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African Journal of  
**Pharmacy and Pharmacology**

22 April, 2019  
ISSN 1996-0816  
DOI: 10.5897/AJPP  
[www.academicjournals.org](http://www.academicjournals.org)



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# Table of Content

**Endopleura uchi (Huber) Cuatrec, a medicinal plant with potential anti-inflammatory activity: A review of its phytochemistry and biological activities**

76

Beatriz Martins de Sá Hyacienth, Brenda Sánchez Ortiz , Arlindo César Matias Pereira, Danilo Cabral de Sá Hyacienth, Josué Arturo Velázquez Moyado, Glória Melisa Gonzales Aduanga, Andrés Navarrete and José Carlos Tavares Carvalho

*Full Length Research Paper*

## ***Endopleura uchi* (Huber) Cuatrec, a medicinal plant with potential anti-inflammatory activity: A review of its phytochemistry and biological activities**

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Received 15 January, 2019; Accepted 16 April, 2019

***Endopleura uchi* (Huber) Cuatrec. is a tree found in the Brazilian Amazon, whose barks are used in folk medicine as an alternative treatment for inflammatory-related diseases. This review, performed using current available international scientific literature, aimed to survey biological activities reported from *E. uchi*, and describes its phytochemistry. In folk medicine, the barks are used to treat a range of conditions such as intestinal infections, inflammations, diabetes, arthritis, among others; the fruits have some unique nutritional benefits. Phytochemical studies with this plant species indicate the presence of tannins, saponins, and mainly bergenin (a coumarin) in the barks. Among biological activities reported using extracts from the barks are: Inhibition of acetylcholinesterase and butylcholinesterase, bacteriostatic and bactericidal activity, antidiabetic activity through inhibition of  $\alpha$ -glucosidase, anti-inflammatory and antioxidant activity. Bergenin, the most abundant molecule, has antimicrobial activity mainly against yeasts and anti-inflammatory activity apparently through mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF- $\kappa$ B) inhibition; its acetylated derivative acetylbergenin has analgesic and more prominent anti-inflammatory activity.**

**Key words:** Anti-inflammatory, bergenin, *Endopleura uchi*, phytochemistry.

### **INTRODUCTION**

Uxi, *Endopleura uchi* (Huber) Cuatrec, is a tree found in the Brazilian Amazon. Barks and seeds of this species

are employed in folk medicine to treat hemorrhoids, intestinal infection, hepatitis, tuberculosis, anemia,

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dysmenorrhea, genitourinary diseases and as a menstrual regulator (Rodrigues, 2007; Santos et al., 2012; Oliveira et al., 2015; Pedrollo et al., 2016).

*E. uchi* fruit is an important food among the Amazonian population, with a high content of Vitamin A and low content of calories (Herrero-Jáuregui et al., 2008; Shanley and Gaia, 2002). During its fruiting period, uxi's fruit is a vital source of income for traditional communities located around the city of Belém, in the Brazilian Amazon (Shanley et al., 2002, 2012).

The seeds of *E. uchi* are also used as a hemostatic agent, and the smoke from burned fruits are used against "evil eye" (Coelho-Ferreira, 2009; Ricardo et al., 2017). In Belém, the fruit is used in the manufacture of liquors, juices, and ice-creams, known by vendors as one of the best seller flavors (Shanley et al., 2002), the fruit is also used in hunting traps. Due to its high demand, there are conflicts for this species (Rist et al., 2012; Neves et al., 2012; Santos et al., 2012; Pedrollo et al., 2016; Yazbek et al., 2016).

Currently, a significant number of studies has been performed with this plant, but no review about it is available. Hence, this review aimed to highlight the importance of *E. uchi* and direct future studies, describing its use in folk medicine, phytochemistry, and biological activities reported.

## METHODOLOGY

A bibliographic survey was performed using the keywords *Endopleura uchi*, *Endopleura uchi* Huber Cuatrec, *Sacoglottis uchi*, and uxi, in international scientific databases such as Medline, Embase, Lilacs, ScienceDirect, CAPES Periodicals, Scopus, and Scielo (Figure 1).

## RESULTS AND DISCUSSION

### Botany

*E. uchi* (Huber) Cuatrec (formerly *Sacoglottis uchi* Hub.) is a plant with tree habit, 25 to 30 m tall, and 38 to 60 cm trunk diameter (Moore and Fisch, 1986; Shanley et al., 2012), found in the Brazilian Amazon; this species belongs to family Humiriaceae (Schultes, 1979; Oliveira and Mori, 1999; Parry et al., 2009), and is popularly known as *uxi amarelo* (Frausin et al., 2015), *uxi* (Smith et al., 1996) *uxi liso* (Rodrigues, 2006; Oliveira et al., 2015), *uchi* (Herrero-Jáuregui et al., 2008) and *uchi pucú* (Parrotta, 1997, 2002). In a study performed by Laurance et al. (2004), the authors estimated this species' average lifetime around 223 years. The trunk of this species has, on average, 0.746 g cm<sup>-3</sup> (Nogueira et al., 2005).

The fruit from *E. uchi* is a drupe, has a double oblong-ellipsoid layer ranging from 5 to 7 cm of length, and 4.2 to

4.6 cm in diameter; it weighs between 55.61 and 60.31 g of fresh mass. The pulp is greenish-yellow, which turns brown when mature (Neves et al., 2012). When it is in its fruiting period, the tree attracts animals toward it (Rylands, 1981; Gonçalves et al., 2010).

The fruiting period lasts between 4 and 5 months, and the fruits are appreciated among people from the city of Belém, who wait for its arrival in the city's central market (Shanley et al., 2002). This fruit has a climacteric behavior (Neves et al., 2015); after falling from the tree and collected, it can be sold until five days. In the Oriental Amazon, uxi's production starts at the end of January and continues until May (Shanley et al., 2002).

Wood management from *E. uchi* should be planned to avoid unsustainable exploitation before the trees are entirely developed, providing this way economic sustainability and better wood quality (Wadsworth and Zweede, 2006). However, local deforestation for land use has made *E. uchi* rarer (Shanley and Gaia, 2002).

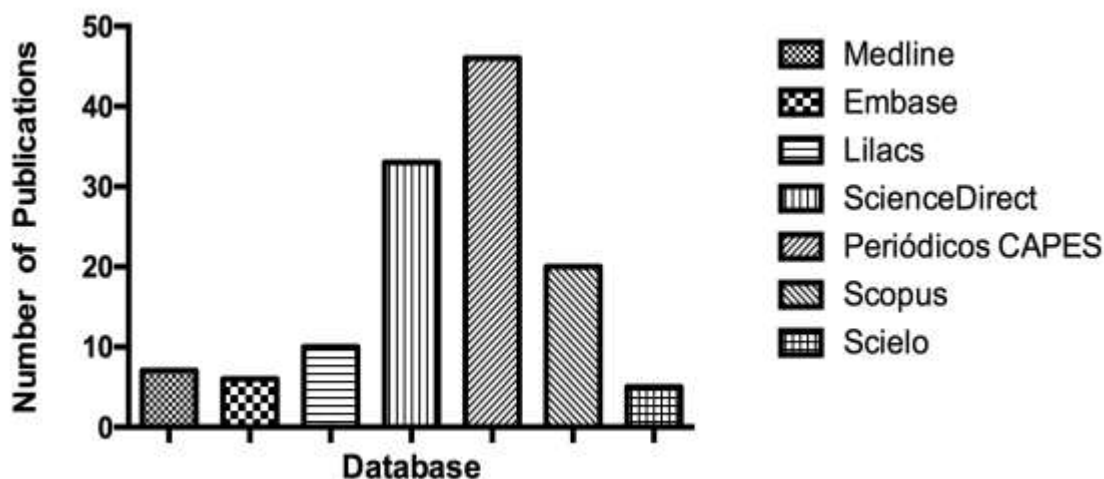
Although domestication of this species could be an option for exploitation, this is unfeasible due to genetic features of this plant that make their development slower, impairing to implement this method (Venturieri, 2013).

### Folk medical use

*E. uchi* is native from the Americas, more precisely, from its tropical zones (Guimaraes et al., 2008). The barks are used therapeutically as teas and macerated preparations for maternity issues and other women-related conditions (Yazbek et al., 2016). *E. uchi* is used during the labor to favor the birth, there is, however, reports of its use also as an abortive agent; hence, it is contraindicated during the pregnancy period (Rodrigues, 2007; Santos et al., 2012).

The barks and seeds are also used for gastralgia, dysentery, hemorrhoids, intestinal infection, inflammations, hepatitis and other liver diseases, tuberculosis, as healing agents, for apathy, anemia, to induce uterus hypertonia, as a lactogenic agent, for dysmenorrhea, genitourinary infections, kidney stone, metrorrhagia, hemorrhage, as a menstrual regulator, and contraceptive (Santos et al., 2012; Pedrollo et al., 2016). In an Amazonian community in the river Urini, local women use the barks to prepare a powerful contraceptive agent (Rodrigues, 2006; Santos et al., 2012; Oliveira et al., 2015).

Associated with barks from *Aspidosperma* species, the barks from *E. uchi* are prepared as an infusion and consumed orally to treat liver diseases, inflammation, and fever (Frausin et al., 2015). This important species is also used to treat animals, for instance, the barks are used topically as a wound healing agent, and grounded seeds mixed to water or food are used to treat diarrhea (Ritter et al., 2012).



**Figure 1.** Number of publications including the terms *Endopleura uchi*, *Endopleura uchi* Huber Cuatrec, *Sacoglottis uchi*, and uxi per database.

## Phytochemical composition

### Barks

Main classes of molecules found in *E. uchi* barks are tannins, coumarins, and saponins (Freitas et al., 2018). Silva and Teixeira (2015) prepared an infusion and a hydroethanolic extract using trunk barks of *E. uchi*. Through high-performance liquid chromatography (HPLC) coupled to diode-array detection (DAD) were detected phenolic compounds, mainly bergenin (Figure 2; compound 1) and its derivatives.

Bergenin is a C-glycoside derived from gallic acid. This compound is formed by three aromatic rings and has two analogs: norbergenin and acetylbergenin (Rastogi and Rawat, 2008). Among bergenin's known biological activities are a hepatoprotective and antioxidant activity (Rastogi and Rawat, 2008), It effectively prevents oxidative stress and crystal deposition in the kidneys, thus preventing urolithiasis (Aggarwal, 2016), and has analgesic and anti-inflammatory activity (Oliveira, 2011).

In a study performed by Abreu et al. (2013), they were identified through nuclear magnetic resonance (RMN) spectroscopy in the ethanol extract from *E. uchi* barks: pentacyclic triterpenes such as 3-oxo-friedelin (compound 2), pseudotaraxasterol (compound 3), lupeol (compound 4),  $\alpha$ -amirin (compound 5), botulin (compound 6), and methyl 2 $\beta$ ,3 $\beta$ -dihydroxy-urs-12-en-28-oate (compound 7); steroids such as sitosterol (compound 8) and stigmasterol (compound 9) were identified as well.

Using plant specimen from Manaus (Brazil), a methanol extract from *E. uchi* barks was obtained, and bergenin was isolated from it through liquid-liquid extraction

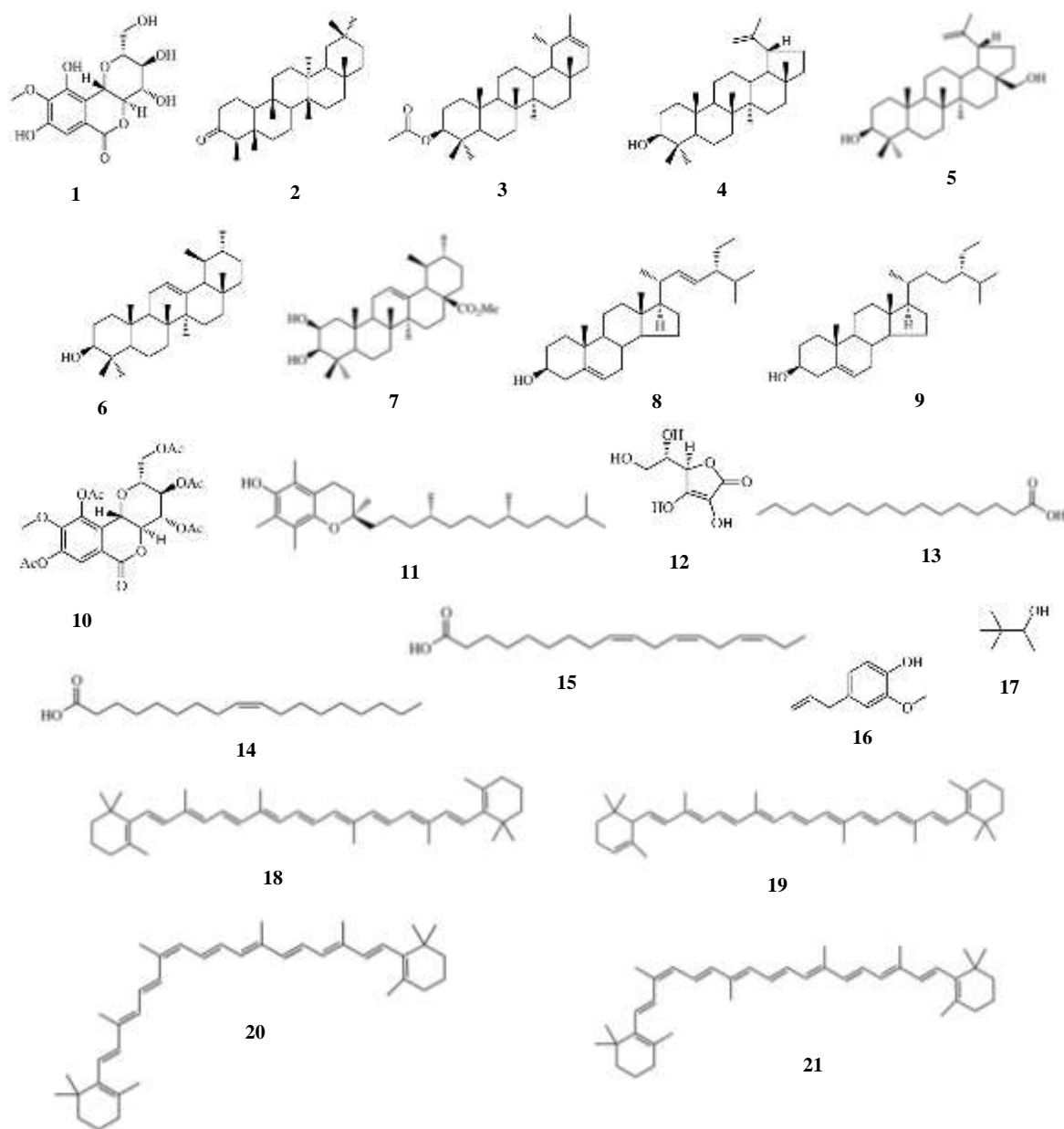
followed by liquid chromatography, then, identified through RMN spectroscopy (Nunomura et al., 2009). Bergenin was also identified through HPLC in the aqueous extract from barks at 3.19% (De Abreu et al., 2008), indicating this molecule as the potential responsible for this species' biological activity when using barks infusion. Bergenin was also isolated from the whole extract using ethyl acetate (da Silva et al., 2009).

Through dynamic maceration under controlled period of extraction, temperature, and solvent concentration (ethanol), Tacon and Freitas (2013) improved the extraction of polyphenols between 31.89 and 47.82%, and bergenin in 35.58% compared to the extract weight and in 4% compared to barks weigh (Tacon and Freitas, 2013).

Acetylbergenin (compound 10) is a bergenin derivative. Borges et al. (2011) obtained this molecule using bergenin (previously isolated from *E. uchi* barks) through acetic anhydride-induced acetylation in the presence of pyridine, yielding 99%.

### Fruits

In fruit, the pulp has the highest content of phytosterols, dietary fibers, mineral salts, vitamin E (compound 11, Figure 2), and vitamin C (compound 12) (Marx et al., 2002; Costa et al., 2010). Moreover, using a spectrophotometric method, Neves et al. (2015) detected a low content of phenolic compounds in pulp and peel; this study showed how the maturity stage influenced the fruits composition and biological activities. Regarding its physical-chemical properties, the pulp has between 43 and 94% of moisture content, while the peel has 43 and



**Figure 2.** Molecules found in *Endopleura uchi*.

87% and seeds have 28 and 69%. The fruit is rich in lipids, carbohydrates and has some protein content. Moreover, it is a source of essential minerals such as magnesium, zinc, iron, sodium, manganese, and copper (Berto et al., 2015). Minerals are crucial for human nutrition, and insufficient intake of them may result in illnesses; this is because of their role in biochemical reactions of our physiology, mainly as enzymes co-factors (Food Ingredients Brasil, 2008).

In the fruit's peel and pulp, there are saturated fatty

acids such as palmitic acid (compound 13, 3.78%), and unsaturated fatty acids such as oleic acid (compound 14, 7.38%). In seeds, there is a higher content of  $\alpha$ -linolenic acid (compound 15) (Marx et al., 2002; Berto et al., 2015).

The oleic acid (compound 14) is monounsaturated (C18:1 cis 9) fatty acid with a long chain of 18 carbons, and its double bond improves its conformational stability (Moreira et al., 2002). This important fatty acid has several nutraceutical benefits, for instance, preventing

cardiovascular diseases antioxidant (Nocella et al., 2018) prevents inflammatory responses, specifically the cellular inflammatory response (Soto-Alarcon et al., 2017).

Using gas chromatography coupled to mass spectroscopy (GC-MS), Marx et al. (2002) analyzed the chemical composition of the fruit's oil and found a total of 42 compounds, predominantly 3,3-dimethyl-2-butanol (compound 16, 18.8%) and eugenol (compound 17, 14.0%).

According to Bianchini et al. (2017), eugenol presents muscle relaxing activity in mollusks of the species *Pomacea canaliculata*. This effect may have important applications for pest control in agriculture.

Other molecules found in the fruit of *E. uchi* were bergenin (an isocoumarin) and  $\beta$ -carotene (compound 18);  $\alpha$ -carotene (compound 19) was found in trace quantities. Regarding  $\beta$ -carotene, its isomers were detected in the following proportion: trans- $\beta$ -carotene at 89.3%, 13-cis- $\beta$ -carotene (compound 20) at 8%, and 9-cis- $\beta$ -carotene (compound 21) at 3% (Magalhães et al., 2007).

The fruit from *E. uchi* can be considered a functional food considering the nutritional importance of carotenoids and other molecules found in its composition. Functional foods are a source of metabolites with nutritional values, such as isoflavones, tannins, fatty acids, vitamins, minerals, proteins, and can provide a carbohydrate-rich diet. Overall, functional foods can improve cardiovascular system health, the immune system and cellular metabolism (Embrapa, 2012).

## Biological activities

### Barks

According to de Oliveira et al. (2017), the tea from *E. uchi* barks is traditionally used to treat diabetes, arthritis, rheumatism and to control cholesterol levels. Hence, these authors tested the activity of different extracts over the inhibition of pancreatic lipase. At 1 mg/mL the acetonic extract inhibited 49.3% of this enzyme activity, and the ethanol extract inhibited 36.8%, while at 2 mg/mL the aqueous extract inhibited 47.5%. Also, the authors reported significant antioxidant activity on the extracts, which were strongly correlated with the total phenolic content.

Also *in vitro*, some relevant biological activities were reported using products from *E. uchi* barks, for instance, the hydroethanolic extract was reported to inhibit the enzyme acetylcholinesterase ( $IC_{25} = 200$  mg/mL) and butylcholinesterase ( $IC_{25} = 309$  mg/mL). Also, the infusion from barks was reported to have bacteriostatic and bactericidal activity against Gram-negative bacteria, mainly *Pseudomonas aeruginosa*, while the hydroethanolic extract was more effective against Gram-

positive bacteria such as *Bacillus cereus*, *Micrococcus luteus*, and *Staphylococcus aureus*. Moreover, a potential antidiabetic activity was evidenced through a dose-dependent  $\alpha$ -glycosidase inhibition by the hydroethanolic extract ( $IC_{50} = 2.2$  mg/mL), and infusion ( $IC_{50} = 2.4$  mg/mL) (Silva and Teixeira, 2015).

The enzyme acetylcholinesterase hydrolyzes acetylcholine, an essential neurotransmitter in cholinergic synapses. Drugs able to inhibit acetylcholinesterase have an essential value in the pharmaceutical market since they can be used to treat diseases conditions such as urinary retention, intestinal atonia, and atonic constipation (if it acts in the peripheral nervous system), and dementia associated with Alzheimer and Parkinson diseases (if it acts in the central nervous system). In this way, to evaluate the potential that compounds present either to inhibit or to reactivate this enzyme, is of great importance for the development of new drugs.

Da Silva et al. (2009) reported a remarkable antimicrobial activity of bergenin, the major compound from *E. uchi* barks, against yeasts, namely *Candida albicans*, *Candida tropicalis*, and *Candida guilliermondii*, with MIC values of 14.9, 14.9, and 29.8  $\mu$ M, respectively. Also, bergenin had moderate inhibitory activity against filamentous fungi such as *Aspergillus flavus*, *Candida niger*, and *Candida nidulans*, with MIC values between 476.1 and 1,093  $\mu$ M. These results can explain the effectiveness of the treatment using *E. uchi* barks' infusion against vaginal infections, such as candidiasis, but other compounds can be involved in this activity besides bergenin.

Antioxidant activity from the barks' extracts was evaluated through 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, both the infusion and the hydroethanolic extract had this activity in a dose-dependent manner; the infusion had a higher effect ( $IC_{50} = 27$  mg/mL) than the hydroethanolic extract ( $IC_{50} = 33$  mg/mL). However, in nitric oxide and superoxide radicals scavenging, the hydroethanolic extract was more effective ( $IC_{50} = 12$  mg/mL) than infusion ( $IC_{50} = 33$  mg/mL) (Silva and Teixeira, 2015).

Politi et al. (2011), using barks from *E. uchi* collected in São Paulo (Brazil), reported that its concentration of tannins ranged from 9.65 to 32.85% depending on the extraction method, decoction, infusion, maceration, percolation, and turbo-extraction. The aqueous solutions from these extracts (5 to 20% w/v) had antioxidant activities values in DPPH assay ranging from 79 to 90%; despite being statistically lower, these values were close of those from control compounds such as gallic acid (97%), rutin (96.83%), and vitamin C (98.14%) at 250  $\mu$ g/mL (in methanol).

Moreover, using an ethanol extract from barks through dynamic maceration, Tacon and Freitas (2013) reported a significant antioxidant activity in the DPPH assay ( $IC_{50}$  values from 4.02 to 5.87  $\mu$ g/mL). The authors attributed

this antioxidant activity to the high content of polyphenols and bergenin from the extract. In accordance with this, De Abreu et al. (2008) showed that bergenin had a significant antioxidant activity at 1 mg/mL in DPPH and methylene blue antioxidant assays.

Another relevant property of bergenin reported is a potential anti-inflammatory activity evidenced by selective inhibition of COX-2 ( $IC_{50} = 1.2 \mu\text{mol}\cdot\text{L}^{-1}$ ). This selectiveness for COX-2 results in fewer collateral effects in the gastrointestinal tract when compared with non-selective COX inhibitors (Nunomura et al., 2009). According to Borges et al. (2017), acetylbergenin has a higher anti-inflammatory activity than bergenin, these authors reported that oral treatment with this molecule at 6.8 mg/kg inhibited 75.6% of croton oil-induced ear edema in rats, inhibited carrageenan-induced paw edema in 35% and dextran-induced paw-edema edema in 33% without stress-induced ulcerogenic activity. The treatment also inhibited 70% of leukocytes migration to the peritoneal cavity. Borges et al. (2011) also reported analgesic activity by acetylbergenin in the writhing test in mice without changes in the hot plate test, suggesting a peripheral analgesic activity.

Shedding light into bergenin's anti-inflammatory mechanism of action, Gao et al. (2015) showed that bergenin decreased LPS-induced mastitis in mice. The treatment downregulated the phosphorylation of nuclear factor  $\kappa\text{B}$  (NF- $\kappa\text{B}$ ) and mitogen-activated protein kinases (MAPK), resulting in decreased infiltration of inflammatory cells, decreased levels of nitric oxide (NO), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and of the pro-inflammatory cytokines IL-1 $\beta$  and IL-6.

Natural compounds with anti-inflammatory activity add value to herbal products containing them, making these products commercially attractive. The use of natural products with useful pharmacological activities has attracted attention in Brazil, where was created the National List of Medicinal Plants of Interest to the Health Unic System (RENISUS) in 2009, evidencing the importance of medicinal plants in therapeutics (Marmitt, 2015). Concerning the plant safety assessments, cytotoxic assays using bark extracts in fibroblast cells showed no toxicity, with 100% of cell survival and  $IC_{50}$  higher than 0.2 mg/mL (Politi et al., 2011). However, the type-II arabinogalactan, isolated from *E. uchi* bark had a cytotoxic effect on HeLa cells, reducing cell viability in 20% over 48 and 72 h in all concentrations tested (5 to 500  $\mu\text{g}/\text{mL}$ ); at 100  $\mu\text{g}/\text{mL}$ , this molecule inhibited HeLa cells proliferation in 25% (Bento et al., 2014).

Sá (2015), tested the subchronic toxicity from the *E. uchi* barks' hydroethanolic extract; for this, the author evaluated biochemical and hematological parameters in Wistar rats. The rats were treated orally over 22 consecutive days with the extract at 500 mg/kg, and then, their biochemical and hematological profile were analyzed. The treatment did not induce any death or

toxicity, such as ponderal growth, and water and food intake. The biochemical and hematological parameter were not affected either, except for the hematimetric values of MCHC in male rats of the treated group, yet, this had no clinical relevance since the values were still within the reference range of the species.

According to Freitas et al. (2018), bergenin has a low water solubility resulting in impaired bioavailability after treatment. The authors suggested a spouted bed system to work around this issue by using bergenin in  $\beta$ -cyclodextrin complexes with lyophilized cooker rice as a solid substrate. This system could greatly improve bergenin solubility with low loss of the bioactive. However, biological activities reports with this system are still lacking and would be of significant value.

### Fruit

The fruit of *E. uchi* collected in the states of Pará, Manaus, and Roraima (Brazil), has a low level of phenolic compounds, but high antioxidant activity (Neves et al., 2012). Corroborating the results from De Souza et al. (2010), who also reported significant antioxidant activity in the DPPH assay, 20%. Also, the extract had significant inhibition of  $\alpha$ -glucosidase, with  $IC_{50} = 0.5 \text{ mg}/\text{mL}$ .

Neves et al. (2015) also showed that the antioxidant activity from the fruit's pulp and peel assessed through DPPH and ORAC methods decreased from fruit collection until 12 days of stocking, and vitamin C content decreased as well.

### CONCLUSION FUTURE PERSPECTIVES

The empirical use of *E. uchi* for therapeutic purposes is widespread among traditional communities, attracting the attention of researchers aiming to learn more about this important Amazonian species that has molecules with useful biological activities, mainly in its barks and fruits. Current studies indicate that *E. uchi* fruit is a functional food, anti-oxidants rich, and in its oil is found eugenol, a molecule with useful applications (e.g., muscle relaxant and analgesic).

Some of the folk medicinal uses of *E. uchi* have empirical support; for instance, among biological activities reported are anti-inflammatory, analgesic, antibacterial, fungicide, anti-diabetic, antioxidant, among others. However, until now, more *in vivo* assays are still lacking for some of the properties reported (e.g., anti-diabetic activity), and future researches with this species should be performed using living models to corroborate the available data from *in vitro* assays. The majority of the studies attribute the biological activity to bergenin, and some were performed with the isolated molecule, although other compounds may be involved as well.

Some frequent reported traditional uses of *E. uchi* that could have useful pharmacological applications still lack experimental research, such as its effect to induce birth during labor, contraceptive activity, and galactogenic activity. Finally, more toxicity studies are needed to ensure their safety. Regarding the pharmacological activities reported, more researches are needed to elucidate their mechanism of action.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

## ACKNOWLEDGEMENT

The authors thank CAPES Pró-Amazonia Proc. Auxpe - 3292/2013 and CNPq – RAPBioFar Proc. 407768/2013-0 for the financial support.

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