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RESEARCH

The Protective Effect of Juçara Fruit (*Euterpe edulis* Martius) Extracts on LPS-Activated J774 Macrophages

Mayara Schulz[1] · Luciano Valdemiro Gonzaga[1] · Ana Clara Nascimento Antunes[1] · Tainá Lubschinski[2] · Eduarda Talita Bramorski Mohr[2] · Eduardo Monguilhott Dalmarco[2] · Carolina Turnes Pasini Deolindo[3] · Rodrigo Barcellos Hoff[3] · Fábio Martinho Zambonim[4] · Ana Carolina Oliveira Costa[1] · Roseane Fett[1]

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Abstract

This study investigated the anti-inflammatory effect of hydrophilic and lipophilic extracts from juçara fruits (*Euterpe edulis* Martius) through measurement of nitric oxide (NOx) and cytokines (IL-12p70, TNF-α, INF-γ, MCP-1, IL-6, and IL-10). J774 macrophages were stimulated with lipopolysaccharides (1 μg/mL) and treated with various concentrations (1–100 μg/mL) of juçara fruits extracts from crude extracts, and hexane, dichloromethane, ethyl acetate, and butanol fractions. Potential relationships between the phenolic composition of the extracts determined by LC-ESI-MS/MS and their anti-inflammatory capacity were also evaluated. Hexane and dichloromethane fractions inhibited NOx and IL-12p70 while increased IL-10. Hexane fractions also decreased IL-6 and IFN-γ production. Hexane and dichloromethane fractions showed a higher number of phenolic compounds (32 and 34, respectively) than the other extracts tested and were also the only ones that presented benzoic acid and pinocembrin. These results suggest juçara fruits compounds as potential anti-inflammatory agents, especially those of a more apolar nature.

Keywords Phenolic Compounds · Inflammation · Anti-inflammatory · Cytokines · Nitric Oxide · Açaí

Introduction

Inflammation is a complex response of cell- and molecular levels to biological, chemical, or physical stimuli, which is necessary for survival. In this response, there is recruit immune cells that modulate the secretion of inflammatory biomarkers that will guide the immune response to resolve inflammation [1]. However, when the initial inflammatory response is unresolved and a persistent inflammation occurs may generate a chronic condition, which has been associated with many diseases, such as arthritis, asthma, atherosclerosis, autoimmune diseases, diabetes, and cancer [1, 2].

Macrophages are among the main cells involved in the inflammatory process. They perform a key role as regulatory cells involved in the phagocytosis of pathogens, necrotic tissue, and secretion of pro- and anti-inflammatory cytokines [3]. Therefore, experimental models using these cells are commonly applied since they allow a fast and reliable initial screening, reducing laboratory animals experiments while seeking new anti-inflammatory agents [4]. Also, to discover pharmacologically active compounds from plants, appropriate extraction methods is necessary to obtain semi-pure extracts, fractions, and, finally, pure compounds. Generally, a solvent that allows the extraction of a greater number of compounds is used to reach the crude extract, and, subsequently, this extract is submitted to a liquid-liquid partition

✉ Mayara Schulz
schulzmay@gmail.com

✉ Roseane Fett
roseane.fett@gmail.com

[1] Department of Food Science and Technology, Federal University of Santa Catarina, Admar Gonzaga 1346, Itacorubi, Florianopolis, SC 88034-001, Brazil

[2] Department of Clinical Analysis, Federal University of Santa Catarina, Florianópolis, SC 88040-900, Brazil

[3] Federal Agricultural Defense Laboratory, Brazilian Ministry of Agriculture, Livestock and Food Supply, São José, SC 91780-580, Brazil

[4] Agricultural Research and Rural Extension Company of Santa Catarina (Epagri)/ Environmental Resources and Hydrometeorology Information Center (Ciram), Florianópolis, SC 88034-901, Brazil

with solvents of increasing polarity, aiming at a semi-purification of the substances by their polarities [5, 6].

Foods rich in bioactive compounds, especially phenolic compounds, have been frequently associated with positive modulation of inflammation. This effect is mainly attributed to inhibition in the production of pro-inflammatory mediators, activation of transcription factors, and control of cell migration and proliferation [5, 7, 8].

Juçara fruits (*Euterpe edulis* Mart.) have been named superfruit due to their rich diversity and contents of phenolic compounds (especially anthocyanins, other flavonoids, and phenolic acids) as well as relevant health-promoting activities, including antioxidant, hypolipidemic, neuroprotective, and chemopreventive [9–12]. These black-violet fruits are native to Atlantic Forest distributed across the Brazilian coast and comparable to Amazonian açaí (*Euterpe oleracea* Mart.) [11].

In vitro [13] and in vivo [14–16] studies demonstrated that juçara fruits were able to modulate inflammation, mainly influencing the secretion of the cytokines TNF-α, IL-6, and IL-10. However, evidence for a possible relationship between the anti-inflammatory potential of the juçara fruits with the phenolic composition is still lacking. Those findings may provide a better understanding of the ability of the juçara extracts to modulate inflammatory mediators, potentially active compounds, besides possible synergistic and antagonistic effects that can influence the anti-inflammatory activity.

Thus, the aim of this study was to evaluate the phenolic composition and the effect of crude extracts and hexane, dichloromethane, ethyl acetate, and butanol fractions from juçara fruits harvested in Florianópolis and São Pedro de Alcântara cities (Santa Catarina state, Brazil) on the production of nitric oxide (NOx) and anti-(IL-10) and pro-(IL-12p70, TNF-α, INF-γ, MCP-1, IL-6) inflammatory cytokines by J774 macrophages stimulated with LPS.

Materials and Methods

The Materials and methods section is showed in supplementary material 1.

Results and Discussion

Phenolic Compounds by LC-ESI-MS/MS

The concentrations of phenolic compounds in the crude extracts and hexane, dichloromethane, ethyl acetate, and butanol fractions from juçara fruits are shown in supplementary material 2. Out of.

Fig. 1 Cytotoxicity and calculated CC_{10} (concentration that kills 10% of the cell line) of crude extracts and fractions from juçara fruits (*Euterpe edulis* Mart.). Blank (**B**) represents cells pretreated with vehicle and stimulated with PBS. Groups 'A' represent the extracts from the São Pedro de Alcântara region and groups 'B' represent the extracts from Florianópolis region, Santa Catarina, Brazil. Cells were pre-treated with crude extracts (**A**) (**B**), hexane fractions (**C**) (**D**), dichloromethane fractions (**E**) (**F**), ethyl acetate fractions (**G**) (**H**), and butanol fractions (**I**) (**J**) at 1–100 µg/mL. Each bar represents the average survival of the macrophages in independent experiments ± S.D. ($n = 3$)

phenolic compounds analyzed, only 4-methylumbelliferone was not detected in any of the extracts. The results were in line with other studies that also evaluated the phenolic composition of these fruits [17–21]. However, it is important to note that of the 34 phenolic compounds found, we showed, for the first time, the presence of isorhamnetin, 2,5-dihydroxybenzoic acid, *p*-aminobenzoic acid, chrysin, hesperidin, naringin, pinobanksin, and coumarin.

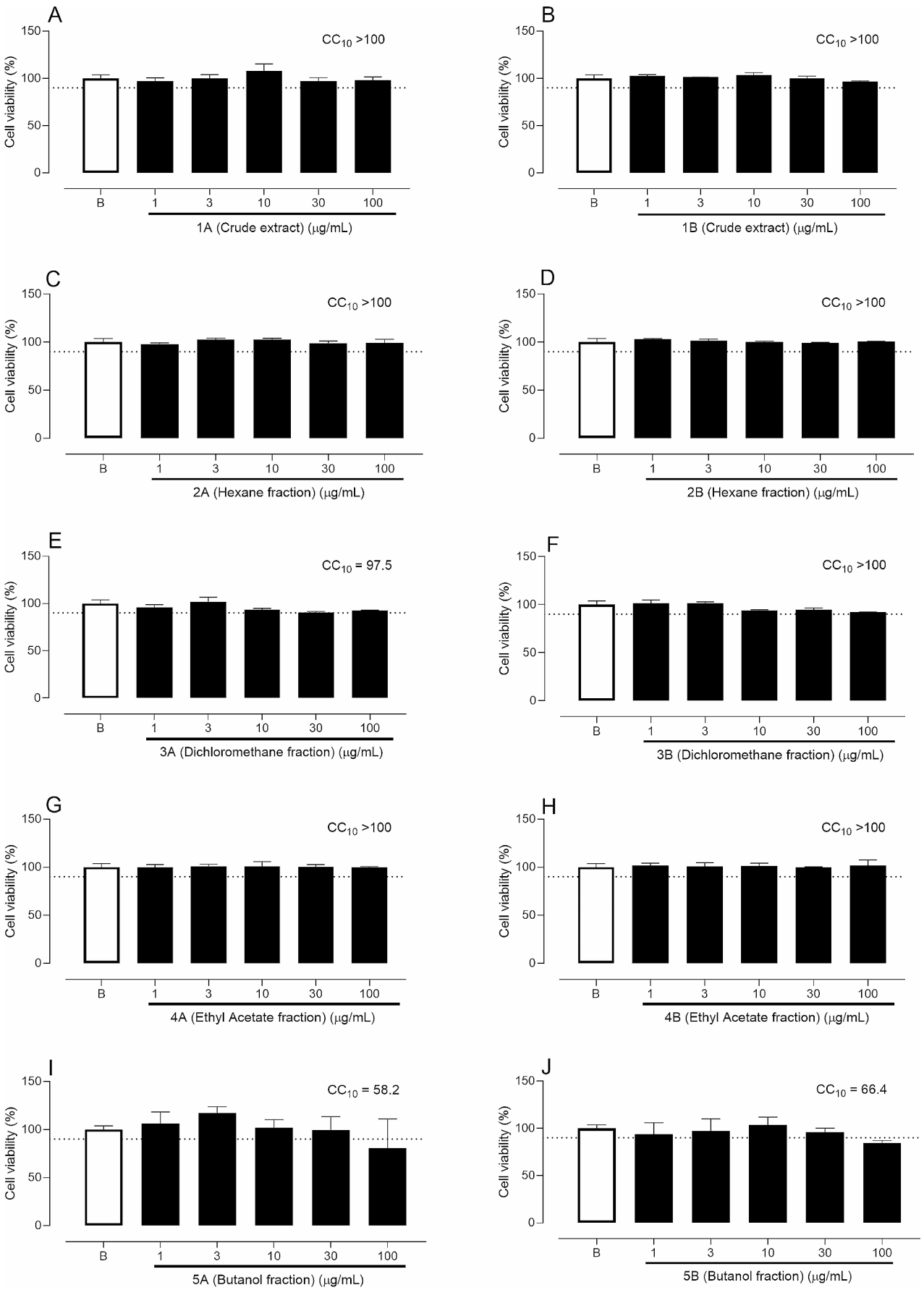
The dichloromethane and hexane fractions showed the highest number of compounds, 34 and 32, respectively. Benzoic acid and pinocembrin were found only in these two fractions, while *p*-coumaric acid and coniferaldehyde were found only in the dichloromethane fraction.

Isoquercetrin and isorhamnetin were found in higher concentrations. Other prominent flavonoids in the crude extracts and in the hexane, ethyl acetate, and butanol fractions were rutin and quercetin, while in the dichloromethane fractions, the flavonoids isoquercetrin, isorhamnetin, and rutin, and the phenolic acids protocatechuic acid, ferulic acid, and 2,5 dihydroxybenzoic acid were the major.

The growing location did not influence the concentrations of *p*-aminobenzoic and 2,5-dihydroxybenzoic acids, apigenin, chrysin, galangin, isorhamnetin, naringin, and coumarin, which was not statistically different between the mean values for crude extracts and fractions (supplementary material 2). However, for most of the phenolic compounds, there was a statistically significant interaction between the type of extract and the growing location of the juçara fruits (supplementary material 3). The dichloromethane fraction B showed higher concentrations of phenolic acids and phenolic aldehydes than the dichloromethane fraction A. This phenolic composition variation in fruits grown in different locations is expected since the differences in edaphoclimatic conditions, affect the biosynthesis of these compounds [22, 23].

Cell Viability Assay and NOx Levels

Crude extracts and fractions from juçara fruits were evaluated for their cytotoxic potential against the J774 macrophages. Figure 1 shows that the cell viability was unaffected by crude extracts, hexane, and ethyl acetate fractions, regardless of the concentration tested (1, 3, 10, 30, and


A
CC10 >100
Cell viability (%)
150
100
50
0
B 1 3 10 30 100
1A (Crude extract) (μg/mL)
B
CC10 >100
Cell viability (%)
B 1 3 10 30 100
1B (Crude extract) (μg/mL)
C
CC10 >100
Cell viability (%)
B 1 3 10 30 100
2A (Hexane fraction) (μg/mL)
D
CC10 >100
Cell viability (%)
B 1 3 10 30 100
2B (Hexane fraction) (μg/mL)
E
CC10 = 97.5
Cell viability (%)
B 1 3 10 30 100
3A (Dichloromethane fraction) (μg/mL)
F
CC10 >100
Cell viability (%)
B 1 3 10 30 100
3B (Dichloromethane fraction) (μg/mL)
G
CC10 >100
Cell viability (%)
B 1 3 10 30 100
4A (Ethyl Acetate fraction) (μg/mL)
H
CC10 >100
Cell viability (%)
B 1 3 10 30 100
4B (Ethyl Acetate fraction) (μg/mL)
I
CC10 = 58.2
Cell viability (%)
B 1 3 10 30 100
5A (Butanol fraction) (μg/mL)
J
CC10 = 66.4
Cell viability (%)
B 1 3 10 30 100
5B (Butanol fraction) (μg/mL)

100 µg/mL). In contrast, dichloromethane fraction (2 A) (Fig. 1E) and butanol fractions (both samples) (Fig. 1I and J) decreased the cell viability at 100 µg/mL. Butanol fractions showed the highest cytotoxicity, with CC_{10} (concentration that kills 10% of the cell line) of 58.2 µg/mL for sample A (Fig. 1I) and 66.4 µg/mL for sample B (Fig. 1J). The dichloromethane fraction demonstrated a CC_{10} of 97.5 µg/mL (Fig. 1E).

Due to the cytotoxicity demonstrated by dichloromethane (3A) and butanol (5A and 5B) fractions, NOx was measured at concentrations of 1, 3, 10, and 30 µg/mL for crude extract and fractions. The ability of the crude extracts and hexane, dichloromethane, ethyl acetate, and butanol fractions to inhibit the production of NOx is shown in Fig. 2. No significant inhibition was observed for crude extracts, ethyl acetate, and butanol fractions. However, hexane (both samples) and dichloromethane (3B) fractions inhibited NOx production. This inhibition occurred at all tested concentrations (1, 3, 10, and 30 µg/mL): inhibition (%) of the hexane fraction 2A: 80.3 ± 3.5; 74.9 ± 5.5; 84.3 ± 11.0; 66.8 ± 4.8 ($p < 0.001$) (Fig. 2C); inhibition (%) of the hexane fraction 2B: 72.9 ± 0.8; 81.3 ± 3.6; 81.8 ± 5.1; 53.3 ± 11.8) ($p < 0.001$) (Fig. 3D); and inhibition (%) of the dichloromethane fraction 3B: 53.5 ± 6.3; 62.1 ± 7.7; 60.4 ± 12.8; 74.4 ± 3.2) ($p < 0.001$) (Fig. 2F).

To the best of our knowledge, only one study was published on the anti-inflammatory activity of juçara fruits using cell culture. Barroso et al. [13] evaluated the effects of juçara aqueous extracts (10–100 µg/mL) from different genotypes on LPS-induced RAW 264.7 macrophages. The percentages of inhibition of nitric oxide metabolites were lower than in the present study, ranging from 0 to 65% [13]. NOx is an important inflammatory mediator since iNOS expression is induced by pro-inflammatory cytokines TNF-α, IL-1, and IFN-γ, as well as by LPS [24]. Nitric oxide is the main responsible to increase the vasodilatation necessary to leukocyte migrate to the inflammatory side, as well as one of the most important sources for production of reactive species of nitrogen, like peroxynitrite, nitroxyl anion and nitrogen dioxide among others that are very dangerous to the cells [25, 26].

Cytokines

The quantification of pro-(TNF-α, IL-6, IL-12p70, MCP-1, and IFN-γ) and anti-(IL-10) inflammatory cytokines was performed for the fractions that inhibited NOx production (hexane fraction 2 A, hexane fraction 2B, and dichloromethane fraction 3B), using the best concentrations of each fraction (hexane 2 A: 1 µg/mL; hexane 2B: 1 µg/mL; dichloromethane 3B: 3 µg/mL).

Fig. 2 Effects of crude extracts and fractions from juçara fruits (*Euterpe edulis* Mart.) on NOx metabolites levels. Blank (**B**) represents cells treated only with the vehicles (DMSO and sterile PBS). LPS represents cells treated only with LPS (1 µg/mL). Dexa represents the group pre-treated with dexamethasone (10 µM) before LPS. Groups 'A' represent the extracts from the São Pedro de Alcântara region and groups 'B' represent the extracts from Florianópolis region, Santa Catarina, Brazil. Cells were pre-treated with crude extracts (**A**) (**B**), hexane fractions (**C**) (**D**), dichloromethane fractions (**E**) (**F**), ethyl acetate fractions (**G**) (**H**), and butanol fractions (**I**) (**J**) at 1, 3, 10 and 30 µg/mL before LPS. The graph bars expressed as mean ± S.D. $n = 3$ (sample size in each group). *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs LPS group (###)

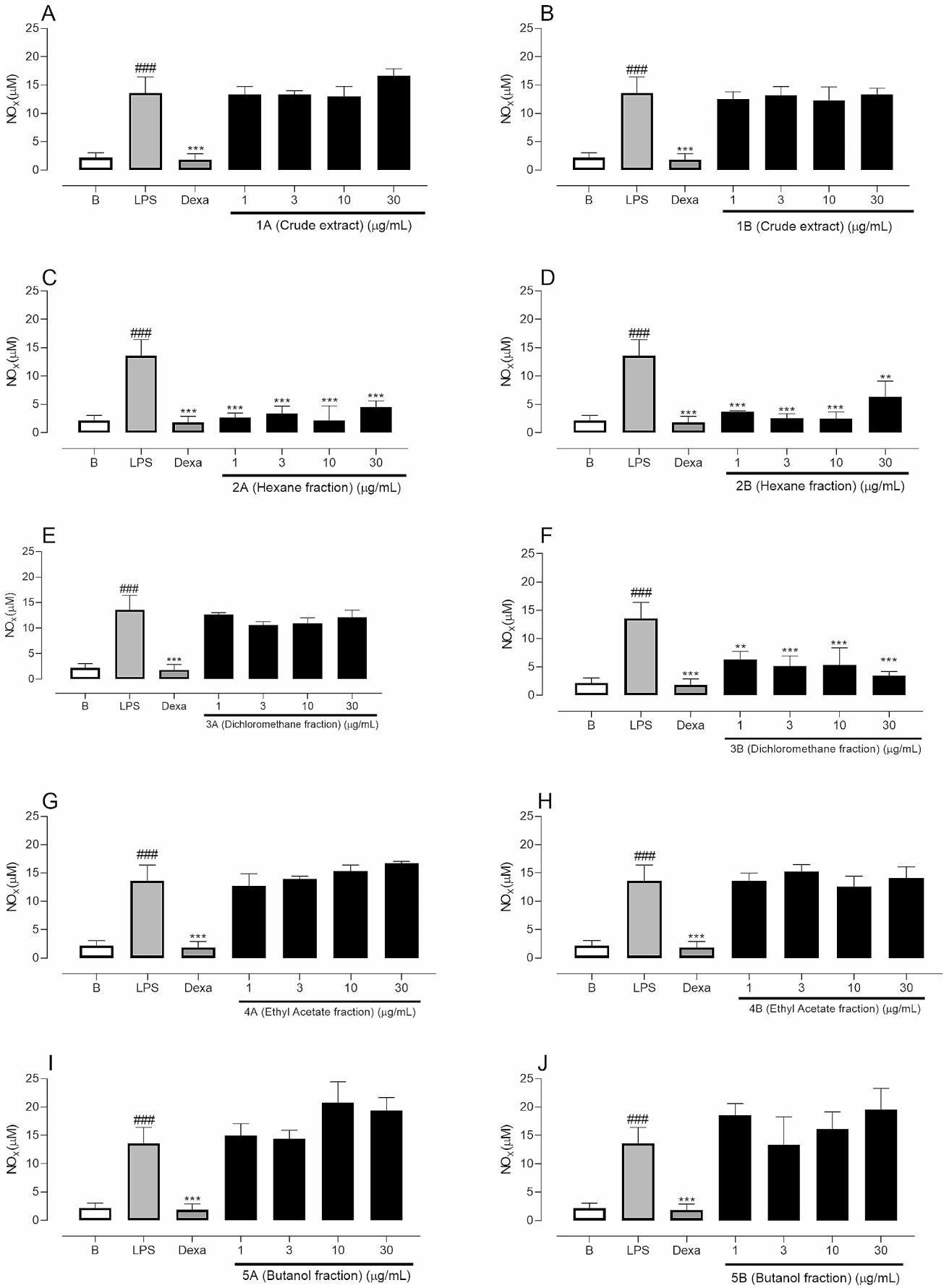
The fractions tested were able to increase the IL-10 production by 107.1 ± 20.2% for hexane fraction 2 A ($p < 0.05$) (Fig. 3A), 96.6 ± 10.3% for hexane fraction 2B ($p < 0.05$) (Fig. 3A), and 133.6 ± 11.4% for dichloromethane fraction 3B ($p < 0.01$) (Fig. 3A). An increase in IL-10 levels was also observed in monocytes isolated from peripheral blood cells of obese humans who received freeze-dried juçara fruit pulp (5 g) for 6 weeks [14]. IL-10, as an anti-inflammatory cytokine, is an inhibitor of pro-inflammatory cytokines, such as IL-2, IL-8, IFN-γ, and TNF-α, promoting inflammation resolution [27, 28].

For pro-inflammatory cytokine IL-12p70, hexane fraction 2 A and dichloromethane fraction 3B significantly reduced the secretion by 51.1 ± 2.1% ($p < 0.05$) (Fig. 3B) and 47.7 ± 6.1% ($p < 0.05$) (Fig. 3b), respectively. This pro-inflammatory interleukin acts as an inductor of the synthesis of IFN-γ and TNF-α and as a differentiation factor on CD4 + T cells [29]. To our knowledge, no studies have reported the action of juçara fruits extracts on IL-12p70 cytokine modulation.

IL-6 production was also inhibited by hexane fraction 2 A (% of inhibition: 48.2 ± 10.2) ($p < 0.01$) (Fig. 3C). In contrast, hexane fraction 2B decreased IFN-γ release (% of inhibition: 68.3 ± 3.4) ($p < 0.01$) (Fig. 3D). IL-6 is also a cytokine with pro-inflammatory function since it stimulates the synthesis of acute-phase proteins [29]. Studies with freeze-dried juçara fruit powder (0.5%) have also demonstrated a down-regulation of IL-6 cytokine. The ingestion of this dose by Wistar rats during pregnancy and lactation promoted a decrease of IL-6 in the retroperitoneal white adipose tissue and liver [16] of 21-day-old offspring in a pro-inflammatory state.

IFN-γ is widely recognized for its pro-inflammatory capability, activating macrophages and natural killers and promoting lymphocyte differentiation and adhesion of CD4 + T lymphocytes [30]. A decrease in IFN-γ levels was also observed in Wistar rats fed defatted lyophilized juçara fruit pulp (10%) for 50 days [15].

In the present study, the differences observed for the effects on inflammatory mediators of the different extracts/fractions studied are possibly related to the phenolic


A
B
C
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NOx(μM)
###
***
**
B
LPS
Dexa
1
3
10
30
1A (Crude extract) (μg/mL)
1B (Crude extract) (μg/mL)
2A (Hexane fraction) (μg/mL)
2B (Hexane fraction) (μg/mL)
3A (Dichloromethane fraction) (μg/mL)
3B (Dichloromethane fraction) (μg/mL)
4A (Ethyl Acetate fraction) (μg/mL)
4B (Ethyl Acetate fraction) (μg/mL)
5A (Butanol fraction) (μg/mL)
5B (Butanol fraction) (μg/mL)

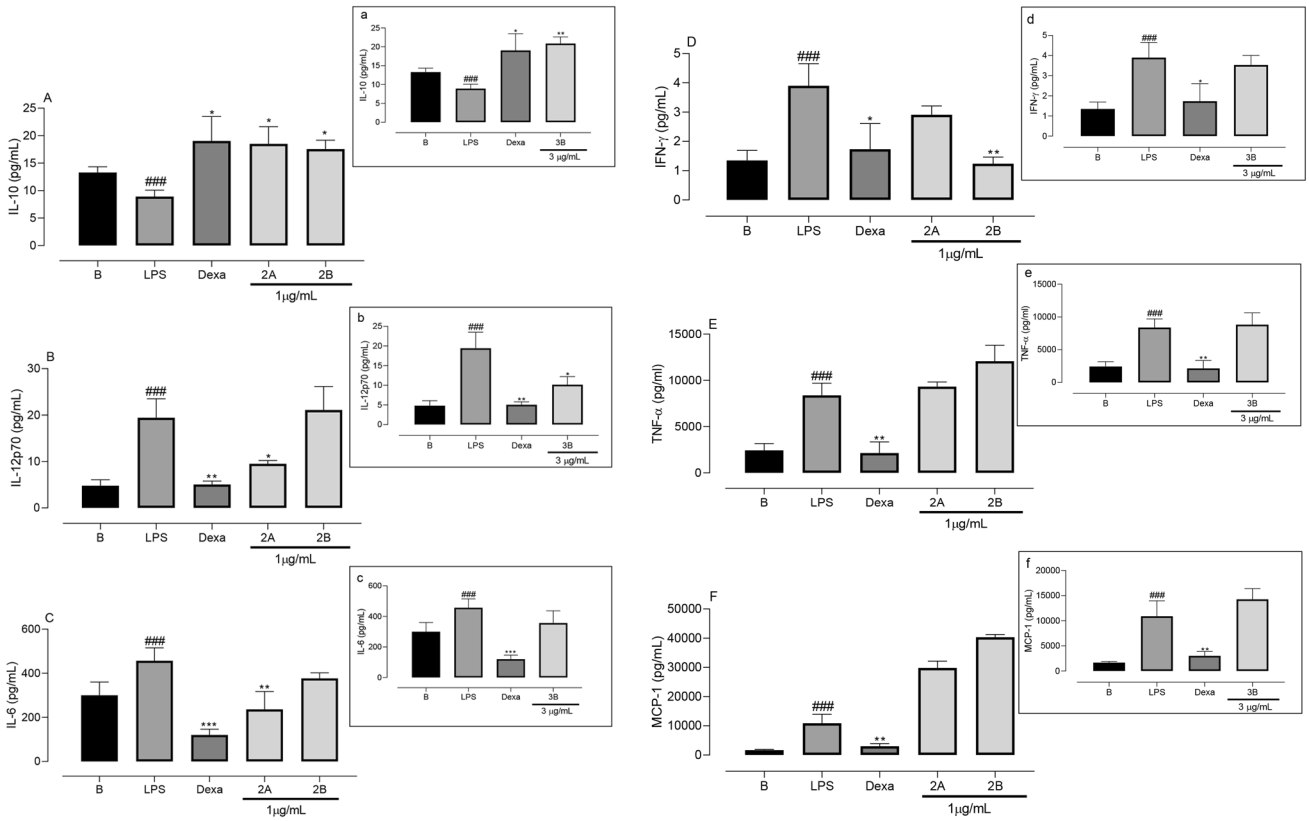

Fig. 3 Effects of the hexane and dichloromethane fractions from juçara fruits (*Euterpe edulis* Mart.) on cytokine levels: IL-10 (**A**) (a), IL-12p70 (**B**) (b), IL-6 (**C**) (c), INF-γ (**D**) (d), TNF-α (**E**) (e), and MCP-1 (**F**) (f). Blank (**B**) represents cells treated only with the vehicles (DMSO and PBS). LPS represents cells treated only with LPS (1 µg/mL). Dexa represents the group pre-treated with dexamethasone (10 µM) before LPS. Groups 'A' represent the extracts from the São Pedro de Alcântara region and groups 'B' represent the extracts from Florianópolis region, Santa Catarina, Brazil. Cells were pre-treated with hexane fractions (2 A, 2B) at 1 µg/mL and with dichloromethane fraction (3B) at 3 µg/mL before LPS. The graph bars expressed as mean ± standard deviation (S.D.); $n = 3$ (sample size in each group); *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* LPS group (###)

composition of each one of them. The positive effects of the phenolic compounds on nitric oxide production and other multiple inflammatory components are already well established in the literature [7, 8].

The anti-inflammatory effects observed only for the hexane and dichloromethane fractions may be related to the higher number of phenolic compounds found in these fractions than the others tested. As previously mentioned, these two fractions were also the only ones that presented benzoic acid and pinocembrin, known for their anti-inflammatory potential [31, 32]. It is also important to highlight the possibility of a synergistic effect between the compounds in these two fractions, conferring a higher biological effect [33]. Still, a possible action of other phenolic compounds that were not evaluated in this study and other classes of compounds also needs to be considered. For instance, juçara fruits are rich in fatty acids, such as oleic and linolenic acids [19], nonpolar compounds that are present in the hexane fraction, and that may have anti-inflammatory effects [34, 35]. As we observed in this study, higher bioactivity of the hexane and dichloromethane fractions was also reported for HT22 cells when the neuroprotective effect of the crude extract and the hexane, dichloromethane, ethyl acetate, and butanol fractions from juçara fruits was studied [21].

Conclusions

Our results showed that juçara fruits extracts have anti-inflammatory potential on inflammation induced by LPS in the J774 macrophages. The hexane and dichloromethane fractions showed an increase in anti-inflammatory cytokine and a decrease in pro-inflammatory mediators, with differences between the two regions studied. These effects can be associated with the phenolic composition of these samples and their fractions, mainly phenolic compounds of a more apolar nature, as well as by the interaction between the compounds, which can act in synergy in the protection against inflammation.

This was the first work that evaluated the protective effects of juçara fruits on J774 macrophages and sequential extracts to better understand the potential relationships between the juçara fruit phenolic composition and its anti-inflammatory capacity. This knowledge furthers the understanding of the juçara fruits health benefits and may lead to novel therapeutic agents to inhibit inflammatory conditions. Additional studies should target which are the active components of the hexane and dichloromethane fractions as well as the signaling pathways involved in the modulation of inflammatory mediators.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11130-024-01204-8.

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Author Contributions MS: Conceptualization, Investigation, Writing-original draft, Writing – review and editing. LVG: Conceptualization, Supervising, Writing – Review & Editing. ACNA: Investigation, Writing – review and editing. TL: Investigation, Writing- original draft. ETBM: Investigation. EMD: Supervising, Writing – Review & Editing. CTPD: Investigation. RBH: Investigation, Supervising. FMZ: Sample collection, Writing – Review & Editing. ACOC: Supervising, Writing – Review & Editing. RF: Conceptualization, Supervising, Writing – Review & Editing.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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