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ORIGINAL PAPER

Obtaining antioxidant compounds from the endophytic fungus *Diaporthe schini* using heat- and ultrasound-assisted extraction

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Abstract
Ultrasound-assisted extraction (UAE) of antioxidant compounds from *Diaporthe schini* biomass using ethanol as solvent was performed and the results were compared with heat-assisted extraction (HAE; conventional technique). Ultrasound intensity (17–85 W cm^{-2}) and pulse cycle (0.50–1.00) were evaluated according to a Central Composite Rotatable Design (CCRD) to obtain the highest extraction yield. The HAE was studied at 30 and 50 °C. In the validation condition (85 W cm^{-2} and 0.93) of the UAE the extraction yield and antioxidant capacity (DPPH) were 22.30 ± 0.47% and 91.35 ± 0.27%, respectively. The best extraction yield (8.34 ± 0.38%) and antioxidant activity (91.32 ± 0.98%) of the HAE were observed at 50 ºC. The GC/MS analysis of the UAE extracts showed the presence of methyl 9,12 octadecadienoate (Z, Z)-, ethyl ester of hexadecanoic acid, ethyl octadec-9-enoate, and 1,4-diaza-2,5-dioxo-3-isobutyl bicyclo[4.3.0]nonane, which could be responsible for the antioxidant activity observed. This study was the first attempt to optimize the UAE parameters for the antioxidant compounds extraction from *Diaporthe schini*. UAE improved the extraction yield and reduced the extraction time in relation to HAE.

Keywords Ultrasound-assisted extraction · Heat-assisted extraction · *Diaporthe schini* · Bioactive compounds · Antioxidant activity

Introduction

Research with antioxidants systems to protect against free radicals has increased in recent years. These systems include some antioxidants produced in the human body and others from the diet, which are needed to decrease the cumulative effects of oxidative damage (Pietta 2000). The production of these antioxidants from microorganisms has increased, especially from endophytic fungi, which are a promising source of natural products (Soria and Villamiel 2010). These microorganisms living in association with plants are the most important way to produce natural products and for drug discovery and development processes (Newman and Cragg 2016). The secondary metabolites produced by these microorganisms show potential interest in industry with applicability in medicine, agriculture, food and cosmetics (Strobel 2002) because some present bioactive compounds, such as those with antioxidant activity.

An extraction process is necessary to obtain bioactive compounds from microorganism biomass. Different methods have been used for the extraction from fungal cells. Maceration, heat-assisted extraction (HAE) and Soxhlet extraction are conventional methods for bioactive compound (antioxidants) extraction. However, these techniques are time-consuming and require a large volume of solvent (Chemat et al. 2017; Wang and Chen 2006; Lin et al. 2018). Innovative methods have been applied in the extraction of compounds, such as supercritical fluid extraction (SFE) and ultrasound-assisted extraction (UAE). Da Rosa et al. (2020) and Mazzutti et al. (2012) extracted antioxidant compounds from *Diaporthe schini* and *Agaricus brasiliensis* biomass, respectively, using SFE with carbon dioxide; however, the extraction yield was low. On the other hand, ultrasound extracted a variety of compounds using different solvents (polar or non-polar) and simpler equipment (Chemat et al. 2017).

UAE can be applied to disrupt cells by the implosion of cavitation bubbles leading to the accumulation of energy, which produces high shear and turbulent energy waves

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improving the mass transfer (Soria and Villamiel 2010). This technology offers some advantages in terms of productivity, yield, and selectivity, with better processing time, enhanced quality, reduced chemical and physical hazards, and can be considered to be environmentally friendly (Chemat et al. 2017). Studies have been performed to evaluate the efficiency of UAE for the extraction of antioxidant compounds from the biomass of plants and fungi or mushrooms, demonstrating the feasibility and potential advantages of this process (Dal Prá et al. 2015; Yildiz et al. 2015; Liu et al. 2019). However, it is necessary to study the effect of ultrasound variables on different matrices, especially those that are most promising for obtaining bioactive compounds. Therefore, the aim of this work was to extract a high yield of metabolites with antioxidant capacity from *Diaporthe schini* biomass using ultrasound-assisted extraction. An experimental design was performed to evaluate the influence of variables (intensity and pulse cycle) on the extraction and the chemical composition of extracts was determined using gas chromatography. A comparison was performed with heat-assisted extraction at different temperatures.

Materials and methods

Fermentation

Diaporthe schini was previously isolated by de Souza et al. (2017). The endophytic fungus was inoculated in potato dextrose agar (PDA) and incubated for 7 days at 28 °C. The fermentation was performed using 150 mL of medium composed of: 17.05% (w/v) corn steep liquor (CSL), 20 g L^{-1} sucrose, 2.0 g L^{-1} ammonium sulfate, 1.0 g L^{-1} ferrous sulfate heptahydrate, 1.0 g L^{-1} manganese sulfate monohydrate, and 0.5 g L^{-1} magnesium sulfate heptahydrate) (dos Reis et al. 2019) in an orbital incubator (Inova 44R, New Brunswick) at 28 °C, 120 rpm for 7 days.

At the end of the fermentation, the biomass and broth were separated by centrifugation at 4000 rpm for 10 min (Centrifuge 5804R, Eppendorf). The cells were lyophilized (L101, Liotop, São Carlos, Brazil) for 48 h, and macerated for the extractions.

Ultrasound-assisted extraction

The extractions were performed using a high-intensity ultrasound processor of 400 W and a frequency of 24 kHz (Hielscher, Model UP 400S, Germany) equipped with a titanium probe (Model H22, Tip 22), with a maximum ultrasound intensity of 85 W cm^{-2}. The experimental apparatus for ultrasound-assisted extraction was described by Sallet et al. (2019).

Extractions were performed using approximately 2.5 g of biomass and 100 mL of ethanol, the temperature was adjusted to 25 °C ± 2 °C by a jacket with circulating water, and the extraction time was fixed at 15 min according to preliminary assays (data not shown). A Central Composite Rotatable Design (CCRD) was performed to evaluate the ultrasound intensity (17–85 W cm^{-2}) and pulse cycle (0.5–1.0) with triplicate at the central point. Table 1 shows the CCRD with real and coded (in parenthesis) variables. Afterward, three additional assays were carried out to validate the results of the experimental design. A control extraction assay was performed without ultrasound under the same experimental conditions (biomass, solvent, and time).

Heat-assisted extraction

Heat-assisted extraction was performed according to López et al. (2018) with some modifications. The biomass (5 g) was placed in an Erlenmeyer flask with 100 mL of ethanol for extraction. A thermostatic water-bath with continuous agitation (Dubnoff Metabolic Bath Reciprocating Shake MA093) was used and the extraction time and agitation were 40 min and 100 rpm, respectively. Assays in triplicate and at different temperatures (30 °C and 50 °C) were evaluated.

After the extractions, the samples from both techniques were centrifuged at 4000 rpm for 10 min, the cell-free fluid was evaporated at 40 °C under vacuum and the solvent was recovered. The extraction yield was determined by the gravimetric method, according to Eq. (1):

Table 1 Extraction yield and antioxidant activity (DPPH) of the extracts from *Diaporthe schini* biomass obtained using ultrasound-assisted extraction

Assay	Ultrasound intensity (W cm^{-2})	Pulse cycle (–)	Extraction yield (%)	DPPH (%)
1	26.89 (– 1)	0.57 (– 1)	10.11	90.67
2	75.11 (1)	0.57 (– 1)	11.62	91.04
3	26.89 (– 1)	0.93 (1)	8.44	90.88
4	75.11 (1)	0.93 (1)	21.05	91.22
5	17.00 (– 1.41)	0.75 (0)	10.43	90.91
6	85.00 (1.41)	0.75 (0)	21.14	90.82
7	51.00 (0)	0.50 (– 1.41)	12.33	91.19
8	51.00 (0)	1.00 (1.41)	15.26	90.48
9	51.00 (0)	0.75 (0)	14.19	90.54
10	51.00 (0)	0.75 (0)	15.06	90.54
11	51.00 (0)	0.75 (0)	14.63	90.57
12[a]	–	–	3.26	56.12

[a]Extraction without ultrasound (control sample)

$$\text{Yield (wt.\%)} = \frac{\text{mass of the extract (g)}}{\text{initial mass of dry biomass (g)}} \times 100 \quad (1)$$

Antioxidant activity (DPPH)

The activity of the assays against DPPH (2,2-diphenyl-1-picrylhydrazyl) radical was monitored as previously described by da Rosa et al. (2020). The percent inhibition against DPPH free radical was calculated by the determination of absorbance at 522 nm.

Gas chromatography/mass spectrometry (GC/MS)

The samples were analyzed with a gas chromatography (GC-2010 Plus, Shimadzu, Kyoto, Japan) and mass spectrometry (GCMS-QP2010 Ultra, Shimadzu, Kyoto, Japan) system, according to the methodology described by dos Reis et al. (2019), with some modifications. Helium was the transport gas at a flow rate of 1.18 mL min^{-1}. A volume of 1 μL of the sample was injected with a 1:40 split ratio.

Statistical analyses

The results were analyzed evaluated using STATISTICA 10.0® (Statsoft Inc., USA) at 95% confidence level ($p < 0.05$). The Tukey test ($p < 0.05$) was used to determine significant differences between extraction techniques evaluated.

Results and discussion

Ultrasound and heat-assisted extractions

Table 1 shows the experimental conditions of the CCRD and the results of yield and antioxidant activity for the ultrasound-assisted extraction. The highest yield of 21.14% (Assay 6) was observed with the highest ultrasound intensity (85 W cm^{-2}) and the pulse cycle of 0.75, and the lowest yield was in Assay 3 (8.44%) with a lower intensity (26.89 W cm^{-2}) and a high pulse cycle (0.93). A control assay was performed to compare with the ultrasound-assisted experiments, which showed a yield of 3.26%, suggesting a positive influence of ultrasound on the extraction yield. This might be attributed to the cavitation events that generate a collapse of bubbles near the surface of the solid matrix and the creation of micro-jets that are strong enough to disrupt the cellular material during the extraction process, intensifying solvent penetration into the cells and mass transfer (Panda and Manickam 2019).

Heat-assisted extractions at different temperatures were performed to compare with the efficiency in the ultrasound-assisted extraction (Table 2). The best extraction yield was 8.34 ± 0.38% at 50 °C; however, according to the Tukey test, the yield observed at 30 °C (6.78 ± 0.97) did not differ statistically ($p > 0.05$). In addition, the yield was lower than the extraction results from the experimental design using ultrasound.

Ultrasound has been studied in the extraction of antioxidant compounds. Zhang et al. (2019a) optimized the extraction variables of bioactive and antioxidants compounds from *Asparagus officinalis* L. and obtained 71.1 mg/g in better conditions. Zhang et al. (2019b) achieved a yield of 32.27% in the extraction of papaya seed oil with functional compounds and antioxidant activity. Moreover, Hashemi et al. (2018) observed the best extract yield (2.8% (w/v)) using ultrasound to extract essential oil from *Aloysia citriodora* Palau leaves with antioxidant activity.

Da Rosa et al. (2020) extracted antioxidant compounds from *Diaporthe schini* biomass with a supercritical fluid and observed a lower yield (3.24 wt.%) when compared to the results obtained in this study using UAE (Table 1). The better yield in UAE could be explained by the increase of mass transfer during the extraction process using ultrasound. This effect may be associated with the formation of cavitation bubbles that provide increased energy and cell disruption, facilitating solvent penetration (Dal Prá et al. 2015). Alzorqi et al. (2017a) and Alzorqi and Manickam (2015) evaluated the scale-up of ultrasound-assisted extraction of a polysaccharide from *Ganoderma lucidum*, since scaling up of UAE has been gaining considerable interest as a result of increased awareness of applying energy-saving, cost-effective, and green technologies in diverse industrial applications. Soria

Table 2 Extraction yield and antioxidant activity of heat-assisted extraction and ultrasound-assisted extraction from *Diaporthe schini* biomass

Extraction method	Ultrasound intensity (W cm^{-2})	Pulse cycle (–)	Temperature (ºC)	Extraction Yield (%)	DPPH (%)
HEA	–	–	30	6.78 ± 0.97[a]	90.78 ± 0.96[a]
HEA	–	–	50	8.34 ± 0.38[a]	91.32 ± 0.89[a]
UAE (validation condition)	85.00	0.93	25	22.30 ± 0.47[b]	91.35 ± 0.27[a]
UAE	85.00	1.00	25	16.95 ± 0.49[c]	90.82 ± 0.23[a]

Same letters in the same column represent no significant difference at 95% ($p > 0.05$) according to Tukey test and Villamiel (2010) using mild operating conditions for the ultrasound-assisted extraction observed no significant changes in the structural/molecular properties and functionality of most bioactive compounds, which is important for the heat-sensitive components. Another advantage of the UAE technique in relation to conventional extraction is the faster extraction rate and more effective energy use (Navarro et al. 2016).

Antioxidant activity

The DPPH radical scavenging assay is one of the most frequently used methods for evaluating antioxidant activity. This method is based on the reduction of DPPH in alcoholic solution by electron/hydrogen (H) donation from an antioxidant, leading to the formation of the non-radical form DPPH-H in the reaction (Gulcin, 2020; Alzorqi et al. 2017b).

All samples obtained by UAE showed high antioxidant activity against DPPH radical (Table 1), which ranged from 90.54 to 91.22%, showing little variation. This indicates that only by changing the operating conditions of the ultrasound it was possible to obtain a higher amount of compounds, while the antioxidant activity was maintained. The use of ultrasound improved the extraction of compounds with antioxidant activity since the DPPH activity of the control sample was 56.12%, a lower result than in all CCRD assays. High antioxidant activity was also observed for HAE, with no significant difference ($p > 0.05$) between the temperatures evaluated (Table 2). These results indicated that it was possible to obtain a similar antioxidant activity with the techniques studied. However, using UAE proved to be more advantageous to achieve a higher yield in a shorter extraction time (15 min).

Ismail et al. (2019) observed a higher antioxidant activity using UAE compared to HAE from baobab (*Adansonia digitata*) seeds. The same was observed by Caleja et al. (2017) in the extraction from *Melissa officinalis* L. of rosmarinic acid, which has antioxidant properties.

Optimization of the extraction yield

Data from Table 1 were used to evaluate the influence of variables (ultrasound intensity and pulse cycle) on the extraction yield and antioxidant activity. The evaluated variables had no significant influence ($p > 0.05$) on the antioxidant activity (DPPH). However, for the extraction yield, an empirical coded equation (Eq. 2) as a function of ultrasound intensity and pulse cycle was obtained, where Y is the extraction yield, UI is the ultrasound intensity, and PC is the pulse cycle.

$$Y(\%) = 14.64 + 7.33 \times UI + 2.98 \times PC + 5.55 \times UI \times PC \quad (2)$$

The analysis of variance (ANOVA) was performed to validate the empirical model at the assumed 5% significance (confidence level of 95%), and the results are shown in Table 3. The empirical model was validated since the coefficient of determination (R^2) was greater than 90%, indicating a satisfactory correlation between the independent variables and the response, and the F_{calc} value (23.47) was higher than the tabulated value (4.35) (Rodrigues and Iemma 2015). Figure 1 shows the response surface and contour diagram for the extraction yield. The significance of each coefficient in the equation was estimated according to the level of p values, thus insignificant parameters ($p > 0.05$) were excluded from the model.

The variables had a positive effect, indicating that the increase in the ultrasound intensity and pulse cycle resulted in an increase in the extraction yield. A validation condition (triplicate) was performed to confirm the result observed according to Fig. 1. In this condition, the ultrasound intensity and pulse cycle were 85 W cm^{-2} and 0.93, respectively, and the extraction yield obtained was $22.30 \pm 0.47\%$ and the antioxidant activity was $91.35 \pm 0.27\%$. According to the Tukey test, these results were statistically different ($p < 0.05$) from the results with HAE. New assays (triplicate) were performed using an ultrasound intensity of 85 W cm^{-2} and a pulse cycle of 1.00, and the result for extraction yield was $16.95 \pm 0.49\%$ and DPPH was $90.82 \pm 0.23\%$. According to this result, it can be observed that the maximum pulse cycle (1.00) was not interesting because, despite the ultrasound intensity being constant, the cavitation bubbles may not have imploded at the same frequency, decreasing the mass transfer.

Table 3 ANOVA for extraction yield from *Diaporthe schini* by ultrasound-assisted extraction

Source of variation	Sum of squares	Degrees of freedom	Mean square	F test	R^2
Regression	155.58	3	51.86	23.47*	0.91
Residual	15.48	7	2.21		
Total	171.06	10			

$^*F_{0.05;3:7} = 4.35$

Analysis of the extracts by gas chromatography

The extracts of the validation assay were analyzed by gas chromatography associated with a mass spectrometer to estimate which compounds were extracted by UAE (Table 4). Figure 2 shows the molecular structure of the main compounds observed. GC/MS identified fatty acid methyl esters such as methyl 9,12-octadecadienoate (Fig. 2a), the ethyl ester of hexadecanoic acid (Fig. 2b), ethyl octadec-9-enoate (Fig. 2c), and diaza-compounds such as 1,4-diaza-2,5-dioxo-3-isobutyl bicyclo[4.3.0]nonane (Fig. 2d). The antioxidant activity observed in this study could be associated with these identified compounds and also with the synergy between them. These compounds are of interest in pharmaceutical and food areas (Elgndi et al. 2017).

Hexadecanoic acid ethyl ester was also identified in essential oil with antioxidant characteristics obtained from *Oxytropis falcate Bunge* (Jiang et al. 2009). Valente et al. (2018) and da Rosa et al. (2020) also observed the presence of the compound 1,4-diaza-2,5-dioxo-3-isobutyl bicyclo[4.3.0]nonane in extracts from the supercritical CO_2 extraction of *Botryosphaeria dothidea* and *Diaporthe schini* biomass, respectively.

Conclusions

Central Composite Rotatable Design was performed to identify the best condition of ultrasound-assisted extraction of antioxidant compounds from the endophytic fungus

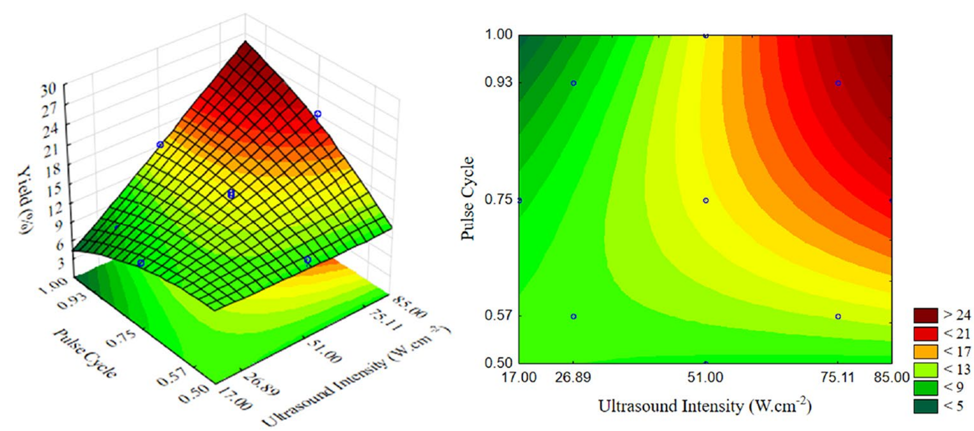

Fig. 1 Response surface and contour diagram for extraction yield

Table 4 Compounds identified by GC/MS in the extracts obtained in the validation condition of UAE

Compounds	Formula	Area %		
		Assay 1	Assay 2	Assay 3
1,4-Diaza-2,5-dioxo-3-isobutyl bicyclo[4.3.0]nonane	$C_{11}H_{18}N_2O_2$	13.75	12.18	13.41
9,12-Octadecadienoic acid (Z,Z)-, methyl ester	$C_{19}H_{34}O_2$	28.98	28.08	19.14
11-Octadecenoic acid, methyl ester (CAS)	$C_{19}H_{36}O_2$	–	–	16.00
Ethyl octadec-9-enoate	$C_{20}H_{38}O_2$	22.59	34.95	24.22
Hexadecanoic acid, ethyl ester (CAS)	$C_{19}H_{38}O_2$	14.64	16.59	15.16
Octadecanoic acid, methyl ester	$C_{19}H_{38}O_2$	–	–	6.73
Tributyl acetylcitrate (Citroflex A)	$C_{20}H_{34}O_8$	20.04	8.20	-
(Z,Z)-3,9-cis-6,7-epoxy-nonadecadiene	$C_{19}H_{34}0$	–	–	5.34

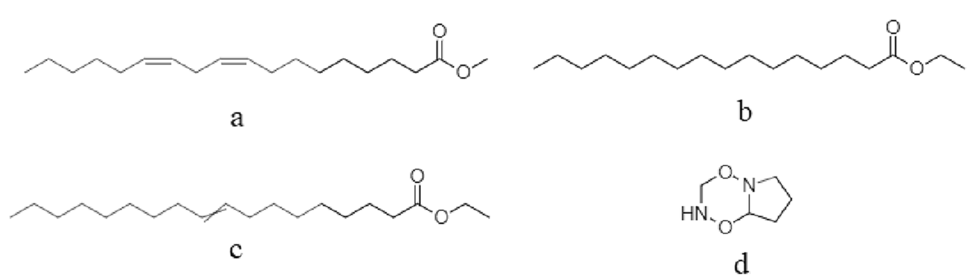

Fig. 2 Molecular structure of compounds obtained by GC/MS. **a** Methyl 9,12 octadecadienoate (Z,Z); **b** ethyl ester of hexadecanoic acid; **c** ethyl octadec-9-enoate; **d** 1,4-diaza-2,5-dioxo-3-isobutyl bicyclo[4.3.0]nonane

Diaporthe schini and then compared with heat-assisted extraction. The validated condition of the UAE (intensity of 85 W cm^{-2} and pulse cycle of 0.93) resulted in an extraction yield of $22.30 \pm 0.47\%$ and an antioxidant activity of $91.35 \pm 0.27\%$. The use of UAE was more efficient and also reduced the extraction time in comparison with the conventional methods of extraction. The compounds identified by GC/MS could be responsible for the antioxidant activity found in the extracts.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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