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EVALUATION OF PHYTOTOXIC ACTIVITY, ANTIOXIDANT AND PHYTOCHEMICAL STUDY OF *Saccharum officinarum* L.

Avaliação da atividade fitotóxica, antioxidante e estudo fitoquímico de Saccharum officinarum L.

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Abstract

In the present work, the phytotoxic activity of ethyl acetate extract of the leaves of *Saccharum officinarum* L. and its fractions were evaluated against the seeds of *Lactuca sativa* L. and *Ipomoea purpurea* (L.) Roth (weed). Then, a phytochemical study and antioxidant activity evaluation were carried out. A chemical profile of the fractions was traced through ESI-MS analysis. Phenolic substances, such as flavonoids, phenolic acids, and polyols, such as quinic acid, a common constituent in the studied fractions, were found. Antioxidant activity was determined through the activity of both ethyl acetate extract and subfaction 3, which corroborated the total phenol content dosage data. Phytotoxic evaluation was based on the effect of fractions and quinic acid on the growth of *L. sativa* seeds. Here, all fractions and quinic acid were active, whereas the growth of *I. purpurea* seeds was only sensitive to fraction 1, with an inhibitory effect on roots growth of 45.1%. In sum, substances with phytotoxic and antioxidant potential were found in the leaves of *S. officinarum*. Therefore, we suggest the use of this residue of the sugar-alcohol industry as raw material for the development of natural herbicides or antioxidant formulations.

Keywords: Phytotoxicity. Residue. Sugarcane.

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Resumo

No presente trabalho, a atividade fitotóxica do extrato em acetato de etila das folhas de *Saccharum officinarum* e suas subfrações foram avaliadas em relação às sementes de *Lactuca sativa* L. e *Ipomoea purpurea* (L.) Roth (erva daninha). Em seguida, o estudo fitoquímico e a avaliação da atividade antioxidante foram conduzidos. Um perfil químico das frações foi traçado através da análise de ESI-EM. Foram encontradas substâncias fenólicas, como flavonoides, ácidos fenólicos e polióis, como o ácido quínico, constituinte comum nas frações estudadas. A atividade antioxidante foi determinada pela atividade da fração em acetato de etila e da subfração 3, o que corroborou com os dados de dosagem do teor de fenólicos totais. A avaliação fitotóxica foi baseada no efeito das frações e do ácido quinico no crescimento de sementes de *L. sativa*. Neste caso, todas as frações e ácido quínico foram ativos, enquanto o crescimento de sementes de *I. purpurea* foi sensível apenas à subfração 1, cuja inibição foi de 45,1% do crescimento das raízes. Em suma, substâncias com potencial fitotóxico e antioxidante foram encontradas nas folhas de *S. officinarum*. Portanto, sugerimos o uso desse resíduo da indústria sucroalcooleira como matéria-prima para o desenvolvimento de herbicidas naturais ou formulações antioxidantes.

Palavras-chave: Fitotoxicidade. Resíduos. Cana-de-açúcar.

Introduction

The species *Saccharum officinarum* L. (sugarcane), belonging to the family Poaceae, is characterized as a perennial plant with unbranched stalks, similar to bamboo (Singh *et al*., 2015). Brazil is the world's largest sugarcane producer, and it also stands out as a world leader in sugar and ethanol production (Conab, 2018). *S. officinarum* is used in traditional medicine in many countries. In India, for example, the use of *S. officinarum* as a diuretic is advocated. In Brazil, leaf decoction is used to lower blood pressure, and the inner stem is used to treat fatigue, anemia, cramps, infections, bronchitis and jaundice (Singh *et al*., 2015; Tribess *et al*., 2015; Boscolo & Valle, 2008; Cartaxo *et al*., 2010). Studies with the leaves of *S officinarum* revealed the presence of policosanols, such as octacosanol (Gámez *et al*., 2007), and fatty acids, such as palmitic, linoleic and stearic acids (Gomes *et al*., 2016). Phenolic acids and flavonoids were also described in the

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leaves. There are reports of hydroxycinnamic, synapic, caffeic, chlorogenic, vanillic, sirinic and ferulic acids in sugarcane leaves (Sampietro *et al*., 2006; Singh *et al*., 2015).

Many of the beneficial effects of phenolic substances on human health are related to their antioxidant and chelating properties. Abbas *et al*. (2014) studied the antioxidant capacity of sugarcane leaves and juice against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and found that phenolic acids and flavonoids, such as ferulic acid and quercitrin, respectively, were involved in antioxidant activity.

Phenolics are known to have a phytotoxic effect. In an agricultural context, weeds are considered fast-growing species that compete with other crops for water, light, nutrients, space and CO_2, thus negatively impacting agricultural production, which then increases the use of synthetic herbicides (Vargas *et al*., 2006) known to have a negative impact on human health and the environment. In this context, new weed control strategies are needed, and natural secondary metabolites are interesting alternatives for the development of sustainable agriculture and weed management.

The sugarcane industry could become a source of different organic substances with high added value obtained from their residues generated by sugarcane processing. Thus, this work sought to identify substances present in sugarcane leaves, otherwise largely discarded in the soil, to evaluate their antioxidant and phytotoxic potential on highly invasive weeds, such as *Ipomoea purpurea* (L.) Roth.

Material and Methods

Plant collection and extract preparation

The leaves of *S. officinarum*, variety SP 711406, were obtained from a food distributor, A. SANTOS DE REZENDE LTDA, located in Itaguaí-RJ, and the extracts were obtained according our previous work (Gomes *et al*., 2016).

The ethyl acetate (600 mg) extract of *S. officinarum* leaves was subjected to the Sephadex LH-20 (35 x 3 cm) chromatographic column. Elution was performed in distilled water (150 mL), giving fraction 1 (535.6 mg), followed by water: methanol (1: 1, v / v, 200 mL) to give fraction 2 (2.4 mg) and methanol (350 mL), which generated fraction 3 (60.3

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mg). Extract and fractions were subjected to thin-layer chromatography (TLC) using silica gel as the stationary phase, elution in butanol-water-acetic acid (4: 5: 1, v / v).

ESI-MS

Ethyl acetate extract and fractions were analyzed by direct infusion ESI-MS in Bruker spectrometer (model 9.4 T Solarix) coupled to a quadrupole analyser with ionization in negative mode. The mass range analyzed was 200-2000 m/z. The parameters used were: nebulizer gas pressure of 0.5-1.0 bar, the capillary voltage of 3-3.5 Kv and capillary temperature transfer of 250 °C. The spectrum was processed using Compass Data Analysis (Bruker). The equivalent of double bonds and rings for each molecule was determined from the DBE (Double Bond Equivalent) value provided by Compass Data Analysis.

Phytotoxicity activity

Germination assays

The ethyl acetate extract, as well as its fractions and quinic acid (Sigma-Aldrich ®) were evaluated in bioassays of phytoxicity activity. Seeds of *L. sativa* were chosen as test species because of their rapid germination and high sensitivity when compared to other organisms (Baratelli, 2006; Macías *et al*., 2000). Subsequently, the fractions were tested on *I. purpurea* seeds.

The ethyl acetate extract and its fractions were dissolved in MeOH, and the volume was adjusted to the concentration 400.7 ppm (Gomes *et al*., 2016). Each Petri dish (d = 6.0 cm, h = 1.5 cm) containing filter paper discs received 0.5 mL of the test solution. After evaporation of the organic solvent at room temperature (for 24 h), 2.5 ml of the 0.1% DMSO solution and 10 *L. sativa* seeds or 5 *I. purpurea* seeds were added. The bioassays were performed in triplicate. Filter paper discs containing 2.5 mL of distilled water or 2.5mL of 0.1% DMSO served as controls without treatment. The bioassays were conducted in a growth chamber in the absence of light, with a temperature around 25 °C. The germination reading was performed 24 h after the introduction of the seeds. The

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germination reading criterion was root protrusion. The percentages of inhibition of germination were calculated by comparison with the control without treatment, using the following calculation: % Inhibition = (CX) / C x 100, where C = number of germinated seeds in control, and X = number of germinated seeds in the test sample.

Growth of hypocotyls and roots

Growth of *L. sativa* seedlings was evaluated by measuring the length of the hypocotyls and radicles on graph paper at 5 days after seed introduction. The percentages of root and hypocotyl growth inhibition were calculated by comparison with the control without treatment, using the following calculation: % Inhibition = (CX) / Cx100, where C = mean hypocotyl / roots length in the control, and X = hypocotyl / roots length in the test sample (Chiapusio et al., 1997). As a positive control, menadione (naphthoquinone) was used at 143 ppm (IC_{50} previously established in our previous work , Baratelli et al., 2012). The same protocol was applied for evaluation of *I. purpurea*. Analysis of variance (ANOVA) was applied to the results, according to Tukey's test, at a significance level of 5% with the use of the GraphPad Prism. An IC_{50} was calculated by nonlinear regression, using the same program.

Evaluation of antioxidant activity

The ethyl acetate extract and fractions from leaves of *S. officinarum* were evaluated for antioxidant capacity by the 2,2-diphenyl-1-picryl-hydrazyl (DPPH) (Sigma-Aldrich®) radical sequestration method. The procedure was performed in 96-well microplates, each with 250 µL capacity. For each sample, a stock solution of 1mg/mL in methanol was prepared. From the stock solution, dilutions were prepared and solutions were obtained at the concentrations of 250, 200, 100, 50 and 25 µg/mL for the ethyl acetate extract; 500, 250, 200, 100, 50, 25 and 5 µg/ml for fraction 1; 250, 200, 100, 50, 25 and 5 µg/ml for fraction 2 and 200, 100, 50, 25 and 5 µg/ml for fraction 3. The DPPH solution was prepared at a concentration of 0.3 mM in methanol. In each well, 125 µL of each sample were pipetted and 50 µL of the DPPH solution in triplicate with three replicates. The blank

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of each concentration was obtained from 50 µL of methanol and 125 µL of the test sample solution. A 50 µL volume of the DPPH solution added to 125 µL of methanol was used as reaction control. For control of the solvent, 175 µL of methanol were used. Quercetin solutions at the concentrations of 50, 25, 10, 5 and 1 µg/mL were used as a positive control. Reactions occurred at room temperature for 30 minutes, and then absorbance readings were taken at 518 nm in an ELISA apparatus. The antioxidant activity (AA) was defined as AA (%) = 100 - {[(Aa - Ab) x 100] / Ac}, where Aa = sample absorbance, Ab = blank absorbance and Ac = absorbance of negative control. The antioxidant activity of each fraction was expressed by determining the EC_{50}, i.e., the sample concentration required to reduce the DPPH moiety by 50%.

Total phenolic content

The ethyl acetate extract and fractions 1-3 of the leaves of *S. officinarum* were performed to determine total phenolic content by the spectrophotometric quantification method using the Folin-Ciocalteu reagent (Sigma-Aldrich®), as described by Singlenton & Rossi (1965). To perform the assay, 500 µg/mL solutions of the ethyl acetate extract and fractions 1-3 were prepared in a methanol to aqueous Folin-Ciocalteu reagent solution in the ratio of 1:10 and 20% Na_2CO_3 solution. In eppendorfs, aliquots of methanol, test sample and Folin-Ciocalteu solution, each in the volume of 100 µL, were added, and 5 min after the addition of the Folin-Ciocalteu reagent, 700 µL of the Na_2CO_3 solution were added. As a blank, the mixture of 200 µL of methanol, 100 µL of the Folin-Ciocalteu solution and 700 µL of the Na_2CO_3 solution was used. The reaction occurred for 20 min at room temperature. Eppendorfs were centrifuged for 5 min. After this time, 250 µL aliquots of eppendorfs contents were transferred to the wells of the microplate in triplicate. The microplates were held out of the light, and the absorbance reading was carried out at 760 nm. The total phenolic content was expressed in gallic acid equivalents (GAE) from the calibration curve. For the construction of the calibration curve, solutions of 1000, 500, 100, 25, 25, 10, 5 and 1 µg/mL of gallic acid were prepared and performed with the same protocol as that of the fraction and fractions noted above.

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Results and Discussion

Phytochemical analysis

The ethyl acetate extract and fractions 1, 2 and 3 were subjected to ESI-MS analysis in negative mode. Data representing molecular ions, formulas and tentative compound identification are presented in Table 1 as follow. ESI-MS spectra are given in each section below.

Table 1
Mass spectral characteristics and identity of compounds present in ethyl acetate extract and its fractions from sugarcane leaves

	Compounds	Formula	$[M-H]^-$	RDB/error (ppm)
Ethy acetate extract	Quinic acid	$C_7H_{12}O_6$	191.0565	2.5/2.1
	Palmitic acid	$C_{16}H_{32}O_2$	255.2328	1,5/0,5
	Chlorogenic acid	$C_{16}H_{18}O_9$	353.0886	8.5/2.1
	7-*O*-methylapigenin-6-*C*-glucoside	$C_{22}H_{22}O_{10}$	445.1161	12.5/2.5
	Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	515.1234	14.5/1.5
Fr 1	Quinic acid	$C_7H_{12}O_6$	191.0568	2.5/2.0
	Palmitic acid	$C_{16}H_{32}O_2$	255.2336	1.5/0.3
Fr 2	Quinic acid	$C_7H_{12}O_6$	191.0569	2.5/2.1
	Feruoylquinic acid		367.1044	8.5/2.7
	diglycosylated stilbene	$C_{26}H_{32}O_{12}$	535.1834	11.5/2.4
Fr 3	Quinic acid	$C_7H_{12}O_6$	191.0567	2.5/2.1
	7-*O*-methylapigenin-6-*C*-glucoside	$C_{22}H_{22}O_{10}$	445.1161	12.5/2.5
	Tricin 7-*O*-glucoside	$C_{27}H_{24}O_9$	491.1345	16.5/0.4
	Schaftoside/Isoschaftoside	$C_{26}H_{28}O_{14}$	563.1525	30.5/1.3

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Ethyl acetate extract

The $[M-H]^-$ 191 ion indicates the presence of quinic acid (Figure 1). Quinic acid is a cyclic polyol, an intermediary of the shikimic acid pathway, often found in its free form or forming esters (Santos-Sánchez *et al*. 2019). Some esterification of quinic acid occurs with chlorogenic and dicaffeoylquinic acid, the molecular formula of which corroborates the ions $[M-H]^-$ 353 and $[M-H]^-$ 515, respectively, both present in the mass spectrum of the ethyl acetate extract from *S. officinarum* leaves. The 3,4- 3,5- and 4,5- isomers of dicaffeoylquinic acid, as well as quinic acid, are quite common in nature, as well as being related to several beneficial health effects, such as antioxidant, anti-inflammatory and hepatoprotective (Baeza *et al*., 2014; van der Werf *et al*., 2014; de Barros *et al*., 2008).

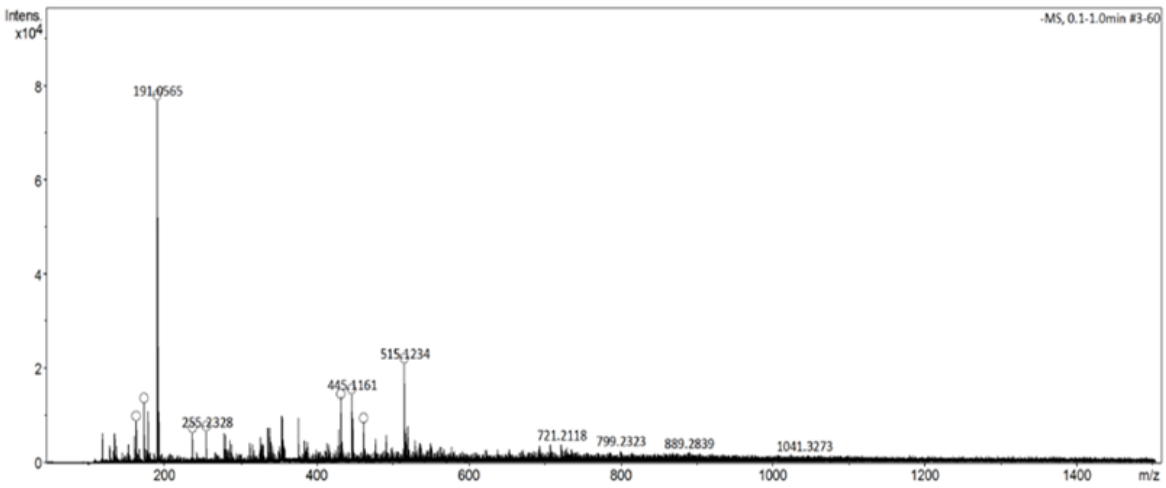

Figure 1: ESI-MS spectrum in negative mode of the ethyl acetate extract of the hydromethanolic extract of *S. officinarum* leaves

Another pseudo-molecular ion was $[M-H]^-$ 255, and its formula refers to palmitic acid (Amorim *et al*., 2009). Fatty acids are constituents frequently found in *epicuticular wax* and leaves of *S. officinarum* (Nuissier et al., 2002). Ion $[M-H]^-$ 445 suggests the presence of flavone 7-*O*-methylapigenin-6-*C*-glucoside. Colombo *et al*. (2009) reported the presence of 7-*O*-methylapigenin-6-*C*-glucoside, also known as swertisin, in sugarcane

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juice. C-glycosylated flavones are quite common in species of the Poaceae family, such as sugarcane, corn and wheat (Colombo *et al*., 2009; Wojakowska *et al*., 2013; Liu *et al*., 2011). This is the first report of the identification of swertisin in leaves of *S. officinarum.*

Fraction 1

The most intense signals of the mass spectra of fraction 1 were related to the pseudo-molecular ions $[M-H]^-$191 and $[M-H]^-$255 (Figure 2), suggesting the presence of quinic and palmitic acids, constituents previously detected in the ethyl acetate extract.

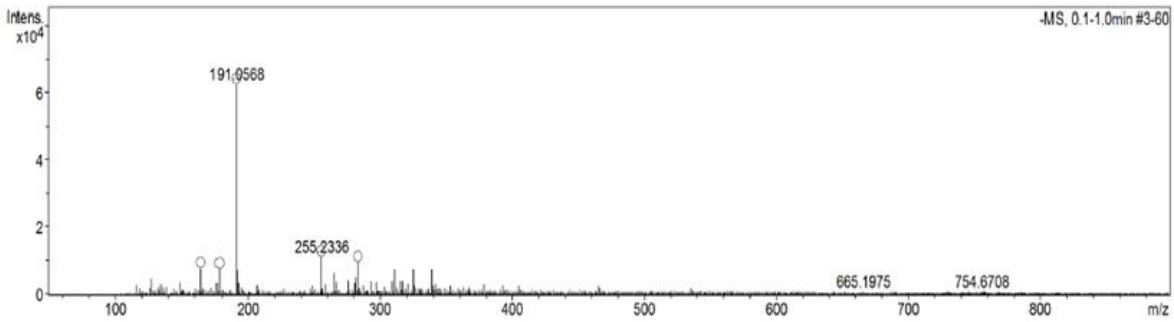

Figure 2: ESI-MS spectrum in negative mode of fraction 1 from the ethyl acetate extract of *S. officinarum* leaves.

Fraction 2

According to the mass spectra of fraction 2 (Figure 3), the most intense signal corresponded to ion $[M-H]^-$ 191, referring to quinic acid. Ion $[M-H]^-$367 suggests the presence of feruoilquinic acid. This is the first report of the identification of this constituent in *S. officinarum* leaves. Other authors reported the presence of ferulic and caffeic acid derivatives in sugarcane juice and molasses; however, they did not reveal the identity of such derivatives (Duarte-Almeida *et al*., 2011). Ion $[M-H]^-$ 535 suggests the molecular formula $C_{26}H_{32}O_{12}$. Studies in the literature describe the occurrence of stilbenes, such as resveratrol, in species of the family Poaceae, such as *S. officinarum* and *Sorghum bicolor*. Boue *et al*. (2013) reported the presence of resveratrol in bark and sugarcane juice, whereas in *Sorghum bicolor*, the presence of a glycosylated stilbene, (*E*) -

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resveratrol-3-*O*-glucopyranoside, was detected (Yu *et al*., 2008). According to reports of the occurrence of glycosylated stilbenes in the Poaceae family, it may be suggested that the $[M-H]^-$ 535 ion corresponds to a diglycosylated derivative of stilbene, such as *trans*-resveratrol-3-*O*-rutinoside. However, further analysis is required to reveal the identity of the proposed molecule. This is the first report of the identification of this stilbene in sugarcane leaves.

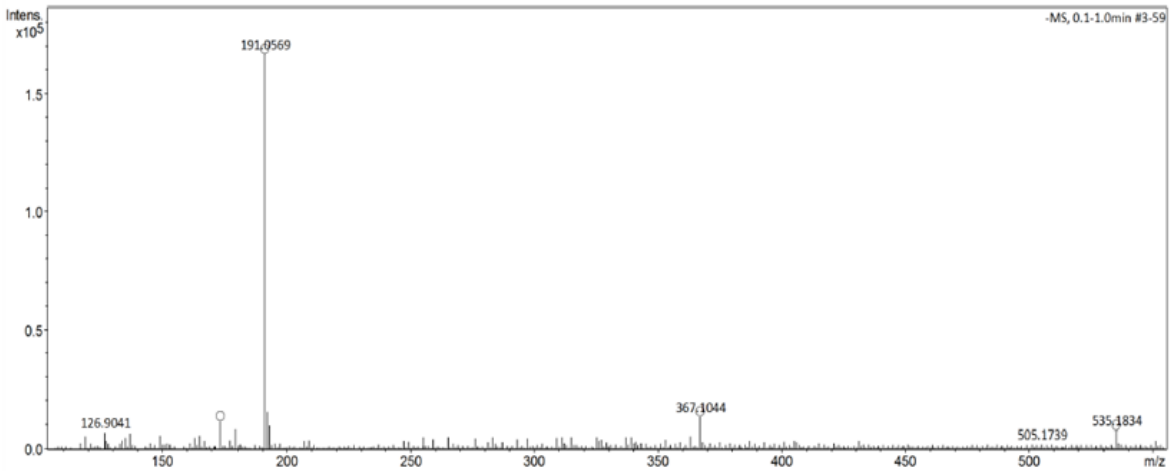

Figure 3: ESI-MS spectrum in negative mode of fraction 2 from the ethyl acetate extract of *S. officinarum* leaves.

Fraction 3

According to the mass spectrum of fraction 3 (Figure 4), $[M-H]^-$ 191 is the major ion, as seen before as quinic acid. The $[M-H]^-$ 445 ion refers to the flavonoid 7-*O*-methylapigenin-6-*C*-glucoside, previously detected in the ethyl acetate extract. The $[M-H]^-$ 491 ion corresponds to the molecular formula $C_{23}H_{24}O_{12}$. Colombo *et al*. (2008) reported the presence of tricin 7-*O*-glucoside ($[M+H]^+$ 493) in the hydromethanolic extract of sugarcane leaves and juice. Thus, the presence of $[M-H]^-$ 491 ion can be attributed to the flavone tricin 7-*O*-glucoside. In *S. officinarum*, as well as other species of the Poaceae family, the occurrence of tricin and its glycosylated derivatives, such as, for example, tricin-7-*O*-neohesperoside-4'-*O*-rhamnoside, tricin-7-*O*-methylglucuronate-4’-O-

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rhamnoside and tricin-7-*O*-methylglucuronide, is common (Colombo *et al*., 2009; Duarte-Almeida *et al*., 2011). The $[M-H]^-$ 563 ion refers to a di-C-glycosylated flavone. Schaftoside and isoschaftoside isomers are frequent in the Poaceae family and have also been identified in sugarcane leaves and juice (Colombo *et al*., 2008; Gomes *et al*., 2020). Therefore, it can then be suggested that the $[M-H]^-$ 563 ion corresponds to one of these isomers.

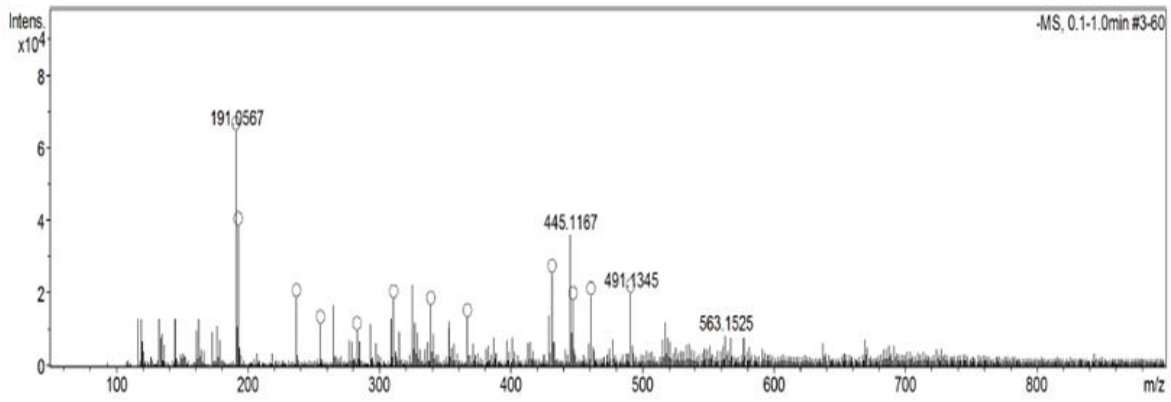

Figure 4: ESI-MS spectrum in negative mode of subfraction 3 from the ethyl acetate extract of *S. officinarum* leaves.

Total phenolic content and antioxidant activity

Total phenolic contents and antioxidant activity of fractions from *S. officinarum* leaves are described in Table 2.

Phenolic content was higher in the ethyl acetate extract (145.98 µg GAE / mg) and fraction 3 (107.41 µg GAE / mg), which suggests that the fractionation occurred in increasing mode for phenolic content. These results corroborate previous analyses that found fraction 1 to be mainly constituted of quinic acid, aside from palmitic acid, thus explaining the low phenolic content obtained. For the first time, the phenolic content is herein reported in *S. officinarum* leaves.

Only the ethyl acetate extract and fractions 2 and 3 reached 50% of antioxidant activity, thus enabling the calculation of their respective EC_{50s}: 48.18, 115.58 and 52.25

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µg/mL, respectively. The results of antioxidant activity corroborate the content of phenolic substances previously determined.

Table 2
Total phenolic content, antioxidant activity and EC_{50} of ethyl acetate extract and its fractions from sugarcane leaves

Fractions	Total Phenolic Content (µg GAE/mg)	% Antioxidant activity							EC_{50} µg/mL
		500 µg/mL	250 µg/mL	200 µg/mL	100 µg/mL	50 µg/mL	25 µg/mL	5 µg/mL	
Ethyl acetate	145.98	-	96.49	95.00	93.59	50.56	15.24	-	48.18
Fr 1	3.75	19.11	14.58	9.88	8.11	3.27	2.35	0.57	>500
Fr 2	11.65	-	71.28	65.71	46.85	21.45	10.83	1.38	115.58
Fr 3	107.41	-	-	83.89	85.95	40.32	19.19	17.57	52.25

From mass spectrometry analyses, it was possible to infer that the ethyl acetate extract and fraction 3 were composed of flavonoids, as well as quinic acid and its derivative, caffeoylquinic acid. However, in the other fractions, the presence of flavonoids was not evident, which accounted for the lower phenol content and, hence, lower antioxidant activity. Yang *et al*. (2013) described the antioxidant activity of quinic acid

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derivatives in the DPPH assay with EC_{50} values ranging from 11.7 – 58.5 µg/mL. Duarte-Almeida *et al*. (2007) identified a glycosylated tricin derivative of sugarcane juice, which was used to evaluate antioxidant activity by the DPPH assay, and it was found that this component exhibited a proton donor capacity of 55.4%, or 23.9 % more than the positive control Trolox®, both at 100 µM. Zheng et al. (2017) found that fractions from sugarcane bagasse having the highest phenolic content (241.42 mg GAE/g) also showed the highest antioxidant activity (90% activity with concentration 2 mg/mL). Antioxidant substances are related to the prevention of various diseases, especially cancer and diabetes and its complications (Parohan *et al*., 2019; Rahimi-Madiseh *et al*., 2016). In 2015, cancer-related deaths reached more than 8.7 million cases worldwide (Fitzmaurice *et al*., 2017). It has been described in the literature that increased consumption of fruits, vegetables, and other foods rich in antioxidant substances has reduced the occurrence of various types of cancer (Chen *et al*., 2016; Li *et al*., 2014; Nakagawa-Senda *et al*., 2017; Vieira *et al*., 2016). In addition, previous studies have shown that combining natural products with antioxidant activity with sunscream products is very beneficial for photoprotection, preventing another major villain: skin cancer (Wroblewska *et al*., 2019). Diabetes is in the top 10 of leading causes of death in the world, and was estimated to have caused four million deaths globally in 2017 (Saeedi *et al*. 2019). These complications are caused by hyperglycemia that leads to a process of oxidative stress, culminating in kidney damage, atherosclerosis, heart disease, nephrotoxicity, hepatotoxicity and neurophatic pain (Rahimi-Madiseh *et al*., 2016; Kandhare *et al*., 2012).

Phytotoxicity activity

According to our previous work (Gomes *et al*., 2016), the ethyl acetate extract showed an IC_{50} = 400.7 ppm for inhibition of *L. sativa* root growth, so this concentration was considered in the present work for the evaluation of phytotoxic activity of ethyl acetate extract and its fractions against *L. sativa* and *I. purpurea* (weed) seeds.

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Germination and growth of *Lactuca sativa* seeds

Twenty-four hours after sowing, germination was evaluated by the presence of radicular protrusion. The evaluated fractions showed no inhibition potential, as there was germination above 84% of seeds (Table 3).

Table 3
Germination of *L. sativa* and *I. purpurea* seeds in the presence of fractions from *S. officinarum* leaves

Extract and fractions 400.7 ppm	*Lactuca sativa*	*Ipomoea purpurea*
	% Germination	
Ethyl acetate	~ 80 (Gomes *et al*., 2016)	98.6
Fr 1	95.6	85.2
Fr 2	92.2	98.8
Fr 3	84.4	97.4

Fraction 1 showed the best inhibitory activity on roots of *L. sativa*, indicating a higher concentration of phytotoxic substances (Figure 5). One of the constituents of this fraction is palmitic acid, as observed by ESI-MS analysis. Fatty acids disturb the lipid bilayer of the membranes through the formation of ionic channels that cause permeability changes associated with loss of K^+ ions, resulting in the destruction of membrane organization (Alamsjah *et al*., 2008; Wu *et al*., 2006). Fraction 2 (Figure 5), which is composed basically of quinic acid and its feruoylquinic derivative, in addition to resveratrol-diglycosylated, showed phytotoxic activity on root growth. Fraction 3 (Figure

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5), which is composed mainly of quinic acid and flavonoids, such as glycosylated derivatives of apigenin and tricin, exhibited an inhibitory effect on roots (46,80 %) and hypocotyl (shoot) (30,98 %) of *L. sativa*. Although showing different inhibitory values, all three fractions were statiscally similar in the inhibitory effect on roots. Fraction 3 was the only one that showed inhibitory effect on the growth of hypocotyls. Quinic acid, which is the major constituent of these fractions, according to ESI-MS analysis, is a very common acid in plants, and it is usually conjugated to phenolic compounds, such as caffeic, coumaric and ferulic acids, giving rise to chlorogenic, coumaroylquinic and feruoylquinic acids, respectively (Kremr *et al*., 2016). Thus, this is the first report correlating phytotoxic activity with fractions whose major constituent is quinic acid.

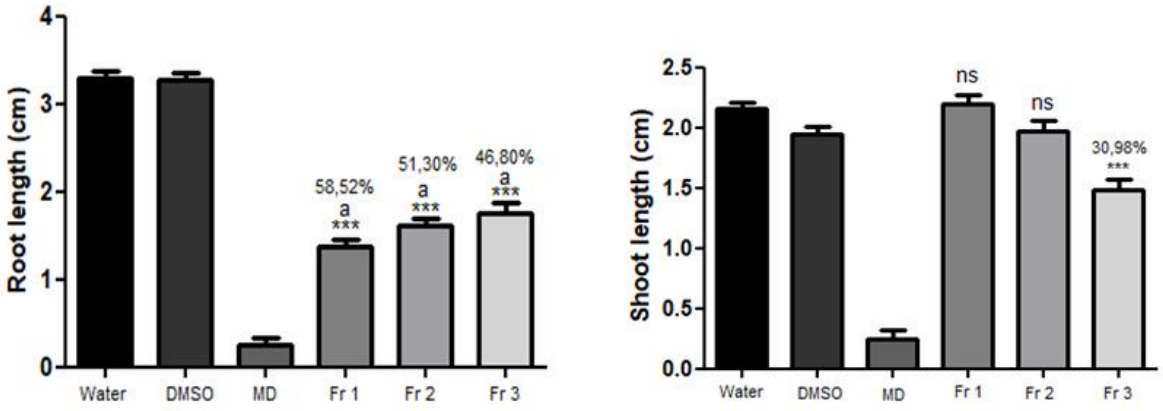

Figure 5: Effects of fractions from *S. offinarum* leaves on lettuce root and hypocotyl (shoot) growth. MD: Menadione (143 ppm); Fr 1: fraction 1; Fr 2: fraction 2; Fr 3: fraction 3. Above each column, results are described as inhibition (%) over control (water). In controls (water and DMSO 0.1%), there was no inhibition. Results are expressed as mean ± S.D. Significance was determined by ANOVA, followed by Tukey's Multiple Comparison Test. Different lowercase letters among treatments indicate significant differences.

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Germination and growth of *Ipomoea purpurea* seeds

Seed germination was above 97%, except for those tested with fraction 1 (85.2%), as shown in Table 3.

In Figure 6, it is noted that fraction 1 inhibited the growth of roots and hypocotyls of *I. purpurea* above 43%. The ethyl acetate extract and fractions 2 and 3 did not show a significant effect on the growth of the roots or on the hypocotyls of *I. purpurea*. Fraction 1, consisting mainly of quinic acid and palmitic acid, inhibited the growth of both *L. sativa* and *I. purpurea* roots. Although quinic acid derivatives have been isolated from *Ipomea pes-caprae* (Teramachi *et al*., 2005), there are no reports in the literature correlating the phytotoxic activity of quinic acid with the *Ipomoea* genus. These results are new for phytotoxic activity literature. Weeds of the genus *Ipomoea* are highly invasive and cause major problems for harvesting because they are capable of altering grain quality owing to moisture and impurity generated in the grain (Pazuch *et al*., 2017; Norsworthy and Oliver, 2002).

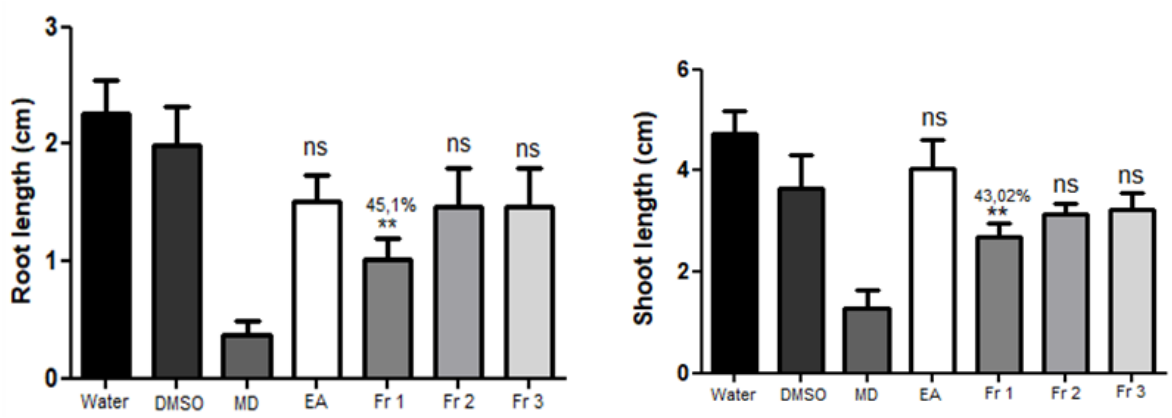

Figure 6: Effects of fractions from *S. offinarum* leaves on Ipomoea purpurea root and hypocotyl (shoot) growth. MD: Menadione (143 ppm); EA: Ethyl acetate extract; Fr 1: fraction 1; Fr 2: fraction 2; Fr 3: fraction 3. Above each column, results are described as inhibition (%) over control (water). In controls (water and DMSO 0.1%), results are expressed as mean ± S.D. Significance was determined by ANOVA, followed by Tukey's Multiple Comparison Test. Different lowercase letters among treatments indicate significant differences.

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Previous studies have identified that grain loss in soybean production as a result of *Ipomoea* contamination can reach 80% (Norsworthy and Oliver, 2002). Glyphosate herbicide is widely used in plantations for weed control, including *Ipomoea* species (Hanke *et al*., 2010). However, the danger of its increasing use has been causing concern. The World Health Organization (WHO) classified glyphosate in 2015 as a carcinogenic substance for humans (Bai and Ogbourne, 2016; EFSA, 2015; Guyton *et al*., 2015; IARC, 2015). Both glyphosate and its breakdown product aminomethyl phosphonic acid (AMPA) are capable of affecting soil, water, animals, plants, humans and microorganisms (Battaglin *et al*., 2014; Séralini *et al*., 2014). Because of this, it is necessary to search for new alternatives to be applied in weed control, and in this context, the leaf constituents of *S. officinarum* stand out as promising candidates. It is worth remembering that the leaves of *S. officinarum* are industrial waste, so their use for weed control is through reuse, characterizing a more sustainable application.

Phytotoxic activity of quinic acid

Quinic acid, the main constituent of fraction 1, inhibited the growth of both *L. sativa* and *I. purpurea* roots; therefore, its phytotoxic activity was tested at different concentrations (400, 200 and 100 ppm) (Figure 7). The germination of *L. sativa* seeds was inhibited at all concentrations (Table 4).

After evaluating quinic acid at different concentrations, it was established an IC_{50} of 182.5 ppm, considering its effect over *L. sativa* roots growth (Figure 8). When tested on the seeds of *I. purpurea* at the same concentration, quinic acid inhibited 14.07 % of roots growth and 10.55 % of hypocotyls growth, which shows that these seeds were not as sensitive to quinic acid effect as lettuce seeds, showing growth values statistically similar to control. In contrast, seed germination was only 53.3% in the presence of quinic acid, suggesting a more intense effect on *I. purpurea* seed germination than seedling growth (Table 4, Figure 9).

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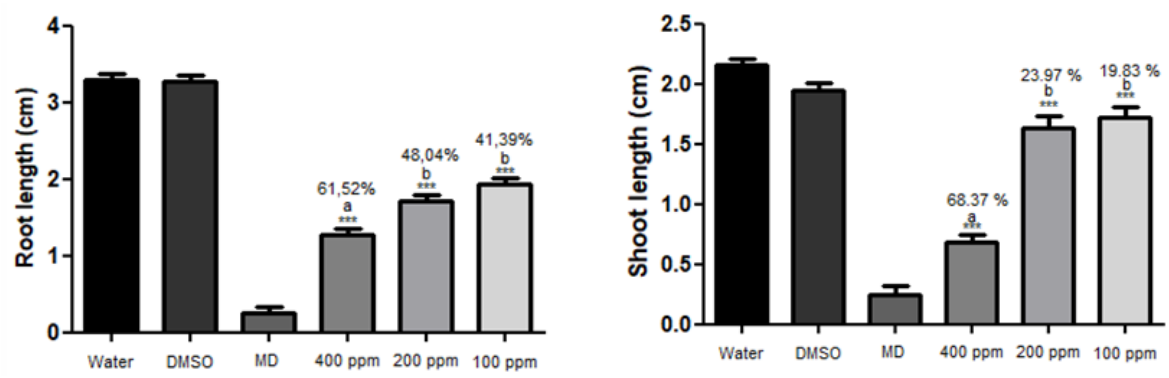

Figure 7: Effects of quinic acid (400, 200 and 100 ppm) on lettuce root and hypocotyl (shoot) growth. MD: Menadione (143 µg/mL). Above each column, results are described as inhibition (%) over control (water). In controls (water and DMSO 0.1%), there was no inhibition. Results are expressed as mean ± S.D. Significance was determined by ANOVA, followed by Tukey's Multiple Comparison Test. Different lowercase letters among treatments indicate significant differences.

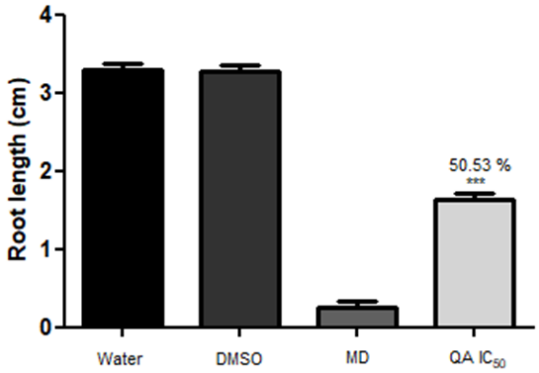

Figure 8: Effect of inhibitory concentration of quinic acid (182.5 ppm) on lettuce root growth. MD: Menadione (143 ppm); QA IC_{50} = quinic acid's inhibitory concentration. Above each column, results are described as inhibition (%) over control (water). In controls (water and DMSO 0.1%), there was no inhibition. Results are expressed as mean ± S.D. Significance was determined by ANOVA, followed by Tukey's Multiple Comparison Test. Different lowercase letters among treatments indicate significant differences.

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Table 4
Germination of *L. sativa* and *I. purpurea* seeds in the presence of quinic acid

Quinic acid	*Lactuca sativa*	*Ipomoea purpurea*
	% Germination	
400 ppm	78.8 %	_
200 ppm	87.7 %	_
100 ppm	92.2 %	_
IC_{50}= 182,5 ppm	84.4 %	53.3 %

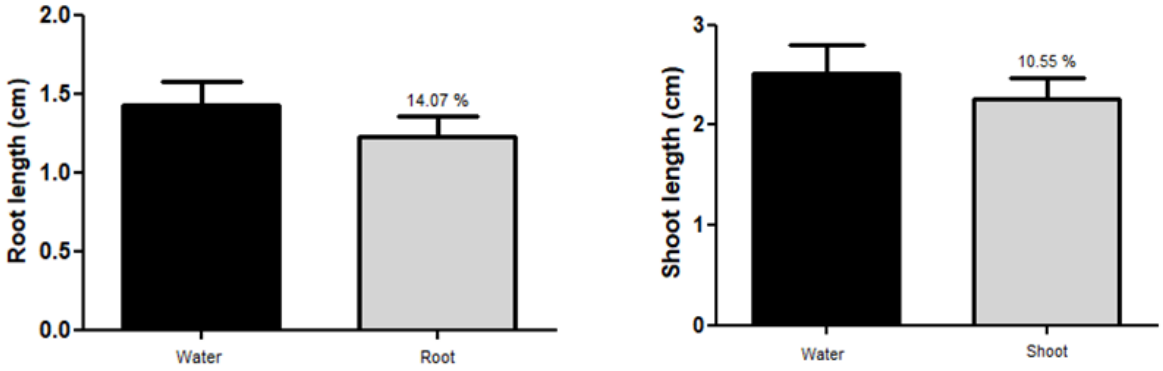

Figure 9: Effect of the inhibitory concentration of quinic acid (182.5 ppm) on *Ipomoea purpurea* root and hypocotyl (shoot) growth. MD: Menadione (143 ppm). Above each column, results are described as inhibition (%) over control (water). In controls (water and DMSO 0.1%), there was no inhibition. Results are expressed as mean ± S.D. Significance was determined by ANOVA, followed by Tukey's Multiple Comparison Test. Different lowercase letters among treatments indicate significant differences.

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It is well known that quinic acid has a precursor in the biosynthetic route of 3-dihydroquinic acid (DHQ). This precursor is responsible for the formation of shikimic acid, also a precursor for the formation of phenolic substances, such as flavonoids and phenolic acids (Santos- Sánchez *et al*., 2019). According to Zulet, Zabalza and Royuela (2013), quinic acid may not have a phytotoxic target site by itself, but it could enter the shikimate pathway and deregulate different processes related to this pathway, including amino acid biosynthesis inhibition, in a manner similar to that of common herbicides, such as glyphosate. Also we may assume that quinic acid has a synergic effect along with others compounds that were found in the *S. officinarum* fractions, which may explain its lower activity on seedling growth of *I. purpurea* when tested isolated. Besides, the seeds of *I. purpurea* are much larger than the seeds of *L. sativa*, and according to Einhelling (1995), a larger seed size may explain why some species are more tolerant to allelochemicals than those whose seeds are smaller. Flavonoids appear to exhibit phytotoxic activity from the inhibition of mitochondrial O_2 capture and can cause perturbation of the mitochondrial membrane, preventing the transport of electrons. They may also inhibit the hydrolysis of ATP catalyzed by Mg^{+} ^{2}-ATPase (Einhellig, 2005). There is evidence in the literature showing that phenolic acids can interfere with several plant enzymes and, in this way, influence most physiological processes, such as phytohormone activity, water balance, stomatal functioning, photosynthesis, respiration, biosynthesis of organic substances and carbon flow (Einhellig, 2004). Some studies have shown that cinnamic, synapic, *p*-coumaric and caffeic acids act by interfering with the capture of inorganic ions, such as NO_3^-, $H_2PO_4^-$, SO_4^{-2}, K^+, Ca^{+2} and Mg^{+2}, and nutrients from the rhizosphere by the roots, which has a negative impact on cellular functions, resulting in blockage of plant growth (Einhellig, 2005; Blum, 1996; Inderjit *et al*., 2002). Other studies have shown that phenolic acids cause damage to plant growth through the inhibition of the phosphorylase, ATPase, peroxidase and phenylalanine ammonia (PAL) enzymes (Li *et al*., 2010; Politycka *et al*., 1998; Devi *et al*., 1992).

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Conclusion

In the production of sugar and ethanol, as well as other products derived from sugarcane processing, the leaves of *S. officinarum* are largely discarded by mills. They are often used in the soil as fertilizers, but tons of leaves are burned, which generates an environmental imbalance from the emission of highly polluting gases such as CO_2. Our work aims to add value to an industrial waste widely found in Brazil, which presents in its content a series of substances with relevant biological activities, such as antioxidants, by the presence of phenolics (flavonoids and phenylpropanoides) and phytotoxicity, mainly related to the presence of quinic acid. It is noteworthy that this is the first study reporting on the phytotoxic activity of quinic acid on the highly invasive weed *I. purpurea*.

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Conflicts of interest

The authors declare no conflicts of interest

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