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BIOMEDICAL SCIENCES

Cytotoxicity, antinociceptive and gastroproiltective potential of the Abuta *selloana* Eichler: a fruit plant from Catarinense flora, Brazil

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Abstract: This study evaluated some biological activities of extracts from *Abuta selloana*. The gastroprotective potential was determined against ethanol/HCl- and indomethacin-induced gastric ulcers, whereas the antinociceptive effect was evaluated by acetic acid-induced abdominal contortions in mice. The cytotoxicity activity was measured against human cancer cell lines: U251 (glioma), MCF-7 (breast cancer) and NCI-H460 (lung cancer). The radical scavenger potential was verified; and preliminary phytochemical analyses were performed. The phytochemical screening revealed higher levels of phenolic compounds in all extracts. Moreover, the methanolic extract from pulp fruit (MEPu), peel fruit (MEPe), branches (MEB) and leaves (MEL) scavenged the DPPH radical at 100 µg/mL. Besides, only MEL presented GI_{50} < 30 µg/mL in all tested cells. Besides, MEPu, MEPe, MEB or MEL at 10 mg/kg (i.p) reduced the abdominal contortions at 47.22%, 63.31%, 84.59% and 37.76%, respectively. The MEPu, MEPe, MEB and MEL reduced the ethanol/HCl- and indomethacin- induced ulcer at 250 mg/kg (p.o). In conclusion, *A. selloana* had interesting biological activities; presenting the leaves as a promising source for compounds with cytotoxic potential, however, further studies should be performed to confirm its antitumoral activity. Besides, the whole plant can be an important source of bioactive compounds associated with gastroprotective and antinociceptive properties.

Key words: fruit plant, gastric ulcer, pain, antiproliferative, free radical scavenger.

INTRODUCTION

Brazil has the highest total of biodiversity in the world, with 20–22% of the total existing plants, but many native and exotic fruit species, with possible biological potential, remain unexplored (Rufino et al. 2010, Souza et al. 2012). In this scenario, fruit species have attracted the attention of some researchers due to the presence of nutrients and bioactive substances, such as vitamins, minerals and phenolic compounds. Some species has shown potential to decrease the risk of developing chronic diseases such as cancer, diabetes, and cardiovascular diseases (Genkinger et al. 2004, Liu 2004, Calixto & Goni 2006).

The *Abuta* genus (Menispermaceae) is composed by 32 fruit species, which are native to tropical Central and South America. In addition, depending on location, *Abuta* plants are one of the components of the arrow poison curare of some indigenous tribes of South America (Correa 1926). Furthermore, the biological activity of some plants from *Abuta* genus has been investigated, however, most, if

not all, using in vitro assays. Of note, the alkaloids stepharine and 5-N-methylmaytenine isolated from branches of *Abuta panurensis* Eichler, an endemic species from the Amazonian rainforest, displays acetylcholinesterase enzyme (AChE) inhibition, cytotoxic against two tumor cell lines (K562 and U937) with IC50 values ranging from 11.77 μM to 28.48 μM, and immunomodulatory effects in vitro (da Silva Mesquita et al. 2020). Besides, bisbenzylisoquinoline alkaloids from Abuta grandfolia (Mart.) Sandwith also presented ability to inhibite AChE and butyrylcholinesterase (BChE) activity (Cometa et al. 2012); whereas tropoloisoquinoline alkaloids from *Abuta rufescens* Aubl. have exhibited the greatest cytotoxicity against tumoral cell lines, especially ACHN and HCT-116 cells (Swaffar et al. 2012).

The species *Abuta selloana* Eichler is popularly known as "pitomba-de-cipó", "baga-de-caboclo" or "abuta" and found in the Brazilian caatinga and Atlantic Forest (Braga 2010). Its roots are used as a tonic, diuretic and febrifuge in Brazilian folk medicine, whereas its fruits are edible with a very sweet taste (Muniz 2017). Furthermore, Boscolo & Galvão (2019) conducted an ethnobotanical survey of medicinal plants in two communities in the mountainous region of Rio de Janeiro and described that *A. selloana* is used to digestive diseases, mainly in stomach. Despite of this, in our knowledge, there are no studies that describe the bioactive potential of extracts from any morphological part of *A. selloana*. Therefore, the aim of this study was performed an initial screen of the pharmacological properties of this selected plant from the flora of Santa Catarina, Brazil.

MATERIALS AND METHODS

Plant material and preparation of the extract

Fruits, branches and leaves of *A. selloana* were collected in September 2012, in Major Gercino, Santa Catarina, Brazil (latitude 27º 25' 05" S; longitude 48º 57' 05" W). The plant material was authenticated by Prof. Oscar Iza and a voucher was deposited at the Herbarium Barbosa Rodrigues (Itajaí, Santa Catarina) under number VC Filho 092. The peels and pulp from the fruits, as well as the branches and leaves were cut into small pieces and macerated separately with methanol at 25° C for 7 days, yielding the methanolic extract from the peels (MEPe; 8.49%), methanolic extract from the pulp (MEPu; 13.37%), methanolic extract from the leaves (MEL; 11.10%) and methanolic extract from the branches (MEB; 6.33%) after solvent evaporation.

Preliminary phytochemical Analysis

Aliquots of the extracts were analysed by thin layer chromatography (TLC), to determine the preliminary phytochemical profile of the extracts from *A. selloana*. Samples were eluted with different solvent systems with increasingly polarity (hexane: acetone and chloroform: methanol) and revealed with specific reagents, such as: sulfuric anisaldehyde to terpenes and steroids; ferric chloride to phenolic compounds; potassium hydroxide to coumarins and *Dragendorff's* reagent to alkaloids (Ugaz 1994).

Estimation of total phenolic content

Total phenols were determined using the Folin–Ciocalteu reagent in accordance with Arnous et al. 2001. In this assay, the extract solution (50-200 μg/mL) of the extracts were added to the Folin–Ciocalteu reagent (1 N) plus sodium carbonate (7.5 % w/v) and incubated at 45 °C for 15 min. The absorbance was read at 750 nm and the total polyphenol concentration was

calculated using a tannic acid curve (10–100 µg/ml) as standard.

2,2-Diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay

The free radical scavenging activity of the extracts was determined as described earlier (Jagtap et al. 2010). Aliquots of the extracts (1-1000 µg/mL), ascorbic acid (50 µg/mL, positive control), or vehicle (distilled water, negative control) were mixed with DPPH methanolic solution (80 µM). The decrease in the absorbance at 517 nm was measured after 5 min and the DPPH levels were calculated using a DPPH curve (10–60 µM) as standard.

In vitro antiproliferative activity

Human cancer cell lines U251 (glioma), MCF-7 (breast cancer), 786-0 (kidney cancer) and NCI-H460 (large cell lung cancer) were kindly provided by National Cancer Institute (NCI, Bethesda, USA). Cells cultures were grown in medium RPMI 1640 supplemented with 5% fetal bovine serum in presence of penicillin (100 U/mL) and streptomycin (100 µg/mL). Cells (100 µL cells well^{-1}) were incubated during 48h with each extract from *A. selloana* (0.25- 250 µg/mL) at 37^{o} C and 5% CO_2. Doxorubicin hydrochloride (0.025-25 µg/mL) was adopted as a positive control. Afterwards, cells were fixed with 50% trichloroacetic acid and cell growth was determined at 540 nm using the sulforhodamine B assay, as previously performed by Campos et al. 2016. The concentration–response curve for each cell line and GI_{50} (50% growth inhibition) values were determined through non-linear regression analysis, using the software ORIGIN 8.0 (OriginLab Corporation).

Animals

Male *Swiss* mice (25–35 g) were from the Central Animal Laboratory of University of Vale do Itajaí were housed in polypropylene cages at 22 ± 2 °C under 12-h light/dark cycle with access to food and water *ad libitum*. The rodents were deprived of food twelve hours prior to the experiments. All experiments were approved in advance by the Institutional Ethics Committee of the UNIVALI, Itajaí, SC, Brazil (approval number 004/14) and were carried out in accordance with the International Standards and the Ethical Guidelines on Animal Welfare (NRC 2011, CCAC 2022).

Antinociceptive activity (acetic acid-induced writhing)

Abdominal constriction was induced by intraperitoneal injection of 0.6% acetic acid (Collier et al. 1968). The animals (n=6) were pre-treated with methanolic extracts from *A. selloana* (10 mg/kg, i.p.). The negative control group were pre-treated with received saline (10 mL/kg, i.p.). Acetylsalicylic acid (10 mg/mL, i.p) and acetaminophen (10 mg/mL, i.p) were used as positive control. Another group, named vehicle received saline (10 mL/kg, i.p.) and not was exposed to acetic acid. Then, 30 min after the pre-treatment the acetic acid injection was performed and the number of abdominal contractions together with stretching was counted cumulatively during 20 min. The % inhibition was calculated using the formula = (1–T/C) × 100; where T represents the number of abdominal contractions along with stretching of the treated groups and C the number from negative control group.

Gastroprotective activity

Acute gastric lesions induced by ethanol/HCl (Mizui & Doteuchi 1983) or indomethacin (Boeing et al. 2016) were performed in fasted mice. The different groups (n=6) and orally pre-treated with cimetidine (positive control, 100 mg/kg), vehicle (negative control, distilled water, 10 mL/

Kg) or methanolic extracts from *A. selloana* (250 mg/Kg). One hour later, all animals received the ulcerogenic agents [60% ethanol plus 0.3 M HCl or indomethacin (100 mg/Kg)] at 10 mL/Kg. The animals were euthanized in CO_2 atmosphere one hour after ethanol/HCl intake or twelve hours after indomethacin administration. In both experiments, the stomachs were removed, opened along the greater curvature and stretched on glass plates to measure the injured area (mm^2) using the software EARP®.

Statistical analysis

The data are reported as means ± standard error of the means (SEM) and were compared using one-way analysis of variance (ANOVA), followed by Dunnett's pairwise test using the software GraphPad Prism 6.0®. In all experiments, $p<0.05$ was considered significant.

RESULTS AND DISCUSSION

There are several methodologies described for the preparation of plant extracts, aiming at the isolation of its chemical constituents. One of the methods widely used for chemical-pharmacological analysis is the preparation of hydroalcoholic extract (ethanol/water 50/50, v/v) because it is analogous to tinctures made in popular culture, where the active parts of plants are mixed with alcoholic beverages (Cirilo 1993). However, the preparation of an extract can also aim to extract the greatest possible diversity of secondary metabolites, especially in an initial studies on the pharmacological properties of a plant species and in this case the most suitable solvent for obtaining the crude extract is methanol, as it allows the extraction of a greater number of compounds (Cechinel-Filho & Yunes 1998) and for this reason the extracts studied here were obtained by methanolic maceration. As depicted in table I, the preliminary phytochemical analysis evidenced the presence of different compounds in each extract from *A. selloana*. Phenolic compounds were markedly present in all extract tested, mainly in leaves and branches. Phytochemicals studies have focused the search for saponins and alkaloids, with significant biological potential, in extracts from *Abuta* genus (Cometa et al. 2012, Sayagh et al. 2012). Indeed, the presence of cholinesterase inhibitory alkaloids in preparations of these species, mainly in *A. grandifolia*, can explain their use in the curare preparation (Cometa et al. 2012). Here, the presence of alkaloids was observed in MEB and more intensely in MEL (Table I).

Given the presence of phenolic compounds in all extracts, a quantitative assay was performed, in which it was possible to verify higher concentration of total phenols, mainly in MEB and MEPe (Table II). Therefore, the accented

Table I. Preliminary phytochemical profile of the methanolic extracts obtained from different parts of *A. selloana*.

Abuta selloana extracts	Terpenes and steroids	Phenolic compounds	Coumarins	Alkaloids
MEPu	+	+	-	-
MEPe	-	+	-	-
MEB	+++	+++	+	+
MEL	+++	+++	+	++

- absence or traces; + weak; ++ medium; +++ strong.

presence of polyphenols in the extracts from *A. selloana* can encourage further research to explore the biological potential of this species in diseases associated with oxidative conditions.

Based on the antioxidant potential of phenolic compounds, the in vitro antioxidant activity of the extracts was verified. In agreement to the total phenols amount, MEB and MEPe showed higher free radical scavenging activity, inhibiting the DPPH radical in up to 87.02% and 71.08%, respectively, at 100 µg/mL (Figure 1). As expected, MEPu [Log of the half maximal inhibitory concentration ($LogIC_{50}$) =1.757] and MEL ($LogIC_{50}$=1.681) were also able to reduce the DPPH radical. These findings are in accordance to elevated phenolic amount on the MEB and MEPe and strengthened the hypothesis about the suitable antioxidant potential of constituents from *A. selloana*. In addition, the peels of the fruits from *A. selloana* represent a valuable source of phenol compounds and the concentration of these phytochemicals in the fruit peel can guarantee a crucial protection against environmental aggressors to the fruit.

Prior studies have shown that phenolic alkaloids isolated from *Abuta rufescens* Auble exhibited cytotoxic activity against human HCT-116 colon, ACHN renal, and A549 lung cancer cells (Swaffar et al. 2012). Therefore, given the presence of alkaloids in MEB and more intensely in MEL, the cytotoxicity of the extracts of *A. selloana* was verified. Indeed, the results of the in vitro antiproliferative activity demonstrated that MEL inhibited the growth of the glioma (U251), breast cancer (MCF-7) and large cell lung cancer cell lines (NCI-H460) whit an IG_{50} value

Table II. Total phenolic content of the methanolic extracts obtained from different parts of *A. selloana*.

Abuta selloana extracts	Concentration (µg/mL)	Phenol compound (T.A.E)
MEPu	50	26.52 ± 1.23
	100	70.22 ± 2.05
	150	80.94 ± 1.25
	200	173.10 ± 35.67
MEPe	50	106.70 ± 4.48
	100	262.10 ± 19.80
	150	491.80 ± 77.01
	200	663.90 ± 0.05
MEB	50	129.50 ± 1.25
	100	237.50 ± 2.27
	150	320.80 ± 5.39
	200	407.90 ± 9.22
MEL	50	19.11 ± 3.79
	100	44.26 ± 2.67
	150	89.26 ± 6.74
	200	130.20 ± 21.15

Results are expressed as means ± SEM of tannic acid equivalents (T.A.E) in µg/mL. MEPu: methanolic extract from pulp fruit; MEPe: methanolic extract from peel fruit; MEB: methanolic extract from branches; MEL: methanolic extract from leaves.

<30 µg/mL (Table III). The cytotoxicity potency of MEL can be attributed to alkaloid content, given that the presence of these compounds has been related to cytotoxic, antiproliferative and antitumor effects for other species of the *Abuta* genus (da Silva Mesquita et al. 2020, Lai et al. 2018, Swaffar et al. 2012). Furthermore, MEPu inhibited the growth of the breast cancer (MCF-7) and large cell lung cancer cell lines (NCI-H460) whit an IG_{50} value <30 µg/mL (Table III). Given that no alkaloids were found in MEPu, the findings about its effects against MCF-7 and NCI-H460 indicate a diversified cytotoxic effect that can be promoted by terpenes, steroids or phenolic compounds present in the fruit pulp of *A. selloana* that may even have chemo preventive potential in neoplasia processes. However, given the limitations of this study, qualitative and quantitative phytochemical tests are needed to identify and quantify the compounds that mediate this action and test them in an in vivo model of neoplasms related to these tumor strains.

In addition to in vitro trials, two pharmacological activities were assessed in this study through in vivo studies, the antinociceptive effect and the gastroprotective potential of the extracts. The current therapeutic treatments to pain still has limited effectiveness and safety, particularly to treat chronic painful diseases and some issues justify the continuity in the search for therapeutic innovations in this field (Walker et al. 2013). Indeed, neuropathic pain is refractory to the current analgesic drugs, including opioids (Colloca et al. 2017) and the repeated use of the non-steroid anti-inflammatory drugs may induce several adverse effects, such as gastrointestinal lesions (Rostom et al. 2002). Over the years, natural products have shown to be an interesting source of molecular diversity leading to drug discovery currently used in modern medicine. However, it is important to emphasize that natural products can also promote side effects and studies that access such possibilities are also needed. Therefore, these issues encouraged us to evaluate the nociceptive potential of the *A. selloana* extract.

The antinociceptive activity using the writhing test demonstrated that *A. selloana* extracts (10 mg/Kg) caused pronounced inhibition

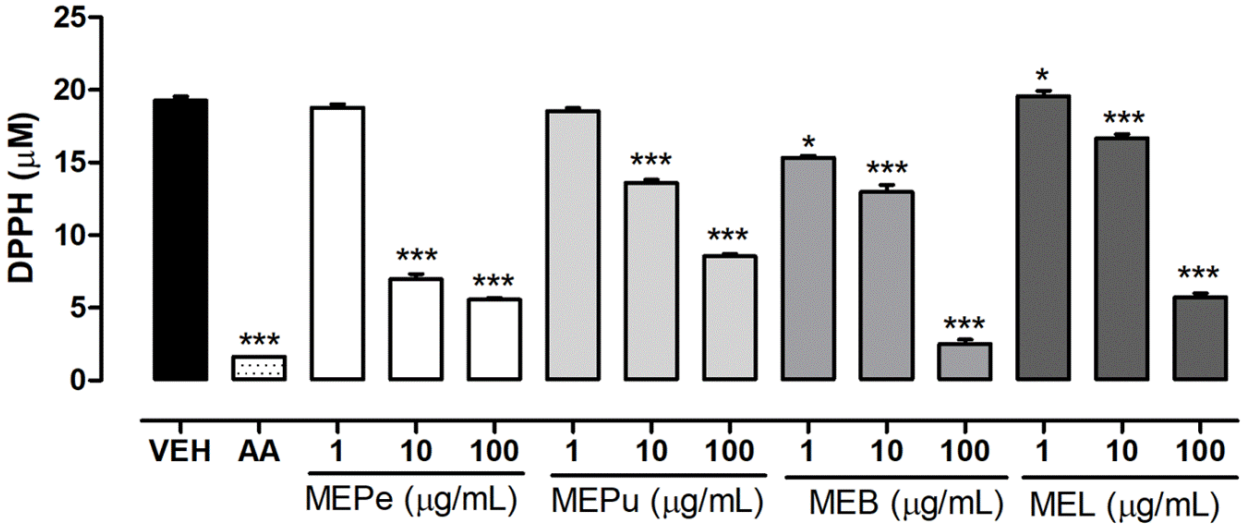

Figure 1. Scavenging effects of the methanol extract of peels from fruit (MEPe), pulp fruit (MEPu), branches (MEB) and leaves (MEL) of the *A. selloana* on DPPH radical. Results are presented as means ± S.E.M. from a triplicate of independent experiments One-way ANOVA followed by Bonferroni test. $^{*}p$ <0.05 and $^{***}p$ <0.001 compared to the vehicle group. VEH: vehicle (10% dimethyl sulfoxide solution), AA: ascorbic acid (50 µg/mL).

of abdominal constrictions. The highest effect was verified after the treatment with MEB with inhibition value of 84.59%, followed by the MEPe with 63.31% (Figure 2a). In this experiment were more effective than some drugs used in the therapy, such as acetylsalicylic acid and acetaminophen, which showed inhibition values of 35% and 38%, respectively, at the same dose of 10 mg/kg (Figure 2a). Interestingly, MEB and MEPe are the extracts with the highest level of phenolic compounds and the scientific literature provides pre-clinical experimental evidence on the antinociceptive effects of polyphenolic compounds, found in plant extracts in animal models of nociceptive, inflammatory, and neuropathic pain, as revised by Boadas-Vaello et al. (2017). Besides, is noteworthy that this is the first time that the antinociceptive effect of preparations from *Abuta sp*. is carried out and that the phenol compounds can justify it. Thus, given this promising result, it is possible that further studies are planned to evaluate the effect of these extracts on models of chronic pain conditions.

Seeing that the nonsteroidal anti-inflammatory drugs (NSAIDs), a widely used class of analgesic drug, can make patient develop gastrointestinal lesions (Katzung et al. 2009, Naidoo & Swan 2009) and the evident antinociceptive effect displayed by the extracts, their effects on the ulcerated mucosa was also investigated. The ethanol is an ulcerogenic agent by its direct harmful effect promoting the depletion of gastric mucus, bicarbonate, and the phospholipids layer in the gastric mucosa (Mózsik & Jávor 1988). Therefore, the ethanol-induced gastric ulcer has been used as a model of easy reproducibility in the search for gastroprotective substance, causing hemorrhagic lesions, extensive submucosal edema, inflammatory cell infiltration, and epithelial cell loss in the stomach. Indeed, macroscopic hemorrhagic lesions were verified in the gastric mucosa of vehicle group exposed to ethanol. In contrary, as depicted in figure 2b, the methanolic extracts obtained from different parts of *A. selloana* (250 mg/kg) demonstrated to be protective against the aggressive agent ethanol, decreasing the injured area when compared to negative control group ($p<0.001$). In addition to their therapeutic effect, is classically established that the non-steroidal anti-inflammatory drugs, such as indomethacin, decrease the prostaglandin bioavailability and the blood flow in the gastric mucosa and lead to ulcers installation in long-term use (Brzozowski et al. 2006, Mózsik 2010). For this reason, the gastroprotective effect of the *A. selloana* was also evaluated against the indomethacin-induced gastric ulcer. Corroborating to findings from ethanol-induced gastric ulcer, the extracts

Table III. Antiproliferative activity the methanol extract of peels from fruit (MEPe), pulp fruit (MEPu), branches (MEB) and leaves (MEL) of the *A. selloana* against human cancer cell lines[a]. GI50 (µg/mL)[b].

Treatments	U251	MCF7	NCI-H460
Doxorubicin	0.025	<0.025	<0.025
MEPu	>250	27.8	9.0
MEPe	>250	32.8	>250
MEB	>250	63.3	>250
MEL	27.5	8.5	26.5

[a]Human cancer cell lines: U251 (glioma); MCF-7 (breast); NCI-H460 (large cell lung cancer). Assessed by the SRB assay. [b]GI50 values represent the concentration required to inhibit 50% of cell growth.

of the fruit plant *A. selloana* also reduced the lesions in the indomethacin-induced gastric ulcer (Figure 2c). These findings corroborate with the ethnobotanical survey of Boscolo & Galvão (2019), which was conducted in two communities in the mountainous region of Rio de Janeiro and described that *A. selloana* is used to treat digestive diseases, mainly in stomach, in that population. The ulcerogenic process reduce the defense mechanisms on the gastric mucosa initially by forming reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and lipid peroxides (Alvarez-Suarez et al. 2011, Saghaei et al. 2012). Therefore, the antioxidant potential displayed by the *A. selloana* extracts, as evidenced by the DPPH test, can be mediated, at least in party, the gastroprotective potential of these extracts.

Taken together the results found in this research are of great novelty given that there is no experimental evidence on the biological potential of extracts from the *A. selloana*; however, some limitations need to be pointed out to direct future studies, especially in the field of phytochemistry, where there is still a need for complete details of the phytochemicals and the quantifications of the majorities in each extract studied. After that, further studies using in vivo

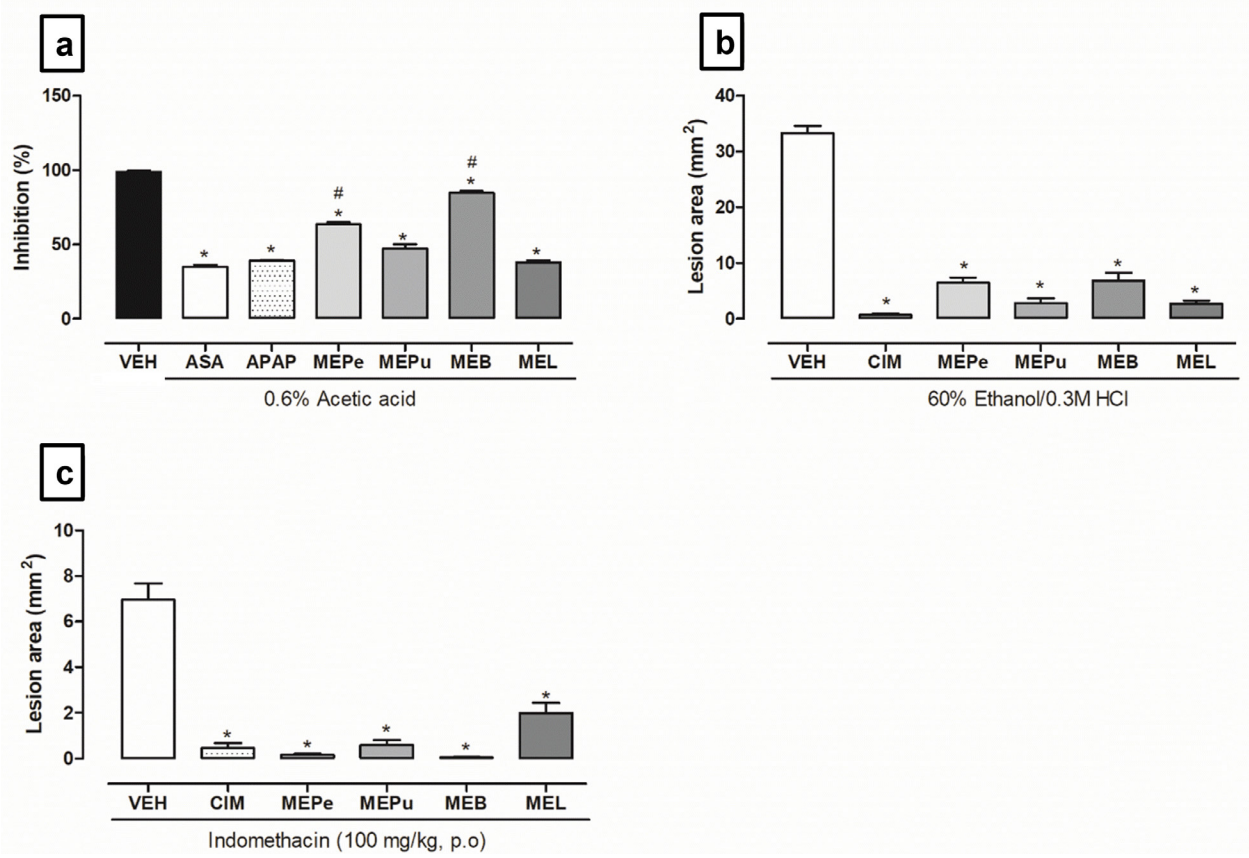

Figure 2. Antinociceptive (a) and gastroprotective effects against ethanol (b) and indomethacin (c) of the methanol extract from peels fruit (MEPe), pulp fruit (MEPu), branches (MEB) and leaves (MEL) of the *A. selloana* in mice. Results are presented as means ± S.E.M. (n=6). One-way ANOVA followed by Bonferroni test. *p <0.001 compared to the vehicle group \#p <0.001 compared to the ASA or APAP group. VEH: vehicle (10% dimethyl sulfoxide solution), ASA: acetylsalicylic acid (10 mg/mL, i.p); APAP: acetaminophen (10 mg/mL, i.p); MEPu: methanolic extract from pulp fruit (10 mg/mL, i.p); MEPe: methanolic extract from peel fruit (10 mg/mL, i.p); MEB: methanolic extract from branches (10 mg/mL, i.p); MEL: methanolic extract from leaves (10 mg/mL, i.p).

models related to cancer, pain and gastric ulcer could be done using a bio monitored approach. Nevertheless, the results achieved here open a wide avenue for future studies that explore the pharmacological potential of this medicinal species of southern Brazilian flora.

CONCLUSION

The results show that the fruit plant *A. selloana* presents different classes of bioactive compounds and possible therapeutic applications, as already evidenced in other species of Menispermaceae family. Interestingly, the methanolic extract of the leaves and pulp exhibited the greatest cytotoxicity against the human cancer cell lines. Further, the findings revealed the antinociceptive and gastroprotetor potentials of the methanolic extracts of *A. selloana* which could be beneficial in alleviating painful inflammatory conditions and in parallel protect the gastric mucosa. However, more studies are needed to identify the bioactive compounds and mechanisms of action of the biological activities initially evidenced in this study.

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LANN, AC, AR, FTM, LNMB conducted experiments. FCB, ALTGR, JEC, VCF and LMS contributed to the experimental design and data analyses. LANN, AC and VCF contributed with phytochemical procedures. LMS wrote the manuscript. All authors read and approved the manuscript.