Brazilian Journal of Botany (2022) 45:41–65
https://doi.org/10.1007/s40415-021-00747-3

BIOCHEMISTRY & PHYSIOLOGY - REVIEW ARTICLE

Esenbeckia (Pilocarpinae, Rutaceae): chemical constituents and biological activities

Juliana C. S. Carvalho[1] · José R. Pirani[1] · Marcelo J. P. Ferreira[1]

Received: 29 June 2021 / Revised: 26 August 2021 / Accepted: 27 August 2021 / Published online: 9 September 2021

Abstract
The Rutaceae Juss. is a plant family known as a producer of bioactive compounds, comprising several species used for disease treatment in folk medicine. Among Rutaceae genera, *Esenbeckia* Kunth includes 28 species distributed from Mexico through Argentina and in the West Indies. Some species such as *E. alata* (Triana) Triana & Planch., *E. febrifuga* (A.St.-Hil.) A.Juss. ex Mart. and *E. yaaxhokob* Lundell are used as medicines to treat fever and gastrointestinal disorders. To date, almost 50 studies provided phytochemical data and biological activities from 19 species of *Esenbeckia*. A comprehensive review of the current state of knowledge of the genus is discussed in this article. A total of 180 compounds distributed into alkaloids, phenolic derivatives (mostly coumarins and flavonoids), steroids and terpenoids were summarized. Moreover, this survey provides data about cytotoxic, antiplasmodial, leishmanicidal, larvicidal, antimicrobial and anti-inflammatory activities found in compounds, fractions and extracts of *Esenbeckia*, highlighting its potential as a producer of bioactive metabolites. In addition, the use of compounds as chemophenetic characters is evaluated into the genus.

Keywords Alkaloids · Coumarins · Galipeeae · Sapindales · Terpenoids

1 Introduction

Rutaceae comprises around 2070 species distributed into 154 genera with a nearly cosmopolitan distribution (Kubitzki et al. 2011; Christenhusz and Bing 2016). Species of the family occur as trees, shrubs and herbs found predominantly in tropical and subtropical habitats (Morton and Telmer 2014). The family has been economically important primarily for edible fruits, especially *Citrus* L., timbers from *Balfourodendron* Mello ex Oliv. and *Zanthoxylum* L., bitter beverages employed to treat fevers (*Angostura* Roem. & Schult and *Galipea* Aubl.) and drugs (*Pilocarpus* Vahl. species) (Groppo et al. 2012).

For over 100 years, pilocarpine, an alkaloid isolated from the Brazilian species *Pilocarpus microphyllus* Stapf ex Wardlew., has been used as a drug to treat glaucoma. Pilocarpine has cholinergic properties and can stimulate the parasympathetic system, acting in the sudoriferous and salivary glands (Debnath et al. 2018; Adejoke et al. 2019).

✉ Marcelo J. P. Ferreira
marcelopena@ib.usp.br

[1] Departamento de Botânica, Instituto de Biociências – Universidade de São Paulo, São Paulo 05508-090, Brazil

A plethora of biological activities have been described for extracts and compounds isolated from Rutaceae species (Li et al. 2017; Forkuo et al. 2020; Passos et al. 2021; Dos Santos et al. 2021; Mbaveng et al. 2021; Ombito et al. 2021). Undoubtedly, the biosynthetic machinery of the family is highly diversified, producing several classes of secondary metabolites. Consequently, thousands of natural products such as alkaloids, coumarins, flavonoids, limonoids and other terpenoids have been identified from Rutaceae species (Epifano et al. 2015; Adamska-Szewczyk et al. 2016; Abotaleb et al. 2020; Coimbra et al. 2020; Wei et al. 2020; Ombito et al. 2021).

The Rutaceae includes two subfamilies (Cneoroideae and Rutoideae), six main clades, the tribes Aurantieae, Diosmeae, Galipeeae, Ruteae, Zanthoxyleae and the AAMAO clade. Of these, the tribe Galipeeae comprises two subtribes Galipeinae and Pilocarpinae, with around 218 species and 25 genera (Cole and Groppo 2020).

Pilocarpinae has Neotropical distribution and currently includes six genera *Balfourodendron* Mello ex Oliv., *Esenbeckia* Kunth, *Helietta* Tul., *Metrodorea* A.St.-Hil., *Pilocarpus* Vahl and *Raulinoa* R.S.Cowan (Cole and Groppo 2020). Phytochemical studies on species of Pilocarpinae include a range of compounds, mainly composed of alkaloids (Santos

and Moreno 2004; Gómez-Calvario et al. 2019) and coumarins (Santos and Moreno 2004; Ferreira et al. 2010; Madeiro et al. 2017).

Esenbeckia comprises 28 species, distributed from Mexico through Argentina, and in the West Indies (Kaastra 1982; Pirani 1999; Dias et al. 2013). The genus is centered in Brazil and Mexico, where 15 species occur in each country (Villaseñor, 2016; Pirani and Groppo 2020). In the monograph of Pilocarpinae, Kaastra (1982) divided *Esenbeckia* into three subgenera: *Esenbeckia*, *Lateriflorens,* and *Oppositifolia* according to leaves' features and side branchlets and position of inflorescences. Additionally, *Esenbeckia* subg. *Esenbeckia* was subdivided into two sections, distinguished by the presence and absence of basal appendage on the staminal filaments as, respectively, *Esenbeckia* subg. *Esenbeckia* sect. *Pachypetalae* and *Esenbeckia* subg. *Esenbeckia* sect. *Esenbeckia* (Kaastra 1982).

In folk medicine, some species of *Esenbeckia* are traditionally used to treat illness. *Esenbeckia yaaxhokob* Lundell is known as "tankas-ché" by communities along the Peninsula of Yucatan (Mexico), and the aerial parts are used to treat gastrointestinal disorders (Mata et al. 1998). Similarly, *Esenbeckia alata* (Triana) Triana & Planch., known as "loro" on the Colombian Atlantic coast, is used as an insecticide and antipyretic (García-Beltrán and Cuca-Suárez 2003). Finally, in the Southwest of Brazil, the bark of *Esenbeckia febrifuga* (A.St.-Hil.) A.Juss. ex Mart. is considered a medicine for fever and a tonic (Brandão et al. 2012; Cosenza et al. 2019).

Due to the traditional uses and pharmacological activities of *Esenbeckia* species and the broad diversity of compounds identified from the genus to date, this review surveys the *Esenbeckia* species' metabolites and associated biological activities, highlighting the importance of this genus as a source of bioactive natural products. Additionally, the meaning of these metabolites for taxonomic purposes is evaluated here, verifying whether they are useful as chemophenetic characters to corroborate the infrageneric taxa currently recognized in *Esenbeckia*.

2 Compounds identified from *Esenbeckia* species

Phytochemical and biological activity studies were searched into SciFinder using as keyword *Esenbeckia*. All papers published in English, Portuguese and Spanish and the abstracts of works written in other languages were compiled until April 2021. To date, chemical constituents isolated or identified from barks, leaves, roots, stems, woods and volatile oils of *Esenbeckia* species were described. The phytochemical profile of the *Esenbeckia* genus furnished 180 compounds, divided into alkaloids and amides (1–52; Table 1 and Figs. 1, 2, 3), phenolic compounds (53–115, Table 2 and Figs. 4, 5, 6, 7), steroids & terpenoids (116–174, Table 3 and Figs. 8, 9, 10) and long-chain compounds (175–180, Table 4 and Fig. 11). Authors of species names are presented in Table 5.

Alkaloids – *Esenbeckia* is a rich source of nitrogenous natural products providing compounds (1–52, Table 1 and Figs. 1, 2, 3) belonging to nine distinct groups: acridone, furanoquinoline, furanoquinolone, indole, β-indolopyridoquinazoline alkaloids, protoalkaloids, pyranoquinolinone, quinoline and quinolinone alkaloids. Also, amides were identified in three species, *E. alata*, *E. almawillia* Kaastra and *E. leiocarpa* Engl.

Despite the description of three acridone alkaloids, only compound **1** was found in more than one species. Similarly, indole and β-indolopyridoquinazoline alkaloids were identified strictly in *E. grandiflora* Mart. and *E. leiocarpa* (Monache et al. 1990, 1991; Januário et al. 2009). Otherwise, furanoquinoline and quinoline alkaloids occur in several species of *Esenbeckia*, and the compounds flindersiamine (8), kokusaginine (10) and skimmianine (12) are ubiquitously distributed among the species. Compounds with quinoline rings have been explored for drug development (Matada et al. 2021).

Phenolic derivatives – *Esenbeckia* species provided 62 phenolic derivatives (53–115, Table 2 and Figs. 4, 5, 6 and 7), distributed among the following natural products classes: chromanone, cinnamic acid derivatives, coumarins, flavonoids, lignoids, phenylpropanoids, simple phenolics and phloroglucinols. Although cinnamic acid derivatives encompass one of the most diverse classes of phenolic compounds (El-Seedi et al. 2012), only three compounds (54–56, Fig. 4) were identified from *Esenbeckia* species (Monache et al. 1990; Guilhon et al. 1994). Similarly, only five lignoids (106–110, Fig. 7) were identified from *E. alata*, *E. leiocarpa,* and *E. yaaxhokob* (Monache et al. 1990; Mata et al.1998; Suárez and Barrera 2007).

Coumarins are widely distributed in the plant kingdom and this natural product class has been described in several species of Apiaceae, Asteraceae and Rutaceae (Borges et al. 2005). Indeed, coumarins are the largest group among phenolic compounds of *Esenbeckia* providing 29 constituents (57–86, Fig. 5). A remarkable characteristic of these compounds is the presence of prenyl moieties at the C-6 position. Consequently, furanocoumarins are often identified in the genus instead of simple and pyranocoumarins. Additional prenyl groups are found at C-7 and C-8 positions. Coumarins were described in *E. alata, E. almawillia, E. febrifuga, E. flava* Brandegee*, E. hartmani* B.L.Rob. & Fernald*, E. hieronymi* Engl*, E. pumila* Pohl and *E. stephanii* Ramos (Table 2).

So far, flavonoids were described exclusively from leaves and roots of *E. almawiillia, E. berlandieri* Baill*, E.*

Table 1 Alkaloids and amides identified into *Esenbeckia* species

	Compounds	*Esenbeckia* spp.	Plant parts	References
	Acridone alkaloids			
1	1-Hydroxy-3,4-dimethoxy-10-methyl-9(10) acridone	*E. litoralis*	Leaves	Rios et al. (2002a)
2	1-Hydroxy-3-methoxy-*N*-methylacridone	*E. febrifuga*	Stem	Dreyer (1980), Dolabela et al. (2008)
		E. litoralis	Bark	Dreyer (1980)
		E. pentaphylla	Wood	Simpson and Jacobs (2005)
		E. pilocarpoides	Wood bark	Bevalot et al. (1984)
3	Arborinine	*E. litoralis*	Leaves	Rios et al. (2002a)
	Furoquinoline alkaloids			
4	Delbine	*E. febrifuga*	Bark	Cosenza et al. (2019)
		E. grandiflora	Leaves	Januário et al. (2009)
		*E. grandiflora**	Root	Trani et al. (2004)
5	Dictamine	*E. alata*	Wood	Cuca-Suarez et al. (2011)
		E. flava	Wood	Dreyer (1980)
		E. leiocarpa	Root	Monache et al. (1990)
		E. litoralis	Wood	Dreyer (1980)
		E. pentaphylla	Wood	Simpson and Jacobs (2005)
6	Evolitrine	*E. litoralis*	Wood	Dreyer (1980)
		E. flava	Wood	Dreyer (1980)
7	γ-Fagarine	*E. alata*	Wood	Cuca-Suarez et al. (2011)
		E. febrifuga	Stem	Dolabela et al. (2008)
		*E. grandiflora**	Root	Trani et al. (2004)
		E. hieronymi	Leaves	Monache et al. (1996)
		E. pentaphylla	Wood	Simpson and Jacobs (2005)
8	Flindersiamine	*E. alata*	Leaves	Cuca-Suarez et al. (2011)
			Leaves	Álvarez-Caballero et al. (2019)
		E. almawillia	Trunk bark	Oliveira et al. (1996)
		E. belizencis	Leaves	Rios and Delgado (1992a,(b)
		E. conspecta	Wood	Rios et al. (2002b)
		E. febrifuga	Bark	Vitagliano and Comin (1970; Cosenza et al. (2019)
			Stem	Dolabela et al. (2008)
		E. flava	Wood	Dreyer (1980)
		*E. grandiflora**	Root	Trani et al. (2004)
		E. grandiflora	Root	Oliveira et al. (1996)
		E. hieronymi	Laves	Monache et al. (1996)
		E. leiocarpa	Stems	Cardoso-Lopes et al. (2010)
			Root	Monache et al. (1990)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. pentaphylla	Wood	Simpson and Jacobs (2005)
		E. pilocarpoides	Wood bark	Bevalot et al. (1984)
		E. yaaxhokob	Leaves	Aguilar-Guadarrama and Rios (2004)
9	Kokusagine	*E. pilocarpoides*	Wood bark	Bevalot et al. (1984)
			Leaves	Bevalot et al. (1984)
10	Kokusaginine	*E. alata*	Wood and leaves	Cuca-Suarez et al. (2011)
			Leaves	Álvarez-Caballero et al. (2019)
		E. belizencis	Leaves	Rios and Delgado (1992a,(b)
		E. febrifuga	Stem	Dolabela et al. (2008)
		E. grandiflora	Root	Oliveira et al. (1996; Januário et al. (2009)
		*E. grandiflora**	Root	Trani et al. (2004)

Table 1 (continued)

	Compounds	*Esenbeckia* spp.	Plant parts	References
		E. hieronymi	Leaves	Monache et al. (1996)
		E. litoralis	Leaves	Rios et al. (2002a)
			Wood and husk	Dreyer (1980)
		E. leiocarpa	Stem	Cardoso-Lopes et al. (2010)
			Root	Monache et al. (1990)
		E. pentaphylla	Wood	Simpson and Jacobs (2005)
		E. pilocarpoides	Wood bark	Bevalot et al. (1984)
			Leaves	Bevalot et al. (1984)
11	Maculine	*E. almawillia*	Root	Barros-filho et al. (2007)
			Bark	Vitagliano and Comin (1970)
		*E. grandiflora***	Root	Nunes et al. (2005a)
		E. grandiflora	Root	Oliveira et al. (1996)
		E. hieronymi	Leaves	Monache et al. (1996)
		E. leiocarpa	Stem	Cardoso-Lopes et al. (2010)
			Root	Monache et al. (1990)
		E. litoralis	Wood	Dreyer (1980)
			Leaves	Rios et al. (2002a)
		E. pilocarpoides	Wood bark	Bevalot et al. (1984)
12	Maculosidine	*E. almawillia*	Trunk bark	Oliveira et al. (1996)
		E. conspecta	Wood	Rios et al. (2002b)
		E. flava	Wood	Dreyer (1980)
		E. hartmanii	Stems and branches	Dreyer et al. 1975
13	Skimmianine	*E. alata*	Leaves	Suárez and Barrera (2007)
		E. febrifuga	Bark	Vitagliano and Comin (1970; Cosenza et al. (2019)
			Stem	Dolabela et al. (2008)
		E. flava	Wood and husk	Dreyer (1980)
		*E. grandiflora**	Root	Trani et al. (2004)
		E. hartmanii	Stems and branches	Dreyer et al. (1972)
		E. hieronymi	Leaves	Monache et al. (1996)
		E. leiocarpa	Stem	Cardoso-Lopes et al. (2010)
		E. litoralis	Wood	Dreyer (1980)
			Leaves	Rios et al. (2002a)
	Furoquinolone alkaloids			
14	Isomasculine	*E. pilocarpoides*	Wood bark	Bevalot et al. (1984)
	Indole alkaloids			
15	1*H*-indole-7-carboxaldehyde	*E. leiocarpa*	Root	Monache et al. (1990)
16	5-(3-methyl-2-buten-1-yl)-1*H*-indole	*E. leiocarpa*	Root	Monache et al. (1990)
17	6-Prenylindole	*E. leiocarpa*	Root	Monache et al. (1990)
18	7-Prenylindole	*E. leiocarpa*	Root	Monache et al. (1990)
19	7-Indolemethanol	*E. leiocarpa*	Root	Monache et al. (1990)
20	Annonidine A	*E. leiocarpa*	Root	Monache et al. (1990)
21	Annonidine C	*E. leiocarpa*	Root	Monache et al. (1990)
22	Dihydrocorynantheol	*E. leiocarpa*	Bark	Liz et al. (2011)
23	Leicarpatriol A	*E. leiocarpa*	–	Monache et al. (1991)
24	Leicarpatriol B	*E. leiocarpa*	–	Monache et al. (1991)
25	(+)-Leiocarpadiol	*E. leiocarpa*	Root	Monache et al. (1990)
26	(-)-Leiocarpol	*E. leiocarpa*	Root	Monache et al. (1990)
27	Leiocarpone	*E. leiocarpa*	–	Monache et al. (1991)
	β-*indolopyridoquinazoline alkaloids*			

Table 1 (continued)

	Compounds	*Esenbeckia* spp.	Plant parts	References
28	1-Hydroxyrutaecarpine	*E. grandiflora*	Leaves	Januário et al. (2009)
29	Euxylophoricine D	*E. grandiflora*	Root	Januário et al. (2009)
30	Rutaecarpine	*E. grandiflora*	Leaves	Januário et al. (2009)
	Protoalkaloids			
31	Geranyl-*N*-dimethylallylanthranilate	*E. yaaxhokob*	Leaves	Aguilar-Guadarrama and Rios (2004)
	Pyranoquinolinone alkaloids			
32	8-Methoxy-*N*-methylflindersine	*E. conspecta*	Wood	Rios et al. (2002b)
33	(-)-Lunacrinol	*E. hieronymi*	Leaves	Monache et al. (1996)
34	N-Methylflindersine	*E. alata*	Wood	Cuca-Suarez et al. (2011)
		E. pentaphylla	Wood	Simpson and Jacobs (2005)
	Quinoline alkaloids			
35	2-(1-ethylpropyl)-4-Methoxyquinoline	*E. leiocarpa*	Roots	Monache et al. (1990)
	Quinolinone alkaloids			
36	3,3-Diisopentenyl-*N*-methyl-2,4-quinoldione	*E. almawillia*	Root	Barros-Filho et al. (2007)
			Wood (EO)	Barros-Filho et al. (2004)
			Wood and root	Nunes et al. (2005b)
		E. flava	Wood	Dreyer (1980)
37	3´-Methoxygraveoline	*E. almawillia*	Root	Barros-Filho et al. (2007)
			Trunk bark	Oliveira et al. (1996)
38	4-Methoxy-1-methyl-2-quinolone	*E. pentaphylla*	Wood	Simpson and Jacobs (2005)
		E. grandiflora	Root	Oliveira et al. (1996)
39	4-Methoxy-3-(3´-methyl-but-2´-enyl)-*N*-methyl-quinolin-2(1*H*)-one	*E. alata*	Wood	Cuca-Suarez et al. (2011)
40	8-Methoxy-1-methyl-tridecyl-4-quinolone	*E. leiocarpa*	–	Monache et al. (1991)
41	8-Methoxy-1-methyl-2-heptyl-4-quinolone	*E. almawillia*	Trunk bark	Guilhon et al. (1994)
42	8-Methoxy-1-methyl-2-hexyl-4-quinolone	*E. almawillia*	Trunk bark	Guilhon et al. (1994)
43	8-Methoxy-1-methyl-2-pentyl-4-quinolone	*E. almawillia*	Trunk bark	Guilhon et al. (1994)
44	8-Methoxy-2(3´-methoxy-4,5-methylenedioxyphenyl)-1-methylquinolin-4-one	*E. almawillia*	Trunk bark	Oliveira et al. (1996)
45	Eduline	*E. pentaphylla*	Bark	Simpson and Jacobs (2005)
46	Leiokinine A	*E. leiocarpa*	Stem	Cardoso-Lopes et al. (2010)
		E. leiocarpa	Leaves	Nakatsu et al. (1990)
47	Leiokinine B	*E. leiocarpa*	Leaves	Nakatsu et al. (1990)
		E. leiocarpa	Roots	Monache et al. (1990)
48	Leptomerine	*E. leiocarpa*	Stem	Cardoso-Lopes et al. (2010)
	Amides			
49	3-(1,3-benzodioxol-5-yl)-*N*-methyl-*N*-(2-phenylethyl)-2-propenamide	*E. leiocarpa*	–	Monache et al. (1990)
50	(*E*)-*N*-isobutyl-3-methoxy-4,5-methylenedioxy-cinnamoyl amide	*E. almawillia*	Root	Barros-Filho et al. (2007)
51	Pellitorin	*E. alata*	Bark	García-Beltrán and Cuca-Suárez (2003)
52	Podocarpamide	*E. leiocarpa*	–	Monache et al. (1991)

**E. grandiflora* subsp. *brevipetiolata*; ***E. grandiflora* subsp. *grandiflora*

grandiflora, E. pumila, E. yaaxhokob. Five groups of flavonoids, i.e., chalcones, catechins, flavanones, flavones and flavanols were identified in the *Esenbeckia* species (87–105, Fig. 6). Flavonoids within the genus occur either as aglycons and glycosides, with hydroxy, methoxy or glycosyl substitution. Also, 8-prenylated flavanones were identified in *E. berlandieri* (Table 2; Cano et al. 2006).

Steroids and terpenoids – Steroids and several classes of terpenoids such as polyprenols, triterpenoids, limonoids,

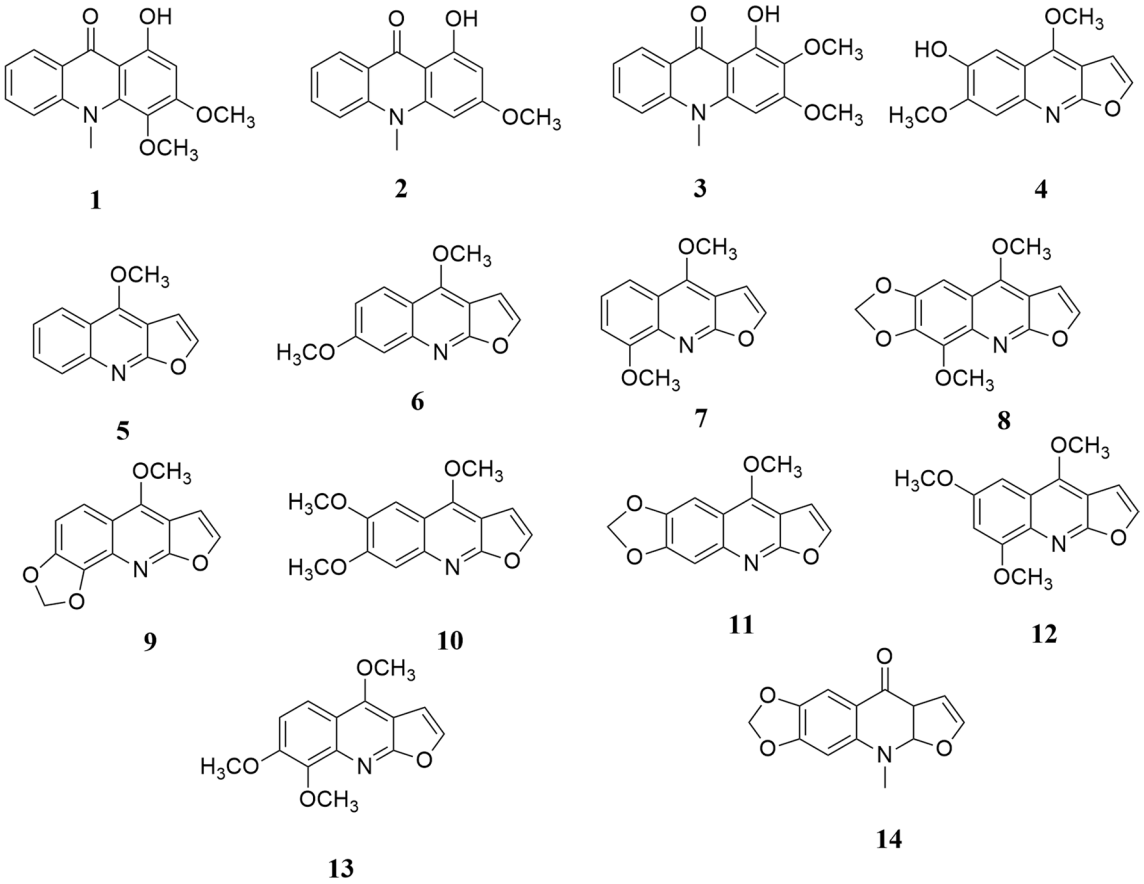


Fig. 1 Acridone (1–3), furoquinoline (4–13) and furoquinolone (14) alkaloids found into *Esenbeckia* species

sesquiterpenoids and monoterpenoids were identified in *Esenbeckia* species.

Steroids (116–120, Fig. 8) were identified into *E. alata*, *E. belizensis* Lundell, *E. conspecta* (Kaastra) Ramos, *E. grandiflora*, *E. hieronymi*, *E. leiocarpa*, *E. litoralis* Donn.Sm., *E. nesiotica* Standl., *E. ovata* Brandegee, *E. stephanii* and *E. yaaxhokob*. However, polyprenols (121–123, Fig. 8) were described only for *E. belizensis*, *E. litoralis*, *E. neositica* and *E. yaaxhokob*.

Triterpenoids (124–140, Fig. 9) belonging to pentacyclic and tetracyclic skeletons were identified into *E. alata, E. belizensis, E. grandiflora*, *E. hartmanii, E. litoralis, E. nesiotica, E. ovata, E. stephanii* and *E. yaaxhokob*. Also, highly oxygenated tetranortriterpenoids, known as limonoids, were described into *E. berlandieri, E. febrifuga, E. hartmanii* and *E. litoralis*. Limonoids are restricted to the order Rutales, and these compounds are frequently described in Meliaceae and Rutaceae (Rios and Aguilar-Guadarrama 2002; Roy and Saraf 2006). Limonoids are biosynthesized through oxidative degradation of C-17 side chain of tetracyclic skeletons, such as euphane or tirucallane, which leads to the loss of four carbon atoms as well as the formation of β-oriented furan ring. Additional oxidation and skeletal rearrangements provide structural modifications on the limonoid skeleton, which occur primarily in Meliaceae. Therefore, Meliaceae exploit different biogenetic pathways, leading to more diverse limonoids than in Rutaceae (Da Silva et al., 2021). Nevertheless, limonoids frequently found in *Citrus* (Rutaceae) have modifications on A and B rings (Roy and Saraf 2006; Tundis et al., 2014), such as Limonin (138) and its derivatives (139 and 140).

Sesquiterpenoids (141–169, Fig. 10) and monoterpenoids (170–174, Fig. 10) are present in essential oils, primarily studied in *E. almawillia*. Within *Esenbeckia*, 32 components were described in two studies of volatile oils; in *E. almawillia* oils are composed of terpenes and one alkaloid (Barros-Filho et al. 2004), while in *E. yaaxhokob* they are mainly composed of ketones (Mata et al. 1998). The extractions from barks, leaves, roots and wood of *E. almawillia* show different compositions within the aerial parts. Many components were found in leaves, whose oils were mainly composed of mono and sesquiterpenes in these aerial parts. Also, extracting essential oil from different parts provided major components such as safrole (112; 60.9–49.17% in barks), selin-11-en-4α-ol (164; 32% in roots), β-caryophyllene (145; 33.75% in leaves) and the alkaloid

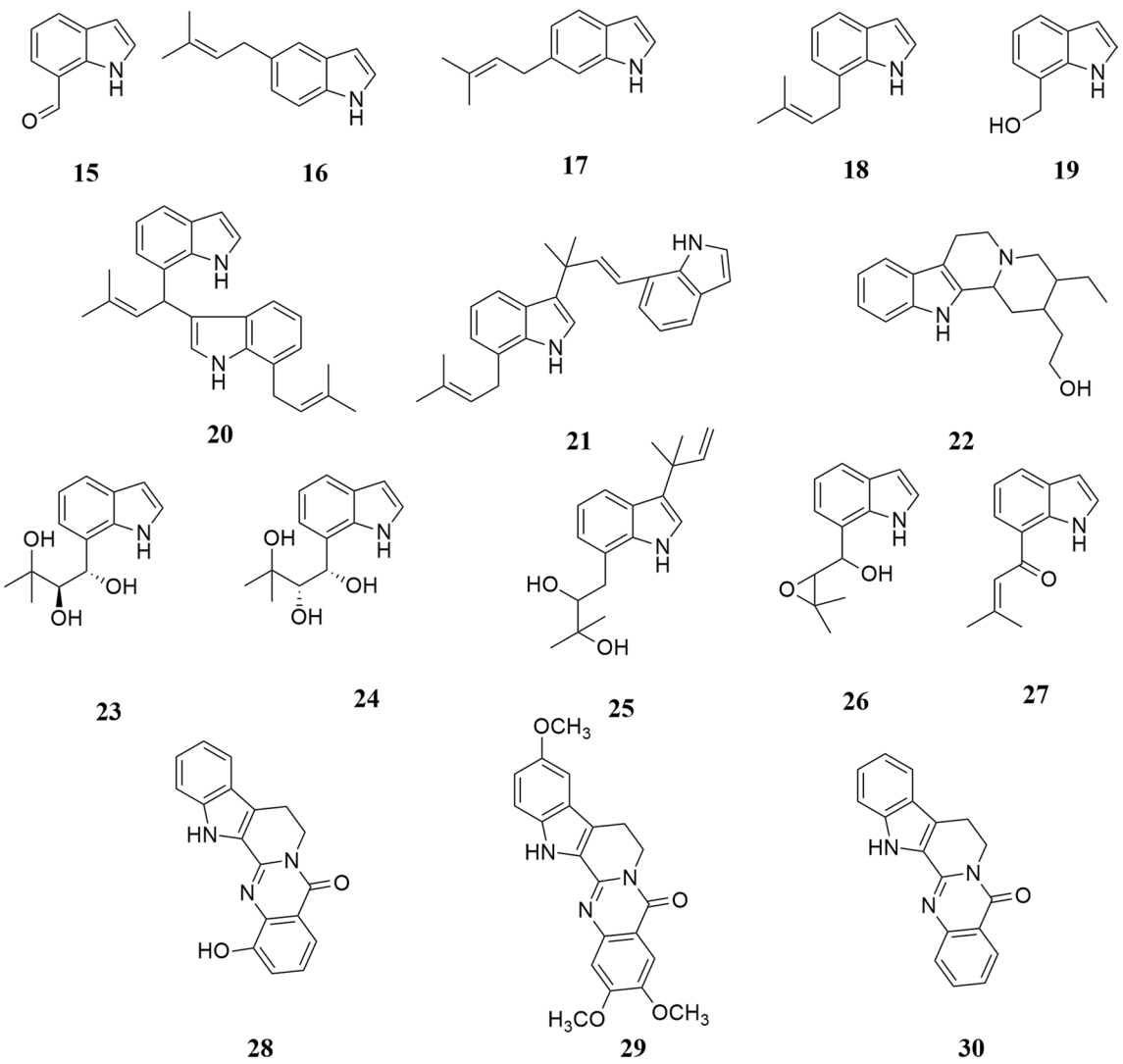


Fig. 2 Indole (15–27), β-indolopyridoquinazoline (28–30) alkaloids identified from *Esenbeckia* species

3,3-diisopentenyl-*N*-methyl-2,4-quinoldione (36; 75.28% in woods) (Barros-Filho et al. 2004). Moreover, three other sesquiterpenes, caryophyllene β-oxide (146), clovandiol (148) and spathulenol (166) were identified in leaves of additional species (*E. almawillia, E. belizensis, E. conspecta, E. hieronymi, E. litoralis, E. nesiotica, E. ovata, E. stephanii* and *E. yaaxhokob*).

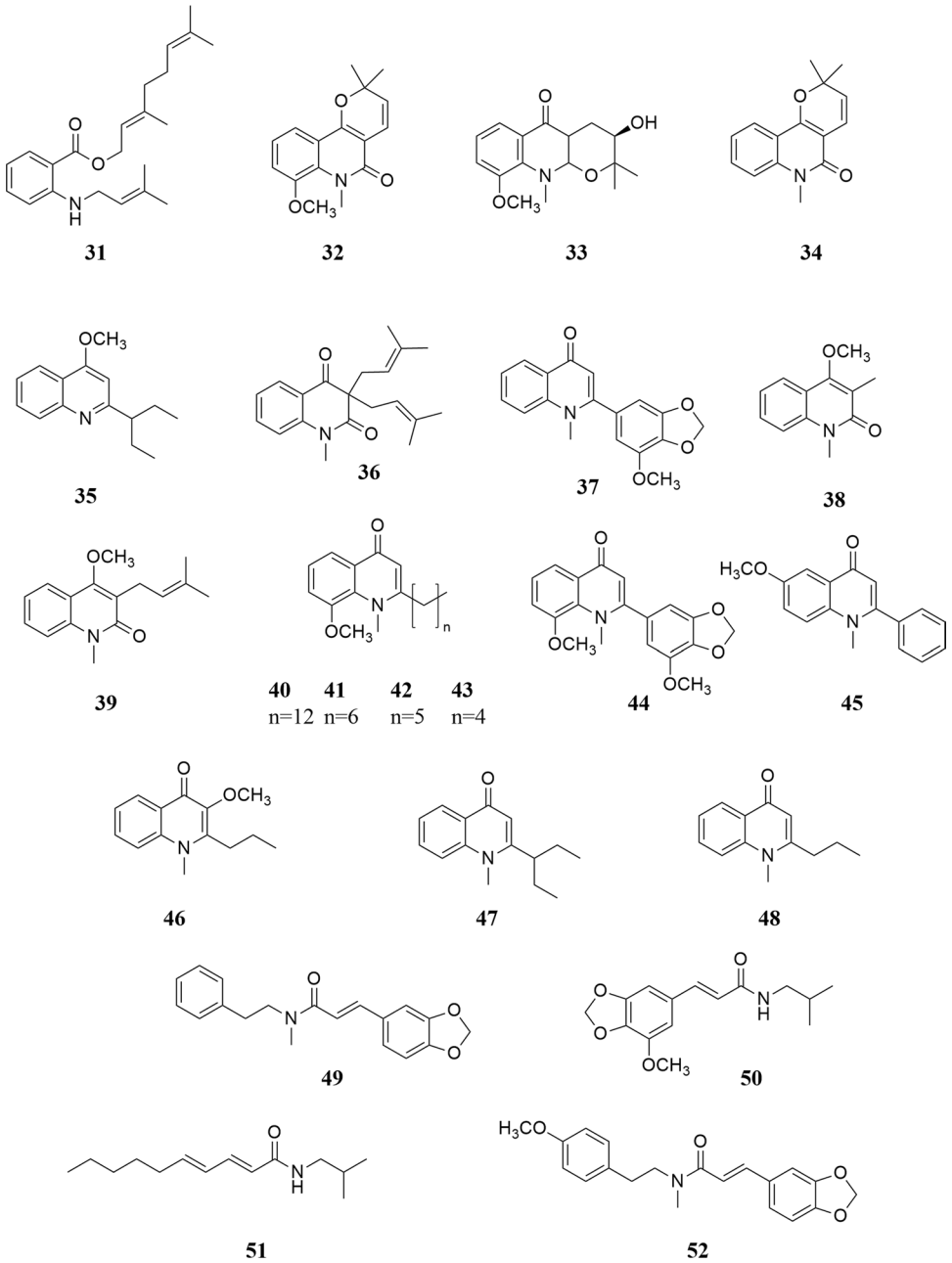


Fig. 3 Protoalkaloid (31), pyranoquinolinones (32–34), quinolines (35), quinolinones (36–48) alkaloids and amides (49–52) identified of *Esenbeckia* species

3 Biological activities of extracts and compounds of *Esenbeckia* species

Antimicrobial activity – Two species of *Esenbeckia* were studied for antimicrobial activity. *E. alata* and *E. yaaxhokob* were evaluated against gram-positive and gram-negative bacteria. Crude acetone extract of *E. yaaxhokob* inhibits the growth of *Staphyloccocus aureus* Rosenbach and *S. faecalis* Andrewes and Horder (Aguilar-Guadarrama and Rios 2004), while hydroethanolic extract from *E. alata* showed low activity in *Micrococcous luteus* (Schroeter) Cohn assay (García-Beltrán and Cuca-Suárez 2003). Both extracts were fractionated by a bioactive-guided approach. Phytochemical study of *E. yaaxhokob* yielded the compounds flindersiamine (8), geranyl-*N*-dimethylallylanthranilate (31) and, spathulenol (166). Compounds 31 and 166 showed minimal inhibitory concentration at 200 μg mL^{-1} (MIC = 200 μg mL^{-1}) against *S. aureus*. Also, compound 8 was active against *S. aureus* (50 μg mL^{-1}) and *S. faecalis* (100 μg mL^{-1}) (Aguilar-Guadarrama and Rios 2004). From *E. alata* four compounds were identified including pellitorine (51), 5-hydroxy-2-methylchromanone (53), asarinin (106) and β-sitosterol (117). However, only asarinin showed promising activity against *Bacillus subtilis* (Ehrenberg) Cohn, *Klebsiella pneumoniae*

Table 2 Phenolic derivatives identified from *Esenbeckia* species

	Compounds	*Esenbeckia* spp.	Plant parts	References
	Chromanone			
53	5-Hydroxy-2-methylchromanone	*E. alata*	Bark	García-Beltrán and Cuca-Suárez (2003)
	Cinnamic acid derivatives			
54	2-Methoxy-4,5-methylenedioxycinnamaldehyde	*E. almawillia*	Trunk bark	Guilhon et al. (1994)
55	3-Methoxy-4,5-methylenedioxycinnamic acid methyl ester	*E. almawillia*	Trunk bark	Guilhon et al. (1994)
56	Methyl-4-isoprenyloxy-*trans*-cinnamate	*E. hieronymi*	Leaves	Monache et al. (1996)
		E. leiocarpa	Root	Monache et al. (1990)
	Coumarins			
	Simple coumarins			
57	7-[(*E*)-7'-Hydroxy-3',7'-dimethylocta-2',5'-dienyloxy]-coumarin	*E. grandiflora***	Leaves and branches	Trani et al. (1997)
58	Anisocoumarin H	*E. grandiflora***	Leaves and branches	Trani et al. (1997)
59	Auraptene	*E. conspecta*	Wood	Rios et al. 2002c
		E. febrífuga	Leaves	Napolitano et al. (2004)
		E. grandiflora	Leaves	Januário et al. (2009)
		E. hieronymi	Leaves	Monache et al. (1996)
60	Daphnetin-7-methyl-8-(3,3-dimethylallyl)ether	*E. grandiflora*	Root	Oliveira et al. (2005)
61	Rutacultin	*E. alata*	Leaves and bark	Garcia-Beltrán and Cuca-Suarez (2005)
62	Scopoletin	*E. pentaphylla*	Wood	Simpson and Jacobs (2005)
63	Umbelliferone	*E. grandiflora*	Leaves	Januário et al. (2009)
	Furanocoumarins			
64	3-(1',1'-dimethylallyl)-columbianetin	*E. grandiflora*	Root	Oliveira et al. (1996, (2005)
		*E. grandiflora**	Root	Trani et al. (2004)
65	3,8-dimethoxyfuro[3,2-g]coumarin	*E. grandiflora***	Root	Nunes et al. (2005a)
66	5-(1'-hydroxy-isopentenyl)-bergapten	*E. grandiflora*	Root	Oliveira et al. (2005)
67	5-Senecioylxanthotoxin	*E. grandiflora*	Root	Oliveira et al. (2005)
		*E. grandiflora**	Root	Trani et al. (2004)
68	8-Hydroxy-bergapten	*E. litoralis*	Bark	Dreyer (1980)
69	Alloimperatorin	*E. litoralis*	Bark	Dreyer (1980)
70	Bergapten	*E. alata*	Leaves	García-Beltrán et al. (2014)
		E. berlandieri	Husks	Dreyer (1980)
		E. febrifuga	Stem	Dolabela et al. (2008)
		E. litoralis	Leaves	Rios et al. (2002a)
			Husk	Dreyer (1980)
		E. ovata	Leaves	Rios and Delgado (2002)
71	Chalepensin	*E. alata*	Leaves	García-Beltrán et al. (2014)
72	Chalepin	*E. almawillia*	Bark	Oliveira et al. (1996)
73	*exo*-Dehydrochalepin	*E. alata*	Leaves and bark	Garcia-Beltrán and Cuca-Suarez (2005)
74	(-)-Heraclenol	*E. grandiflora***	Leaves and branches	Trani et al. (1997)
75	Imperatorin	*E. grandiflora***	Leaves	Trani et al. (1997)
		E. litoralis	Bark	Dreyer (1980)
		E. pentaphylla	Wood	Simpson and Jacobs (2005)
		E. yaaxhokob	Aerial parts	Mata et al. (1998)
76	Isoangenomilin	*E. alata*	Wood	García-Beltrán et al. (2014)
77	Isopimpinellin	*E. almawillia*	Trunk bark	Guilhon et al. (1994)
		E. febrífuga	Stem	Dolabela et al. (2008)
		E. grandiflora	Root	Oliveira et al. (2005)
		*E. grandiflora**	Root	Trani et al. (2004)
		E. litoralis	Leaves	Rios et al. (2002a)

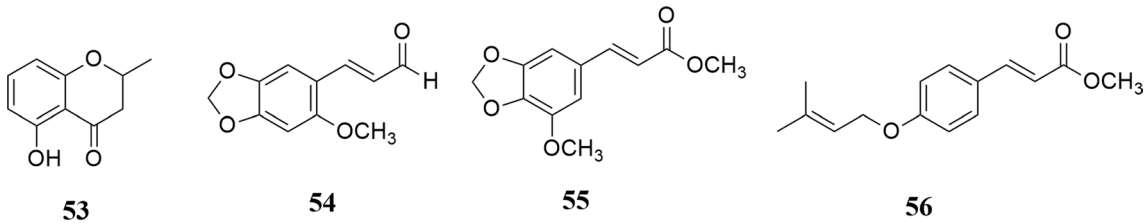
Table 2 (continued)

	Compounds	*Esenbeckia* spp.	Plant parts	References
			Husk and bark	Dreyer (1980)
		E. ovata	Leaves	Rios and Delgado (2002)
78	Leptophyllidin	*E. alata*	Wood	García-Beltrán et al. (2014)
79	Phellopterin	*E. conspecta*	Wood	Rios et al. (2002b)
		E. litoralis	Wood and bark	Dreyer (1980)
		E. ovata	Leaves	Rios and Delgado (2002)
80	Pimpinellin	*E. grandiflora*	Root	Januário et al. (2009)
			Root	Oliveira et al. (2004, (2005)
			Bark	Oliveira et al. (1996)
		*E. grandiflora**	Root	Trani et al. (2004)
81	Psoralen	*E. alata*	Leaves	Suárez and Barrera (2007)
82	(+)-Marmesin	*E. leiocarpa*	Root	Monache et al. (1990)
83	Methoxyrutaretin	*E. litoralis*	Leaves	Rios et al. (2002a)
84	Swietenocoumarin B	*E. grandiflora*	Root	Oliveira et al. (2005)
85	Xanthotoxin	*E. alata*	Leaves	Suárez and Barrera (2007)
		E. grandiflora	Root	Oliveira et al. (2005; Januário et al. (2009)
		*E. grandiflora**	Root	Trani et al. (2004)
		E. hieronymi	Leaves	Monache et al., 1995
		E. litoralis	Leaves	Rios et al. (2002a)
		E. ovata	Leaves	Rios and Delgado (2002)
	Pyranocoumarin			
86	Xanthyletin	*E. alata*	Leaves	Suárez and Barrera (2007)
	Flavonoids			
	Catechin			
87	(-)-Epigallocatechin	*E. grandiflora***	Leaves	Trani et al. (1997)
	Chalcones			
88	1-[3-[(2*E*)-3,7-dimethyl-2,6-octadien-1-yl]-2,4,6-trihydroxyphenyl]-3-(8-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-yl)-1-propanone	*E. grandiflora**	Leaves and branches	Trani et al. (2004)
89	3-[3,4-dihydroxy-5-(3-methyl-2-buten-1-yl)phenyl]-1-[2,4,6-trihydroxy-3-(3-methyl-2-buten-1-yl) phenyl]-1-propanone	*E. grandiflora**	Leaves and branches	Trani et al. (1997)
90	3-[3,4-dihydroxy-5-(3-methyl-2-butenyl)phenyl]-1-[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]-1-propanone	*E. grandiflora**	Leaves and branches	Trani et al. (1997)
91	Dihydrochalcone M-1	*E. grandiflora***	Leaves	Trani et al. (2004)
92	Dihydrochalcone M-2	*E. grandiflora***	Leaves	Trani et al. (2004)
	Flavanones			
93	5,4'-dihydroxy-7-methoxy-8-(2,3-dihydroxy-3-methylbutyl)flavanone	*E. berlandieri*▲	Aerial parts	Cano et al. (2006)
94	5,7,4'-trihydroxy-8-(2,3-dihydroxy-3-methylbutyl) flavanone	*E. berlandieri*▲	Aerial parts	Cano et al. (2006)
95	5,7-dihydroxy-8-(2,3-epoxy-3-methylbutyl)flavanone	*E. berlandieri*▲	Aerial parts	Cano et al. (2006)
96	7-O-Methylglabranin	*E. berlandieri*▲	Aerial parts	Cano et al. (2006)
97	8-Prenylnaringenin	*E. berlandieri*▲	Aerial parts	Cano et al. (2006)
98	Flowerine	*E. berlandieri*▲	Aerial parts	Cano et al. (2006)
99	Glabranin	*E. berlandieri*▲	Aerial parts	Cano et al. (2006)
100	Hesperidin	*E. febrifuga*	Bark	Cosenza et al. (2019)
		E. yaaxhokob	Aerial parts	Mata et al. (1998)
	Flavones			
101	Gardenine B	*E. almawillia*	Root	Barros-Filho et al. (2007)

Table 2 (continued)

	Compounds	*Esenbeckia* spp.	Plant parts	References
102	Nevadensin	*E. almawillia*	Root	Barros-Filho et al. (2007)
	Flavonols			
103	Afzelin	*E. grandiflora***	Leaves and branches	Trani et al. (1997)
		*E. grandiflora**	Leaves	Trani et al. (2004)
104	Quercitrin	*E. grandiflora***	Leaves and branches	Trani et al. (1997)
		*E. grandiflora**	Leaves	Trani et al. (2004)
105	Rutin	*E. pumila*	Leaves	Kubo et al. (1990)
	Lignoids			
106	Asarinin	*E. alata*	Bark	García-Beltrán and Cuca-Suárez (2003)
		E. yaaxhokob	Aerial parts	Mata et al. (1998)
107	Lirioresunol B dimethyl ether	*E. leiocarpa*	Root	Monache et al. (1990)
108	Methylpiperitol	*E. leiocarpa*	Root	Monache et al. (1990)
109	(+)-Sesamin	*E. leiocarpa*	Root	Monache et al. (1990)
110	(-)-Sesamin	*E. alata*	Leaves	Suárez and Barrera (2007)
	Phenylpropanoid and Simple Phenolic			
111	3,5-dimethoxy-4-hydroxy-benzaldehyde	*E. pentaphylla*	Wood	Simpson and Jacobs (2005)
112	Safrole	*E. almawillia*	Trunk wood (VO)	Barros-Filho et al. (2004)
	Phloroglucinols			
113	3-geranyl-1-(2-methylbutanoyl)-phloroglucinol	*E. nesiotica*	Leaves	Rios and Delgado (1992b)
114	3-geranyl-1-(3-methylbutanoyl)-phloroglucinol	*E. nesiotica*	Leaves	Rios and Delgado (1992b)
115	3-geranyl-1-(2-methylpropanoyl)-phloroglucinol	*E. nesiotica*	Leaves	Rios and Delgado (1992b)

**E. grandiflora* subsp. *brevipetiolata*; ***E. grandiflora* subsp. *grandiflora*; ▲*E. berlandieri* subsp. *acapulcensis*; VO: volatile oil



53 54 55 56

Fig. 4 Chromanone (53) and cinnamic acid derivatives (54–56) identified from *Esenbeckia* species

(Schroeter) Trevisan and *Pseudomonas aeruginosa* (Schroeter) Migula (García-Beltrán and Cuca-Suárez 2003).

Cytotoxic activity – Bioactive-guided studies by MTT assay using three *Esenbeckia* species evaluated alkaloids (Nunes et al. 2005b; Álvarez-Caballero et al. 2019), triterpenoids (Victor et al. 2017) and synthetic derivatives (Nunes et al. 2005b; Victor et al. 2017) against different tumor cell lines. These studies highlight structure-relationships of *Esenbeckia* compounds to enhance cytotoxic activities.

Methanol extract from roots and woods of *E. almawillia* and its fractions were tested against five tumor cells lines (HL-60 and CEM, human leukemia, B-16 murine melanoma, HCT-8 human colon and MCF-7 human breast). Antitumoral activity was inversely proportional to the polarity of the solvent used in the extraction procedure. Therefore, the most active extract was obtained using hexane as solvent. From this fraction, 3,3-diisopentenyl-*N*-methyl-2,4-quinoldione (36) was isolated as a primary compound (Nunes et al. 2005b). Although the activity of 36 was tested in all cell lineages, the results demonstrated other non-identified compounds responsible for good activity in the hexane fraction. Also, several modifications in the alkaloid structure leading to O-acyl, O-alkyl and isoprenyl derivatives were obtained, enhancing the activity from the isolated alkaloid and verify structure–activity relationships. Through this study, it was possible to correlate the increase in antitumoral activity with the presence of carbonyl and isoprenyl groups in the structure (Nunes et al. 2005b).

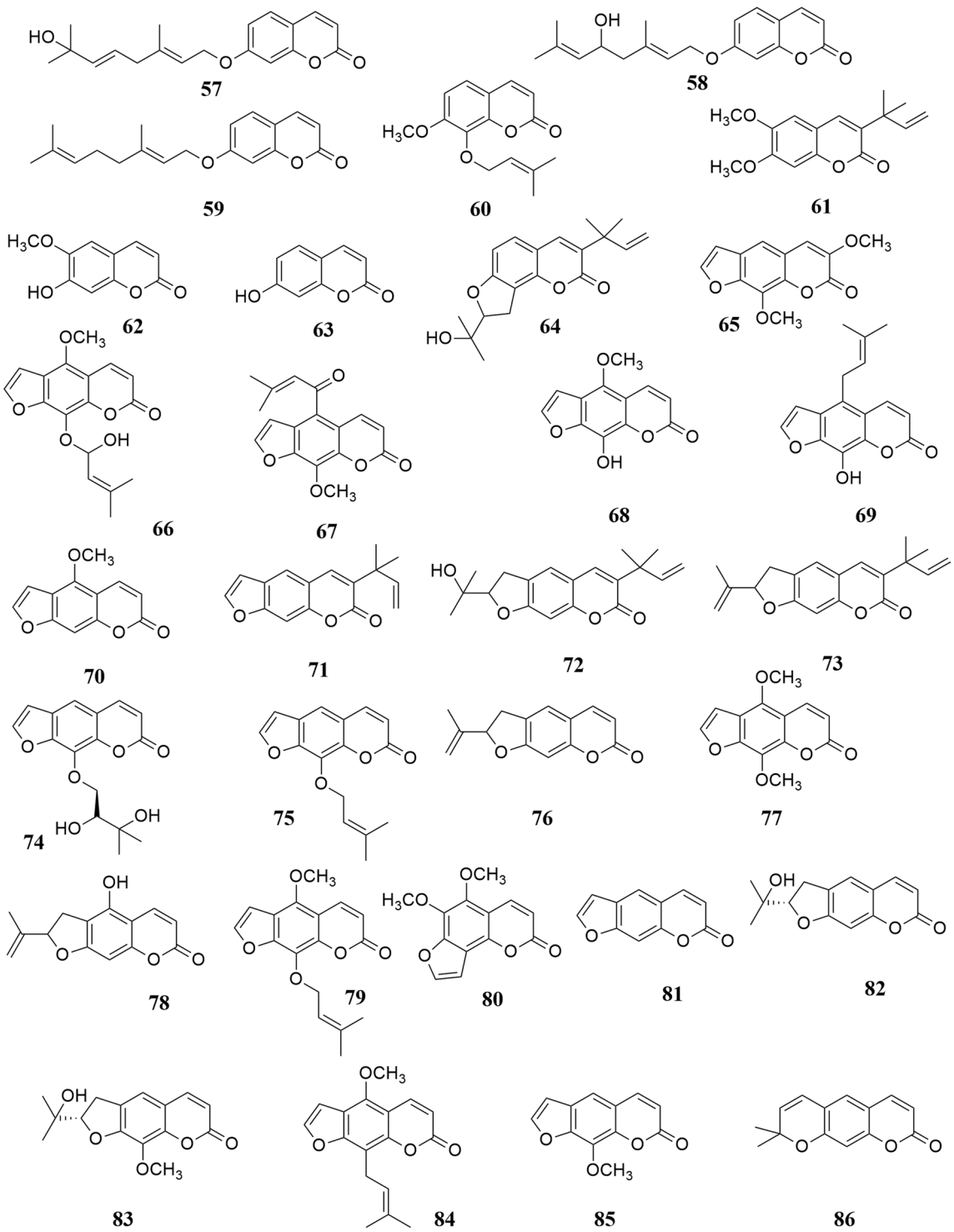


Fig. 5 Simple coumarins (57–59), furanocoumarins (64–85) and pyranocoumarin (86) described from *Esenbeckia* species

Similarly, structure-relationship studies were performed with α- and β-amyrin derivatives isolated from *E. grandiflora*. Both compounds were esterified and subsequently treated with amines affording amino acetyl derivatives. These compounds were evaluated by three human tumor cell lines (HCT-116, colon; HL-60, leukemia; and PC-3, prostate) using MTT assay. This study concluded that diethylamine and imidazole derivatives exhibit higher cytotoxic

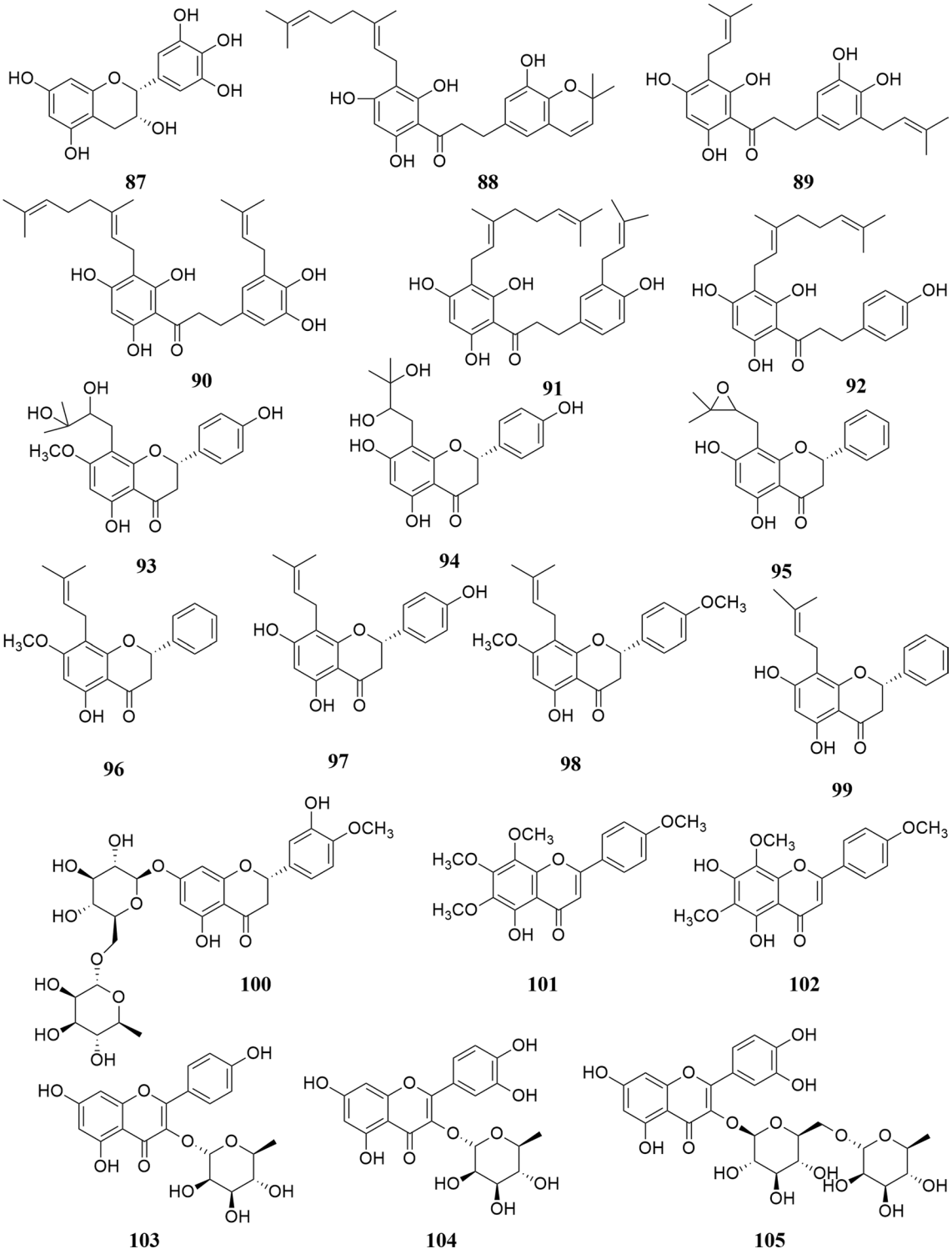


Fig. 6 Catechin (87), chalcones (88–92), flavanones (93–100), flavones (101–102) and flavonols (103–105) identified of *Esenbeckia* species

Table 3 Steroids and terpenoids isolated from *Esenbeckia* species

	Compounds	*Esenbeckia* spp.	Plant parts	References
	Steroids			
116	Campesterol	*E. grandiflora*	Leaves	Januário et al. (2009)
117	β-Sitosterol	*E. alata*	Bark	García-Beltrán and Cuca-Suárez 200
		E. belizencis	Leaves	Rios and Delgado (1992a)
		E. conspecta	Wood	Rios et al. (2002b)
		E. grandiflora	Leaves and stems	Januário et al. (2009)
			Root	Oliveira et al. (2005)
		E. leiocarpa	Bark	Liz et al. (2011, (2013)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. nesiotica	Leaves	Rios and Delgado (1992b)
		E. ovata	Leaves	Rios and Delgado (2002)
		E. stephani	Leaves	Rios and Aguilar-Guadarrama (2002)
		E. yaaxhokob	Leaves	Aguilar-Guadarrama and Rios (2004)
118	Sitostenone	*E. grandiflora*	Root	Oliveira et al. (2005)
119	β-Sitosteryl glucoside	*E. conspecta*	Wood	Rios et al. (2002b)
		E. grandiflora	Leaves	Januário et al. (2009)
120	Stigmasterol	*E. grandiflora*	Leaves	Januário et al. (2009)
		E. hieronymi	Leaves	Monache et al. (1996)
	Polyprenols			
121	[3*E*,6*Z*]-10-Prenol	*E. nesiotica*	Leaves	Rios and Delgado (1992b)
122	[3*E*,9*Z*]-13-Prenol	*E. nesiotica*	Leaves	Rios and Delgado (1992b)
123	Decaprenol	*E. belizencis*	Leaves	Rios and Delgado (1992a)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. yaaxhokob	Leaves	Aguilar-Guadarrama and Rios (2004)
	Triterpenoids			
124	(24*S*)-24-Methyl-dammara-20,25-diene-3β-yl-acetate	*E. yaaxhokob*	Aerial parts	Mata et al. (1998)
125	3α-Hydroxy-12,13-epoxy-oleanane	*E. grandiflora*	Leaves	Januário et al. (2009)
126	3α-Hydroxy-ursan-12-one	*E. grandiflora*	Leaves	Januário et al. (2009)
127	α-Amyrenonol	*E. grandiflora*	Leaves	Januário et al. (2009)
128	α-Amyrin	*E. grandiflora***	Leaves	Nunes et al. (2005a)
		E. grandiflora	Leaves and stems	Januário et al. (2009)
129	β-Amyrin	*E. grandiflora***	Laves	Nunes et al. (2005a)
		E. grandiflora	Leaves and stems	Januário et al. (2009)
130	β-Amyrenonol	*E. grandiflora*	Leaves	Januário et al. (2009)
131	Friedelanol	*E. alata*	Leaves	Cuca-Suarez et al. (2011)
		E. belizencis	Leaves	Rios and Delgado (1992a)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. yaaxhokob	Leaves	Aguilar-Guadarrama and Rios (2004)
132	Friedeline	*E. alata*	Leaves	Cuca-Suarez et al. (2011)
		E. belizencis	Leaves	Rios and Delgado (1992a)
		E. berlandieri▲	Aerial parts	Cano et al. (2006)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. nesiotica	Leaves	Rios and Delgado (1992b)
		E. ovata	Leaves	Rios and Delgado (2002)
		E. stephani	Leaves	Rios and Aguilar-Guadarrama (2002)
		E. yaaxhokob	Leaves	Aguilar-Guadarrama and Rios (2004)
133	Fridelanyl acetate	*E. alata*	Leaves	Cuca-Suarez et al. (2011)
134	Lupenone	*E. belizencis*	Leaves	Rios and Delgado (1992a)
		E. ovata	Leaves	Rios and Delgado (2002)

Table 3 (continued)

	Compounds	*Esenbeckia* spp.	Plant parts	References
135	Lupeol	*E. alata*	Leaves	Suarez et al. 2007
		E. nesiotica	Leaves	Rios and Delgado (1992b)
		E. ovata	Leaves	Rios and Delgado (2002)
		E. yaaxhokob	Aerial parts	Mata et al. (1998)
136	Wallenol	*E. stephani*	Leaves	Rios and Aguilar-Guadarrama (2002)
137	Wallenone	*E. stephani*	Leaves	Rios and Aguilar-Guadarrama (2002)
	Limonoids			
138	Limonin	*E. hartmanii*	Stems and branches	Dreyer et al. (1972)
		E. litoralis	Seed	Dreyer (1980)
139	Limonin diosphenol	*E. flava*	Seed	Dreyer et al. (1972)
		E. hartmanii	Stems and branches	Dreyer et al. (1972)
140	Rutaevin	*E. berlandieri*	Seed	Dreyer (1980)
		E. flava	Seed	Dreyer (1980)
		E. febrifuga	Stem	Dolabela et al. (2008)
			Bark	Vitagliano and Comin (1970)
		E. hartmanii	Stems and branches	Dreyer et al. (1972)
		E. litoralis	Seed	Dreyer (1980)
	Sesquiterpenoids			
141	10-epi-γ-Eudesmol	*E. almawillia*	Trunk bark and root (VO)	Barros-Filho et al. (2004)
142	α-Acorenol	*E. almawillia*	Bark (VO)	Barros-Filho et al. (2004)
143	δ-Cadinene	*E. almawillia*	Leaves and bark (VO)	Barros-Filho et al. (2004)
144	Caryolanne-5β,8β-diol	*E. yaaxhokob*	Leaves	Aguilar-Guadarrama and Rios (2004)
145	β-Caryophyllene	*E. almawillia*	Leaves and bark (VO)	Barros-Filho et al. (2004)
146	Caryophyllene β-oxide	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
		E. belizencis	Leaves	Rios and Delgado (1992a)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. nesiotica	Leaves	Rios and Delgado (1992b)
		E. ovata	Leaves	Rios and Delgado (2002)
		E. stephani	Leaves	Rios and Aguilar-Guadarrama (2002)
		E. yaaxhokob	Laves	Aguilar-Guadarrama and Rios (2004)
147	β-Chamigrene	*E. almawillia*	Leaves, bark and root	Barros-Filho et al. (2004)
148	Clovandiol	*E. conspecta*	Wood	Rios et al. (2002b)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. nesiotica	Leaves	Rios and Delgado (1992b)
149	Cryptomeridiol	*E. ovata*	Leaves	Rios and Delgado (2002)
150	ar-Dihydroturmerone	*E. almawillia*	Bark (VO)	Barros-Filho et al. (2004)
151	Drima-7,9(11)-diene	*E. almawillia*	Rot (VO)	Barros-Filho et al. (2004)
152	β-Elemene	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
153	Elemol	*E. almawillia*	Bark and root (VO)	Barros-Filho et al. (2004)
154	Eremophilene	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
155	*cis*-α-Farnesene	*E. hieronymi*	Leaves	Monache et al. (1996)
156	*trans*-β-Guaiene	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
157	α-Humulene	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
158	Intermediol	*E. almawillia*	Root	Barros-filho et al., (2007)
159	Z-Lanceol	*E. almawillia*	Bark and root (VO)	Barros-Filho et al. (2004)
160	Muurolol[a]	*E. almawillia*	Leaves and bark (VO)	Barros-Filho et al. (2004)
161	γ-Muurolene	*E. almawillia*	Leaves and bark (VO)	Barros-Filho et al. (2004)
162	*E*-Nerolidol	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
163	Patchulane	*E. almawillia*	Bark and root (VO)	Barros-Filho et al. (2004)
164	Selin-11-en-4α-ol	*E. almawillia*	Root (VO)	Barros-Filho et al. (2004)

Table 3 (continued)

	Compounds	*Esenbeckia* spp.	Plant parts	References
165	epi-α-Selinene	*E. almawillia*	Bark and root (VO)	Barros-Filho et al. (2004)
166	Spathulenol	*E. belizencis*	Leaves	Rios and Delgado (1992a)
		E. litoralis	Leaves	Rios et al. (2002a)
		E. conspecta	Wood	Rios et al. (2002b)
		E. yaaxhokob	Leaves	Aguilar-Guadarrama and Rios (2004)
167	Turmerol	*E. almawillia*	Bark (VO)	Barros-Filho et al. (2004)
168	ar-Turmerone	*E. almawillia*	Bark (VO)	Barros-Filho et al. (2004)
169	Valencene	*E. almawillia*	Leaves bark and root (VO)	Barros-Filho et al. (2004)
	Monoterpenoids			
170	Myrcene	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
171	*E*-Ocimenone	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
172	*Z*-Ocimenone	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
173	β-Phellandrene	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)
174	α-Pinene	*E. almawillia*	Leaves (VO)	Barros-Filho et al. (2004)

**E. grandiflora* subsp. *brevipetiolata*; ***E. grandiflora* subsp. *grandiflora*; ▲*E. berlandieri* subsp. *acapulcensis*; VO: volatile oil; [a]Isomer not defined

activity, mainly against HL-60 cell line. Additionally, the alkyl chain in dimethylamine and the second coordination atom in the imidazole ring were essential features for this activity (Victor et al. 2017).

Also, the cytotoxic activity of *E. alata* was evaluated in several tumor cell lines (U251, central nervous system, PC-3 prostate, HCT-15 colon, MCF-7 breast, SKLU-1 lung and K562 myeloid leukemia). The ethanol extract of *E. alata* at a concentration of 50 μg mL^{-1} shows 60% activity against K562, PC-3, MCF-7 and SKLU-1 cell lines. The most expressive activity was observed on K562 (97%), indicating a good selectivity of the extract. This pattern was also found for flindersiamine (8) and kokusaginine (10) (86–96% against K562). Comparing both furanoquinoline alkaloids, 10 exhibited higher activity in all tested tumor cell lines, except SKLU-1. Both furanoquinoline alkaloids demonstrated a positive interaction profile with UBA-5 (ubiquitin-activating enzyme 5), as well as binding modes to E1 inhibitor, indicating that studies with furanoquinoline alkaloids are promising for antitumoral therapy development (Álvarez-Caballero et al. 2019).

Leishmanicidal, antiplasmodial and larvicidal activities – Compounds of *E. febrifuga* and *E. grandifolia* furnished positive results as natural treatments against vector-borne diseases such as malaria, dengue, yellow fever, leishmaniasis and Chagas disease.

Esenbeckia febrifuga was a source of compounds against *Leishmania major* and two strains of *Plasmodium falciparum* Welch (sensitive to chloroquine, CQS and resistant to chloroquine, CQR). The ethanol extract of *E. febrifuga* showed activity against CQS and CQR strains $IC_{50} = 21.0 \pm 1.4$ and 15.5 ± 0.7 μM, respectively; however arborinine (3) and rutaevin (140) were considered inactive. On the other hand, γ-fagarine (7) and skimmianine (13) exhibited moderate activity, indicating a synergistic effect contributing to observed activity in the extract (Dolabela et al. 2008). Also, auraptene (59), isolated from *E. febrifuga*, significantly inhibits promastigote forms of *Leishmania major* Yakimoff & Schokhor (LD = 30 μM). The molecular configuration of 59 showed that planarity and intermolecular interactions were similar to other inhibitors of *Leishmania* (Napolitano et al. 2004).

Coumarins isolated from *E. grandifolia* were good agents against *Aedes aegypti* L. larvae. Mixtures of isopimpinellin (77) and pimpinellin (80) as well as 80 and swietenocoumarin B (84) were also effective against larvae ($LC_{50} = 45.77$ and 62.23 ppm, respectively). Both mixtures may represent an alternative source to *A. aegypti* control (Oliveira et al. 2005).

Anti-inflammatory activity – *Esenbeckia leiocarpa* has been pointed out as a promisor anti-inflammatory agent. Hydroethanolic extract showed relevant properties as a mediator in inflammatory response. The extract was able to significantly reduce NO, IL-1β and TNF-α levels and inhibit myeloperoxidase (MPO) and adenosine deaminase (ADA) enzymes involved in activation of neutrophils and mononuclear leukocytes (Liz et al. 2011). Indeed, activation of human polymorphonuclear neutrophils by this extract was proven by actin polymerization, cell events signaling and cleavage of cytoskeletal proteins (Pozzatti et al. 2011), together with induction of neutrophil apoptosis (Liz et al. 2012a). To isolate and test compounds produced by *E. leiocarpa,*

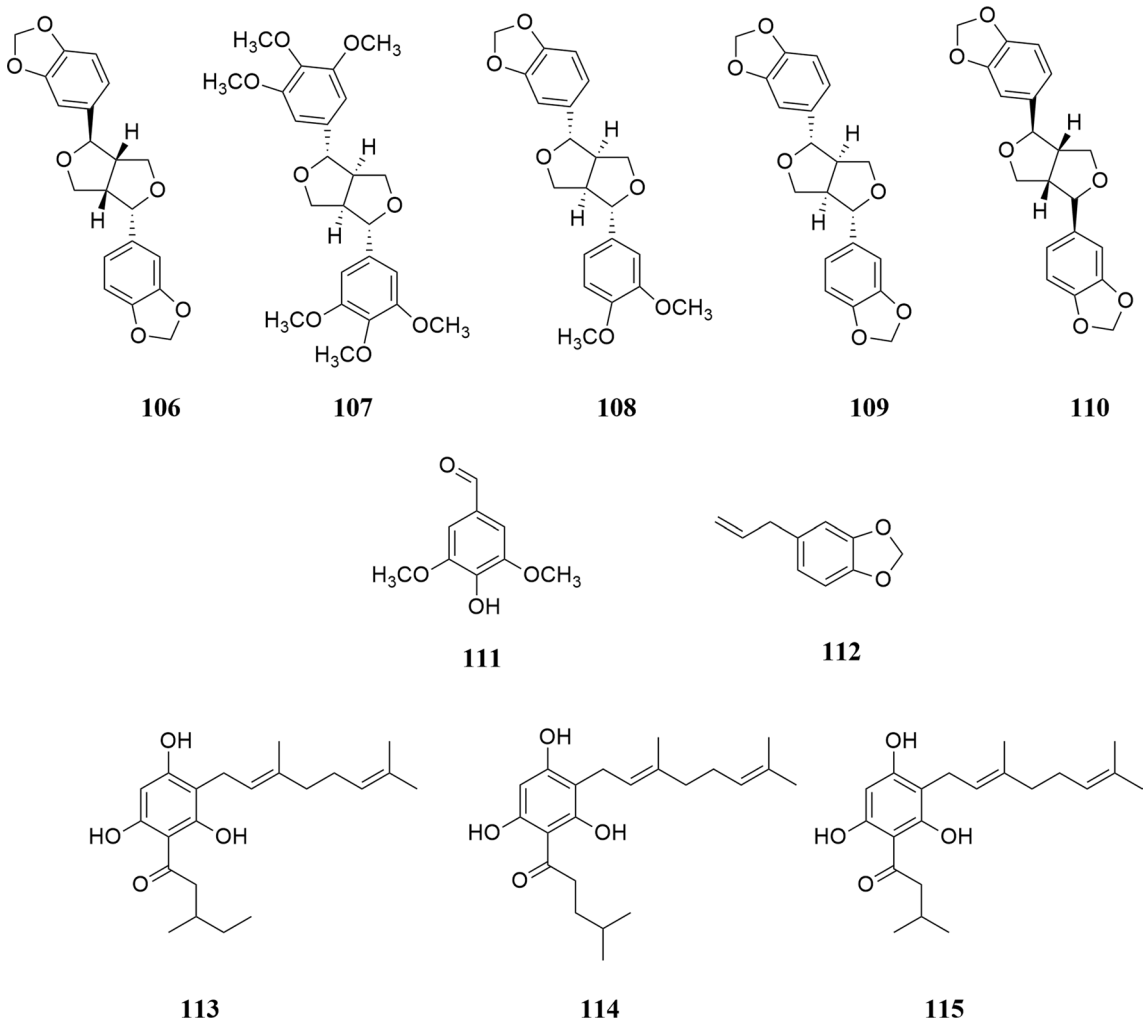


Fig. 7 Lignoids (106–110), phenylpropanoid and simple phenolic (111–112) and phloroglucinols (113–115) described from *Esenbeckia* species

hydroethanolic crude extract was fractionated through an acid-basic extraction, leading to an enriched alkaloid fraction, treated with ethyl ether and yielding soluble and insoluble subfractions (Liz et al. 2011, 2012b, 2013; Pozzatti et al. 2011). The soluble subfraction was the most active and furnished dihydrocorynantheol (22) and β-sitosterol (117) (Liz et al. 2011, 2013; Pozzatti et al. 2011). Both compounds inhibited inflammation induced by carageen (Liz et al. 2011). However, in vitro and in vivo assays demonstrated a pleiotropic effect of compound 117 in a dose-dependent manner and showing anti-inflammatory effectiveness only in higher doses (Liz et al. 2013).

Allelopathic and antifeedant activities – Essential oils extracted from aerial parts of *E. yaaxhokob* inhibited radicle growth of *Lycopersicum esculentum* Mill. (89.4%, 1000 μg mL^{-1}) and germination of *Echonochloa crusgalli* (L.) P. Beauv. (88.3%, 1000 μg mL^{-1}), *Lactuca sativa* L. (86.5%, 1000 μg mL^{-1}) and *Lycopersicum esculentum* (82.5%, 1000 μg mL^{-1}). This extract was mainly composed of 2-tridecanone (179; 84%), which also exhibit high phytotoxicity (Mata et al. 1998). Similarly, imperatorin (75) was also identified into *E. yaaxhokob* and was considered an allelopathic agent and phytogrowth inhibitor. These characteristics are shown through ATP synthesis inhibition ($IC_{50} = 71.5 \pm 1.3$ μM) and as an uncoupling agent, activating Mg^{2+} ATPase by 614% (Mata et al. 1998).

Antifeedant activity was described into two quinoline alkaloids isolated from *E. leiocarpa*. Leiokinine B (47) and leptomerine (48) showed antifeedant activity against a pink bollworm *Pectinophora gossypiela* Saunders (Nakatsu et al. 1990).

Anticholinesterase activity – *Esenbeckia leiocarpa* furnished compounds with anticholinesterase activity, which is pointed out as a possible alternative for the treatment of Alzheimer's disease. The alkaloids skimmianine (13) and leiokinine A (46) inhibited acetylcholinesterase (AChE)

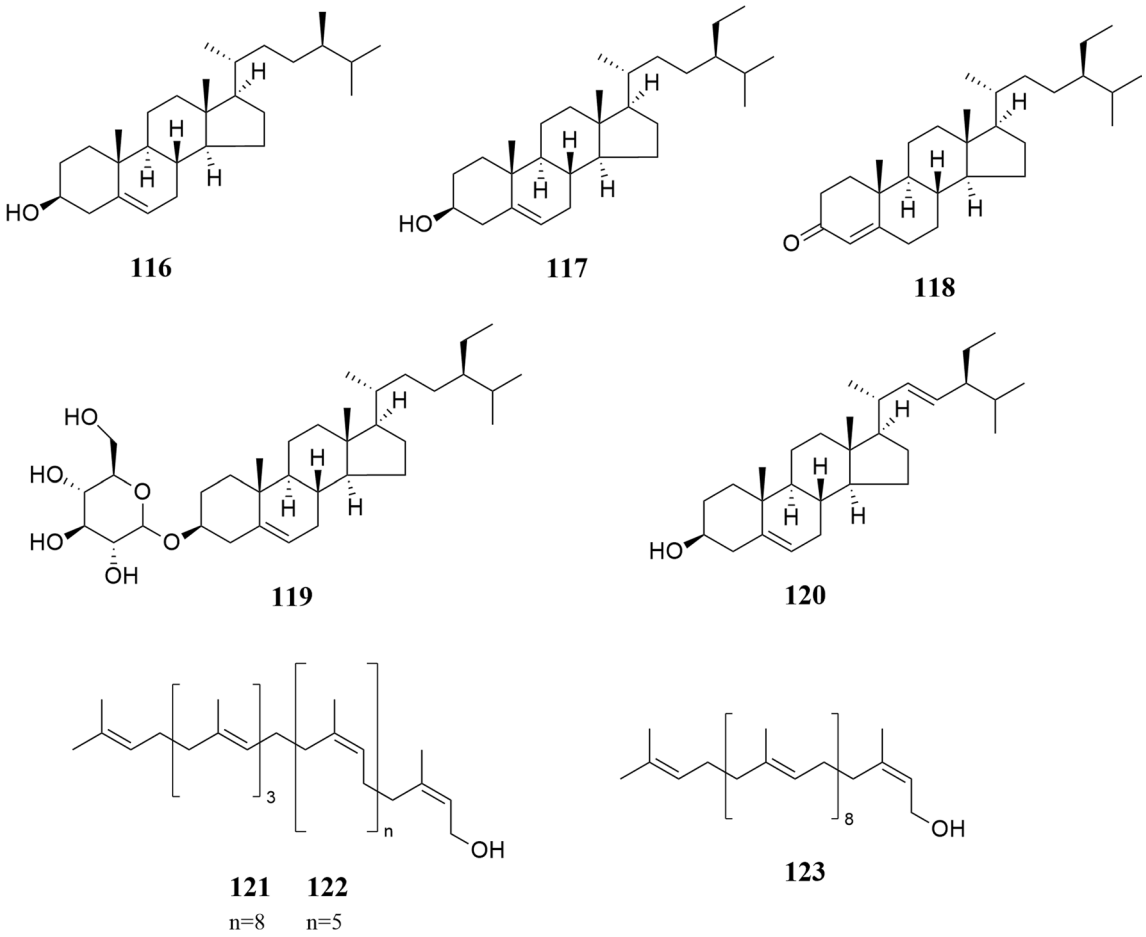


Fig. 8 Steroids (116–120) and polyprenols (121–123) identified from *Esenbeckia* species

(IC_{50} = 0.21 mM). Also, kokusaginine (10; IC_{50} = 46 µM) and leptomerine (48; IC_{50} = 2.5 µM) were similar to galantamine and physostigmine, reference drugs to anticholinesterase activity (Cardoso-Lopes et al. 2010).

4 Chemophenetic characters of *Esenbeckia* species

Compounds identified in *Esenbeckia* species are distributed in Table 5 according to division into subgenera and sections proposed by Kaastra (1982). The chemical data do not corroborate the taxa below genus level proposed for *Esenbeckia*, since it is not possible to find compounds that characterize any subgenus or section.

According to the distribution of metabolite classes, *E. pumila* is an outgroup because it has been under investigated chemically. Only the flavonoid rutin (105) was described for *E. pumila*.

Alkaloids were widespread in *Esenbeckia*, however they were not identified into *E. berlandieri*, *E. nesiotica*, *E. ovata* and *E. stephanii*. Further investigation should be carried out to ensure the absence of alkaloids in these species. Quinolinone alkaloids have previously been suggested as a chemotaxonomic marker of the genus (Barros-Filho et al. 2004). However, these compounds were only identified in *E. almawillia*, *E. flava*, *E. grandiflora*, *E. leiocarpa* and *E pentaphylla* (MacFad.) Griseb. Furanoquinolines alkaloids were considered important characters in *Esenbeckia* (Rios et al. 2002a). These compounds were identified in all alkaloid producers' species. Also, flindersiamine (8), kokusaginine (10) and, skimmianine (13) are widely distributed in *Esenbeckia*. On the other hand, indole and β-indolopyridoquinazoline alkaloids were identified only of *E. leiocarpa* and *E. grandiflora*, respectively. Acridone, pyranoquinoline and quinolinone alkaloids are of restricted occurrence among *Esenbeckia* species (Table 5). Thus, these alkaloid types could be useful to distinguish groups of species.

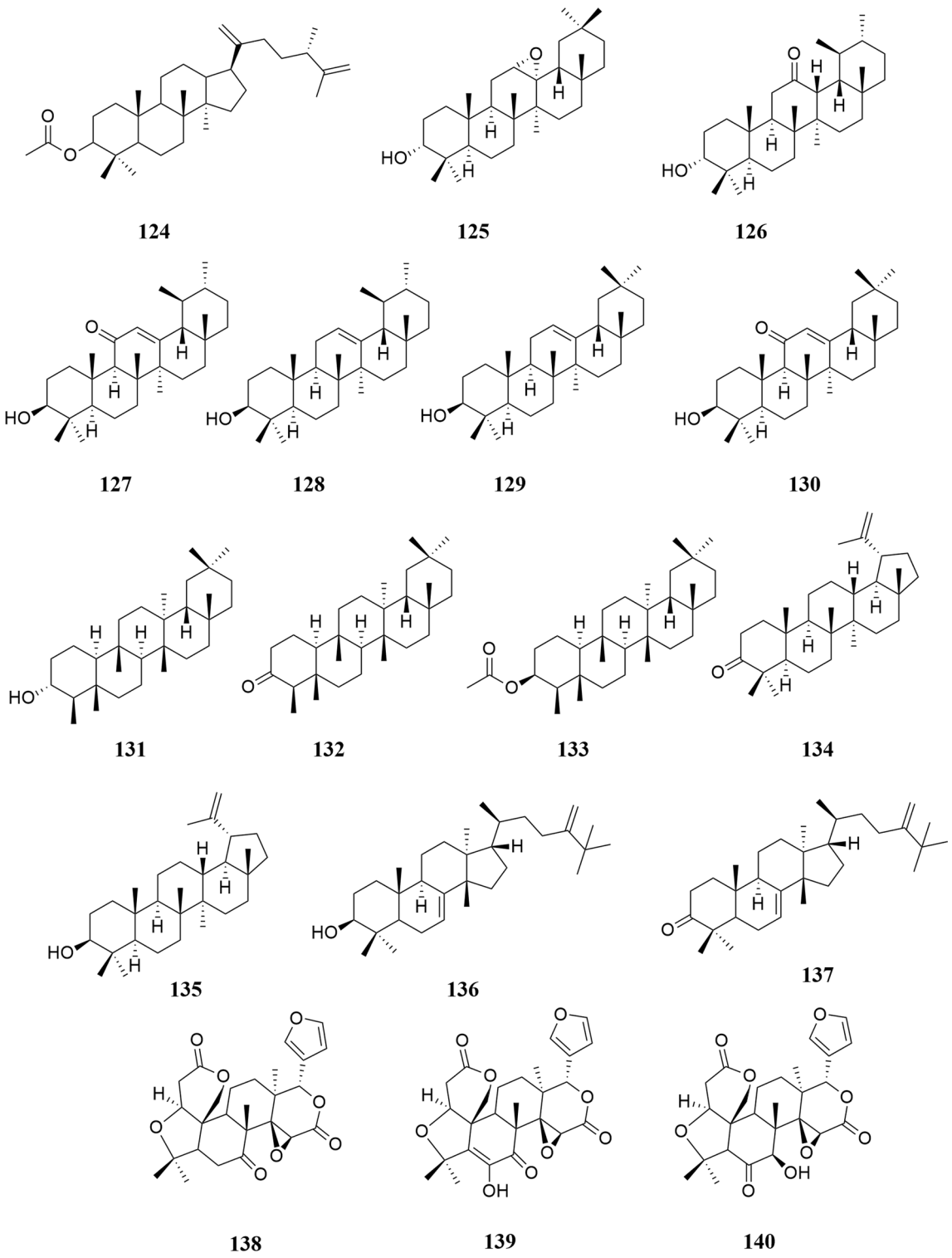


Fig. 9 Triterpenoids (124–137) and limonoids (138–140) identified from *Esenbeckia* species

Table 4 Long-chain compounds identified from *Esenbeckia* spp.

	Compounds	*Esenbeckia* spp.	Plant parts	References
	Aldehydes			
175	Decadienal[a]	*E. almawillia*	Trunk wood	Barros-Filho et al. (2004)
	Fatty acids			
176	Oleic acid	*E. conspecta*	Wood	Rios et al. (2002b)
177	Palmitic acid	*E. conspecta*	Wood	Rios et al. (2002b)
	Ketones			
178	2-Pentadecanone	*E. yaaxhokob*	Aerial parts (VO)	Mata et al. (1998)
179	2-Tridecanone	*E. almawillia*	Wood (EO)	Barros-Filho et al. (2004)
		E. yaaxhokob	Aerial parts (VO)	Mata et al. (1998)
180	6,10,14-trimethyl-2-pentadecanone	*E. yaaxhokob*	Aerial parts (VO)	Mata et al. (1998)

[a]Double bond position is undefined, so this compound is not represented in Fig. 11; VO: Volatile Oil

Previous works demonstrated that simple and furanocoumarins are widely distributed in *Esenbeckia* (Rios et al. 2002a; Simpson and Jacobs 2005). Although several coumarins were isolated through phytochemical studies on the genus, *E. belizencis*, *E. flava*, *E. hartmanii*, *E. nesiotica*, *E. pilocarpoides* Kunth and *E. stephanii* there is no description of such compounds. Furanocoumarins were identified in all other studied species, however, simple coumarins were identified only of *E. alata*, *E. conspecta*, *E. febrifuga*, *E. grandiflora*, *E. hieronymi* and *E. pentaphylla*.

Due to restricted occurrence, it has been suggested that once a limonoid is identified in a species, it is highly probable that the whole genus is limonoid-producer (Dreyer 1980). However, to date, limonoids were only identified at *E. berlandieri*, *E. febrifuga*, *E. flava*, *E. hartmanii* and *E. litoralis*. This suggests that the limonoids may be restricted to a group (or groups) of *Esenbeckia* species, but the lack of a phylogeny of the genus prevents any conclusion so far. Additionally, oxidation levels of limonoids correlates well with Rutaceae subfamilies' distribution (Dreyer et al. 1972). *Esenbeckia* belongs to the Rutoideae subfamily (Cole and Groppo 2020), which is characterized by oxidation at the C-19 methyl group (Dreyer et al. 1972). This oxidation pattern was also observed in limonoids (138–140) identified in *Esenbeckia*. In general, the limonoids in the Rutaceae do not show the structural diversity and abundance observed in the Meliaceae (Da Silva et al. 2021).

5 Prospects

The review summarized 180 identified compounds and several biological activities described in 19 species of *Esenbeckia*. Alkaloids, phenolic derivatives, terpenoids and long-chain compounds were the main classes of metabolites extracted from the genus. Some compounds can be used as chemophenetic characters to define groups of species. However, these groups do not agree with the subgenera and sections proposed for *Esenbeckia*. Moreover, a phylogenetic study of the genus is not available yet. Therefore, these chemophenetic characters should be reevaluated on a phylogenetic framework within *Esenbeckia*.

Also, the review of compounds in *Esenbeckia* highlight this genus as a good source of biological activities, primarily due to furanocoumarin, furoquinoline alkaloids and terpenes production. Compounds with quinoline rings are widely studied through several biological activities and have been an essential source for drug development. Also, extracts and fractions of *Esenbeckia* species are reported for potential activity in controlling against vector-borne

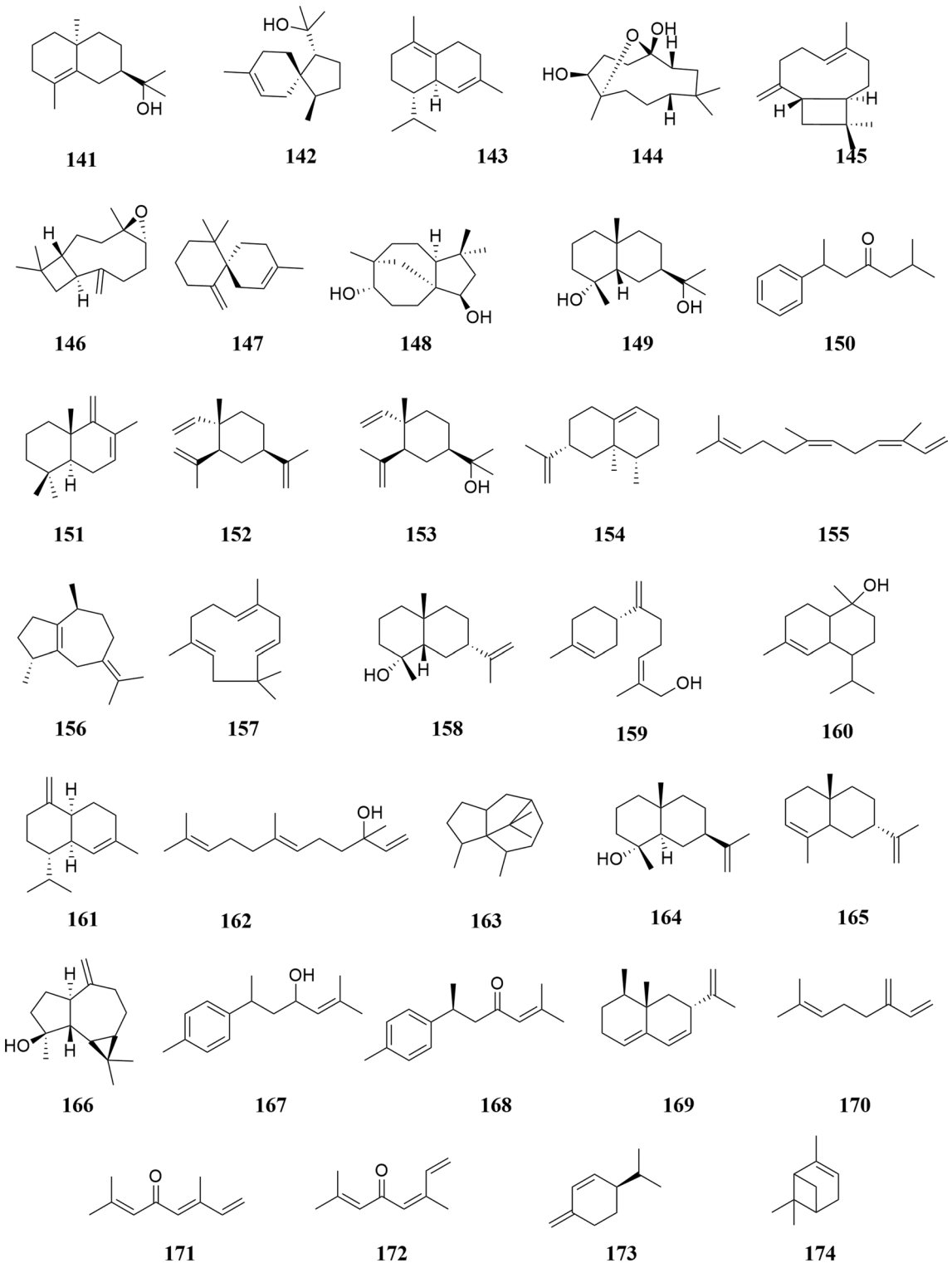
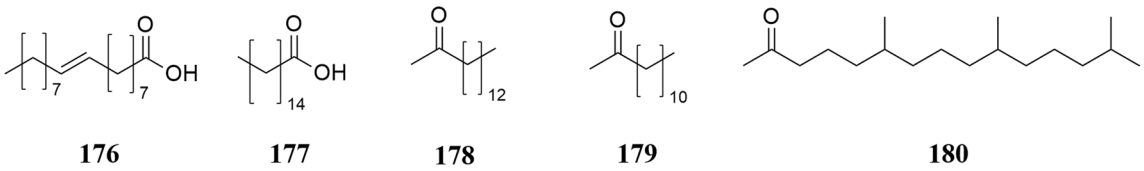


Fig. 10 Sesquiterpenoids (141–169) and monoterpenoids (170–174) identified from *Esenbeckia* species

Table 5 Compounds identified in *Esenbeckia* species; subgenera and sections proposed by Kaastra (1982) are indicated for each species

Esenbeckia spp.	Subg/Sect*	Compounds
E. alata (Triana) Triana & Planch	EE	5, 7, 8, 10, 13, 34, 39, 51, 53, 61, 70, 71, 73, 76, 78, 81, 85, 86, 106, 110, 117, 131, 132, 133, 135
E. almawillia Kaastra	L	8, 11–12, 36–37, 41–44, 50, 54–55, 72, 77, 101–102, 112, 141–143, 145–147, 150–154, 156–165, 167–175, 179
E. belizensis Lundell	EP	8, 10, 117, 123, 131, 132, 134, 146, 166
E. berlandieri Baill	EP	70, 140
E. berlandieri subsp. *acapulcensis* (Rose) Kaastra	EP	93–99, 132
E. conspecta (Kaastra) Ramos	EP	8, 12, 32, 59, 79, 117, 119, 148, 166, 176, 177
E. febrifuga (A.St.-Hil.) A.Juss. ex Mart	O	2, 4, 7, 8, 10, 13, 59, 70, 77, 100, 140
E. flava Brandegee	EP	5, 6, 8, 12, 13, 36, 138, 140
E. grandiflora Mart	EP	4, 8, 10, 11, 28–30, 38, 59, 60, 63, 64, 66, 67, 77, 80, 84, 85, 116–120, 125–130
E. grandiflora Mart. subsp. *grandiflora*	EP	11, 57, 58, 65, 74, 75, 87, 89, 90, 103, 104, 128, 129
E. grandiflora subsp. *brevipetiolata* Kaastra	EP	4, 7, 8, 10, 13, 64, 67, 77, 80, 85, 88, 91, 92, 103, 104
E. hartmanii B.L.Rob. & Fernald	EP	12, 13, 138–140
E. hieronymi Engl	O	7, 8, 10, 11, 13, 33, 56, 59, 85, 120, 155
E. leiocarpa Engl	EP	5, 8, 10, 11, 13, 15–27, 35, 40, 46–49, 52, 56, 82, 107–109, 117
E. litoralis Donn.Sm	EP	1–3, 5, 6, 8, 10, 11, 13, 68–70, 75, 77, 79, 83, 85, 117, 123, 131, 132, 138, 140, 146, 148, 166
E. nesiotica Standl	EP	113–115, 117, 121, 122, 132, 135, 146, 148
E. ovata Brandegee	EP	70, 77, 79, 85, 117, 132, 134, 135, 146, 149
E. pentaphylla (MacFad.) Griseb	EP	2, 5, 7, 8, 10, 34, 38, 45, 62, 75, 111
E. pilocarpoides Kunth	EE	2, 8–11, 14
E. pumila Pohl	EP	105
E. stephanii Ramos	-	117, 132, 136, 137, 146
E. yaaxhokob Lundell	EP	8, 31, 75, 100, 106, 117, 123, 124, 131, 132, 135, 144, 146, 166, 178–180

*Subg/Sect = Subgenera & Sections: EE = subg. *Esenbeckia* sect. *Esenbeckia*; EP: subg. *Esenbeckia* sect. *Pachypetalae*; L: subg. *Lateriflorens*; O: subg. *Oppositifolia*



176 **177** **178** **179** **180**

Fig. 11 Fatty acids (176 and 177) and ketones (178–180) identified from *Esenbeckia* species

diseases and antimicrobial, anti-inflammatory and cytotoxic properties. Undoubtedly, the phytochemical studies of the genus are an opportunity for future discoveries of new natural products, once 20% of compounds described of *Esenbeckia* are unique structures.

Acknowledgements The authors thank the following funding agencies: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Financial Code 001), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, 140120/2018-1, 308952/2020-0 and 307655/2015-6) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, 2014/18002-2 and 2014/21593-2).

Author Contribution Statement JCSC contributed to formal analysis, methodology, investigation and writing—original draft. JRP contributed to writing—review and editing. MJPF contributed to conceptualization, methodology, investigation and writing—review and editing.

Declaration

Conflict of Interest The authors declare that they have no conflict of interest.

References

Abotaleb M, Liskova A, Kubatka P, Büsselberg D (2020) Therapeutic potential of plant phenolic acids in the treatment of cancer. Biomolecules 10:1–23. https://doi.org/10.3390/biom10020221

Adamska-Szewczyk A, Glowniak K, Baj T (2016) Furochinoline alkaloids in plants from Rutaceae family—a review. Curr Issues Pharm Med Sci 29:33–38. https://doi.org/10.1515/cipms-2016-0008

Adejoke HT, Louis H, Amusan OO, Apebende G (2019) A review on classes, extraction, purification and pharmaceutical importance of plants alkaloid. J Med Chem Sci 2019:130–139. https://doi.org/10.26655/JMCHEMSCI.2019.8.2

Aguilar-Guadarrama AB, Rios MY (2004) Geranyl N-Dimethylallylanthranilate, a new compound from *Esenbeckia yaaxhokob*. Planta Med 70:85–86. https://doi.org/10.1055/s-2004-815465

Álvarez-Caballero JM, Cuca-Suárez LE, Coy-Barrera E (2019) Bioguided fractionation of ethanol extract of leaves of *Esenbeckia alata* Kunt (Rutaceae) led to the isolation of two cytotoxic quinoline alkaloids: Evidence of selectivity against leukemia cells. Biomolecules 9:585. https://doi.org/10.3390/biom9100585

Barros-Filho BA, Nunes FM, De Oliveira MCF et al (2004) Volatile constituents from *Esenbeckia almawillia* (Rutaceae). Biochem Syst Ecol 32:817–821. https://doi.org/10.1016/j.bse.2004.02.003

Barros-Filho BA, Nunes FM, De OCF et al (2007) Metabólitos secundários de *Esenbeckia almawillia* Kaastra. (Rutaceae). Quim Nova 30:1589–1591. https://doi.org/10.1590/S0100-40422007000700017

Bevalot F, Fournet A, Moretti C, Vaquette J (1984) Alkaloids from *Esenbeckia pilocarpoides*. Planta Med 50:522–523. https://doi.org/10.1055/s-2007-969789

Borges F, Roleira F, Milhazes N et al (2005) Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. Curr Med Chem 12:887–916. https://doi.org/10.2174/0929867053507315

Brandão MGL, Pignal M, Romaniuc S et al (2012) Useful Brazilian plants listed in the field books of the French naturalist Auguste de Saint-Hilaire (1779–1853). J Ethnopharmacol 143:488–500. https://doi.org/10.1016/j.jep.2012.06.052

Cano A, Espinoza M, Ramos CH, Delgado G (2006) New prenylated flavanones from *Esenbeckia berlandieri* ssp. *acapulcensis*. J Mex Chem Soc 50:71–75. http://www.scielo.org.mx/pdf/jmcs/v50n2/v50n2a4.pdf

Cardoso-Lopes EM, Maier JA, Da Silva MR et al (2010) Alkaloids from stems of *Esenbeckia leiocarpa* Engl. (Rutaceae) as potential treatment for Alzheimer disease. Molecules 15:9205–9213. https://doi.org/10.3390/molecules15129205

Christenhusz MJM, Byng JW (2016) The number of known plant species in the world and its annual increase. Phytotaxa 261:201–217. https://doi.org/10.11646/phytotaxa.261.3.1.

Coimbra AT, Ferreira S, Duarte AP (2020) Genus *Ruta*: a natural source of high value products with biological and pharmacological properties. J Ethnopharmacol 260:113076. https://doi.org/10.1016/j.jep.2020.113076

Cole TCH, Groppo M (2020) Rutaceae phylogeny poster. Freie Univesität Berlin https://www.researchgate.net/publication/324647641_RUTACEAE_Phylogeny_Poster_2020. Accessed 27 May 2021

Cosenza GP, Viana CTR, Campos PP et al (2019) Chemical characterization, antihyperlipidaemic and antihyperglycemic effects of Brazilian bitter quina species in mice consuming a high-refined carbohydrate diet. J Funct Foods 54:220–230. https://doi.org/10.1016/j.jff.2019.01.030

Cuca-Suarez LE, David E, Barrera C et al (2011) Quinoline alkaloids and friedelane-type triterpenes isolated from leaves and wood of *Esenbeckia alata* Kunt. (Rutaceae). Quim Nova 34:984–986. https://doi.org/10.1590/S0100-40422011000600013

Da Silva MFGF, Pinto LS, Amaral JC et al (2021) Nortriterpenes, chromones, anthraquinones, and their chemosystematics significance in Meliaceae, Rutaceae, and Simaroubaceae (Sapindales). Braz J Bot. https://doi.org/10.1007/s40415-021-00733-9 (in press)

Debnath B, Singh WS, Das M et al (2018) Role of plant alkaloids on human health: a review of biological activities. Mater Today Chem 9:56–72. https://doi.org/10.1016/j.mtchem.2018.05.001

Dias P, Udulutsch RG, Pirani JR (2013) *Esenbeckia cowanii* (Rutaceae), epitypification and emendation. Novon 22:288–291. https://doi.org/10.3417/2007052

Dolabela MF, Oliveira SG, Nascimento JM et al (2008) *In vitro* antiplasmodial activity of extract and constituents from *Esenbeckia febrifuga*, a plant traditionally used to treat malaria in the Brazilian Amazon. Phytomedicine 15:367–372. https://doi.org/10.1016/j.phymed.2008.02.001

Dos Santos BM, Ferreira GM, Tavares JC et al (2021) Antiophidic activity of the secondary metabolite lupeol identified from *Zanthoxylum monogynum*. Toxicon 193:38–47. https://doi.org/10.1016/j.toxicon.2021.01.018

Dreyer DL (1980) Alkaloids, limonoids and furocoumarins from three Mexican *Esenbeckia* species. Phytochemistry 19:941–944. https://doi.org/10.1016/0031-9422(80)85142-9

Dreyer DL, Pickering MV, Cohan P (1972) Distribution of limonoids in the Rutaceae. Phytochemistry 11:705–713. https://doi.org/10.1016/0031-9422(72)80036-0

El-Seedi HR, El-Said AMA, Khalifa SAM et al (2012) Biosynthesis, natural sources, dietary intake, pharmacokinetic properties, and biological activities of hydroxycinnamic acids. J Agric Food Chem 60:10877–10895. https://doi.org/10.1021/jf301807g

Epifano F, Fiorito S, Genovese S et al (2015) Phytochemistry of the genus *Skimmia* (Rutaceae). Phytochemistry 115:27–43. https://doi.org/10.1016/j.phytochem.2015.02.014

Ferreira ME, Rojas de Arias A, Yaluff G et al (2010) Antileishmanial activity of furoquinolines and coumarins from *Helietta apiculata*. Phytomedicine 17:375–378. https://doi.org/10.1016/j.phymed.2009.09.009

Forkuo AD, Mensah KB, Ameyaw EO, Antwi AO, Kusi-Boadum NK, Ansah C (2020). Antiplasmodial and antipyretic activity and safety evaluation of the methanolic leaf extract of *Murraya exotica* (L.). J Parasitol Res 2020:1308541. https://doi.org/10.1155/2020/1308541

García-Beltrán O, Areche C, Cassels BK, Cuca-Suárez LE (2014) Coumarins isolated from *Esenbeckia alata* (Rutaceae). Biochem Syst Ecol 52:38–40. https://doi.org/10.1016/j.bse.2013.12.011

García-Beltrán O, Cuca-Suárez LE (2003) Constituyentes no polares de la corteza de *Esenbeckia alata* y actividad antimicrobiana. Rev Colomb Química 32:23–28. https://revistas.unal.edu.co/index.php/rcolquim/article/view/743

Garcia-Beltrán OJ, Cuca-Suarez LE (2005) NMR spectroscopy as a tool in structural elucidation of substituted 3(1',1'-dimethylallyl) coumarins isolated from *Esenbeckia alata* (Karst & Triana) Tr. & Pl. (Rutaceae). Actual Biol 27:71–74

Gómez-Calvario V, Ramírez-Cisneros MÁ, Acevedo-Quiroz M, Rios MY (2019) Chemical composition of *Helietta parvifolia* and its in vitro anticholinesterase activity. Nat Prod Res 33:889–892. https://doi.org/10.1080/14786419.2017.1410808

Groppo M, Kallunki JA, Pirani JR, Antonelli A (2012) Chilean *Pitavia* more closely related to Oceania and Old World Rutaceae than to Neotropical groups: evidence from two cpDNA non-coding regions, with a new subfamilial classification of the family. PhytoKeys 19:9–29. https://doi.org/10.3897/phytokeys.19.3912

Guilhon GMSP, Baetas ACS, Maia GJ, Conserva LM (1994) 2-alkyl-4-quinolone alkaloids and cinnamic acid derivatives from

Esenbeckia almawillia. Phytochemistry 37:1193–1195. https://doi.org/10.1016/S0031-9422(00)89556-4

Januário AH, Vieira PC, Fátima M et al (2009) Alcaloides β indolopiridoquinazolinicos de *Esenbeckia grandiflora* Mart. (Rutaceae). Quim Nova 32:2034–2038. https://doi.org/10.1590/S0100-40422009000800010

Kaastra RC (1982) Pilocarpinae (Rutaceae) Flora Neotropica 33:1–197. https://www.jstor.org/stable/4393763

Kubitzki K, Kallunki JA, Dureto M, Wilson PG (2011) Rutaceae. In: Kubitzki K (ed) The families and genera of vascular plants, vol 10. Springer, New York, pp 276–356

Kubo I, Vieira PC, Fukuhara K (1990) Efficient isolation of the insect growth inhibitory flavone glycoside rutin from two tropical medicinal plants by rotation locular countercurrent chromatography (rlcc). J Liq Chromatogr 13:2441–2448. https://doi.org/10.1080/01483919008049044

Li H, Zhe-Ling F, Yi-Tao W, Li-Gen L (2017) Anticancer carbazole alkaloids and coumarins from *Clausena* plants: a review. Chin J Nat Med 15:881–888. https://doi.org/10.1016/S1875-5364(18)30003-7

Liz R, Pereira DF, Horst H et al (2011) Protected effect of *Esenbeckia leiocarpa* upon the inflammatory response induced by carrageenan in a murine air pouch model. Int Immunopharmacol 11:1991–1999. https://doi.org/10.1016/j.intimp.2011.08.009

Liz R, Horst H, Pizzolatti MG et al (2012a) Activation of human neutrophils by the anti-inflammatory mediator *Esenbeckia leiocarpa* leads to atypical apoptosis. Mediators Inflamm 2012:1–10. https://doi.org/10.1155/2012/198382

Liz R, Horst H, Pizzolatti MG et al (2012b) Activation of human neutrophils by *Esenbeckia leiocarpa*: Comparison between the crude hydroalcoholic extract (CHE) and an alkaloid (Alk) fraction. J Inflamm (united Kingdom) 9:1–9. https://doi.org/10.1186/1476-9255-9-19

Liz R, Zanatta L, Dos Reis GO et al (2013) Acute effect of β-sitosterol on calcium uptake mediates anti-inflammatory effect in murine activated neutrophils. J Pharm Pharmacol 65:115–122. https://doi.org/10.1111/j.2042-7158.2012.01568.x

Madeiro SAL, Borges NHPB, Souto AL et al (2017) Modulation of the antibiotic activity against multidrug resistant strains of coumarins isolated from Rutaceae species. Microb Pathog 104:151–154. https://doi.org/10.1016/j.micpath.2017.01.028

Mata R, Macías ML, Rojas IS et al (1998) Phytotoxic compounds from *Esenbeckia yaxhoob*. Phytochemistry 49:441–449. https://doi.org/10.1016/S0031-9422(98)00110-1

Matada BS, Pattanashettar R, Yernale NG (2021) A comprehensive review on the biological interest of quinoline and its derivatives. Bioorg Med Chem 32:115973. https://doi.org/10.1016/j.bmc.2020.115973

Mbaveng AT, Noulala CGT, Samba ARM, Tankeo SB, Fotso GW, Happi EN, Ngadjui BT, Beng VP, Kuete V, Efferth T (2021) Cytotoxicity of botanicals and isolated phytochemicals from *Araliopsis soyauxii* Engl. (Rutaceae) towards a panel of human cancer cells. J Ethnopharmacol 267:113535. https://doi.org/10.1016/j.jep.2020.113535

Monache FD, Monache GD, Moraes De, e Souza MA, Cavalcanti MS, Chiappeta A (1990) Isopentenylindole derivatives and other components of *Esenbeckia leiocarpa*. Gazz Chim Ital 119:1989

Monache FD, Di Benedetto R, Moraes De, e Souza MA, Sandor P (1991) Esenbeckia leiocarpa. II Further Components Gazz Chim Ital 120:387–389

Monache FD, Trani M, Yunes RA, Falkenberg D (1996) (-)-Lunacrinol from *Esenbeckia hieronimi*. Fitoterapia 66:474

Morton CM, Telmer C (2014) New subfamily classification for the Rutaceae. Ann Missouri Bot Gard 99:620–641. https://doi.org/10.3417/2010034

Nakatsu T, Johns T, Kubo I et al (1990) Isolation, structure, and synthesis of novel 4-quinolinone alkaloids. J Nat Prod 53:1508–1513. https://doi.org/10.1021/np50072a017

Napolitano HB, Silva M, Ellena J et al (2004) Aurapten, a coumarin with growth inhibition against *Leishmania major* promastigotes. Braz J Med Biol Res 37:1847–1852. https://doi.org/10.1590/S0100-879X2004001200010

Nunes FM, Barros-Filho BA, De Oliveira MCF et al (2005a) 1H and 13C NMR spectra of 3,8-dimethoxyfuro[3,2-g] coumarin and maculine from *Esenbeckia grandiflora* Martius (Rutaceae). Magn Reson Chem 43:864–866. https://doi.org/10.1002/mrc.1621

Nunes FM, Barros-Filho BA, Oliveira MCF (2005b) 3,3-Diisopentenyl-N-methyl-2,4-quinoldione from *Esenbeckia almawillia*: The antitumor activity of this alkaloid and its derivative. Nat Prod Commun 1:313–318. https://doi.org/10.1177/1934578X0600100409

Oliveira FM, Santana AEG, Conserva LM et al (1996) Alkaloids and coumarins from *Esenbeckia* species. Phytochemistry 41:647–649. https://doi.org/10.1016/0031-9422(95)00564-1

Oliveira PES, Conserva LM, De Simone CA et al (2004) A pimpinellin monomer and dimer isolated from the roots of *Esenbeckia grandiflora*. Acta Crystallogr Sect C Cryst Struct Commun 60:900–902. https://doi.org/10.1107/S0108270104023777

Oliveira PES, Conserva LM, Brito AC, Lemos RPL (2005) Coumarin derivatives from *Esenbeckia grandiflora* and its larvicidal activity against *Aedes aegypti*. Pharm Biol 43:53–57. https://doi.org/10.1080/13880200590903363

Ombito JO, Chi GF, Wansi JD (2021) Ethnomedicinal uses, phytochemistry, and pharmacology of the genus *Vepris* (Rutaceae): A review. J Ethnopharmacol 267:113622. https://doi.org/10.1016/j.jep.2020.113622

Passos MS, Nogueira TSR, Azevedo AO, Vieira MGC, Terra WS, Braz-Filho R, Vieira IJC (2021) Limonoids from the genus *Trichilia* and biological activities: review. Phytochem Rev, pp 1–32. https://doi.org/10.1007/s11101-020-09737-x

Pirani JR (1999) Two new species of *Esenbeckia* (Rutaceae, Pilocarpinae) from Brazil and Bolivia. Bot J Linn Soc 129:305–313. https://doi.org/10.1006/bojl.1998.0212

Pirani JR, Groppo M (2020) Rutaceae in Flora do Brasil 2020. Jardim Botânico do Rio de Janeiro. http://floradobrasil.jbrj.gov.br/reflora/floradobrasil/FB572. Accessed 27 May 2021.

Pozzatti P, Dos Reis GO, Pereira DF et al (2011) *Esenbeckia leiocarpa* Engl. inhibits inflammation in a carrageenan-induced murine model of pleurisy. J Pharm Pharmacol 63:1091–1102. https://doi.org/10.1111/j.2042-7158.2011.01311.x

Rios MY, Aguilar-Guadarrama AB (2002) Terpenes and a new bishomotriterpene from *Esenbeckia stephani* (Rutaceae). Biochem Syst Ecol 30:1006–1008. https://doi.org/10.1016/S0305-1978(02)00041-8

Rios MY, Delgado G (1992a) Terpenoids and alkaloids from *Esenbeckia belizencis*. Spontaneous oxidation of furoquinoline alkaloids. J Nat Prod 55:1307–1309. https://doi.org/10.1021/np50087a020

Rios MY, Delgado G (1992b) Polyprenols and acylphloroglucinols from *Esenbeckia nesiotica*. Phytochemistry 31:3491–3494. https://doi.org/10.1016/0031-9422(92)83713-9

Rios MY, Delgado G (2002) Furocoumarins, terpenes and sterols from *Esenbeckia ovata* Kunth (Rutaceae). Biochem Syst Ecol 30:697–699. https://doi.org/10.1016/S0305-1978(01)00138-7

Rios MY, Aguilar-Guadarrama AB, Delgado G (2002a) Furoquinoline alkaloids, furocoumarins and terpenes from *Esenbeckia litoralis* (Rutaceae). Biochem Syst Ecol 30:977–979. https://doi.org/10.1016/S0305-1978(02)00042-X

Rios MY, Rosas-Alonso E, Aguilar-Guadarrama AB (2002b) Alkaloids, coumarins and sesquiterpenes from *Esenbeckia conspecta*

Kunt (Rutaceae). Biochem Syst Ecol 30:367–369. https://doi.org/10.1016/S0305-1978(01)00096-5

Roy A, Saraf S (2006) Limonoids: overview of significant bioactive triterpenes distributed in plants kingdom. Biol Pharm Bull 29:191–201. https://doi.org/10.1248/bpb.29.191

Santos AP, Moreno PRH (2004) *Pilocarpus spp*.: a survey of its chemical constituents and biological activities. Rev Bras Ciencias Farm 40:115–137. https://doi.org/10.1590/s1516-93322004000200002

Simpson DS, Jacobs H (2005) Alkaloids and coumarins from *Esenbeckia pentaphylla* (Rutaceae). Biochem Syst Ecol 33:841–844. https://doi.org/10.1016/j.bse.2004.12.022

Suárez LEC, Barrera CAC (2007) Metabolites isolated from *Esenbeckia alata* (Karst & Triana) (Rutaceae). Biochem Syst Ecol 35:386–388. https://doi.org/10.1016/j.bse.2006.12.004

Trani M, Monache FD, Monache GD et al (1997) Chemistry of *Esenbeckia* genus. IV. Dihydrochalcones and coumarins of *Esenbeckia grandiflora* subsp. *grandiflora*. Gazz Chim Ital 127:415–418. https://doi.org/10.1016/j.fitote.2003.08.004

Trani M, Carbonetti A, Delle Monache G, Delle Monache F (2004) Dihydrochalcones and coumarins of *Esenbeckia grandiflora* subsp. *brevipetiolata*. Fitoterapia 75:99–102. https://doi.org/10.1016/j.fitote.2003.08.004

Tundis R, Loizzo MR, Menichini F (2014) An overview on chemical aspects and potential health benefits of Limonoids and their derivatives. Crit Rev Food Sci Nutr 54:225–250. https://doi.org/10.1080/10408398.2011.581400

Victor MM, David JM, Dos Santos MAS, et al (2017) Synthesis and evaluation of cytotoxic effects of amino-ester derivatives of natural α,β-amyrin mixture. J Braz Chem Soc 28:2155–2162. https://doi.org/10.21577/0103-50

Villaseñor JL (2016) Checklist of the native vascular plants of Mexico. Rev Mex Biodivers 87:559–902. https://doi.org/10.1016/j.rmb.2016.06.017

Vitagliano JC, Comin J (1970) Argentine plant studies. XXIX. Limonoids from *Esenbeckia febrifuga* and *Helietta longifoliata*. An Assoc Quim Argentina 58:273–275

Wei W-J, Chen X-H, Guo T et al (2020) A review on classification and biological activities of alkaloids from the genus *Zanthoxylum* species. Mini-Rev Med Chem 21:336–361. https://doi.org/10.2174/1389557520666200910091905