I error (α) defined as 0.05, and type II error (β) as 0.2 (Cohen, 2013).

The analysis results for microbial growth kinetics and biofilm were expressed as mean ± standard deviation (SD) and the differences between groups were analyzed using one-way (ANOVA), followed by Tukey's post-hoc tests. The results were considered significant when $p \leq 0.05$. GraphPad Prism® software version 7.03 for Windows (GraphPad Software, San Diego, CA, USA) was used for statistical analysis.

3. Results

The concentrations of the principal macronutrients identified in the *Coriandrum sativum* L. sample is presents in Table 1, it is important to highlight that it is an organic product.

Phytochemical analysis by chromatography coupled to a mass spectrometer (CG - MS) (the main EO constituents) is presented in Table 2. In general, there is an expressive presence of alcohols, such as dec-2-in-1-ol and 1-decanol, in addition to aldehydes, such as decanal, undecanal, and tetradec-2-enal, among others.

The antifungal action of *Coriandrum sativum* L. was evidenced for the tested fungal species. The minimum inhibitory concentration (MIC), and minimum fungicidal concentration (MFC) values for *C. sativum* L. and nystatin are

Table 1. Principal macronutrient concentrations identified in the *Coriandrum sativum* L. sample.

Macronutrients	Concentration	Adequate Concentration
Nitrogen (N)	47.08 g kg^{-1}	40 to 60 g kg^{-1}
Phosphorus (P)	5.30 g kg^{-1}	4 to 6 g kg^{-1}
Potassium (K)	50.46 g kg^{-1}	40 to 60 g kg^{-1}

Table 2. Identification of the main compounds present in the essential oil of *C. sativum* L. by GC-MS.

R_t (min)	Area	Area Percentage	Name
3.071	939545	1.87	Cyclopentane, 1-ethyl-3-methyl-
3.110	1051015	2.09	Cyclopentane, 1-ethyl-3-methyl-
3.159	4440888	8.85	Octane
3.212	953168	1.90	Cyclohexane, 1,2-dimethyl-, trans-
3.305	763317	1.52	Cyclohexane, 1,3-dimethyl-, trans-
3.386	101019	0.20	Cyclopentane, (1-methylethyl)
3.465	82325	0.16	3,4,5-Trimethylheptane
3.556	499529	1.00	Octane, 5-ethyl-2-methyl-
3.670	668024	1.33	Cyclopropane, nonyl-
3.724	884799	1.76	Cyclohexane, ethyl-
3.771	741041	1.48	1,2-Diethylcyclohexane
3.940	121751	0.24	Cyclohexane, 1,2,3-trimethyl-
4.026	211759	0.42	1-undecene, 8-methyl-
4.162	321060	0.64	Decane, 5,6-dimethyl-
4.304	113088	0.23	Octane, 3-methyl-
4.368	78654	0.16	-
4.635	77038	0.15	Cyclododecane
4.706	134203	0.27	2-Pentene, 2,3-dimethyl-
4.885	410871	0.82	Nonane
4.958	60711	0.12	1-Hexyn-3-ol
5.084	351587	0.70	2-Pentanethiol, 2-methyl-
5.170	113559	0.23	Cyclohexane, bromo-
5.516	365106	0.73	3-butenyl hexyl ether
5.699	69344	0.14	(1-propylnonyl)cyclohexane
6.081	117636	0.23	Hydroperoxide, 1-ethylbutyl
6.340	144941	0.29	Ethanol, 2-(hexyloxy)-
6.736	843068	1.68	3-Hexen-2-one
7.553	87868	0.18	Mesitylene
7.638	59594	0.12	Decane
7.794	60853	0.12	Octanal
11.338	77702	0.15	Undecane
15.605	106865	0.21	Dodecane
15.919	4121268	8.21	Decanal
18.413	3370666	6.71	Dec-(2E)-enal
18.758	1402235	2.79	Dec-2-en-1-ol
18.878	2128368	4.24	1-Decanol
19.896	7465971	14.87	Phenol, 5-methyl-2-(1-methylethyl)-
20.434	551888	1.10	Undecanal
22.937	648586	1.29	Undec-(8Z)-enal
24.884	1185439	2.36	Dodecanal
25.428	1421246	2.83	trans-Caryophyllene
27.338	3866765	7.70	Tetradec-2-enal <trans->

Table 2. Continued...

R_t (min)	Area	Area Percentage	Name
27.569	261448	0.52	Dodec-2-en-1-ol <trans->
28.051	328320	0.65	Germacrene-D
28.663	334548	0.67	Viridiflorene
29.157	230384	0.46	Bisabolene <beta->
29.527	258681	0.52	Methyl (Z)-dec-2-en-4,6-diynoate
29.790	347388	0.69	Cedrene <beta->
31.566	201858	0.40	Tetradec-2-enal <trans->
32.275	260028	0.52	Caryophyllene oxide
33.284	328834	0.66	Hexadecanal
35.591	3339800	6.65	Tetradec-2-enal <trans->
41.239	201374	0.40	Cyclononasiloxane, octadecamethyl-
43.732	123135	0.25	Heptasiloxane, hexadecamethyl-
46.451	308428	0.61	Cyclononasiloxane, octadecamethyl-
48.794	165796	0.33	Heptasiloxane, hexadecamethyl-
51.234	468684	0.93	Tetracosamethylcyclododecasiloxane
53.434	173054	0.34	Heptasiloxane, hexadecamethyl-
55.587	654188	1.30	Cyclononasiloxane, octadecamethyl-
57.717	162373	0.32	Heptasiloxane, hexadecamethyl-
59.599	833619	1.66	Cyclononasiloxane, octadecamethyl-

Table 3. Minimum inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of *C. sativum* L. and nystatin against. The MIC and MFC values are expressed in µg/mL.

Strain	***C. sativum* L. (µg/mL)**			**Nystatin (µg/mL)**		
	MIC	**MFC**	**MFC/MIC***	**MIC**	**MFC**	**MFC/MIC***
C. albicans ATCC 60193	250	250	1	12	12	1
C. albicans ATCC 10231	62.5	62.5	1	3	3	1
C. albicans ATCC 90028	31.25	31.25	1	12	12	1
C. albicans CBS 562	125	125	1	0.375	1.5	4
C. tropicalis ATCC 750	250	250	1	6	6	1
C. tropicalis CBS 94	31.25	31.25	1	1.5	1.5	1
C. guilliermondii 207	125	125	1	3	3	1
C. utilis CBS 5609	31.25	31.25	1	3	3	1
C. glabrata ATCC 2001	62.5	62.5	1	3	3	1
C. krusei ATCC 34135	125	125	1	6	6	1
C. krusei CBS 573	31.25	31.25	1	1.85	1.85	1

presented in Table 3. The MIC and MFC values for *C. sativum* L. and nystatin varied, respectively from 31.25 µg/mL to 250 µg/mL, and from 0.375 µg/mL to 12 µg/mL. There was no fungal growth interference by the vehicles (distilled water and Tween 80), and for all strains tested, *C. sativum* L. presented fungicidal effect, as shown by the MFC/MIC ratio.

Microbial growth inhibition kinetics are essential to evaluate the interaction between microorganisms and a tested substance, with a demonstration of growth inhibition over 24 hours. This makes it possible to establish differences and variations for test substance concentrations over the test time.

Applying EO in concentrations of (250 µg/mL, 125 µg/mL and 62.5 µg/mL), the growth of the strains was observed using time-death curves for *C. albicans* ATCC 90028, as can be seen in Figure 1.

In the control group, the *C. albicans* strain began to grow significantly after 8 hours, with exponential growth

starting at 12 h. *Coriandrum sativum* L. (in all concentrations) inhibited fungal growth during the 24 hours of exposure tested, verifying the fungicidal characteristic of the substance ($p \leq 0.05$).

As can be seen in Figure 2, *Coriandrum sativum* L. presented anti-biofilm activity (10 - 70%) varying between concentrations (20 mg/mL to 80 mg/mL), with significant differences ($p \leq 0.05$). The effect was dose-dependent, as the 80 mg/mL concentration promoted the greatest reduction in multispecies biofilm, with 70% of inhibition. Nystatin, used as a positive control, also presented anti-biofilm activity at concentrations from 10 µg/mL to 100 µg/mL (a 64.2% reduction) (Figure 3).

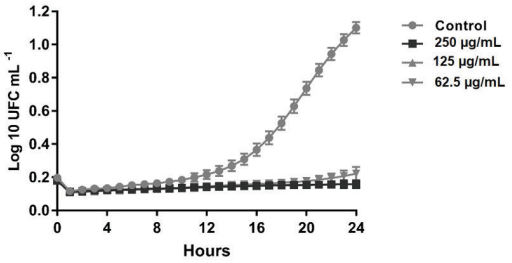

Figure 1. Growth inhibition curve of *Candida albicans* exposed to the essential oil of *Coriandrum sativum* L.

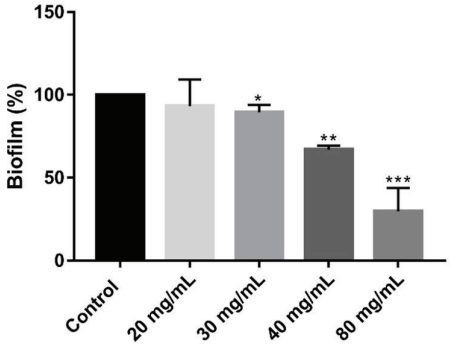

Figure 2. Effect of *Coriandrum sativum* L. on the reduction of multi-species *Candida* biofilm. *p<0.05, **p<0.01, ***p<0.001.

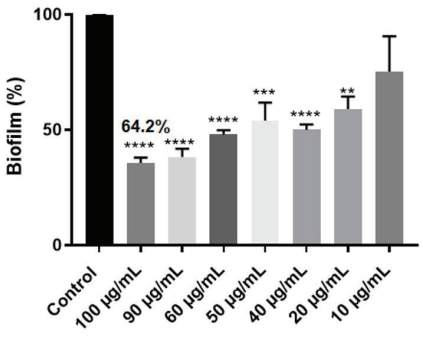

Figure 3. Effect of nystatin on the reduction of multi-species *Candida* biofilm. **p<0.01, ***p<0.001, ****p<0.0001.

4. Discussion

Coriandrum sativum L. is the second most consumed vegetable in Brazil, thus having great economic and social importance (Bertini et al., 2010). The environment in which a plant grows can promote a difference in its yield and/or chemical composition (Alves et al., 2014; Ferraz et al., 2014; Trani et al., 2014). According to the literature, its composition was satisfactory (Trani et al., 2014), this analysis evidences the proper functioning of the plant metabolism in producing the secondary metabolites found in the essential oil extracted from its leaves.

This result was expected, considering that previous research had already reported the presence of alcohols and aldehydes; among the chemical components of *C. sativum* EO (Freires et al., 2014). Decanal, an organic compound with the chemical formula $C_9H_{19}CHO$, is the simplest ten-carbon aldehyde, and is used in fragrances and aromatization (Oueslati et al., 2018).

In other studies, involving analysis of *C. sativum* L. constituents, a similar phytochemical profile to that found by us has been demonstrated. Decanals (19.09%), trans-2-decennial (17.54%), 2-decen-1-ol (12.33%), and cyclodecane (12.15%) (Freires et al., 2014) have been reported, and another study identified the presence of 1-decanol (15.30%), 2-tetradecenol (13.58%), 2-dodecenol (11.26%), decanal (10.97%), and dodecanal (7.53%) (Furletti et al., 2011). Yet other authors have demonstrated the presence of: 2-decennial, 2-dodecenal, tetradecanol, dodecanal, decanol, and undecenal; phytochemicals with respective percentages (18.02%), (8.72%), (6.09%), (5.81%), (5.77%) and (2.60%) (Padalia et al., 2011). A previous study also identified: (E) -2-decenal, linalool (E) -2-dodecenal, (E) -2-tetradecenal, 2-decen-1-ol, (E) -2-indecenal, and dodecanal (Kačániová et al., 2020).

The presence of terpenes in the essential oil of the leaves may well be related to the antifungal activity observed. It has been shown that there is synergistic activity between the chemical compounds in *C. sativum* L. EO when compared to its isolated constituents (Freires et al., 2014, 2015). Active fractions of the essential oil present less antimicrobial effect (Freires et al., 2014; Furletti et al., 2011; Galvão et al., 2012).

Other studies demonstrate the potential antifungal action of *C. sativum* L. with MIC and MFC values similar to those found in this study, such as *C. albicans* CBS 562, *C. krusei* CBS 573, and *C. tropicalis* CBS 94 with respective MIC values of 15.6 µg/mL, 15.6 µg/mL, 31.2 µg/mL (Freires et al., 2014). In a previous study, the MIC and MFC of *C. sativum* L. essential oil against strains of *Candida* spp. respectively ranged from 310 to 620 and 620 to 1,250 µg/mL, demonstrating good antifungal activity (Freires et al., 2015). In another study, MIC was determined using *C. sativum* L. EO for certain strains of *Candida* spp. that were also used in the present study. The authors found respective MIC values of 500 µg/mL, 250 µg/mL, and > 1000 µg/mL when the product was tested on strains of *C. albicans* CBS 562, *C. krusei* CBS 573, and *C. tropicalis* CBS 94 (Begnami et al., 2010).

In general, when MIC values are equal to or less than 500 µg/mL (Duarte et al., 2007; Freires et al., 2015;

Sartoratto et al., 2004), natural products are considered potent inhibitors of microbial activity. Thus, *C. sativum* L. can be considered a promising natural product for clinical trials to prove and establish protocols for its future use in the treatment of oral candidiasis.

In recent studies, growth inhibition curves for *C. sativum* essential oil have been investigated, and at concentrations MIC and 2x MIC, fungicidal activity has been conferred; the higher the essential oil concentration, the shorter the time required for fungicidal activity (Sousa et al., 2016). In this study, *C. sativum* L. EO inhibited *C. albicans* fungal growth (regardless of concentration) sufficiently to maintain a fungicidal profile. In relation to our growth inhibition kinetics test, antibacterial activity has been observed in other studies, demonstrating similar behavior (Bag and Chattopadhyay, 2015). The synergistic antibacterial activity of *C. sativum* L. EO continued during the 24h, maintaining the number of colony-forming units at a low level.

In species of *Candida*, there is an association between biofilm formation and increased virulence (Ramage et al., 2009). Antifungal agents are less effective against *C. albicans* biofilms than against planktonic cells (Chandra et al., 2001; de Almeida Rochelle et al., 2016). Biofilm is considered a heterogeneous structure composed of planktonic and mycelial yeast forms and surrounded by extracellular polymeric substances. The structure provides greater protection to microorganisms, increases resistance to antifungal agents, and makes therapy more difficult. Low toxicity substances that reduce biofilm formation are valued for optimizing treatments (Rajkowska et al., 2019).

C. sativum essential oil demonstrates strong activity against *Candida* spp., in both planktonic cells and biofilm (Alves et al., 2016; Bersan et al., 2014; Freires et al., 2014, 2015; Furletti et al., 2011). Low concentrations (62.5 µg/mL) were able to promote inhibition of *Candida spp*. in planktonic and biofilm form, and possibly acts on the fungal membrane (binding to ergosterol), while reducing the proteolytic activity of these microorganisms. In addition, low toxicity to human cells has been confirmed (Freires et al., 2014).

Increases in the number of immunocompromised patients and the number of resistant *Candida* spp. strains has affected the epidemiological scenario for fungal infections, and emphasized the need to develop new drugs (Moraes and Ferreira-Pereira, 2019; Peyton et al., 2015).

In conclusion, the results obtained in this study, associated with the fact that there are a limited number of antifungal drugs on the market (Arendrup and Patterson, 2017; Moraes and Ferreira-Pereira, 2019), encourage further research, investigating mechanisms of action against resistant fungal cells, evaluating the cytotoxic potential of each substance, and considering antimicrobial activity in both *in vivo* and clinical tests.

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