PHYTOCHEMICAL STUDIES AND PHARMACOLOGICAL POTENTIAL OF *ENDOPLEURA UCHI* AND ITS ISOLATED CONSTITUENTS

Gutemberg Lopes Soares[1]; Matheus Kleber de Jesus Souza[2]; Grasiely Faria de Sousa[3]; Clarice de Carvalho Veloso Moura[4]

[1]Mestre em Ciências Farmacêuticas pela Universidade Federal do Amazonas, Manaus-AM
[2]Graduando em Farmácia pela Universidade Federal do Amazonas, Manaus-AM
[3]Professora Adjunto do Departamento de Química, Instituto de Ciências Exatas pela Universidade Federal de Minas Gerais, Belo Horizonte-MG
[4]Professora Adjunto da Faculdade de Ciências Farmacêuticas pela Universidade Federal do Amazonas, Manaus-AM. E-mail: claricecv@gmail.com

Recebido em: 15/11/2021 – Aprovado em: 15/12/2021 – Publicado em: 30/12/2021
DOI: 10.18677/EnciBio_2021D41

ABSTRACT

The search for new drugs derived from natural products is an important field of research that brings us into various bioactive compounds. Because of the survival process, many biological compounds are produced by medicinal plants, which are used to prepare teas or infusions, for example, and may produce beneficial effects for those who see in this folk knowledge a way to cure and prevent health problems. Among such important medicinal species is the *Endopleura uchi* used for the treatment of inflammatory diseases. Throughout the years, some works have been concluded to characterize the chemical profile and the biological activities of *E. uchi* extracts, demonstrating how promising this plant may be for discovering new medicines. This review paper aims to gather important information on *E. uchi* concerning its isolated chemical compounds and the biological activities so far, besides providing some basic reflection, which may be useful to expand the discoveries related to this species' future research.
KEYWORDS: Amazon; Ethnopharmacology; Phytochemical studies; Biological assays.

ESTUDOS FITOQUÍMICOS E POTENCIAL FARMACOLÓGICO DA ENDOPLEURA UCHI E COMPOSTOS ISOLADOS

RESUMO

A busca por novos medicamentos derivados de produtos naturais é um importante campo de pesquisa que nos leva a uma variedade de compostos bioativos. Deviso ao processo de sobrevivência, muitos compostos biológicos são produzidos por plantas medicinais, que são utilizadas no preparo de chás ou infusões, por exemplo, e podem produzir efeitos benéficos para quem vê nesse saber popular uma forma de curar e prevenir problemas de saúde. Dentre essas importantes espécies medicinais, está a Endopleura uchi, utilizada no tratamento de doenças inflamatórias. Ao longo dos anos, alguns trabalhos foram concluídos para caracterizar o perfil químico e as atividades biológicas dos extratos de E. uchi, demonstrando o quão promissora esta planta pode ser para a descoberta de novos medicamentos. O objetivo desde artigo de revisão é reunir informações importantes de E. uchi sobre seus compostos

químicos isolados e as atividades biológicas até o momento, além de fornecer algumas reflexões básicas, que podem ser úteis para expandir as descobertas relacionadas às pesquisas futuras desta espécie.
PALAVRAS-CHAVE: Amazon; Etnofarmacologia; Estudos fitoquímicos; Ensaios biológicos.

INTRODUCTION

Medicinal plants have always been used in the history of humankind for the combat and relief of diseases. In many places, the use of plants in teas consolidates as a complementary therapeutic alternative to medicines produced by the pharmaceutical industry (SILVA; TEXEIRA, 2015).

Natural products isolated from plants and other living beings play a significant role in searching for new drugs (NEWMAN; CRAGG, 2016). These compounds contain functional groups and fit stereochemistry to interact with enzymes and other biological targets (LI; VEDERAS, 2009). Such interactions may result in pharmacological effects of interest. Microorganisms, plants, sea organisms, terrestrial vertebrates, invertebrates, and other natural products sources have been used in researches to obtain bioactive compounds (NEWMAN *et al*., 2000). Most of the drugs present in commercial medicines were derived or inspired by nature. According to Newman and Cragg (2016), from 1981 to 2014, Food and Drug Administration (FDA) and other regulatory agencies approved 1562 new medicines. Among these, 25% presented drugs based on natural products and obtained from total synthesis, 26% had unchanged natural products or minor structural modifications, 22% were vaccines and peptides, and 27% contained fully synthetic drugs. Therefore, in the analyzed period, 73% of approved medicines were related to natural products.

Catharanthus roseus (L) G. Don is an example of a plant that led to the obtainment of drugs used in the current therapeutics. The species, known as “vinca”, is popularly used for diabetes treatment. After confirming the activity of *C. roseus* in leukemia and lymphoma models, the alkaloids vinblastine and vincristine, which are anti-cancer agents used to treat Hodkin’s lymphoma, Kopsi’s sarcoma, and other conditions, have been isolated (BRANDÃO *et al.,* 2010). These drugs present complex structures and are obtained from the *C. roseus* leaves extraction for medicine production (PALEM *et al*., 2016).

Other examples of drugs obtained from plants are morphine, opioid painkiller isolated from poppy (*Papaver somniferum*); escin, a saponin with anti-inflammatory activity isolated from horse-chestnut (*Aesculus hippocastanum*); digoxin, a cardiotonic glycoside extracted from *Digitalis sp*; artemisinin, an antimalarial drug from *Artemisia annua*; and the alkaloids atropine and scopolamine, which are anticholinergic drugs obtained from *Atropa belladonna* (MARTINEZ *et al*., 2009).

Endemic plants may be sources of phytochemical products, offering a range of biological activities. In the tropical climate, these species produce many secondary metabolites with the objective of protection against unfavorable factors such as temperature variation, degradation by ultraviolet rays, and presence of herbivores (SILVA; TEXEIRA, 2015). Concomitantly, Brazil has a great biodiversity of medicinal plants, and many of them have not been studied yet (TACON; FREITAS, 2013). The sustainable study of Amazon is a great opportunity and represents a challenge to Brazil that surely will result in more scientific knowledge. The Amazonian biodiversity comprises species with many chemical compounds potentially relevant for research, contributing to new biological activities (NUNOMURA *et al.,* 2009).

Endopleura uchi is a plant native to Amazon used in folk medicine to treat various types of diseases, for example, arthritis, cholesterol, diabetes, inflammation, intestinal diseases, and cancer (POLITI *et al.,* 2010; BORGES *et al.,* 2011; BENTO *et al*., 2014).

The species, known as “uxi-amarelo”, “uxi-liso”, “uchi”, “cumatê”, “pururu”, “uxi-ordinário” or “uchi-pucu”, has few chemical studies and those already made are focused in its fruit, much appreciated by the local population (NUNOMURA *et al.*, 2009; SILVA *et al.*, 2009; POLITI *et al.*, 2010).

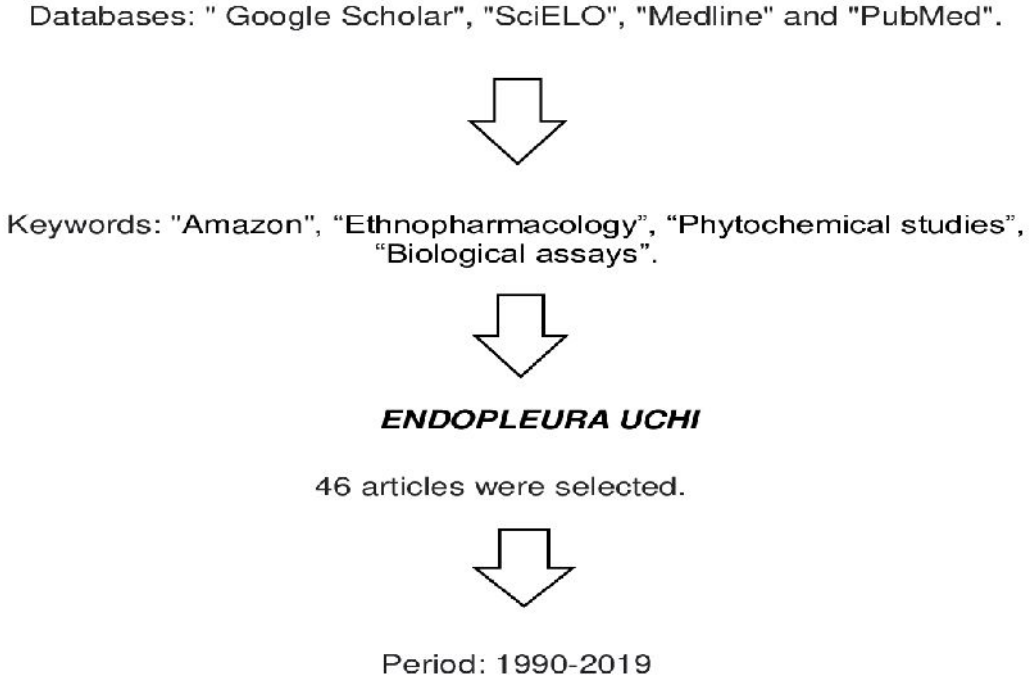
The present review article aims to provide reliable information about *Endopleura uchi* in relation to the studies carried out concerning its phytochemical prospection, isolated and identified compounds, besides its pharmacological activities.

MATERIAL AND METHODS

Data survey

The aim of this study was to carry out a literature review on the chosen topic (FIGURE 1). The bibliographic research methodology was adopted and conducted using as databases available for institutional access “Google Scholar”, “SciELO”, Medline” and “Pubmed”, using the following keywords as descriptors: “Amazon”, “Ethnopharmacology”, “Phytochemical studies”, “Biological assays”, using the Boolean operators “AND” and “OR”, from which 46 articles published in the period 1990 to 2019 were selected. The inclusion criteria were papers in Portuguese, Spanish and English, and their respective abstracts were available. The choice of articles was performed by reading the abstracts in order to confirm the proposed theme with participation of all authors. Information was collected related to the main phytochemical compounds that were isolated and characterized in the identified species, in addition to the biological and pharmacological studies carried out for the species under study. The exclusion criteria were studies that did not refer to at least one of the research themes, with articles from 1990 to 2019.

FIGURE 1- Flowchart of the methodology adopted in preparing the literature review.



The genus *Endopleura* is formed by nine species mostly found in the American continent as large trees and small scrubs on tropical and neotropical places. The species that occur only in Africa refers to *Sacoglottis gabonensis*" (ABREU *et al.*, 2013).

Also known by its synonymy "*Sacoglottis uchi*", *Endopleura uchi* belongs to the Humiriaceae family and is native to Amazon. This species is present mainly in Amazonas and Pará states and all over the Amazonian Basin in the firm land woods. Its flowers grow at the end of the rainy season, in June and July, while its fruits mature between December and June (MARX *et al.*, 2002; ABREU *et al.*, 2013). Its fruit weighs from 50 to 70 grams, has 3 to 4 centimeters in diameter, and presents a yellowish-green or dark brown color (MAGALHÃES *et al.*, 2007). The fruit pulp is very nutritious, being consumed pure or with manioc flour, and is also used to manufacture liqueurs and ice cream. As the forest animals consume fruits, hunters use them as bait in traps (MAGALHÃES *et al.*, 2007).

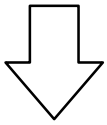
The name "Endopleura" has Greek origin and is formed by "Endon", which means within, and "Pleuron", which means rib. The word has to do with the fruit structure, whose seeds are stored in the endocarp in compartments similar to ribs (BADHANI, 2015).

Although there are few studies concerning the composition and bioactive compounds of *Endopleura uchi*, the "uchi" barks are sold in fairs, markets, and magistral pharmacies to treat arthritis, cholesterol, diabetes, inflammation, and intestinal diseases. The plant is also used to combat myoma, and its barks are used in tea for tumors, uterine inflammations, and female disorders (POLITI *et al.*, 2010; BORGES *et al.*, 2011; BENTO *et al*., 2014). The barks are the main part of *Endopleura uchi* sold into bottles infusions to treat inflammatory disorders, but also the roots are used in these products (KASHIWADA *et al.*, 1990).

FIGURE 2 - Uses of Endopleura uchi in folk medicine.

Endopleura uchi

"uchi"



Arthritis;
Cholesterol;
Diabetes;
Inflammation;
Intestinal diseases;
Myoma;
Tumors;
Uterine inflammations;
Inflammatory disorders.

FIGURE 3 - Fruit of the *Endopleura uchi* collected in April 2017 in the municipality of Novo Ayrão/AM, Brazil.

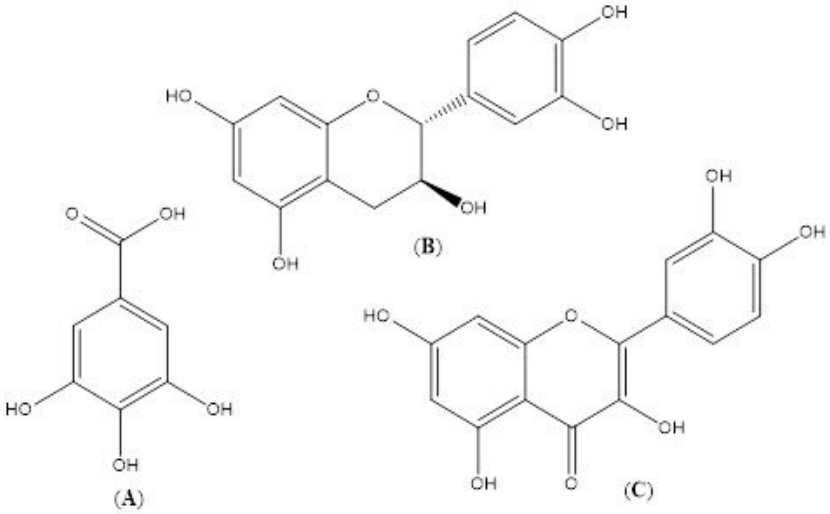
SOURCE: THE AUTHORS

PHYTOCHEMICAL PROSPECTION AND ISOLATED COMPOUNDS FROM *E. UCHI*

Saponins, coumarins, and tannins are the secondary metabolites found in the *E. uchi* barks. The tannins were approached in a comparative study in which these compounds were quantified in extracts obtained from decoction, maceration, infusion, percolation, and turbo extraction. In the study, the percolation method was the most effective, with total tannins content of 32,85% (± 1,62) in the 10% extract (w/v) (CHANG *et al*., 2000).

Among phenolic compounds, gallic acid (**FIGURE 4A**) (BADHANI, 2015), catechin (**FIGURE 4B**) (KASHIWADA *et al*., 1990), quercetin (**FIGURE 4C**) (CHANG *et al*., 2000) are present in *Endopleura uchi*.

FIGURE 4. Some phenolic compounds found in *Endopleura uchi*: Gallic acid (**A**) (BADHANI, 2015), catechin (**B**) (KASHIWADA *et al*., 1990), and quercetin (**C**) (CHANG *et al*., 2000).



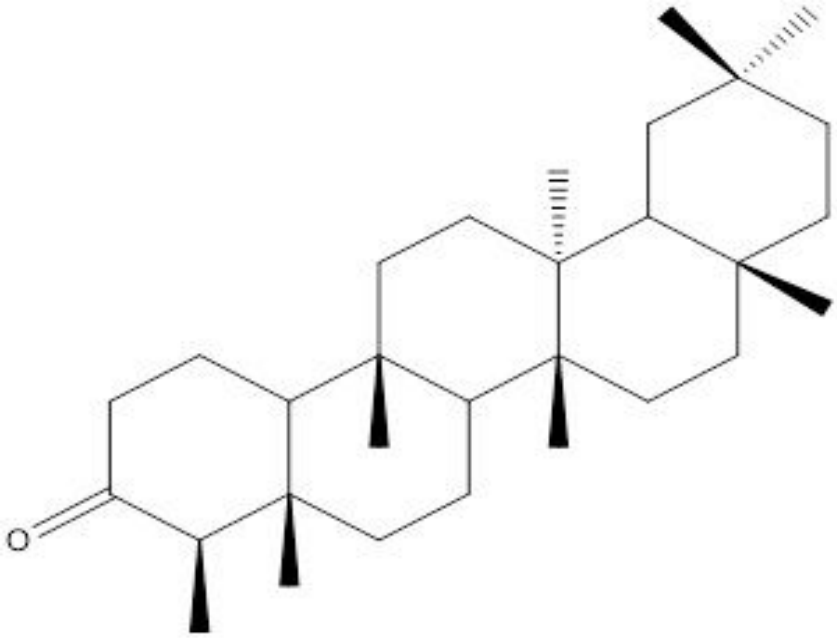
The “uxi” pulp is very fatty. It is mainly composed of fatty acids such as oleic acid and palmitic acid, besides carotenoids, phytosterols, tocopherols, vitamin C, and vitamin E (MAGALHÃES *et al.*, 2007). Costa *et al*. (2010) identified and quantified phytosterols and tocopherols in pulps of *E. uchi*. Among the found phytosterols, brassicasterol, campesterol, stigmasterol, *β*-sistosterol, and sitostanol were present; *α*-tocopherol and *y*-tocopherol were also detected among the analyzed tocopherols.

Magalhães *et al*. (2007) identified carotenoids in “uxi” pulp, being *β*-carotene more abundant than *α*-carotene, and concluded that the fruit is a vitamin A source.

Abreu *et al*. (2013) isolated the pentacyclic triterpenes *3*-oxo-friedelin, pseudotaraxasterol, lupeol, *α*-amyrin, betulin, and methyl *2β,3β*-dihydroxy-urs-*12*-en-*28*-oate from “uxi” barks. Furthermore, a mixture of the steroids sitosterol and stigmasterol were identified by nuclear magnetic resonance (NMR) technique in the same raw material.

Friedelin (**FIGURE 5**), a triterpene identified in the stem bark of *Endopleura uchi* is also isolated from other species such as *Vismia laurentii* and *Maytenus salicifolia* (ABREU *et al.,* 2013). This compound is interesting since it has cytotoxicity activity against human tumor cells and leishmanicidal and antiulcerogenic activities (MOSSI *et al.*, 2004; TORRES-SANTOS *et al.*, 2004; ABREU *et al.*, 2013).

FIGURE 5. Chemical structure of friedelin (ABREU *et al.,* 2013).



The other compounds isolated by Abreu *et al*. (2013) from “uxi” barks, such as pseudotaraxasterol, lupeol, *α*-amyrin, and botulin, show antimicrobial, anti-inflammatory, antitumor, anti-arthritic, insecticide, and antiviral activities. In other words, the biological activities coming from the *Endopleura uchi* extracts may be attributed to these compounds, among others.

Secondary metabolites are present in aqueous extracts of medicinal plants, and most of them are alkaloids and polyphenols. On the other hand, primary metabolites are represented by polysaccharides. Among them, arabinogalactans stand out because they have pharmacological properties such as antitumor, antiviral, immunomodulatory, antiulcer, anti-inflammatory, hypoglycemic, and anticoagulant activities (MONOBE *et al.*, 2008; BAGGIO *et al.*, 2012; THAKUR *et al.*, 2012).

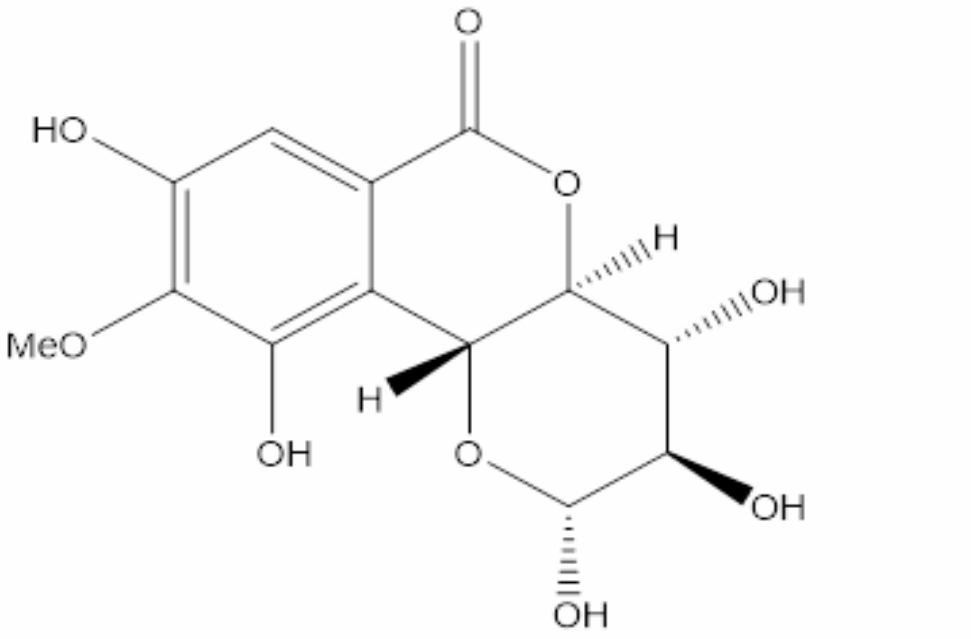
Bento *et al*. (2014) accomplished a work in which they isolated a type II arabinogalactan from the decoction of *E. uchi* barks and evaluated the antiproliferative effect of this polysaccharide against cancer cells. Besides “uchi” arabinogalactans have already been isolated from flowers, roots, seeds, and fruits of other species like *Larix occidentalis*, *Panax ginseng,* and *Coffea arabica* (BENTO *et al*., 2014).

Bergenin, a *C*-glycoside derived from the gallic acid *4-O*-methyl, was isolated from fruits and barks of *E. uchi* and it is considered to be the major constituent from the cortex of “uxi”. Anti-inflammatory, antioxidant, anti-hepatotoxic, antifungal, anti-arthritic, antidiarrheal, antiulcerogenic, antitussive, and hypolipidemic activities were related to the bergenin (BORGES *et al.*, 2011; ABREU *et al.*, 2013, BORGES *et al.*, 2017). The range of biological activities associated with bergenin is related to its chemical structure, which consists of five hydroxyl groups and are considered to be potentially active (AMBIKA; SARAVANAN, 2016).

Borges *et al*. (2011) isolated bergenin (**FIGURE 6**) from “uxi” barks and, after an acetylation reaction in order to increase its lipophilicity and physiological activity, they obtained acetylbergenin, which was assessed for its possible antinociceptive activity (BORGES *et al.*, 2011).

In **PICTURE 1** were presented main components present in the species *Endopleura uchi*.

FIGURE 6. Chemical structure of bergenin (BORGES *et al.,* 2011).



PICTURE 1: Main components present in the species *Endopleura uchi*.

COMPONENTS	PAPERS
Gallic acid	BADHANI (2015)
Type II arabinogalactan	Bento *et al*. (2014)
3-oxo-friedelin, pseudotaraxasterol, lupeol, *α*-amyrin, betulin, methyl *2β,3β*-dihydroxy-urs-*12*-en-*28*-oate and a mixture of the steroids sitosterol and stigmasterol, friedelin, lupeol, *α*-amyrin, and botulin	ABREU *et al*. (2013)
Bergenin	Borges *et al*. (2011)
Brassicasterol, campesterol, stigmasterol, *β*-sistosterol, sitostanol, *α*-tocopherol and *γ*-tocopherol	COSTA *et al*. (2010)
Oleic acid, palmitic acid, carotenoids, phytosterols, tocopherols, vitamin C, vitamin E, *β*-carotene, *α*-carotene, vitamin A	MAGALHÃES *et al.* (2007)
Quercetin	CHANG *et al*. (2000)
Catechin	KASHIWADA *et al*. (1990)

SOURCE: THE AUTHORS

PHARMACOLOGICAL ACTIVITIES OF *ENDOPLEURA UCHI*

Bergenin, isolated from the *E. uchi* barks, was evaluated for antimicrobial activity. In that work, all tested gram-positive and gram-negative bacteria were resistant to the bergenin action. However, yeasts and filamentous fungi were sensible (SILVA *et al.*, 2009). Bergenin isolated from *Flueggea microcarpa* also exhibited antifungal activity against all the fungi tested (PRITHIVIRAJ *et al.,* 1997). Nunomura *et al*. (2009) related the anti-inflammatory activity of bergenin isolated from the “uxi” barks with the compound’s meaningful ability to inhibit cyclooxygenase selectively (COX)-2 when compared to the positive control niflumic acid.

The antinociceptive activity of acetylbergenin was pointed out by Borges *et al*. (2011). This compound was obtained by the structural modification of bergenin isolated from the barks of *E. uchi*. In the study, the acetylbergenin administration decreased abdominal writhing induced by acid acetic in mice and reduced the licking time in the late phase in the formalin test. Once this compound did not show any effect on the hot plate test, it indicates that the antinociceptive effect of acetylbergenin acts only on peripheral tissues, interfering with the release of prostaglandins through the COX inhibition.

Politi *et al*. (2011) performed assays to verify the antioxidant ability of extracts obtained from “uxi” barks. As a result, the extracts prepared using distilled water or ethanol-water mixture presented similar antioxidant activity, but they were less

effective when compared to gallic acid, rutin, ascorbic acid, and *Ginkgo biloba* extract.

Branco *et al*. (2018) verified that after a period of oral treatment using the *Endopleura uchi* tea, rats submitted to a hyperlipidemic diet had a significant reduction in body mass gain and reduction in macro and microvesicular hepatic steatosis, besides the reduction in the inflammatory infiltrate and the total cholesterol levels.

Silva and Teixeira (2015) demonstrated the *α*-glicosidase inhibition activity of "uxi" barks. The hydroethanolic extract and infusion showed an IC_{50} value of 2,2 µg/mL and 2,4 µg/mL, respectively, superior to the acarbose positive control, which presented IC_{50} of 284 µg/mL.

Politi *et al*. (2011) also reported the absence of cytotoxicity of "uxi" barks tea. The prepared extracts did not show the effects of cytotoxicity on fibroblasts cells, which means that the tea can be safely consumed.

A previous study demonstrated the antiproliferative activity of type II arabinogalactan isolated from *E. uchi* barks against human cervical cancer cells. In that study, the effect was not dose-dependent, and there was not induced death mechanism in the neoplastic cells, allowing to infer that the mechanism in which this compound act does not involve the cellular cycle but possibly immunomodulation (OOI; LIU, 2000; BENTO *et al*., 2014). Other biological activities have already been attributed to this chemical structure, such as dehydrogenase stimulation, healing activity through fibroblasts stimulation, and gastroprotective activity (BENTO *et al*., 2014; SEYFRIED *et al*., 2016).

As shown in **PICTURE 2**, many other biological activities have been reported for the isolated compounds found in Endopleura *uchi*, especially bergenin, which stands out for the great range of pharmacological effects.

PICTURE 2: Isolated compounds isolated from "uxi" and their reported biological activities.

Isolated compounds	Part of *Endopleura uchi*	Biological activities	References
Friedelin	Stem barks	Cytotoxicity, antiulcerogenic,	Abreu *et al*. (2013), Torres-Santos *et al*. (2004), Antonisamy *et al*. (2015), Subash-Babu *et al*. (2017)
Pseudotaraxasterol	Stem barks	Antimicrobial	Abreu *et al*. (2013), Xie *et al*. (2005).
Lupeol	Stem barks	antimicrobial	Abreu *et al*. (2013), Siddique and Saleem (2011)
Betulin	Stem barks	Antiviral, antitumor	Abreu *et al*. (2013), Pavlova *et al*. (2003), Zhao *et al*. (2018)
α-amyrin	Stem barks	Anti-inflammatory	Abreu *et al*. (2013), Okoye *et*

			al. (2014)
Bergenin	Barks	Antioxidant, anti-inflammatory, anti-anxiety, neuroprotective, antimalarial, antidiabetic, antiulcerogenic, antitumor, antiarrhythmic, anti-hepatotoxic, antiviral, antifungal, antitussive, antiplasmodial	Abreu *et al*. (2013), Oliveira *et al*. (2017), Ren *et al*. (2016), Singh *et al*. (2017), Barai *et al*. (2019), Liang *et al*. (2014), Bajracharya (2015)

SOURCE: THE AUTHORS

FINAL CONSIDERATIONS

Endopleura uchi shows itself as an Amazonian species with great chemical and pharmacological potential, considering the research results obtained over the years. Concerning biological effects, is possible mention antimicrobial, antiproliferative, antioxidante, hypolipidemic, among others. In this aspect, the anti-inflammatory activity attributed to bergenin, a chemical constituent of the barks and pul of the fruit, stants out. Bergenin presented a great anti-inflammatory action specific for COX-2, an important pro-inflammatory enzyme. In addition, other substances already isolated from the species showed promising results. Therefore, new biological activities associated with Endopleura uchi may be discovered due to different compounds present in this species.

REFERENCES

ABREU V.G.C.; CORRÊA G.M.; LAGOS I.A.S.; SILVA R.R.; ALCÂNTARA A.F.C. Pentacyclic triterpenes and steroids from the stem bark of uchi (*Sacoglottis uchi*, Humiriaceae). **Acta Amazonica**, v. 43, p. 525-8, 2013. Disponível em: <https://doi.org/10.1590/S0044-59672013000400015>.

AMBIKA S.; SARAVANAN R. Antihyperglycemic and antihyperlipidemic effect of bergenin on C57BL/6J mice with high fat-diet induced type 2 diabetes. **Journal of Pharmacy Research**, v. 10, p. 126-32, 2016.

ANTONISAMY P.; DURAIPANDIYAN V.; ARAVINTHAN A.; AL-DHABI N.A.; IGNACIMUTHU S. *et al.* Protective effects of friedelin isolated from *Azima tetracantha* Lam. against ethanol-induced gastric ulcer in rats and possible underlying mechanisms. **European Journal of Pharmacology**, v. 750, p. 167-75, 2015. doi: 10.1016/j.ejphar.2015.01.015

BADHANI B.; SHARMA N.; KAKKAR R. Gallic acid: a versatile antioxidant with promising therapeutic and industrial applications. **RSC Advances**, v. 5, p. 27540-57, 2015. Disponível em: <https://doi.org/10.1039/C5RA01911G>.

BAGGIO C.H.; FREITAS C.S.; TWARDOWSCHY A.; DOS SANTOSA A.C.; MAYER B. *et al*. In vivo/ in vitro studies of the Effects of the Type II Arabinogalactan Isolated from *Maytenus ilicifolia* Mart. ex Reissek on the Gastrointestinal Tract of Rats. **Zeitschrift fur Naturforschung. C, Journal of Biosciences**, v. 67, p. 405-10, 2012. doi: 10.1515/znc-2012-7-808.

BAJRACHARYA G.B. Diversity, pharmacology and synthesis of bergenin and its derivatives: potential materials for therapeutic usages. **Fitoterapia**, v. 101, p. 133-52, 2015. doi: 10.1016/j.fitote.2015.01.001.

BARAI P.; RAVAL N.; ACHARYA S.; BORISA A.; BHATT H. *et al*. Neuroprotective effects of bergenin in Alzheimer's disease: Investigation through molecular docking, in vitro and in vivo studies. **Behavioural Brain Research**, v. 356, p. 18-40, 2019. doi: 10.1016/j.bbr.2018.08.010.

BENTO J.F.; NOLETO G.R.; OLIVEIRA PETKOWICZ C.L. Isolation of an arabinogalactan from *Endopleura uchi* bark decoction and its effect on HeLa cells. **Carbohydrate Polymers**, v. 101, p. 871-7, 2014. doi: 10.1016/j.carbpol.2013.10.014.

BORGES J.C.M.; RIPARDO FILHO H.S.; GUILHON G.M.S.P.; CARVALHO C.J.T.; SANTOS L.S. *et al*. Antinociceptive Activity of Acetylbergenin in Mice. **Latin American Journal of Pharmacy**, v. 30, p. 1303-8, 2011.

BORGES J.C.M.; AGUIAR R.W.S.; SOUZA J.F.; FILHO H.S.R.; GUILHOM G.S.P. *et al*. Anti-inflammatory and non ulcerogenic activities of acetylbergenin. **African Journal of Pharmacy and Pharmacology**, v. 11, p. 402-10, 2017. Disponível em: <https://doi.org/10.5897/AJPP2017.4819>.

BRANCO N.V.C.; HALAGIA H.F.; LUNA F.M.S.; FREITAS D.M.O.; FONSECA F.C.F. *et al*. Efeito do chá de uxi (*Endopleura uchi*) na esteatose hepática. **Revista da Sociedade Brasileira de Clínica Médica**, v.16, p. 25-9, 2018. Disponível em: < https://docs.bvsalud.org/biblioref/2018/06/884989/dezesseis_vinte_cinco.pdf>.

BRANDÃO H.N.; DAVID J.P.; COUTO R.D.; NASCIMENTO J.A.P.; DAVID J.M. Química e farmacologia de quimioterápicos antineoplásicos derivados de plantas. **Química Nova**, v. 33, p. 1359-69, 2010. Disponível em: <https://doi.org/10.1590/S0100-40422010000600026>.

CHANG Y.C.; CHANG F.R.; WU Y.C. The constituents of *Lindera glauca*. **Journal of the Chinese Chemical Society**, v. 47, p. 373-80, 2000. Disponível em: <https://doi.org/10.1002/jccs.200000050>.

COSTA P.A.; BALLUS C.A.; TEIXEIRA-FILHO J.; GODOY H.T. Phytosterols and tocopherols content of pulps and nuts of Brazilian fruits. **Food Research International**, v. 43, p. 1603-6, 2010. Disponível em: <https://doi.org/10.1016/j.foodres.2010.04.025>

KASHIWADA Y.; IIZUKA H.; YOSHIOKA K.; CHEN R.F.; NONAKA G. *et al*. Tannins and related compounds. XCIII.: Occurrence of enantiomeric proanthocyanidins in the Leguminosae plants, *Cassia fistula* L. and *C. javanica* L. **Chemical and Pharmaceutical Bulletin**, v. 38, p. 888-93, 1990.

LI J.W.; VEDERAS J.C. Drug Discovery and Natural Products: End of an Era or an Endless Frontier. **Science**, v. 325, p. 161-5, 2009. doi: 10.1126/science.1168243

LIANG J.; LI Y.; LIU X.; HUANG Y.; SHEN Y. *et al*. In vivo and in vitro antimalarial activity of bergenin. **Biomedical Reports**, v. 2, p. 260-4, 2014. Disponível em: <https://doi.org/10.3892/br.2013.207>.

MAGALHÃES L.A.M.; LIMA M.P.; MARINHO H.A.; FERREIRA A.G. Identificação de bergenina e carotenoides no fruto de uchi (*Endopleura uchi*, Humiriaceae). **Acta Amazonica**., v. 37, p. 447-50, 2007. Disponível em: <https://doi.org/10.1590/S0044-59672007000300016>.

MARTINEZ S.T.; ALMEIDA M.R.; PINTO A.C. Alucinógenos naturais: um voo da Europa Medieval ao Brasil. **Química Nova**, v. 32, p. 2501-7, 2009.

MARX F.; ANDRADE E.H.A.; ZOGHBI M.G.B.; MAIA J.G.S. Studies of edible Amazonian plants. Part 5: Chemical characterization of Amazonian *Endopleura uchi* fruits. **European Food Research Technology**, v. 214, p. 331-4, 2002.

MONOBE M.; EMA K.; KATO F.; MAEDA-YAMAMOTO M. Immunostimulating activity of a crude polysaccharide derived from green tea (*Camellia sinensis*) extract. **Journal of Agricutural Food Chemistry**, v. 56, p. 1423-7, 2008. doi: 10.1021/jf073127h.

MOSSI A.J.; CANSIAN R.L.; CARVALHO A.Z.; DARIVA C.; OLIVEIRA J.V. *et al*. Extraction and characterization of volatile compounds in *Maytenus ilicifolia*, using high-pressure CO_2. **Fitoterapia**, v. 75, p. 168-78, 2004. doi: 10.1016/j.fitote.2003.12.006.

NEWMAN D.J.; CRAGG G.M.; SNADER K.M. The influence of natural products upon drug discovery. **Natural Product Reports**, v. 17, p. 215-34, 2000. doi: 10.1039/a902202c.

NEWMAN D.J.; CRAGG G.M. Natural Products as Sources of New Drugs from 1981 to 2014. **Journal of Natural Products**., v. 79, p. 629-61, 2016. Disponível em: <https://doi.org/10.1021/acs.jnatprod.5b01055>.

NUNOMURA R.C.S.; OLIVEIRA V.G.; DA SILVA S.L.; NUNOMURA S.M. Characterization of bergenin in *Endopleura uchi* bark and its anti-inflammatory activity. **Journal of the Brazilian Chemical Society**, v. 20, p. 1060-4, 2009. Disponível em: <https://doi.org/10.1590/S0103-50532009000600009>.

OKOYE N.N.; AJAGHAKU D.L.; OKEKE H.N.; ILODIGWE E.E.; NWORU C.S. *et al*. beta-Amyrin and alpha-amyrin acetate isolated from the stem bark of *Alstonia boonei*

display profound anti-inflammatory activity. **Pharmaceutical Biology**., v. 52, p. 1478-86, 2014. doi: 10.3109/13880209.2014.898078.

OLIVEIRA G.A.L.; OLIVEIRA G.L.S.; NICOLAU L.A.D.; MAFUD A.C.; BATISTA L.F. *et al*. Bergenin from *Peltophorum dubium*: Isolation, Characterization, and Antioxidant Activities in Non-Biological Systems and Erythrocytes. **Medicinal Chemistry**, v. 13, p. 592-603, 2017. doi: 10.2174/1573406413666170306120152

OOI V.E.; LIU F. Immunomodulation and anti-cancer activity of polysaccharide-protein complexes. **Current Medicinal Chemistry**, v. 7, p. 715-29, 2000. doi: 10.2174/0929867003374705.

PALEM P.P.; KURIAKOSE G.C.; JAYABASKARAN C. An Endophytic Fungus, *Talaromyces radicus*, Isolated from *Catharanthus roseus*, Produces Vincristine and Vinblastine, Which Induce Apoptotic Cell Death. **PLoS One**, v. 11(4), p. e0153111, 2016. Disponível em: <https://doi.org/10.1371/journal.pone.0144476>.

PAVLOVA N.I.; SAVINOVA O.V.; NIKOLAEVA S.N.; BOREKO E.I.; FLEKHTER O.B. Antiviral activity of betulin, betulinic and betulonic acids against some enveloped and non-enveloped viruses. **Fitoterapia**, v. 74, p. 489-92, 2003. doi: 10.1016/s0367-326x(03)00123-0.

POLITI F.A.; MELLO J.C.; MIGLIATO K.F.; NEPOMUCENO A.L.; MOREIRA R.R. *et al*. Antimicrobial, Cytotoxic and Antioxidant Activities and Determination of the Total Tannin Content of Bark Extracts *Endopleura uchi*. **International Journal of Molecular Sciences**, v. 12, p. 2757-68, 2011. doi: 10.3390/ijms12042757.

POLITI F.A.S.; SALGADO H.R.N.; MOREIRA R.R.D.; PIETRO R.C.L.R. Preliminary tests on acute oral toxicity and intestinal motility with extract of pulverized bark of *Endopleura uchi* (Huber) Cuatrec. (Humiriaceae) in mice. **Revista Pan-Amazônica de Saúde,** v. 1, p. 187-9, 2010. Disponível em: <http://dx.doi.org/10.5123/S2176-62232010000100026>.

PRITHIVIRAJ B.; SINGH U.P.; MANICKAM M.; SRIVASTAVA J.S.; RAY A.B. Antifungal activity of bergenin, a constituent of *Flueggea microcarpa*. **Plant Pathology,** v. 46, p. 224-8, 1997.

REN X.; MA S.; WANG J.; TIAN S.; FU X. *et al*. Comparative effects of dexamethasone and bergenin on chronic bronchitis and their anti-inflammatory mechanisms based on NMR metabolomics. **Molecular Biosystems**, v. 12, p. 1938-47, 2016. doi: 10.1039/c6mb00041j.

SEYFRIED M.; SOLDERA-SILVA A.; BOVO F.; STEVAN-HANCKE F.R.; MAURER J.B.B. *et al*. Pectins of medicinal plants: structural characteristics and immunomodulatory activities. **Revista Brasileira de Plantas Medicinais**, v. 18, p. 201-14, 2016. doi: 10.1590/1983-084x/15_078

SIDDIQUE H.R.; SALEEM M. Beneficial health effects of lupeol triterpene: a review of preclinical studies. **Life Sciences**, v. 88, p. 285-93, 2011. doi: 10.1016/j.lfs.2010.11.020.

SILVA L.R.; TEXEIRA R. Phenolic profile and biological potential of *Endopleura uchi* extracts. **Asian Pacific Journal of Tropical Medicine**, v. 8, p. 889-97, 2015. doi: 10.1016/j.apjtm.2015.10.013

SILVA S.L.; OLIVEIRA V.G.; YANO T.; NUNOMURA R.C.S. Antimicrobial activity of bergenin from *Endopleura uchi* (Huber) Cuatrec. **Acta Amazonica**, v. 39, p. 187- 91, 2009. Disponível em: <https://doi.org/10.1590/S0044-59672009000100019>.

SINGH J.; KUMAR A.; SHARMA A. Anti-anxiety activity guided isolation and characterization of bergenin from *Caesalpinia digyna* Rottler roots. **Journal of Ethnopharmacology**, v. 195, p. 182-7, 2017. doi: 10.1016/j.jep.2016.11.016.

SUBASH-BABU P.; LI D.K.; ALSHATWI A.A. In vitro cytotoxic potential of friedelin in human MCF-7 breast cancer cell: Regulate early expression of Cdkn2a and pRb1, neutralize mdm2-p53 amalgamation and functional stabilization of p53. **Experimental and Toxicology Pathology**, v. 69, p. 630-6, 2017. doi: 10.1016/j.etp.2017.05.011.

TACON L.A.; FREITAS L.A.P. Box-Behnken design to study the bergenin content and antioxidant activity of *Endopleura uchi* bark extracts obtained by dynamic maceration. **Brazilian Journal of Pharmacognosy**, v. 23, p. 65-71, 2013. Disponível em: <https://doi.org/10.1590/S0102-695X2012005000134>.

THAKUR M.; WENG A.; FUCHS H.; SHARMA V.; BHARGAVA C.S. *et al.* Rasayana properties of Ayurvedic herbs: are polysaccharides a major contributor. **Carbohydrate Polymers**, v. 87, p. 3-15, 2012. Disponível em: <https://doi.org/10.1016/j.carbpol.2011.08.035>.

TORRES-SANTOS E.C.; LOPES D.; OLIVEIRA R.R.; CARAUTA J.P.P.; FALCAO C.A.B. *et al*. Antileishmanial activity of isolated triterpenoids from *Pourouma guianensis*. **Phytomedicine**, v. 11, p. 114-20, 2004. doi: 10.1078/0944-7113-00381.

XIE W.D.; ZHANG Q.; LI P.L.; JIA Z.J. Two triterpenoids and other constituents from *Petasites tricholobus*. **Phytochemistry**, v. 66, p. 2340-45, 2005. doi: 10.1016/j.phytochem.2005.03.032.

ZHAO J.; LI R.; PAWLAK A.; HENKLEWSKA M.; SYSAK A., *et al*. Antitumor Activity of Betulinic Acid and Betulin in Canine Cancer Cell Lines. **In Vivo**, v. 32, p. 1081-8, 2018. doi: 10.21873/invivo.11349.