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BIOMEDICAL SCIENCES

Biological Activities of Species of the Genus *Clusia* L (Clusiaceae): A General Approach

MÁRCIA PIETROLUONGO, MARIA CAROLINA ANHOLETI, ANDRÉ L. FULY, ALESSANDRA L. VALVERDE & SELMA R. DE PAIVA

Abstract: The genus *Clusia* L. is highly diverse in Central and South America, comprising about 300 species, including trees and shrubs, hemiepiphytes, epiphytes, and lianas. This genus deserves attention due to its wide range of biological activities. *Clusia* belongs to the Clusiaceae family, chemically characterized by the presence of xanthones, benzophenones, flavonoids, coumarins, terpenoids, and other substances with bioactive activity already described. This review aims to highlight the biological activity associated to extracts and isolated substances from species of the *Clusia* genus, including anti-HIV, antimicrobial, antioxidant, antinociceptive, antitumor, leishmanicidal, modulator of inflammatory processes, neutralization of toxic effects caused by snake bites, and others. This review gathered information on biological activities associated with different types of extracts and isolated substances of the genus *Clusia*, traditional use, chemical profile, and biological properties of plants of the genus, published in the last 23 years (1998 to 2021) and that can provide support for future research. The paper aims to provide an overview of existing knowledge about the biological properties of the genus *Clusia* plant species.

Key words: Biological activity, *Clusia* sp., Clusiaceae, extraction, isolation, natural products.

INTRODUCTION

Among plants with therapeutic contribution, a considerable number are known through popular wisdom, but knowledge about the chemical and bioactive constitution is limited. The Clusiaceae Lindl. family (= Guttiferae Juss.) fall into this context and comprises approximately 14 genera and 800 species of wide geographical distribution, with significant occurrence in the tropics (Anholeti et al. 2017). The family is chemically characterized by the presence of xanthones, benzophenones, flavonoids, coumarins, terpenoids, steroids, among other substances of importance in the plant's biology and in studies of potential biological activity (Sacramento et al. 2007, Wu et al. 2014, Alves et al. 1999, 2000).

Arawakia L. Marinho, *Chrysochlamys* Poepp., *Clusia* L., *Garcinia* L., *Lorostemon* Ducke, *Mammea* L., *Moronobea* Aubl., *Platonia* Mart., *Symphonia* L.f., *Tovomita* Aubl., *Tovomitopsis* Planch. & Triana, *Dystovomita* (Engl.) D'Arcycom are the genera that occur in regions of Brazil with phylogenetic domains in the Amazon, Caatinga, Cerrado, and Atlantic Forest (Gasparotto Júnior et al. 2005).

The genus *Clusia* is highly diversified in Central and South America comprising about 300-400 species including trees and shrubs, hemiepiphytes, epiphytes, and lianas (Oliveira et al. 1999). *Clusia* species have entire, coriaceous and succulent leaves and the fruits are capsules,

with five or five to ten persistent stigmas, each corresponding to a store in which the seeds are located. The seeds are oval, with a smooth surface of yellowish or vinaceous color, always coated by an orange membranous aryl. Despite the uniformity observed in the leaves, in other aspects, there is a great diversity among the species of this genus, as well as huge metabolic plasticity (Winter et al. 2008).

These plants are resistant to water scarcity and highly adaptable to adverse conditions. Succulent leaves, latex production, and the ability to change photosynthetic metabolism provide the genus the advantages needed to remain all over the planet (Oliveira et al. 1999, Luttge 2006, Winter et al. 2008). *Clusia* is the only genus of tree eudicotyledons capable of performing crassulacean acid metabolism (CAM). Most species of this genus can change their C3 metabolism (the photosynthetic mechanism that involves an intermediate formed by three carbons) to CAM under water restriction conditions, while others are constitutive CAM species (Winter et al. 2008, 2009).

The vast majority of *Clusia* species are dioecious. The production of resins in the stamens and/or pistils of their flowers acts as a reward for female bees who, when seeking for material the construction of their nests, perform pollination (Porto et al. 2000). Research involving the chemical composition of *Clusia* floral resins revealed that they are mainly composed of polyisoprenylated benzophenones and fatty acids. Some species can also produce staminal oils to reduce the viscosity of floral resins so that their composition can vary considerably among the species that make up the genus. (Oliveira et al. 1999, Porto et al. 2000, Luttge 2006, Winter et al. 2008, 2009, Anholeti et al. 2015b).

The literature data revealed that *Clusia* species have several biological activities, including anti-HIV, antimicrobial, antioxidant, antinociceptive, antitumor, leishmanicidal, modulating activity of inflammatory processes, and neutralization of toxic effects caused by venomous snake bites. Furthermore, several species of the genus have been used in traditional medicine. Among the species we can highlight: *Clusia amazonica*, *C. coclensis*, *C. grandifolia*, *C. insignis*, *C. lineata*, *C. opaca*, *C. palmicida*, *C. planchoniana* and *C. purpurea*. A summary of their traditional usage is presented in Table I

Natural products' chemical diversity and biological properties have been the target of studies for many years. Advances in bioassay techniques, phytochemical studies, and high-performance analytical methods increased the possibilities of discovering new natural compounds with therapeutic potential, boosting studies in this sense (Valli et al. 2018). Despite the growing interest in the classes of substances present in the genus *Clusia*, there is a lack of review articles gathering aspects related to the biological activity of these compounds. Therefore, this review aims to highlight the biological activity of extracts and substances isolated from species of the genus.

MATERIALS AND METHODS

This is a study with data collection carried out from secondary data through a bibliographic survey, search and database analysis. The search used the keywords defined for the object of study and the period ranged from January 1992 to September 2021. This review used the keywords in different scientific literature databases: National Library of Medicine / NLM (PubMed), Science Direct, Web of Science, Scopus, and Scientific Electronic Library Online (SciELO). The keywords were: Biological activity; Extraction; Isolation; Natural products; *Clusia* L., Clusiaceae. The following pairs were used to

Table I. Some species of *Clusia* used in folk medicine.

***Clusia* species**	**Local name**	**Country**	**Plant Organ**	**Traditional use**	**Ref.**
C. flava	-	México	Leaves	Carminative, headaches, wounds and to treat syphilis	Barrios et al. 1991
C. salvinii	Orelha de coyote	México	-	Treat gonorrhea and kidney pain	Yasunaka et al. 2005
C. coclensis	Azahar de monte; copey, and copeicillo	Costa Rica	Leaves	Treat hypertension	Gárcia-González et al. 1998
C. insignis	-	Colombia	Floral resins	Relief from toothache	Langenhein 2003
	Apuí; cebola-brava, and guapoí	Brazil	Resin	Treat constipation and healing of fissures in the breasts	
	Mê miomio kangô	Brazil	-	Treat infant oral candidiasis	
C. lineata	Came	Peru	Barks and stems	Treat rheumatism	Fenner et al. 2006
C. opaca	-	Colombia	Resiniferous barks	Mixed with the oil from the palm tree *Oenocarpus bataua* to treat twists and sore joints	Sanz-Biset et al. 2009, Fenner et al. 2006
		Brazil	Resin	Applied on wounds to accelerate healing	
C. palmicida	Came	Peru	Barks	Treat rheumatism, inguinal hernia, and broken bones	Fenner et al. 2006
C. planchoniana	-	Colombia	Resin	Treat toothaches	Sanz-Biset et al. 2009
C. purpurea	Cebola-brava	Brazil	Inner bark	Antiseptic and wound scarrant	Fenner et al. 2006
Clusia sp.	Came	Peru	Barks	Macerated in rum with *Calliandra angustifolia*, *Monteverdia macrocarpa (=Maytenus macrocarpa)*, *Tovomita foldatsii* and *Tovomita stylosa* used as a tonic	Sanz-Biset et al. 2009
Clusia sp.	Came	Peru	Barks and stems	Treat rheumatism	Sanz-Biset et al. 2009

refine the search: *Clusia* L. AND Biological activity. As an exclusion criterion, all articles that did not address the study's subject and were not written in Portuguese, English, or Spanish were removed from the search. Subsequently, the eligibility of the studies identified in the search was assessed by reading the titles and abstracts. All those that addressed the biological activity of the genus *Clusia* were read in full. The analysis of scientific publications focused on searching for experimental or observational articles that describe studies with the recognized biological activity of the genus *Clusia*.

RESULTS

After reading the 243 abstracts, 97 articles were selected, which were read in full and dealt with *Clusia* L. and biological activity. Of these, 73 articles were selected and discussed. The articles were analyzed, presented, and their descriptive data discussed. The analysis of

scientific publications was carried out with a focus on seeking articles with an experimental or observational design that described studies with the recognized biological activity of the genus *Clusia*.

The Table II describes the biological activities of extracts and substances (Figure 1) isolated from species of the genus *Clusia* (Clusiaceae).

Anti-HIV activity

Acquired Immunodeficiency Syndrome (AIDS), an infectious disease caused by the Human Immunodeficiency Virus (HIV) that drastically reduces the number of CD4 T cells, is still a worldwide concern. Although the replication cycle of HIV is well known and antiretroviral drugs are available, efforts to develop new pharmaceutical alternatives, which started a long time ago, continue to be conducted, and plant sources have aroused the interest of researchers (Salehi et al. 2018, Reutrakul et al. 2007, Márquez et al. 2005, Rukachaisirikul et al. 2003, Spino et al. 1998). The species of *Clusia* have been described as a promising matrix of bioactive substances for this purpose.

In 1992, studies conducted by Gustafson and collaborators, tracking HIV activity in extracts of plant species, found a series of compounds with potential activity, and phytochemical studies led to the isolation of a series of new polyisoprenylated benzophenone derivatives called guttiferones with the ability to inhibit the cytopathic effects of HIV infection *in vitro*. The study describes that the organic extract ($CHCl_2$:MeOH, 1:1) of leaves of *Clusia rosea*, collected in the Dominican Republic, is mainly composed of guttiferone E and xantochymol. The active compounds inhibited the cytopathic effects of HIV infection *in vitro* in lymphoblastoid CEM-SS cells, with an EC_{50} value of 1-10 µg/mL. In comparison, cytotoxicity occurred at higher concentrations of 50 µg/mL. However, it did not inhibit the activity of the reverse transcriptase enzyme (RT) involved in the AIDS infection mechanism.

Huerta-Reyes et al. 2004 tested organic extracts of leaves in dichloromethane and methanol ($CHCl_2$:MeOH, 1:1, 50 mg/mL) of 10 species of the *Clusia* genus, abundant in Mexico, to verify the ability to inhibit the reverse transcriptase enzyme (RT) involved in HIV-1 infection, through immuno-radioactive and colorimetric assay. Leaves extracts of *Clusia guatemalensis* and *C. massoniana* showed 70.8% and 72.9% of inhibition, respectively, which was considered a high percentage of inhibition (≥ 70%). The species *C. quadrangula* (leaves extract) presented inhibition of 65.6%, considered as moderately active. However, when submitted to the inhibition test of replication of HIV-1 IIIb / LAV, the *C. quadrangula* extracts exhibited less than 52% inhibition.

Piccinelli et al. 2005 described potential HIV activity in *C. torresii*, an endemic species in Costa Rica. The study was conducted with polyisoprenylated benzophenone isolated from the hexanic extract of the fruits, and the results corroborate Huerta-Reyes' studies presenting promising anti-HIV results. Nemorosone and 7-epi-Clusianone showed moderately potent anti-HIV activity with EC_{50} 0.80 and 2.0 µM, respectively. A study of the mechanism of action showed that the benzophenone derivatives, Clusianone and 7-epi-Clusianone, inhibited gp120-s CD4 interaction suggesting interference at the onset of HIV infection and potential preventive activity with neutralization of infectivity by more than 99% when incubated with the virus at 0.05 and 10 µM, respectively, for 60 minutes at 37 ºC, suggesting Clusianone and 7-epi-Clusianone as promising candidates for other studies of HIV infection (Piccinelli et al. 2005, Huerta-Reyes et al. 2004).

Table II. Biological activities described for extracts and substances isolated from species of the genus *Clusia* (Clusiaceae).

Species	Extracts/ substances	Plant organ (solvent)	Biological activities	Dose	IC_{50}	MIC / MBC	Ref.
C. coclensis	Extract	Leaves (H_2O)	Hypotensive effect on normotensive and hypertensive rats	40 mg/Kg	ND	ND	Gárcia-González et al. 1998, Gárcia-González et al. 1996
C. columnaris	Extract	Stems (CH_3OH:CH_2Cl_2)	Antimicrobial activity against *Enterococcus faecalis* (EF) and *Pseudomonas aeruginosa* (PA)	ND	ND	EF: MIC = 180 µg/mL; MBC = 270 µg/mL PA: MIC = 140 µg/mL; MBC > 200 µg/mL	Suffredini et al. 2006, Bittar et al.2000
	I3, II8-Binaringerin (**1**)	Leaves (CH_3OH)	Antinociceptive effect in mice	ND	IC_{50} (writhing test)= 22µmol/kg IC_{50} (formalin test) = 28µmol/kg	ND	
C. grandiflora	Resins	Staminate flowers	Antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans* in bioautography assay	ND	ND	ND	Porto et al. 2000, Lokvam et al. 2000, Diaz-Carballo et al. 2012
	Resins	Pistillate flowers	Antimicrobial activity against *S. aureus* and *B. subtilis*, in bioautography assay	ND	ND	ND	
	Nemorosone II (**2**)	Trunk latex ($(C_2H_5)_2O$	Antimicrobial activity against *Paenibacillus larvae* and *P. alvei* in bioautography assay	ND	ND	ND	
	Chamone I (**3**)	Pistillate flower ($(C_2H_5)_2O$					
	7-*epi*-nemorosone (**4**)	Floral resins ($(C_2H_5)_2O$	Anticancer activity in prostate carcinoma	ND	IC_{50} (LNCaP WT) = 4.12±0.19µM IC_{50} (LNCaP ETO MDR1+) = 4.81±0.68µM IC_{50} (PC-3 WT) = 5.01±0.07µM IC_{50} (PC-3 ETO MDR1+) = 5.1±0.1µM IC_{50} (DU-145) = 7.3±0.07µM IC_{50} (DU-145 MDR1+) = 6.8±0.45µM	ND	
C. guatemalensis	Extract	Leaves (CH_3OH:CH_2Cl_2)	Inhibition of HIV-1 virus reverse transcriptase	50 µg/mL	IC_{50} (HIV-1 RT) = 42 µg/ml IC_{50} (HIV-1 IIIb/LAV) = 124.1 µg/ml	ND	Huerta-Reyes et al. 2004
C. massoniana				50 µg/mL	ND		
C. quadrangula				50 µg/mL	ND		
C. hilariana	Extract	Staminate flowers (CH_3OH)	Antifeedant effect on *Rhodnius prolixus* larvae, and promotion of ecdise delay.	100µg/mL	ND	ND	Kelecom et al. 2002
	Oleanolic acid (**5**)		Toxicity on *R. prolixus* larvae, and promotion of ecdise delay.	1, 10 e 100µg/mL			
	Nemorosone (**6**)		Promotion of ecdise delay on *R. prolixus* larvae	10µg/mL			

Table II. Continuation.

Species	Extracts/ substances	Plant organ (solvent)	Biological activities	Dose	IC_{50}	MIC / MBC	Ref.
C. insignis	Resins	Staminate flowers	Antimicrobial activity against *S. aureus* and *B. subtilis* in bioautography assay	ND	ND	ND	Porto et al. 2000
C. lanceolata	Resins	Staminate flowers	Antimicrobial activity against *S. aureus*, *B. subtilis* and *C. albicans* in bioautography assay	ND	ND	ND	Porto et al. 2000
	Extract	Non-galled and galled leaves (CH_3OH)	Antioxidant activity in β-carotene/ linoleic acid assay	57 µg/mL	ND	ND	Ferreira et al. 2014
C. nemorosa	Resins	Hermaphrodite flowers	Antimicrobial activity against *S. aureus* and *B. subtilis* in bioautography assay	ND	ND	ND	Porto et al. 2000
	Extract	Leaves (C_6H_{14})	Anti-inflammatory and antinociceptive effects on male Swiss mice	62 mg/kg	IC_{50} (writhing test) = 62mg/kg	ND	Ferro et al. 2013
			Inhibition of protein exudation, leukocyte influx and TNFα levels on pleurisy induced by carrageenan on male Swiss mice	100 and 200 mg/kg	ND	ND	Farias et al. 2012
	Betulinic acid (**7**)	Roots (H_2O)	Decrease of body weights, abdominal fat accumulation, blood glucose, plasma triglycerides, and total cholesterol on male Swiss mice	50 mg/L	ND	ND	Melo et al. 2009
C. palmana	Extract	Leaves and flower buds (CH_3CH_2OH:H_2O); Leaves and fruits ($CH_3CO_2C_2H_5$ fraction)	Neutralization of the hemorrhagic effect induced by *Bothrops asper* venom in rats	1:50 (poison / extract ratio)	ND	ND	Castro et al. 1999
C. paralicola	Clusiparalicoline A (**8**)	Roots (CH_3CH_2OH)	Scission-promoting activity on DNA strands; cytotoxicity in KB cells; growth promotion of neuritas in fetal cortical neurons of rats.	neurite outgrowth promoting activity at 1.0 M	ND	ND	Seo et al. 1999, Takaoka et al. 2002
	Clusiparalicoline B (**9**)		Scission-promoting activity on DNA strands; cytotoxicity in the KB cells			ND	
	Clusiparalicoline C (**10**)		cytotoxicity in the KB cells			ND	
	Extract	Unripe fruits (CH_3CH_2OH)	Antioxidant activity	ND	EC_{50}(DPPH) = 12.7±0.1; EC_{50}(ABTS) = 7.4±0.4;	ND	Oliveira et al. 2012
C. renggerioides	Resins	Staminate flowers	Antimicrobial activity against *S. aureus* and *B. subtilis* in bioautography assay	ND	ND	ND	Porto et al. 2000
C. rosea	Guttiferone E (**11**) and xanthochymol (**12**)	Leaves (CH_2Cl_2:CH_3OH)	Inhibition of the cytopathic effects of HIV virus in human lymphoblastoid cells	ND	1-10 µg/mL	ND	Gustafson et al. 1992

Table II. Continuation.

Species	Extracts/ substances	Plant organ (solvent)	Biological activities	Dose	IC_{50}	MIC / MBC	Ref.
C. rosea	Nemorosone (**6**)	Floral resin (CH_3CH_2OH)	Cytotoxicity against human cancer cell lines	ND	IC_{50}(HELA): 3.3±0.17μM; 1.6±0.08μg/mL IC_{50}(HeP-2): 3.1±0.17μM; 1.5±0.08μg/mL IC_{50}(PC-3): 7.2±1.3μM; 3.6±0.65μg/mL IC_{50}(U251): 3.9±1.4μM; 1.9±0.70μg/mL IC_{50} (neuroblastoma cells): 3.10±0.15 - 6.3±0.21μM IC_{50} (MCF-7): 0.03 - 0.1μM	ND	Cuesta-Rubio et al. 2002, Díaz-Carballo et al. 2008, Popolo et al. 2011
	7-*epi*-nemorosone (**4**)	Resins of pistillate flowers	Antiestrogenic activity	10, 20 and 40 μg/well	ND	ND	Camargo et al. 2013
C. spiritu-sanctensis	Nemorosone (**6**)	Resins of staminate flowers	Antimicrobial activity against *S. aureus* and *B. subtilis* in bioautography assay	ND	ND	ND	Porto et al. 2000
C. torresii	Extracts	Leaves and flowers (CH_3CH_2OH:H_2O) Leaves and fruits ($CH_3CO_2C_2H_5$ fraction)	Neutralization of the hemorrhagic effect induced by *B. asper* venom in rats	1:50 (poison / extract ratio)	ND	ND	Castro et al. 1999
	Clusianone (**13**)	Fruits (C_6H_{14})	Inhibition of HIV-1 virus infection in lymphoblastoid T cells (C8166)	ND	IC_{50} = 0.020±0.003 μM	ND	Piccinelli et al. 2005
	7-*epi*-clusianone (**14**)			ND	IC_{50} = 2.0±0.07 μM	ND	
C. weddelliana	Resins	Staminate flowers	Antimicrobial activity against *S. aureus* and *B. subtilis* in bioautography assay	ND	ND	ND	Porto et al. 2000
C. fluminensis	Extract	Stems; Leaves; Fruits (H_2O)	Antiophidic				Da Silva et al. 2019
	Zeaxanthin (**15**)	Fruits (not described)	Antioxidant and macular degeneration protector.				Mazza et al. 2019
	Extract	Staminate flowers (C_6H_{14}) Fruits (C_6H_{14})	Significant reduction of the survival of the insect *Oncopeltus fasciatus*	1.0 mg/ mL (1.0μg/ insect)	ND	ND	Duprat et al. 2017
	Clusianone (**13**)	Floral extract (C_6H_{14})	Reduction on the survival of the insect *Dysdercus peruvianus*	0.7 mg/ mL (0.7μg/ insect)			
	Lanosterol (**16**)	Fruit extract (C_6H_{14})	Significant reduction on both survival and development of the insects *O. fasciatus* and *D. peruvianus*				

Table II. Continuation.

Species	Extracts/ substances	Plant organ (solvent)	Biological activities	Dose	IC_{50}	MIC / MBC	Ref.
C. fluminensis	Extract	Leaves (C_6H_{14}; CH_3OH)	Inhibitory effect of on proteolysis caused by *B. jararaca* venom	venom / extract ratio: 1:5; 1:10; 1:20; and 1:50	$IC_{50(hexane)}$: 567µg/mL $IC_{50(methanol)}$: 447µg/mL	ND	Oliveira et al. 2014
		Stems (CH_3OH) ($(CH_3)_2CO$)			$IC_{50(methanol)}$: 245µg/mL $IC_{50(acetone)}$: 180µg/mL		
		Fruits (C_6H_{14}) ($(CH_3)_2CO$)			$IC_{50(n\text{-}hexane)}$: 736µg/mL $IC_{50(acetone)}$: 90µg/mL		
		Staminate flowers (C_6H_{14}; CH_2Cl_2)			$IC_{50(n\text{-}hexane)}$: 220µg/mL $IC_{50(dichloromethane)}$: 630µg/mL		
	Extract	Staminate flowers (C_6H_{14})	Significant delay on the development of *Aedes aegypti*	50 mg/L	ND	ND	Anholeti et al. 2015a
	Clusianone (**13**)	Staminate flowers (C_6H_{14})	Significant inhibition of survival and complete blockage of development *Ae. aegypti*				
C. criuva	Extracts	Leaves (C_6H_{14}; CH_3OH)	Antioxidant activity in DPPH assay	ND	$EC_{50(n\text{-}hexane)}$: 34.66 ± 19.42 g extract/g DPPH $EC_{50(methanol)}$: 12.54 ± 1.43 g extract/g DPPH	ND	Da Silva et al. 2017
		Pericarp (C_6H_{14}; CH_3OH)			$EC_{50(n\text{-}hexane)}$: 10.94 ± 0.36 g extract/g DPPH $EC_{50(methanol)}$: 5.01 ± 0.16g extract/g DPPH		
		Seeds (C_6H_{14}; CH_3OH)			$EC_{50(n\text{-}hexane)}$: 8.32 ± 0.30g extract/g DPPH $EC_{50(methanol)}$: 4.06 ± 1.12g extract/g DPPH		
C. burlemarxii	Extract	Leaves (CH_3CH_2OH)	Antimicrobial activity against *B. subtilis* and *S. aureus*	ND	ND	MIC (*B. subtilis*): 31.25µg/mL MIC (*S. aureus*): 62.50µg/mL	Ribeiro et al. 2011
		Trunk (CH_3OH)	Antimicrobial activity against *B. subtilis*, *Streptococcus mutans* and *Micrococcus luteus*			MIC (*B. subtilis*): 62.50µg/mL MIC (*S. mutans*): 62.50µg/mL MIC (*M. luteus*): 31.25µg/mL	

Table II. Continuation.

Species	Extracts/ substances	Plant organ (solvent)	Biological activities	Dose	IC_{50}	MIC / MBC	Ref.
	2,2-dimethyl-3,5-dihydroxy-7-(4-hydroxyphenyl) chromane (**17**)	Trunk (CH_3OH)	Antimicrobial activity against *B. subtilis*, *S. aureus*, *S. mutans* and *M. luteus*	ND	ND	MIC (*B. subtilis*): 100µg/mL MIC (*S. aureus*): 50µg/mL MIC (*S. mutans*): 100µg/mL MIC (*M. luteus*): 25µg/mL	
	Lyoniresinol (**18**)	Leaves (CH_3CH_2OH)	Antimicrobial activity against *S. aureus*			MIC (*S. aureus*): 25µg/mL	
	Rhamnopyranosyl kaempferol (**19**)		Antimicrobial activity against *B. subtilis* and *S. aureus*			MIC (*B. subtilis*): 50µg/mL MIC (*S. aureus*): 100µg/mL	
C. gundlachii	Gundlachiione A (**20**)	Fruits (CH_3OH)	Leishmanicidal activity against *P. falciparum*	ND	$IC_{50(promastigote)}$: 11.30µg/mL $IC_{50(amastigote)}$: 0.84µg/mL	ND	Zhang et al. 2018
	Gundlachiione B (**21**)				$IC_{50(promastigote)}$: 30.12µg/mL $IC_{50(amastigote)}$: 5.92µg/mL		
	Gundlachiione C (**22**)				$IC_{50(promastigote)}$: 9.63µg/mL $IC_{50(amastigote)}$: 2.32µg/mL		
C. latipes	Extract	Leaves (C_6H_{14}; $CH_3CO_2C_2H_5$; CH_3OH)	Cytotoxic activity against human cancer cell lines (PC-3, RKO, D-384 and MCF-7)	50µg/ml	ND	ND	Bailón-Moscoso et al. 2016
Clusia minor	Extract	Leaves (CH_2OH)	Antinociceptive effect on mice	150 and 300 mg/kg	ND	ND	Mangas et al. 2019
Clusia flava	Extract	Leaves (CH_3OH)	Leishmanicidal activity against *P. falciparum*	ND	$IC_{50(promastigote)}$: 32µg/mL	ND	Peraza-Sánchez et al. 2007
C. pernanbucensis	Extract	Stem bark ($CH_3CO_2C_2H_5$))	Leishmanicidal activity against *P. falciparum*	ND	$IC_{50(amastigote)}$: 65µg/mL	ND	Silva et al. 2013
	Clusiaxanthone (**23**)				$IC_{50(amastigote)}$: 66.9µM		
C. amazonica	Extract	Leaves and stems (H_2O)	Leishmanicide				Odonne et al. 2009

Legend: IC_{50} - Half maximal inhibitory concentration; MIC - Minimum inhibitory concentration; MBC - Minimum bactericidal concentration; ND - Not determined; (H_2O) water; ($CH_3CO_2C_2H_5$) ethyl acetate; (CH_3OH) methanol; ($(CH_3)_2CO$) acetone; (CH_3CH_2OH) ethanol; (CH_2Cl_2) dichloromethane; (C_6H_6) benzene ; (C_6H_{14}) *n*-hexane; $(C_2H_5)_2O$ diethyl ether.

Studies carried out by Meneses et al., 2015, with extracts and substances isolated from *C. fluminensis*, showed anti-HIV-1 RT activity. Among the crude extracts, methanolic extracts from leaves and stems showed activity, demonstrating inhibition of about 42 and 20%, respectively, of the HIV-1-RT. In this study, the efavirenz, a reverse transcriptase inhibitor drug used to combat HIV-1 infection, was used as a control, which showed inhibition of about 92%. Two isolated substances were also tested (clusianone and lanosterol) and the triterpenoid lanosterol showed a moderate inhibitory effect (77.31% ± 10.74). The weak inhibition on HIV-1-RT of the benzophenone clusianone (37.6% ± 1.73) complements the study of Piccinelli et al. 2005, indicating that the inhibition of the reverse transcriptase enzyme does not represent the main mechanism of action of this substance.

Antimicrobial activity

The indiscriminate use of antimicrobials added to the transmission of genetic resistance among bacterial strains has led to the emergence of resistant bacteria in the available therapeutic arsenal. Therefore, searching for new alternatives is necessary, and natural sources have been studied (Jayasuriya et al. 1991, Nguemeving et al. 2006, Nkengfack et al. 2002, Pecchio et al. 2006, Yimdjo et al. 2004). The *Clusia* genus, the target of this review, has shown antimicrobial activity, especially against gram-positive bacteria.

Suffredini et al. 2006 analyzed organic extracts in dichloromethane and methanol (1:1) produced from *Clusia columnaris* using broth microdilution assay to trace antimicrobial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis*, and the results were significant (MIC or MBC ≤ 200 µg / mL). The extracts were submitted to the determination of the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) using gentamicin and tetracycline as standard drugs (García-González & Matamoros 1996). *Pseudomonas aeruginosa* and *E. faecalis* are bacteria related to human infectious diseases, and the results suggest the continuity of studies with the species of *Clusia* and reinforce plants as a source of a new class of antimicrobials.

Studies were conducted to verify the antimicrobial activity of metabolites isolated from resin and latex of *Clusia grandiflora*. The polyisoprenylated benzophenones chamone I and II were isolated from the latex of the trunk of *C. grandiflora,* while nemorosone II from the reward resin of the pollinator of pistillate flowers of the same plant. The bioassays were carried out with *Paenibacillus larvae* and *Paenibacillus alvei*, pathogens that cause diseases in beekeeping and prevent the formation of hives. The substances tested demonstrated potent antibacterial activity against the aforementioned pathogens. The work also described that the abundance of bioactive benzophenones in the resin compared to latex indicates that these compounds benefit bees (Lokvam et al. 2000).

Porto et al. 2000 researched the bioactivity of floral resins of seven species of *Clusia* cultivated at the Agronomic Institute of Campinas, Campinas, São Paulo, Brazil: *C. grandiflora*, *C. insignis*, *C. lanceolata*, *C. nemorosa*, *C. spiritu-sanctensis*, *C. renggerioides*, and *C. weddelliana*. The study was conducted with pistillate and staminate species and considered the influence of methylation of polyisoprenylated benzophenones on antimicrobial potential. Antimicrobial activity was tested using the bioautography test with *Aspergillus niger*, *Bacillus subtilis*, *Candida albicans*, *E. Escherichia coli*, *Rhodococcus equi*, and *S. Staphylococcus aureus*. Chloramphenicol (antibacterial) and nystatin (antifungal) were used for comparison. Bioautography, a trial capable of providing quantitative and

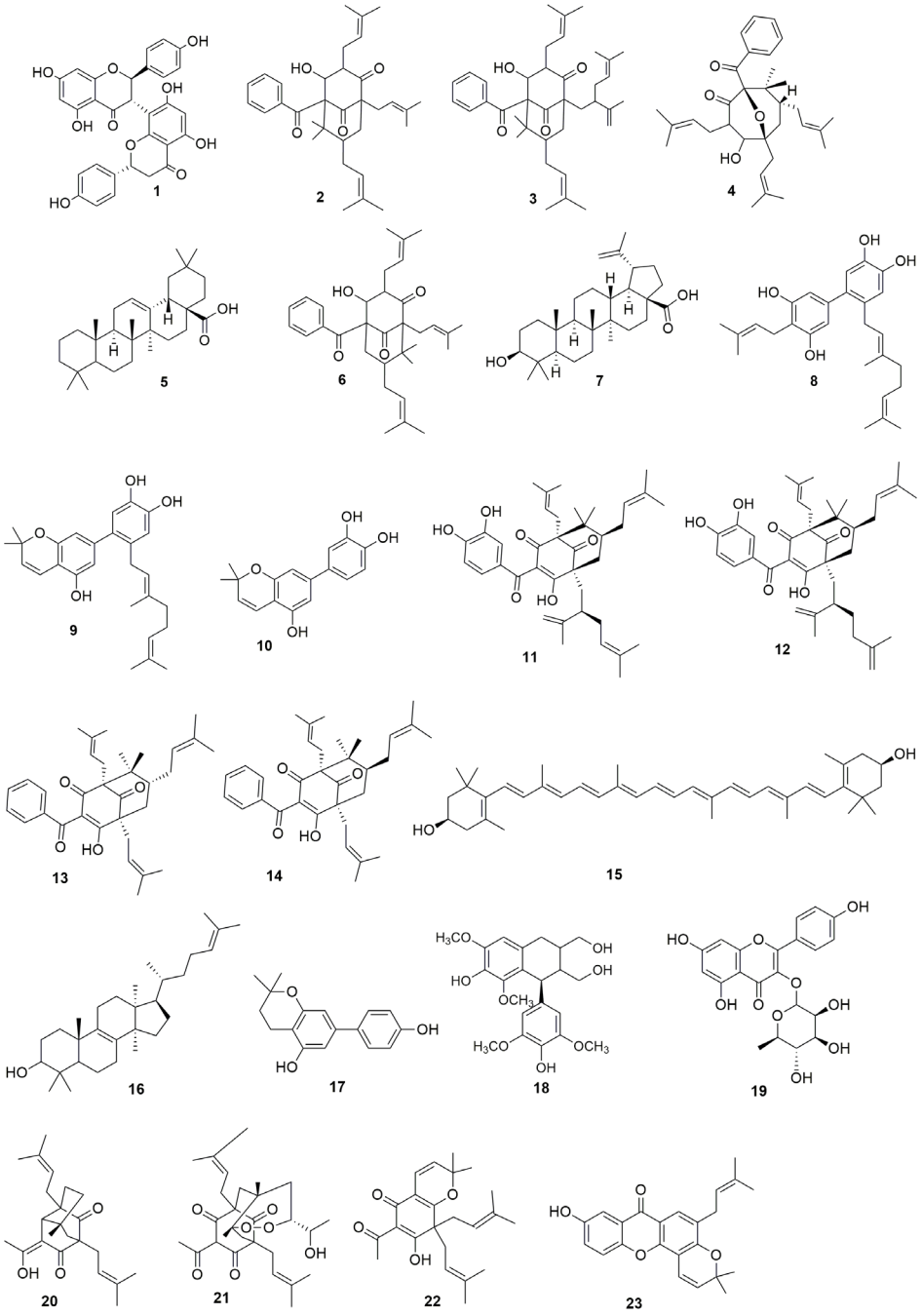

Figure 1. Substances isolated from species of the genus *Clusia* (Clusiaceae) with biological activity. (1) I3, II8-Binaringerin (2) Nemorosone II (3) Chamone I (4) 7-epi-nemorosone (5) Oleanolic acid (6) Nemorosone (7) Betulinic acid (8) Clusiparalicoline A (9) Clusiparalicoline B (10) Clusiparalicoline C (11) Guttiferone E (12) Xanthochymol (13) Clusianone (14) 7-epi-Clusianone (15) Zeaxanthin (16) Lanosterol (17) 2,2-dimethyl-3,5-dihydroxy-7-(4-hydroxyphenyl)chromane (18) Lyoniresinol (19) Rhamnopyranosyl kaempferol (20) Gundlachiione A (21) Gundlachiione B (22) Gundlachiione C (23) Clusiaxanthone.

qualitative information, revealed that non-methylated polyisoprenylated benzophenones have greater antimicrobial activity. The results indicated in the resin of *C. grandiflora* pistillate flowers had higher activity than the resin of *C. grandiflora* staminate flowers and it is due to the higher concentration of active compounds (polyisoprenylated benzophenones) in the resins of the pistillate flowers. The floral resins of most *Clusia* species tested presented antimicrobial

activity, especially in Gram-positive bacteria *S. aureus* and *B. subtilis* (Porto et al. 2000, Neves et al. 2007, Almeida et al. 2008).

Clusia burlemarxii, shrub vegetation found in Chapada Diamantina, Bahia, Brazil, was studied by Ribeiro et al. 2011. In addition to phytochemical research, the authors evaluated the antimicrobial activity of extracts and pure compounds against *Streptococcus mutans*, *S. aureus*, *B. subtilis*, *Micrococcus luteus*, *E. coli*, *Salmonela cholera*, *Pseudomonas aeruginosa*, *Aspergillus niger*, and *Cladosporium cladosporioides*. The extracts, as well as the isolated compounds, presented antimicrobial activity against Gram-positive bacteria, corroborating the results of different species of *Clusia* (Porto et al. 2000, Lokvam et al. 2000, Ribeiro et al. 2011).

The microdilution test on plates determined the MIC of extracts and isolated compounds. Nutrient broth and chloramphenicol were used as a culture medium for bacteria, malt, and olamine ciclopirox for fungi. The MIC was determined by the emergence of turbidity in the wells. Extracts were considered active when there was inhibition in concentration below or equal to 500 µg/mL and substances when there was inhibition below or equal to 100 µg/mL. The ethanolic extract of *C. burlemarxii* demonstrated a very promising activity against *B. subtilis* (31.25µg/mL) and *S. aureus* (62.50 µg/mL) and the methanolic extract from the trunk against *B. subtilis* (62.50µg/mL), *S. mutans* (62.50µg/mL) and *M. luteus*. Four of the nine isolated substances presented strong antimicrobial activity with MIC of 25 µg/mL and moderate activity with MIC of 50 µg/mL (Ribeiro et al. 2011).

Antitumoral activity

Some isolated compounds of different species of *Clusia* have shown promising results in the search for new substances with antitumoral activity. Nemorosone is one of these compounds and has been the target of studies by different research groups. Cuesta-Rubio et al. 2002 described *C. rosea* floral resin as a rich source of polyisoprenylated benzophenones, and after selective extraction of benzophenones and confirmation of a large amount of nemorosone, cytotoxic evaluation tests were performed where the compound was active for epithelioid carcinoma, prostate cancer, and central nervous system cancer (Camargo et al. 2015).

The criteria followed the recommendation of the National Cancer Institute of USA, which considers the significant activity of a product when the IC_{50} is reached with a concentration less than 4 µg/mL. For epithelioid carcinoma, the IC_{50} was 1.6 µg/mL for nemorosone; for prostate cancer, 3.6 µg/mL and for central nervous system cancer, 1.9 µg/mL (Cordell et al. 1993).

In search of pharmaceutical alternatives derived from natural products, the substance nemorosone was isolated from alcoholic extracts of *C. rosea* resins collected in Florida. The studies focused on neuroblastoma, a solid tumor common in childhood and characterized by rapid disease progression. The compound exerted intense activity in neuroblastoma cell lines, both in the matrix cell and in its clones selected for resistance to adriamycin, cisplatin, etoposide, or 5-fluorouracil, medicines widely used in the treatment of cancer (Díaz-Carballo et al. 2008). They found that the cytotoxic effect was due to apoptosis, thus not inducing an inflammatory response. This study demonstrated that nemorosone is a modulator or inhibitor of pathways that play roles in the transduction and integration of extracellular and intracellular oncogenic signals, making it a potential candidate for molecular therapy. The study also demonstrated that nemorosone exhibited cytotoxicity on leukemic cells, affecting protein levels, cell cycle progression, and low

cytotoxicity on non-tumor cells. *In vivo* studies have suggested that nemorosone significantly affected hematopoiesis in mice, making further studies even more attractive (Díaz-Carballo et al. 2008). Corroborating with previous studies, Popolo et al. 2011 also isolated nemorosone from *C. rosea* floral resins in search of therapeutic alternatives for breast cancer. The study reported that the substance could significantly inhibit cell growth at low concentrations, signaling to be a promising estrogen receptor antagonist and act in the prevention and treatment of breast cancer. Considering the potential of nemorosone and the need to test chemotherapy not only for anticancer or antitumor activity but also for potential mutagenicity, Camargo et al. 2013 carried out a study to determine the mutagenic and antimutagenic activity of the substance using the Ames test, using the TA97a, TA98, TA100 and the TA102 strains of *Salmonella typhimurium*, subjected to four different concentrations of the compound. The results indicated an absence of mutagenic activity.

The tests were carried out by associating nemorosone with direct (NPD and MMC) and indirect (AFL) mutagens in strains TA98, ta102, and TA100. The association of strain TA98 + NPD did not reduce the number of restricted colonies; TA100 + AFL caused a moderate protective effect with 31% inhibition. An expressive result was verified in the association of the strain TA102 + MMC, which presented a strong protective effect with an inhibition of 53%. The results suggest that nemorosone can potentially reduce the mutagenic damage of anticancer drug therapy, but further studies should be carried out to clarify its mechanism of action (Piccinelli et al. 2005). Another polyisoprenylated benzophenone, isolated from *C. rosea* and *C. grandiflora*, is 7-epi-nemorosone (4). The substance was described, in 2012, by Díaz-Carballo and collaborators as a potent antitumor agent with action on prostate carcinoma. The study contributed to the search for new substances derived from plants to treat well-known diseases. Prostate cancer is a frequently diagnosed neoplasia and the second leading cause of cancer death in men due to metastases in distant organs due to resistance to available chemotherapy. The authors presented 7-epi-nemorosone (4) as a promising potential candidate to treat prostate cancer, with androgen-dependent cytotoxicity and absence of cross-resistance (Díaz-Carballo et al. 2012, Da Silva et al. 2019, Neves et al. 2007).

Nemorosone, as well as other polyisoprenylated benzophenones with a bicyclo[3.3.1]nonane-2,4,9-trione nucleus, have been the object of studies, demonstrating a great antitumor potential.

Bailón-Moscoso et al. 2016 studied the chemical composition of organic extracts from *Clusia latipes* leaves collected in Ecuador and evaluated the *in vitro* cytotoxicity and genotoxicity in human prostate cancer cells, colon cancer cells, astrocytoma cells, and breast cancer cells. The group presented results of purification and identification of friedelin, friedolan-3-ol and hesperidin, cytotoxic compounds active in the hexane extract. The three substances isolated were antiproliferative in selected cancer cells; however, the hexane extract of *C. latipes* induced a significant increase in DNA damage in exposed lymphocytes. The genotoxicity detected by the comet assay and the damage detected by this method is repairable DNA damage, requiring, according to the authors, further experiments to determine genotoxic effects and provide more consistent results. *Clusia paralicola* is another species of the genus that shows possible antitumor activity. Seo and coworkers isolated three biphenyl-derived compounds, clusiparalicoline A, B, and C, from the roots extracts by bioassay-guided fractionation using the DNA strand scission and human cancer cell

line KB cytotoxicity assays (Seo et al. 1999). The research showed that clusiparalicoline A and B were active in the DNA strand scission assay, while all three compounds exhibited modest cytotoxicity against the KB cell line. Further, *in vivo* biological studies will be needed to assess the antineoplastic potential of isolated compounds (Seo et al. 1999, Takaoka et al. 2002).

Antioxidant activity

The search for compounds with antioxidant activity is necessary since oxidative stress involves processes that cause imbalances in the human body, such as cancer, aging, and degenerative processes. Studies conducted with *Clusia* species (*C. lanceolata*, *C. paralicola*, *C. criuva* and *C. fluminensis*) focused on antioxidant activity have shown promising results. (Ferreira et al. 2014, Mazza et al. 2019, López-Alarcón & Denicola 2013, Athanasas et al. 2004, Wolf et al. 2017, Silva & Paiva 2012).

Ferreira et al. 2014 verified that extracts of leaves with galls of *C. lanceolata* presented higher antioxidant activity than those not galled and attributed this difference to the higher content of phenolic compounds and proanthocyanidins.

Seo et al. 1999 demonstrated that the ethanol extract from green fruits of *C. paralicola*, its fractions, and the isolated biflavonoids have potent antioxidant activity. Moreover, *C. criuva* also showed antioxidant potential. The methanolic extract of the fruit pericarps presented the highest percentage of maximum antioxidant activity at 250 µg / mL (Zhang et al. 2018). Silva and Paiva investigated the antioxidant potential of crude extracts of *Clusia fluminensis* through the neutralization of the stable free radical DPPH and the quantification of flavone and flavonoid content (Silva & Paiva 2012). The results pointed out a positive correlation between the presence of flavonoids and the antioxidant activity of these extracts, and the researchers concluded that the acetonic extract of fruits of *C. fluminensis* is an exciting target for the search for substances with antioxidant activity, especially flavonoids (Athanasas et al. 2004, Silva & Paiva. 2012).

Although most studies link antioxidant activity to the presence of flavonoids, which is favored by the characteristic of its chemical structure, the study conducted by Silva et al. 2017 demonstrated that the antioxidant activity exhibited by *C. criuva* did not present a direct correlation with the presence of this type of substance. The authors suggest that the high values of the flavonoid content observed in hexane extracts may represent; in fact, to the presence of benzophenones that could have interacted with the aluminum chloride used in the quantification methodology.

Antinociceptive activity

The search for new substances with analgesic properties has grown in recent years. Antinociceptive activity was also observed in the *Clusia* species. Bittar et al. 2000 described the antinociceptive effects of I3, II8-binaringerin isolated from the methanol extract of *C. columnaris* collected in Venezuela. The substance did not increase the latency period of pain induced by thermal stimuli by discarding the relationship of its mechanism of action with opioid systems. However, it exhibited potent and dose-related antinociceptive properties, with ID_{50} values of 22 µmol / kg in the writhing test and 28 µmol / kg in the second phase of the formalin test, values that suggest that the substance is more potent than some drugs clinically used as analgesics (Cordell et al. 1993).

Ferro et al. 2013 demonstrated the antinociceptive activity of hexane extract from *Clusia nemorosa* leaves in chemical pain models through mechanisms that suggest

the participation of the adrenergic systems pathways. The extract prevented visceral pain induced by acetic acid in mice for at least two hours. The study suggests that the mechanism may be partially linked to the inhibition of cyclooxygenase and lipoxygenase products and other inflammatory mediators in peripheral tissues, thus interfering in the signal transduction mechanism in primary afferent nociceptors.

To corroborate with studies of the antinociceptive activity of *Clusia* species, Mangas et al. 2019 evaluated the chemical composition and the potential antinociceptive effect of ethanol extract of *Clusia minor* leaves. Previous studies also demonstrated mechanical hypernociception induced by intraplantar carrageenan, tumor necrosis factor α (TNFα), and prostaglandin E2 (PGE2). The extract proved to be effective in reducing pain in a dose-dependent manner, in addition to inhibiting mechanical hypernociception of the paw, suggesting that the antinociceptive effect of *C. minor* occurs by the interaction of various mechanisms through central and peripheral pathways, capable of inflammatory and neurogenic pain.

Leishmanicidal activity

Leishmaniasis is an anthropozoonosis caused by approximately 20 species of a protozoa of the *Leishmania* genus, belonging to the family Trypasonomatidae, and transmitted by a bite of hematophagous female sandflies belonging to the Phlebotominae family. This is considered a neglected disease and one of the significant public health problems in the world, which affects 98 countries, 12 million cases, and 350 million people at risk of developing leishmaniasis, with 1.5 to 2 million new cases per year. Cases of leishmaniasis with the human immunodeficiency virus (HIV) co-infection are increasing and have been described in 35 countries (Wolf et al. 2017, Silva & Paiva 2012).

The leishmanicidal activity of methanol extracts from *Clusia flava* leaves was verified through *in vitro* bioassay. The extract of *C. flava* was able to inhibit the growth of promastigotes of *L. mexicana* with IC_{50} 32 µg/mL. As known of literature, IC_{50} values between 3 and 49 µg/mL are considered as a good inhibition of the microorganism (Peraza-Sánchez et al. 2007). Another study selected plant species used by chayahuite to cure cutaneous leishmaniasis. Forty extracts were evaluated, and among them, the aqueous extract of *Clusia amazonica* was considered with good IC_{50} values, 32.9 µg/mL (stems) and 34.6 µg/mL (leaves) (Odonne et al. 2009).

Fruits of *Clusia gundlachii*, collected in Puerto Rico, were studied by Zhang et al. 2018 and, after fractionation, produced five new polycyclic chloroglucine derivatives that presented activity against intracellular amastigotes of macrophages and promastigotes of *Leishmania donovani*. The activity is comparable to those observed for the standard pentamidine drug.

Clusia pernambucensis, coming from the Brazilian cerrado, was the target of studies conducted by Silva et al. 2013. From the extract in ethyl acetate of the bark of the stem, it was possible to isolate Clusiaxanthone. The substance was able to control macrophage infection with *Leishmania amazonensis* amastigotes. These results indicate that the species is a potential source of new compounds with leishmanicidal activity (Da Silva et al. 2017, Wolf et al. 2017).

Modulation of inflammatory processes

Clusia nemorosa is a common species in coastal forests of northeastern Brazil. Farias et al. 2012 evaluated the anti-inflammatory effect of this species leaves' hexane extract using carrageenan-induced mice pleurisy and cotton pellet-induced mice granuloma using the Boyden chamber assay and flow cytometry (Ferro et al. 2013).

The results were promising as they inhibited exudation, total leukocytes and neutrophils influx, and TNFα levels in carrageenan-induced pleurisy. Although the extract did not suppress the granulomatous tissue formation in the cotton pellet-induced granuloma test, the experiments showed that they revealed that the hexane extract of *C. nemorosa* inhibited neutrophil chemotaxis induced by CXCL1 in a dose-dependent manner, inhibited the chemoattraction of human neutrophils induced by formyl-methionyl-leucyl-phenylalanine (fMLP), leukotriene B4 (LTB4) and platelet activation factor (PAF). Further, *in vivo*, biological studies will be needed to assess the antineoplastic potential of isolated compounds (Seo et al. 1999, Takaoka et al. 2002).

Neutralization of toxic effects caused by *Bothrops* snake accidents

Researches related to neglected diseases are urgent and, as with malaria, dengue, tuberculosis and many other diseases, the risk of snakebite is always present, mainly in poorer areas, being an occupational and environmental risk added to poverty. Serum therapy, recommended in cases of snakebite accidents, acts on the systemic effects caused by the venom. However, the local effects, responsible for example for the amputations, draw attention to the need to search for antivenom support therapies. Extracts from different species of *Clusia*, such as *C. torressi*, *C. palmana* and *C. fluminensis* demonstrated positive effects in neutralizing the effects caused by snake venoms, exhibiting, for example, proteolytic, hemolytic and anti-hemorrhagic activity (Castro et al., 1999, Da Silva et al. 2019).

Da Silva et al. 2019 showed promising results in inhibiting the activities of *Bothrops jararaca* and *B. jararacussu* venoms, regardless of the experimental protocol used or the route of administration of the extracts. The presence of tannins, flavonoids, saponins, steroids, and terpenoids was described. These results suggest that *C. fluminensis* extracts can be effective against some toxic effects of *B. jararaca* or *B. jararacussu* venom, a promising tool for treating accidents caused by such snakes. Thus, anti-venom properties of *C. fluminensis* extracts deserve further investigation (Da Silva et al. 2019).

Other activities

The hypotensive effect of *Clusia coclensis* aqueous extract was tested in normotensive and hypertensive animals, and a significant reduction in venous return was found in both rat strains. The extract caused a peripheral vasoconstrictor effect so the hypotensive and antihypertensive effect was attributed to a direct effect on the myocardium by a decrease in the strength of cardiac contraction (García-González & Matamoros 1998, 1996).

Mazza et al. 2019 described the presence of potentially bioactive compounds in aril extracts from *Clusia fluminensis* fruits, including the carotenoid zeaxanthin, described as an important macular protector and regenerator. The concentration of zeaxanthin (0,823 mg/g), higher than that found in other plant matrices, indicates that the species may be a potential source of bioactive substances. Other studies with *Clusia fluminensis* identified biopesticide activity in hexane extracts of fruits and flowers, and the Clusianone was isolated from the species. The study measured the larvicidal potential of extracts and substances, contributing to the search for less toxic natural insecticides for humans and the environment as alternatives to traditional control of the culicid (Duprat et al. 2017).

Anholeti et al. 2015a also evaluated the effects of the hexane extracts of the fruits and flowers of *Clusia fluminensis* and the

main component of flower extract, a purified benzophenone Clusianone, against *Aedes aegypti*. Although the treatment of larvae with fruit and flower extracts of *C. fluminensis* did not affect the survival of *A. aegypti* (50 mg / L), it significantly delayed the development of the mosquito. The Clusianone isolated (50 mg / L) of flower extract killed 93.3% of larvae and completely blocked the development of *A. aegypti*. The results reinforce the importance of developing Clusianone as a biopesticide to control vectors of insects of tropical diseases (Duprat et al. 2017).

Clusia hilariana was the target of studies conducted by Kelecom et al. 2002. The methanolic extracts of staminate flowers promoted food inhibition in 4th stage larvae of *Rhodnius prolixus* (one of the vectors of Chagas Disease) in addition to the delay of ecdysis. Isolated oleanolic acid promoted toxicity over larvae of the 4th stage of *R. prolixus* and was also able to delay ecdysis. The mixture of benzophenones isolated from the species also promoted the delay in the ecdysis of larvae of the 4th stage of *R. prolixus*.

Corroborating the biological potential of *Clusia paralicola*, previously reported with antitumor activity (Seo et al. 1999), the species was also studied by Takaoka et al. 2002 who found that clusiparalicoline A, a prenylated and geranylated biphenyl compound isolated from the roots of *C. paralicola* through sequential Stille reactions and palladium-catalyzed Suzuki-Miyaura reactions, exhibited potent activity for promoting neurite outgrowth in a primary culture of fetal rat cortical neurons. The results presented encourage further studies on the structure-activity relationship of compounds isolated from the species to elucidate mechanisms of action and the biological activity of therapeutic prototypes of plant origin.

CONCLUSION

The value of plant species as a source of molecules with therapeutic potential is historically known. The challenges associated with the process capable of transforming the plant into medicine are numerous and can only be overcome with interdisciplinary knowledge. In this review, we seek to provide information about some approaches of the research of the genus *Clusia*, focusing on biological activities. The genus was found to have bioactive properties, including antibacterial, antitumor, antivenom, insecticide, anti-inflammatory, antioxidant, smooth muscle relaxant, neuroprotective and antiprotozoal.

The studies demonstrated were conducted with extracts and compounds isolated from different parts of the *Clusia* species, and the promising results deserve further investigation. A summary of the information related to the therapeutic potential of *Clusia* will undoubtedly add value to research on the genus.

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MÁRCIA PIETROLUONGO[1,2]
https://orcid.org/0000-0002-3944-6486

MARIA CAROLINA ANHOLETI[3]
https://orcid.org/0000-0003-1552-9161

ANDRÉ L. FULY[4]
https://orcid.org/0000-0002-5265-52580

ALESSANDRA L. VALVERDE[2,5]
https://orcid.org/0000-0002-1250-1051

SELMA R. DE PAIVA[2,6]
https://orcid.org/0000-0002-8295-7011

[1]Vice-diretoria de Pesquisa, Ensino e Inovação, Instituto de Tecnologia em Fármacos, Fundação Oswaldo Cruz, Laboratório de Farmacotécnica Experimental, Rua Sizenando Nabuco, 100, Manguinhos, 21041-250 Rio de Janeiro, RJ, Brazil

[2]Programa de Pós-Graduação em Ciências aplicadas à Produtos para Saúde/PPGCAPS, Universidade Federal Fluminense, Faculdade de Farmácia, Rua Dr. Mário Vianna, 523, Santa Rosa, 24241-000 Niterói, RJ, Brazil

[3]Universidade Federal do Paraná, Setor de Ciências da Saúde, Departamento de Farmácia, Avenida Prefeito Lothário Meissner, 632, Jardim Botânico, 80210-170 Curitiba, PR, Brazil

[4]Universidade Federal Fluminense, Instituto de Biologia, Departamento de Biologia Celular e Molecular, Rua Prof. Marcos Waldemar de Freitas Reis, s/n, São Domingos, 24210-201 Niterói, RJ, Brazil

[5]Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Outeiro de São João Batista, s/n, Campus do Valonguinho, 24020-141 Niterói, RJ, Brazil

[6]Universidade Federal Fluminense,Instituto de Biologia, Departamento de Biologia Geral, Rua Prof. Marcos Waldemar de Freitas Reis, s/n, São Domingos, 24210-201 Niterói, RJ, Brazil

Correspondence to: **Márcia Pietroluongo**
E-mail: marcia.pietroluongo@fiocruz.br

Author contributions

Conceptualization, methodology, writing—original draft M.P., M.C.A., A.L.V. and S.R.P.; funding acquisition, A.L.V., A.L.F. and S.R.P; investigation, writing—review and editing, M.P., M.C.A., A.L.F., A.L.V. and S.R.P.; resources, A.L.V. and S.R.P.; supervision, M.C.A., A.L.V. and S.R.P.; All authors have read and agreed to the published version of the manuscript.