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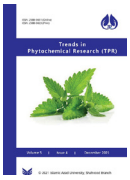

Review Article

Siparuna Aublet genus (Siparunaceae): From folk medicine to chemical composition and biological activity

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ABSTRACT

Species of the genus *Siparuna* Aublet are found in Neotropical regions, mainly in the Andes. In the Brazilian folk medicine, some *Siparuna* species are used to combat fever, inflammation, pain, and infections. This paper presents a review of phytochemical studies and biological activities of species of this genus. Phytochemical studies of 18 species led to the isolation of mainly flavonoids (quercetin and kaempferol derivatives) as well as alkaloids (aporphinic derivatives). Essential oils were reported for 8 species among which *S. guianensis* is the most studied species. Numerous reports provide evidence of antimicrobial, antiplasmodic, larvicidal, cytotoxic, and antioxidant activities for some species of *Siparuna* genus. The reports of phytochemical studies and biological activities motivate the continued research of other species of the genus, remembering that a large part of the identified species are unknown from the natural products chemistry point of view.

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1. Introduction

For generations, natural products have been used by humans in search of relief and cures for diseases. Ingesting herbs and leaves may have been one of the first ways that natural products were used. Countless civilizations have used natural products, made of plant extracts, to cure illnesses, to paint their bodies according to their culture, or to dye artifacts. Brazilian history, for example, is related to the trade of natural products in the form of spices, and the Portuguese's interest in Brazilwood (*Paubrasilia echinata* Lam.), which yielded a red dye, frequently used in clothes and writing ink (Viegas Júnior et al., 2006). We have learned from primitive peoples how to cure diseases using plants, as well as how to avoid those that may be toxic. This knowledge, acquired from different ethnic groups, has brought valuable contributions to the development of research on natural products. The biodiversity of tropical forests provides the prime scenario to discover medicinal plants and, subsequently, to detect specific plants containing biological activity (Braz Filho, 2010). The occurrence of *Siparuna*, of the Siparunaceae family, has been reported throughout the Brazilian Atlantic Forest. These species are used in popular and indigenous medicine to cure several illnesses, and have become the object of study concerning the isolation of secondary metabolites, such as alkaloids and flavonoids, among others. This study presents a review of phytochemical reports, essential oils (EOs), and biological activities of species of the genus *Siparuna*, as of the 1970s.

2. Methodology

A comprehensive research was conducted on the

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PubMed, Sciencedirect, Scopus, Scielo databases and CAPES' journals. Our investigation was also carried out on the annals of events, selecting works published between 1976 and the beginning of 2021. The aforementioned searches used the following keywords: "Siparunaceae" and "*Siparuna*", either separately or combined with the keywords "biological activity", "antioxidant activity", "antibacterial activity", "phytochemistry", "pharmacology", and "chemical composition", both in English and Portuguese.

3. The Siparunaceae family

Species of the Siparunaceae (A. DC.) Schodde family can be found in the Atlantic Forest biome. This family belongs to the Laurales order, with approximately 7 families and 4.559 species (GBIF, 2021). It is divided into two genera, *Glossocalyx*, a genus found in West Africa, and *Siparuna*, with approximately 65 species found in the Neotropical region, mostly in the Andes (Renner and Hausner, 2005). In Brazil, the Siparunaceae family is currently made up of approximately 47 species, all of which belong to the *Siparuna* genus (Reflora, 2020). They are shrubby or arboreal plants, with simple leaves, which may be stipulated, opposite, or star-shaped, occasionally found in an anisophyllous pair, and are usually aromatic, due to oil cells distributed throughout the plant (Hall and Meirelles, 2017). These plants, *e.g., S. cymosa*, *S. guianensis*, and *S. brasiliensis* (Fig. 1) can be found throughout Brazil, especially in the North region, where 19 species have been identified (Reflora, 2020). Many people use medicinal plants to treat a variety of persistent diseases. In traditional communities, the use of medicinal plants is sometimes the only way to treat the illnesses (Gomez et al., 2016), mainly in low-income families. A variety of valuable natural compounds have been characterized in a number of previously published papers in the literature dealing with the characterization of different medicinal and herbal plants (Mohammadhosseini et al., 2021a; Mohammadhosseini et al., 2021b; Nahar et al., 2021). These bioactive compounds usually belong to flavonoids, terepenoids and other natural compound groups.

A: S. *cymosa* ; B: *S. guianensis* ; C: *S. brasiliensis*

Fig. 1. Some pictures of the *Siparuna* species.

4. The *Siparuna* Aublet genus

4.1. Folk medicine

Species of *Siparuna* Aublet genus occur in tropical and subtropical regions of the Southern hemisphere (Leitão et al., 2000). Many species are found on the coast of the state of Bahia, while some *Siparuna* plants are endemic to the southern regions of Bahia. There are several reports in the literature on the use of *Siparuna* species to treat ailments related to folk medicine. Medicinal plants in this genus are used in folk and traditional indigenous medicine in both South and Central America to treat several diseases (Leitão et al., 1999). In the Southern parts of the state of Bahia, plants in this family are known as "Tetrex", and their leaves are used in local tea, which is drunk to treat fevers, infections, wounds, inflammation, and pain (Gomez et al., 2016). So far, *S. guianensis* Aublet is the species for which the highest number of studies have been published. In this sense, Valentini et al. (2010a) published the first review article on this species. Known as "Negramina" in the state of Mato Grosso, its leaves are used to treat sinusitis, body aches, weakness, and nose bleeds in the form of drinks (decoction). In French Guyana, the leaves are used to treat fevers and as intimate and postpartum washes by "Quilombola" women (Tareau et al., 2017). In the Amazon, indigenous peoples use *S. guianensis* leaves to relieve rheumatic pains (Schultes and Raffauf, 1990). *S. aspera* (Ruiz & Pav) A. DC., popularly known as "Mejentsuna", and *S. radiata* (Poepp. & Endl.) A DC. (synonym: *S. sessiliflora* (Kunth) A. DC.), are native species of Peru. Steam baths using their leaves are used to treat fever and asthenia (Valadeau et al., 2009). *S. macrotepala* Perkins infused leaves, also a plant native to Ecuador, are used to treat malaria and influenza (Noriega et al., 2019). *S. andina* (Tul.) A. DC. (synonym: *S. thecaphora* (Poepp. & Endl.) A. DC.) leaves are used to treat fever and malaria (Frei et al., 1998). *S. gilgiana* Perkins (synonym: *S. thecaphora* (Poepp. & Endl.) A. DC.) leaves have been used to treat stomachaches and female sterility (Chiu et al., 1982). *Siparuna thecaphora* (Poepp. & Endl.) A. DC. is used in Guatemala to treat swelling, anemia, muscle cramps, coughs, headaches and eye infections (Hitziger et al., 2016). The leaves are used in folk medicine

to treat pain and skin diseases (Lentz et al., 1998). *S. apiosyce* (Mart. Ex. Tul.) A. DC. (synonym: *S. brasiliensis* (Spreng.) A. DC.), known in traditional medicine as "Limoeiro bravo", is often used for skin diseases, colds, fever, headaches, and rheumatism, in addition to being used to treat snakebites (Leitão et al., 2000). Its leaves are fragrant and are used to cure gastric and respiratory diseases, flatulence, cough, bronchitis, laryngitis, and wounds (Fischer et al., 1999). In Ecuador, the infusion of *S. eggersii* Hieron leaves is used to treat diabetes, stroke, fractures, and rheumatism. The infusion of *S. muricata* (Ruiz & Pav. A. DC.) stems and leaves is used as an antacid (Tene et al., 2007). *S. pauciflora* (Beurl.) A. DC is another species in this genus, which is a small tree known as "Limoncillo" in Costa Rica due to its characteristic lime smell. Its leaves, in the form of a decoction, are used to treat fever by indigenous peoples in Panama (Jenett-Siems et al., 2003). The macerated leaves of *S. gesnerioides* (Kunth) A. DC. are used to treat snakebites in the region of Antioquia, Colombia (Vásquez et al., 2013). The decoction of *S. asperula* (Tul.) A. DC. (Synonym: *S. tomentosa* (Ruiz & Pav.) A. DC.) leaves is used as a cure for the flu. The macerated fruit is used to treat worm bites (Bourdy et al., 2000). Based on these reports, *Siparuna* species are used in folk medicine to treat various illnesses, such as fevers (*S. guianensis*, *S. aspera*, *S. radiata*, *S. thecaphora*, *S. apiosyce* and *S. pauciflora*), malaria (*S. macrotepala*, *S. thecaphora*), respiratory problems (*S. guianensis* and *S. apiosyce*), pain (*S. guianensis* and *S. thecaphora*), rheumatism (*S. guianensis*, *S. apiosyce* and *S. eggersii*) and weakness (*S. guianensis, S. aspera* and *S. radiata*).

4.2. Phytochemical studies

There are only few studies involving the isolation of secondary metabolites and biological activity tests for species of the *Siparuna* genus (Noriega et al., 2019). This may be associated with the distribution of these species in forest regions, which are often difficult to access. Nevertheless, phytochemical studies report the isolation and identification of substances belonging to the alkaloid, steroid, flavonoid, and sesquiterpene classes, in addition to EOs. Phytochemical studies of 18 species of *Siparuna* (Table 1) led to the isolation of 74 substances. Of these, 35 are flavonols, derived from quercetin and kaempferol. Many occur in the glycosidic form, the most common being the glucose and rhamnose units. Twenty-eight of the isolated substances (Table 1, Fig. 2) are alkaloids, 16 of which are derived from the aporphine nucleus. Liriodenine was the most isolated alkaloid among the species. This class of compounds is known to have several pharmacological properties, including antiparasitic, anticancer, and antibacterial behaviors (Dos santos et al., 2019). *S. pauciflora* (Beurl) A. DC, for instance, has some aporphine alkaloids (Jenett-Siems et al., 2003). The first botanical description of the *Siparuna* in Brazil was conducted by Peckolt and Peckolt (1988), with the species *S. apiosyce* (Mart. Ex. Tul.) A. DC. (synonym: *S. brasiliensis* (Spreng.) A. DC.). In 1976, the oxoaporphine alkaloids liriodenine **(5)** and cassamedine **(39)** were isolated from the hexanic extract of the stem of *S. guianensis* Aublet (Braz Filho et al., 1976). These two alkaloids are considered to be common ones in the *Siparuna* genus (Jennet-Siems et al., 2003). Liriodenine **(5)** was also isolated from the ethanolic extract obtained from the branches of *S. nicaraguenses* Hemsl. (synonym: *S. thecaphora* (Poepp. & Endl.), collected in Panama (Gerard et al., 1986), and by Fischer and coworkers (1999) from the aerial parts of *S. apiosyce* (Mart. Ex. Tul.) A. DC. (synonym: *S. brasiliensis* (Spreng.) A. DC.) . A relevant research on *S. dresslerana* T. Antonio was conducted by Gerard et al. (1986) leading to the isolation of flavinantine **(17)** and *O*-methylflavinantine **(18)**, as well. Flavonoids are polyphenols of great biological importance and are quite diversified among natural products. They are responsible for several functions in plants, such as protection against ultraviolet rays, insects, fungi, viruses, and bacteria, as well as the ability to attract pollinator animals. Many of these compounds have important pharmacological properties, such as antiviral, anti-inflammatory, antioxidant, antimicrobial and antitumoral properties (Santos and Rodrigues, 2017). Recently, three flavonoids were isolated from *S. cristata* (Poepp. & Endl.) A. DC. leaves: 3,3′,4′-tri-*O*-methyl-quercetin **(12)**, retusin **(13)** and kumatakenin **(14)**. Retusin and kumatakenin inhibited SARS-CoV-2 replication in Vero E6 and Calu-3 cells, with a higher selective index than the controls used, being a promising result in the search for antiviral drugs for adjuvant therapy in the treatment of COVID-19 (Leal et al., 2021). Derivatives of quercetin and kaempferol were the most isolated compounds among the studied *Siparuna* species, mainly from the species *S. gigantotepala* S.S Renner & Hausner, *S. glycycarpa* (Ducke) S.S. Renner & Hausner and *S. guianensis* Aublet. The flavonoids lucenin-2 **(40)**, vicenin-2 **(41)**, quercetin-3-*O*-rutinoside-7-*O*-rhamnoside **(42)**, quercetin-3-*O*-pentosyl-pentoside-*O*-rhamnoside **(43)**, quercetin-3,7-di-*O*-rhamnoside **(44)**, kaempferol-3-*O*-pentosyl-pentoside-7-*O*-rhamnoside **(45)**, kaempferol-3,7-di-*O*-rhamnoside **(46)** and quercetin-3-*O*-pentosyl-rhamnoside-7-*O*-rhamnoside **(47)** were isolated from the leaves extract of *S. guianensis* Aublet (Negri et al., 2012). Other kaempferol-type flavonoids were isolated by Facundo et al (2012). There are also reports on the isolation of sesquiterpenes in this genus. The sesquiterpenes 7-hydroxy-1-oxy-14-norcalamenene **(57)**, (+)-8-hydroxycalamenene **(58)**, τ-cadinol **(59)**, and 7,14-dihydroxycalamenene **(60)** were isolated from *S. macrotepala* Perkins leaves and branches (El Seedi, 1999), while the sesquiterpenes sipaucin A **(19)**, sipaucin B **(64)**, and sipaucin C **(65)** were isolated from the *S. pauciflora* (Beurl.) A. DC leaves by Jenett-Siems et al. (2003). There is a structural variety of secondary metabolites according to the organ of the studied plant, the location of collection, and the polarity of the solvent used in the extraction. Reports found on studies of polar extracts obtained from *S. guianensis* Aublet leaves, collected in different regions of Brazil and in French Guyana, led to the isolation of 19 flavonoids.

Ethyl acetate extracts of *S. decipiens* (Tul.) A. DC., *S. guianensis* Aublet, *S. pachyantha* A. C. Sm., *S. poeppigi* (Tul.) A. DC. and *S. sessiliflora* leaves were promising in the isolation of alkaloids. Table 1 shows the survey of the studied species, isolated compounds, location of collection, in addition to the method used to isolate the substances; in the period from 1976 to date. The isolated compound structures were numbered and subsequently presented (Fig. 2).

Table 1
Compounds isolated from species of the genus *Siparuna*.

Species name	Distribution	Organ of plant (Type of extracts)	Extraction/ Purification	Compounds[1]	References
S. andina (Tul.) A. DC[2]	Coclé, Panama	Leaves (Petroleum ether/EtOAc)	CC/HPLC acetonitrile-H_2O 40:60 (v/v)	Sipandinolide **(1),** (-)-*cis*-3-acetoxy-4′-5-7-trihydroxyflavanone **(2)**	Jenett-Siems et al., (2000)
S. apiosyce (Mart. Ex Tul.) A. DC[2]	Minas Gerais, Brazil	Aerial parts	CC	Asimilobine **(3)**, stigmasterol **(4)**	(Fischer et al., 1999)
	Rio de Janeiro, Brazil	Leaves (Hex/ MeOH)	Liquid-liquid partition/CC	Liriodenine **(5)**, reticuline **(6)**, 3,7,4'-tri-*O*-methylkaempferol **(7)**, tiliroside **(8)**, siparunoside **(9)**	Leitão et al., 2000)
		Wood/wood bark (Hex/ MeOH)	Liquid-liquid partition/CC	Liriodenine **(5)**, reticuline **(6)**, *N*-methyllaurotetanine **(10)**, laurotetanine **(11)**	Leitão et al., 2000)
S. cristata (Poepp. & Endl.) A. DC.	Manaus, Brazil	Leaves/EtOH	Counter-current chromatography (CCC)	3,3′,4′-tri-*O*-Methyl-quercetin **(12)**, retusin **(13)**, kumatakenin **(14)**	Leal et al., (2021)
S. decipiens (Tul.) A. DC	French Guiana	Leaves (EtOAc)	HPLC UV-Vis; MALDI-TOF	Boldine **(15)**, (+)-*N*-nornuciferine **(16)**	Marti et al., (2013)
S. dressleriana T. Antonio	Cerro Jefe, Panama	Leaves (MeOH)	Soxhlet; CC/ HPLC reverse phase MeOH-H_2O (17:3)	Liriodenine **(5)**, flavinantine **(17)**, *O*-methylflavinantine **(18)**	Gerard et al., (1986)
S. echinata (Kunth) A. DC.	Loja, Ecuador	Leaves (EtOAc)	GC-MS	Sipaucin A **(19)**	García et al., (2020)
S. gigantotepala S. S Renner & Hausner	Valle del Cauca, Colombia	Leaves (MeOH)	Liquid-liquid partition; CC/ ESI-MS; HR-ESI-MS	Kaempferol 3-*O*-β-xylopyranosyl-(1→2)-α-arabinofuranoside **(20)**, kaempferol 3,7-di-*O*-methyl-4′-*O*-α-rhamnopyranosyl-(1→2)-β-glucopyranoside **(21)**, rutin **(22)**, kaempferol 3-*O*-rutinoside **(23)**, kaempferol 3,7-di-*O*-methyl-4′-*O*-rutinoside **(24)**, quercetin **(25)**, kaempferol 3,7-dimethyl kaempferol 3,7-dimethyl ether **(26)**, kaempferol 3,7,4′-trimethyl ether **(27)**	Casteñeda et al., (2016)
S. gilgiana Perkins[2]	Peru	Roots (MeOH)	Lloyd-type extractor	Liriodenine **(5)**, oxonantenine **(28)**	Chiu et al., (1982)

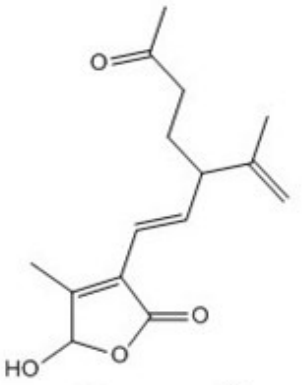
Table 1 Continued

Species name	Distribution	Organ of plant (Type of extracts)	Extraction/ Purification	Compounds[1]	References
S. glycycarpa (Ducke) S. S Renner & Hausner	Amazonas, Brazil	Leaves (MeOH)	Counter-current chromatography (CCC)	Quercetin-3-*O*-rutinoside **(29)**, quercetin-7-*O*-rutinoside **(30)**, kaempferol-3-*O*-β-glucopyranoside **(31)**, kaempferol-3-*O*-β-rhamnopyranoside **(32)**, kaempferol-3-*O*-β-D-6''(p-coumaroyl) glucopyranoside **(33)**, protocatechuic acid **(34)**, quercetin-3-*O*-β-glucopyranoside **(35)**, 2',6'-dihydroxy-4,4'-dimethoxy-dihydrochalcone **(36)**	Costa et al., (2013)
S. griseo-flavescens (Kunth) A. DC. (Syn: *S. gisnerioides* (Kunth) A. DC.)[2]	Alajuea, Costa Rica	Stem (MeOH)	CC; preparative TLC/EI-MS	Asimilobine **(3)**, *N*-methyllaurotenanine **(10)**, nantenine **(37)**, isocorydine **(38)**	López (1993)
S. guianensis Aublet	Amazonas, Brazil	Trunk wood (Hex)	CC	Liriodenine **(5)**, cassamedine **(39)**	Braz Filho et al., (1976)
		Leaves (hydroethanolic)	HPLC-DAD-ESI-MS/MS	Lucenin-2 **(40)**, vicenin-2 **(41)**, quercetin-3-*O*-rutinoside-7-*O*-rhamnoside **(42)**, quercetin-3-*O*-pentosylpentoside-7-*O*-rhamnoside **(43)**, quercetin-3,7-di-*O*-rhamnoside **(44)**, kaempferol-3-*O*-pentosyl-pentoside-7-*O*-rhamnoside **(45)**, kaempferol-3,7-di-*O*-rhamnoside **(46)**, quercetin-3-*O*-pentosyl-rhamnoside-7-*O*-rhamnoside **(47)**	Negri et al., (2012)
	Ceará, Brazil	Leaves (EtOAc)	CCC; HPLC (acetonitrile/ H2O)	Quercetin **(25)**, 3-*O*-β-D-glucopyranosyl (6→1)-rhamnoside **(48)**, quercentin-7-*O*-rutinoside **(30)**, kaempferol **(49)**	Leitão et al. (2005)
	French Guiana	Leaves (EtOAc)	HPLC UV-Vis; MALDI-TOF	Bulbocapnine **(50)**, (+)-actinodaphnine **(51)**, N-methylindcarpine **(52)**, (+)-11-methoxynorneolistine **(53)**	Marti et al., (2013)
	Minas Gerais, Brazil	Leaves (EtOH)	CC; EI-MS	Kaempferol-3,7,3'-trimethyl-ether **(54)**, kaempferol-3,7-dimethyl-ether **(55)**	Facundo et al., (2012)
		Leaves (EtOH)	UHPLC-MS	Kaempferitrin **(56)**, kaempferol-pentosyl-pentoside-rhamnoside3, kaempferol-pentosyl-rhamnoside, rhamnosyl-kaempferol3, kaempferol dimethyl ether3	Conegundes et al., (2021)

Table 1 Continued

Species name	Distribution	Organ of plant (Type of extracts)	Extraction/ Purification	Compounds[1]	References
S. macrotepala Perkins	Napo, Ecuador	Twigs and leaves (EtOH)	CC/HPLC reverse phase MeOH-H_2O (19:1)	7-Hydroxy-1-oxo-14-norcalamenene **(57)**, (+)-8-hydroxycalamenene **(58)**, (+)-*C*-cadinol **(59)**, 7,14-dihydroxycalamenene **(60)**	El Seedi et al., (1999)
S. pachyantha A. C. Sm.	French Guiana	Leaves (EtOAc)	HPLC UV-Vis; MALDI-TOF	Liriodenine **(5)**, corydine **(61)**, roemerine **(62)**	Marti et al., (2013)
S. pauciflora (Beurl) A. DC.	Cerro Caracoral, Panama	Leaves (Petroleum ether/MeOH)	CC/HPLC; HR-EI-MS	*N*-Methyllaurotenanine **(10)**, laurotetanine **(11)**, boldine **(15)**, sipaucin A **(19)**, *nor*-boldine **(63)**, sipaucin B **(64)** , sipaucin C **(65)**	Jenett- Siems et al., (2003)
S. poeppigi (Tul.) A. DC.	French Guiana	Leaves (EtOAc)	HPLC UV-Vis; MALDI-TOF	Liriodenine **(5)**, lysicamine (66), (+)-*O*-methylisopiline **(67)**	Marti et al., (2013)
S. poeppigi (Tul.) A. DC.	Pará, Brazil	Barks (EtOH)	UPLC-PDA-ESI-MS/MS	Liriodenine **(5)**	Pina et al., (2016)
S. sessiliflora (Kunth) A. DC.	Cundinamarca, Colombia	Leaves (EtOAc)	Soxhlet; CC/ GC-MS	Ushinsunine **(68)**, 4′-*O*-methyl-*N*-methylcoclaurineare **(69)**, liriodenine **(5)**, corydine **(61)**, *N*-methyllaurotetanine **(10)**, boldine **(15)**, *N*-methylcoclaurine **(70)**, stepholidine **(71)**, nantenine **(37)**	Guevara et al., (2016)
S. thecaphora (Poepp. & Endl.) A. DC.	Puerto Napo, Ecuador	Leaves (MeOH)	Sephadex LH-20/RP-HPLC MeOH-H_2O (2:3)	*trans*-Thujane-1α,7-diol 1-*O*-β-D-glucopyranoside **(72)**	Saltos et al., (2014)
S. tonduziana Perkins (syn: *S. grandiflora* (Kunth) Perkins)[2]	Cartago, Costa Rica	Stem bark, woods and roots (EtOH)	Liquid-liquid partition/CC; preparative TLC	Asimilobine **(3)**, liriodenine **(5)**, reticuline **(6)**, (+)-*N*-methyllaurotetanine **(10)**, laurotetanine **(11)**, oxonantenine **(28)**, nantenine **(37)**, anonaine **(73)**	López et al., (1989)

[1]The structures were elucidated using one-dimensional and two-dimensional ^{1}H and ^{13}C NMR techniques and chromatographic, spectrometric and spectroscopic techniques. [2]The taxonomy of plant species is complex, and depending on botanical studies, the species names undergo changes. Some of the species mentioned in this article currently have synonyms (syn) and/or names not accepted by botanists. Synonyms can be checked on The Plant List website (www.theplantlist.org). [3]It was not possible to conclude the position of the substituents on the structures.



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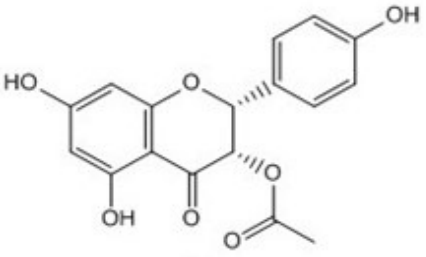

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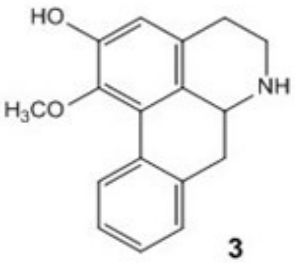

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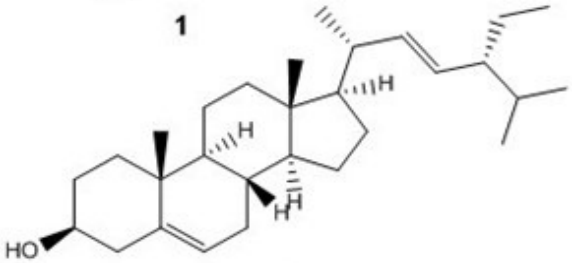

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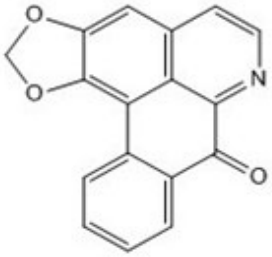

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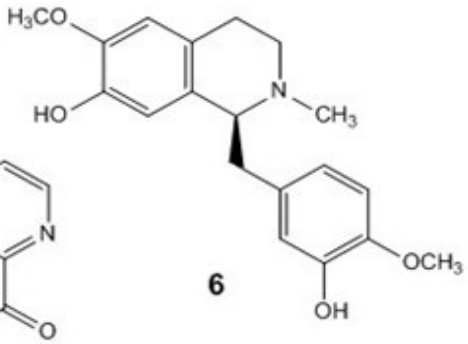

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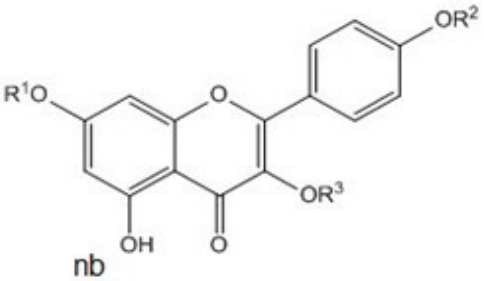

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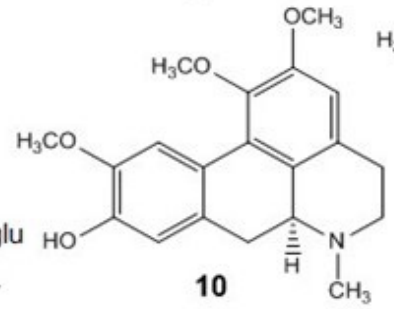
7 R^1= R^2=R^3 = CH_3

8 R^1= R^2=R^3 = (6''-*O*-*p*-coumaroyl)-glu

9 R^1=R^3= H, R^2= -β-[α-rham-(1→2)-glucopyranosyl



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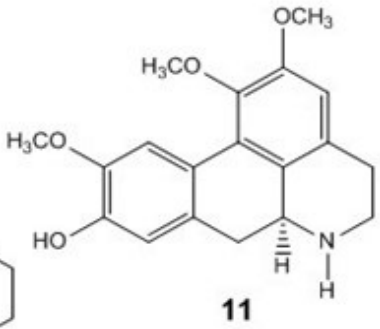

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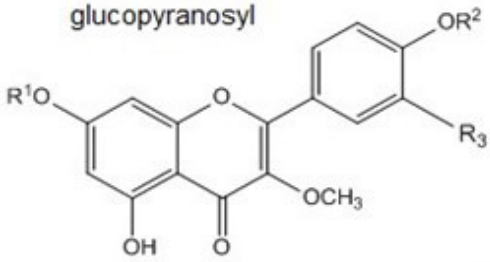
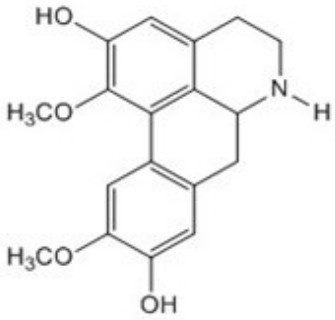


12 R^1= H, R^2 = CH_3, R^3=OCH_3

13 R^1=R^2= CH_3, R^3= OCH_3

14 R^1= CH_3, R^2=R^3= H



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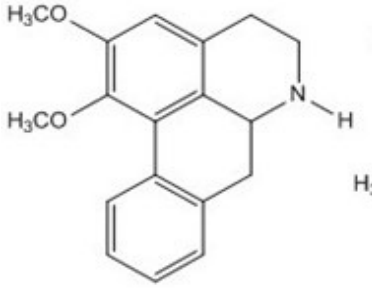

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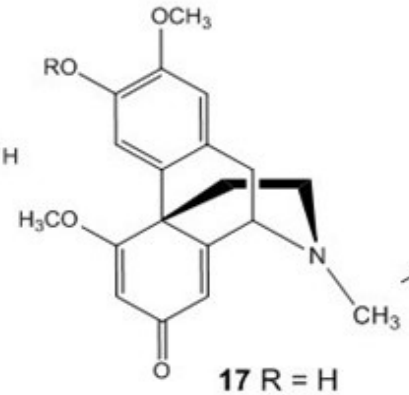
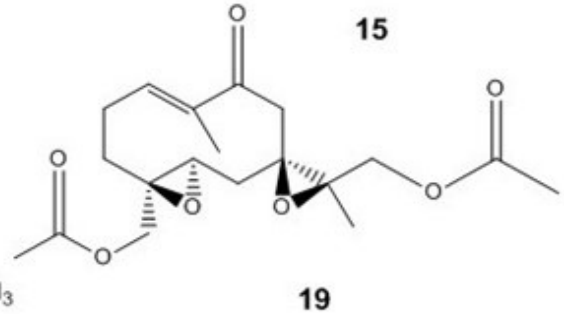


17 R = H

18 R = CH_3



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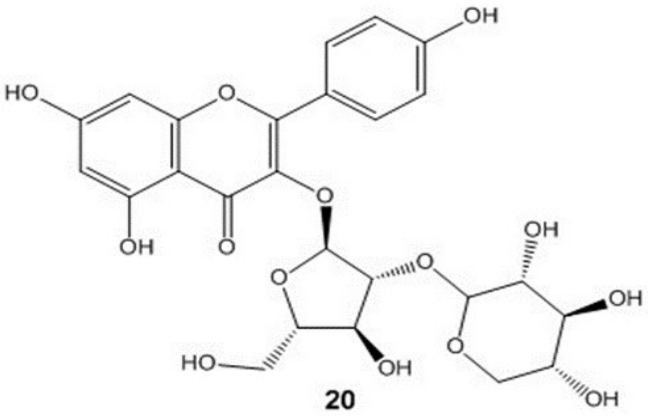

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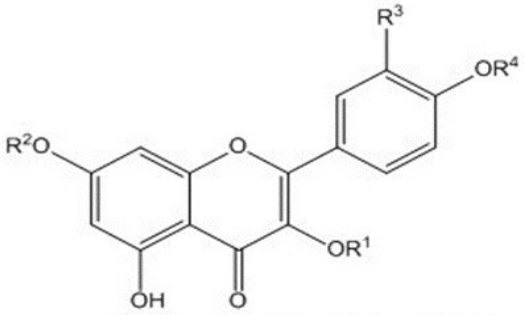
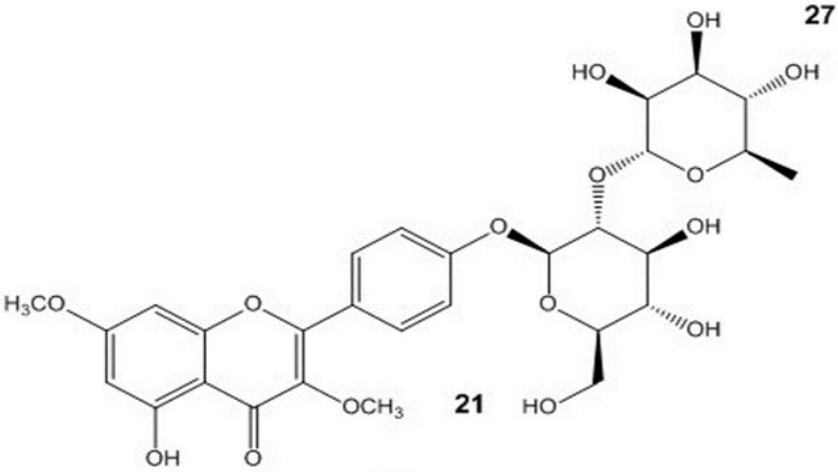


22 R^1 = rut, R^2 =R^4= H, R^3 = OH
23 R^1 = rut, R^2=R^3=R^4= H
24 R^1=R^2=CH_3, R^3= H, R^4 = rut
25 R^1=R^2=R^3=H, R^4 = OH
26 R^1=R^2= CH_3, R^3=R^4= H
27 R^1=R^2=R^4= CH_3, R^3=H



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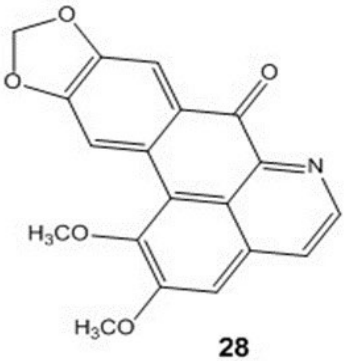

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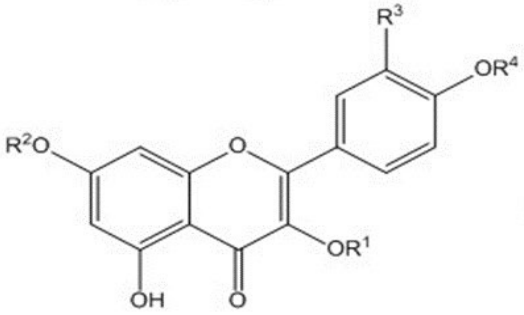
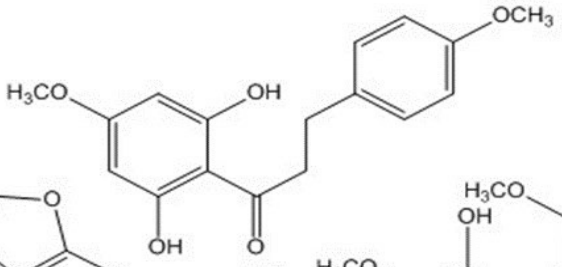


29 R^1= R^2= OH, R^3 = *O*-glu-Rha
30 R^1=R^3= OH, R^2= *O*-glu
31 R^1=H, R^2= *O*-glu, R^3= OH
32 R^1 = H, R^2= *O*-Rha, R^3= OH
33 R^1= H, R^2= *O*-glu-*p*-cinamoyl, R^3= OH
35 R^1= R^3= OH, R^2= *O*-glu



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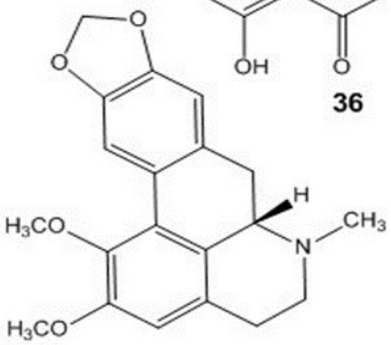

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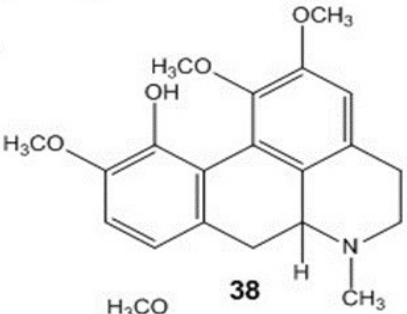

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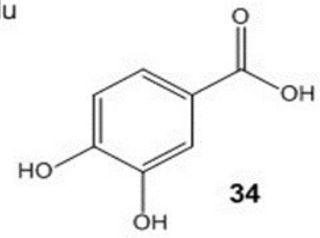

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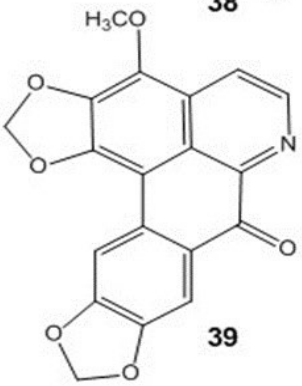

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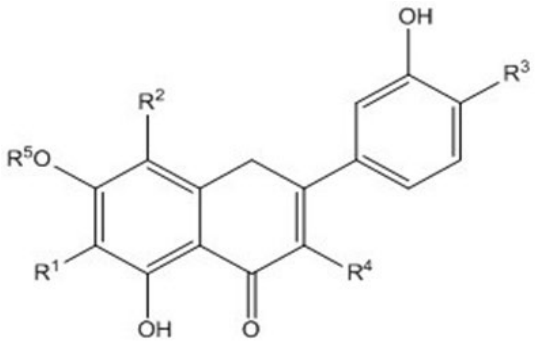
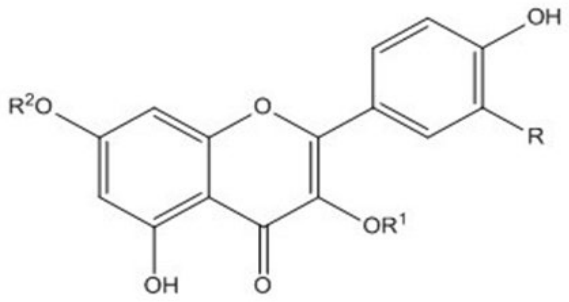
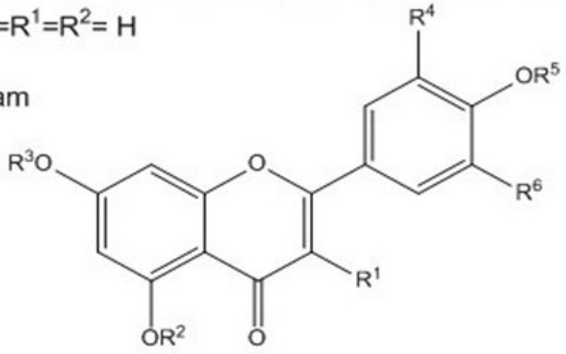
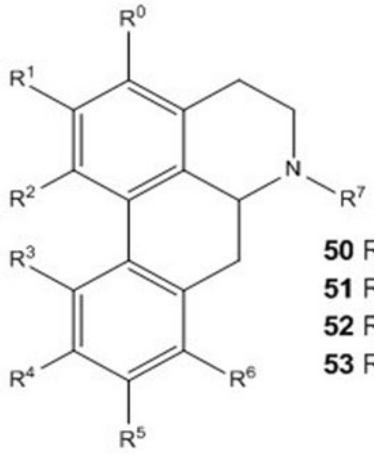


40 R^1=R^2= glu, R^3= OH, R^4=R^5= H
41 R^1=R^2= glu, R^3=R^4=R^5= H
42 R^1=R^2= H, R^3= OH, R^4= rut, R^5= rham
43 R^1=R^2= H, R^3= OH, R^4= pentosyl-pentoside, R^5= rham
44 R^1=R^2= H, R^3= OH, R^4=R^5= rham
45 R^1=R^2=R^3= H, R^4= pentosyl-pentoside, R^5= rham
46 R^1=R^2=R^3= H, R^4=R^5= rham
47 R^1=R^2= H, R^3=OH, R^4= pentosyl-rham, R^5= rham



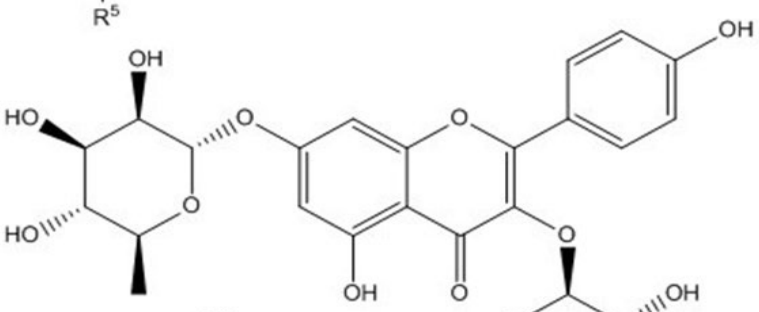
48 R= OH, R^1= β-D-glucopiranosyl (6→1)-rham, R^2= H
49 R=R^1=R^2= H





54 R^1= OCH_3, R^2=R^4=R^5=R^6= H, R^3 = CH_3
55 R^1= OCH_3, R^2=R^4=R^6= H, R^3=R^5= CH_3

50 R^0= R^5=R^6= H, R^1=R^2= O-CH_2-O, R^3= OH, R^4= OCH_3, R^7= CH_3
51 R^0=R^3=R^5=R^7= H, R^1=R^2= O-CH_2-O, R^4= OCH_3, R^5= OH
52 R^0=R^5=R^6= H, R^1=R^3= OH, R^2=R^4= OCH_3, R7= CH_3
53 R^0=R^6=R^7= H, R^1=R^2=R^4=R^5= O-CH_2-O, R^3= OCH_3



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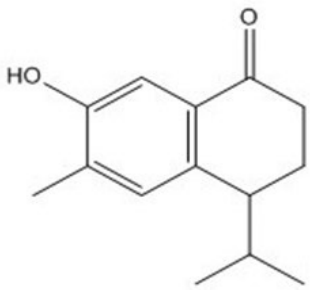

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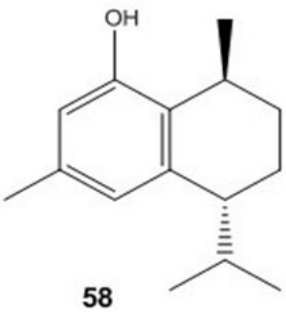

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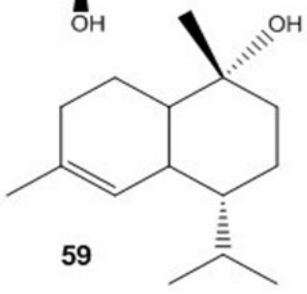

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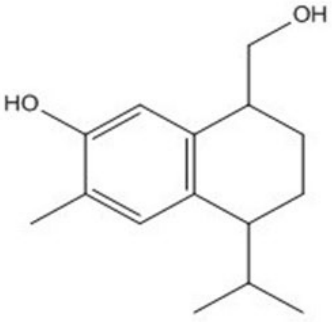

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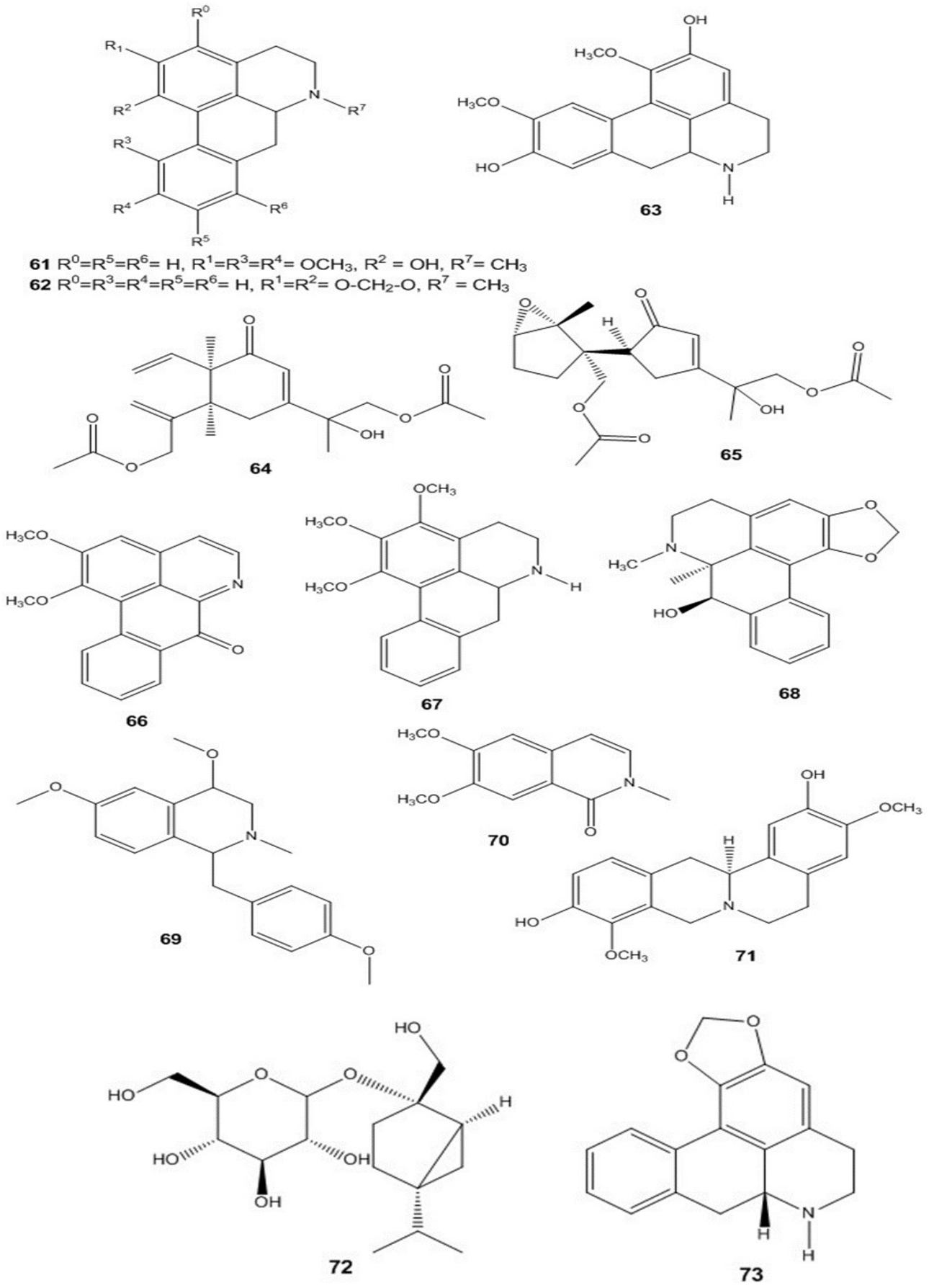


Fig. 2. Structures of chemical components isolated from plant species of the genus *Siparuna*.

4.3. Essential oils (EOs)

EOs usually consist of a mixture of components, *e.g.,* terpenes and phenylpropanoids (Ootani et al., 2013). They are responsible for a plant's smell and flavor characteristics (Bakkali et al., 2008; Camilo et al., 2017; Nunes and Miguel, 2017; Wansi et al., 2018). There are different methods of extracting EOs, including steam distillation, hydro-diffusion, and water distillation (Attokaran, 2017). After the separation process, the components of EOs can be identified by gas chromatography (GC) coupled to a mass spectrometric detector (MS). The GC analysis results in a very powerful tool for EO characterization (Stashenko e Martinez, 2017). *Siparuna* species are mostly known for emitting a pleasant citric smell. Studies involving EOs from these species relate to the identification of some monoterpenes, sesquiterpenes, and bicyclic terpenes. Of the studied *Siparuna* species, there are reports of only 8 species that produce EOs (Table 2), with the extraction of EOs from the leaves being most common. Among the prevalent major compounds, studies conducted between 1984 to 2020 include α-bisabolol **(80)**, and spathulenol **(81)**, germacrene d **(94)** and myrcene **(100)** (Table 2). This survey shows a structural diversity of components present in these EOs, which may become a source for research and application in the pharmaceutical and cosmetic industries, and the industrial sector. The compound structures were numbered and subsequently presented. The most studied species regarding the composition of EO is *S. guianensis* Aublet, in which the presence of sesquiterpenic compounds is remarkable. The leaves of this species were studied in different locations of Brazil, mainly in Minas Gerais and Tocantins. Of the major components identified in the *S. guianensis* EO, the presence of myrcene, 2-undecanone, and germacrene D was notable, which may be associated with the activities presented in this EO (Table 3). The structures of the components identified in the EOs reported for the *Siparuna* species are shown in Fig. 3.

Table 2
Main chemical components identified in essential oils (EOs) of *Siparuna* species.

Species	Localization	Organ of plant	Compounds	References
S. camporum (Tul.) A. DC (syn: *S. guianensis* Aublet)[1]	Maranhão, Brazil	Leaves	α-Phellandrene (12.8%) **(74)**, 6,9-guaiadiene (9.2%) **(75)**, γ-patchouline (28.6%) **(76)**	Dias et al., (2015)
S. conica S. S Renner & Hausner	Choco, Colombia	Leaves	β-Elemene (38.3%) **(77)**, γ-gurjenene (7.6%) **(78)**, δ-cadinene (15.7%) **(79)**	Caballero-Gallardo et al., (2014)
S. cymosa Tolm.	Bahia, Brazil	Leaves	α-Bisabolol (68.9%) **(80)**, spathulenol (3.7%) **(81)**, *p*-cymen-9-ol (7.9%) **(82)**	Da Silva et al., (2020)
S. echinata (Kunth) A. DC	Loja, Ecuador	Leaves	Limonene (10.0%) **(83)**, α-pinene (24.3%) **(84)**, *trans*-ocimene (8.9%) **(85)**, *cis*-ocimene (8.5%) **(86)**	García et al., (2020)
S. guianensis Aublet	Amapá, Brazil	Leaves, nano-emulsified	Curzerenone (18.9%) **(87)**, α-muurolol (11.8%) **(88)**, curzerene (10.5%) **(89)**, γ-muurolene (7.4%) **(90)**, γ-cadinene (5.3%) **(91)**	Ferreira et al., (2020)
	Amazon, Brazil	Leaves	Curzerene (7.1%) **(89)**, atractylone (18.7%) **(92)**, *trans*-β-elemenone (11.8%) **(93)**, germacrene D (7.6%) **(94)**, γ-elemene (7.0%) **(95)**	De Oliveira et al., (2020)
		Leaves, stem, stem bark, root and fruits	*epi*-α-Cadinol (11.0-39.9%) **(96)**, terpinolene (33.4%) **(97)**	Viana et al., (2002)

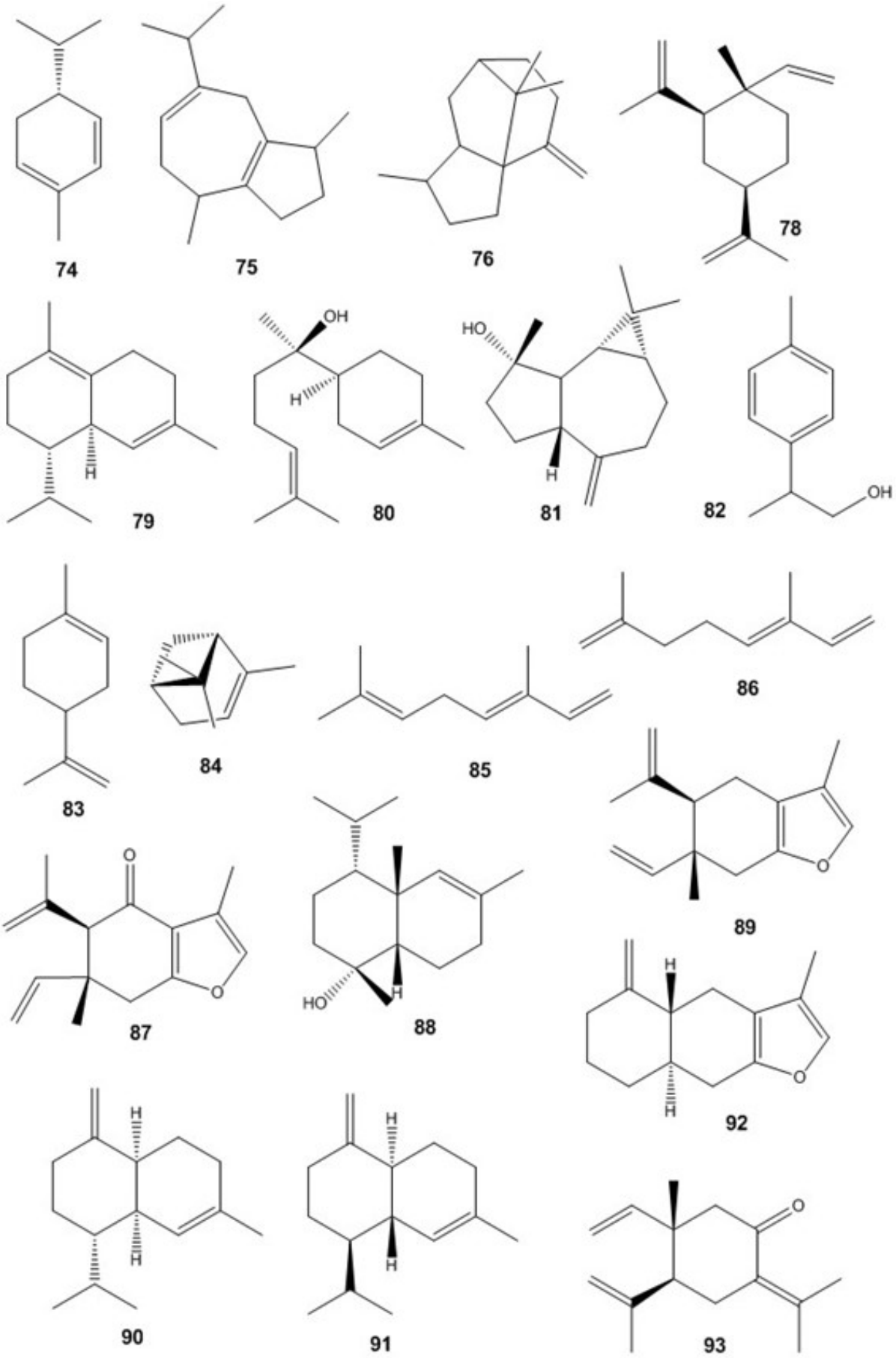
Table 2 Continued

Species	Localization	Organ of plant	Compounds	References
S. guianensis Aublet	Minas Gerais, Brazil	Leaves	Siparunone (30.0-50.0%) **(98)**	Valentini et al., (2010b)
		Leaves	Germacrene D (10.0%) **(94)**, siparunone (14.6 %) **(98)**, (*E*,*E*)-farnesol (18.0%) **(99)**, myrcene (16.0%) **(100)**	De Melo et al., (2017)
		Leaves	Germacrene D (8.7%) **(94)**, myrcene (13.1%) **(100)**, bicyclogermacrene (16.7%) **(101)**	Andrade et al., (2013)
	Panama	Leaves	Curzeronone (25.6%) **(85)**, myristicin (7.9%) **(101)**	Antonio (1984)
	Pará, Brazil	Aerial parts	α-Bisabolol (25.1%) **(80)**, spathulenol (15.7) **(81)**	Zoghbi et al., (1998)
	São Paulo, Brazil	Leaves and fruits	Limonene (13.6%) **(83)**, β-pinene (19.6%) **(103)**, decanoic acid (46.6%) **(104)**, 2-undecanone (31.7%) **(105)**	Fischer et al., (2005)
	Tocantins, Brazil	Leaves	Germacrene D (14.4%) **(94)**, myrcene (39.7%) **(100)**, germacrene B (2.9%) **(106)**, *epi*-curzerenone (18.2%) **(107)**	Moura et al., (2020)
		Leaves	Myrcene (74.9%) **(100)**, 2-undecanone (9.6%) **(105)**	Arruda et al. (2019)
		Leaves and twigs	Myrcene (67.3%) **(100)**, 2-undecanone (8.4%) **(105)**	Portella et al., (2014)
		Leaves	Myrcene (79.7%) **(100)**, 2-undecanone (14.3%) **(105)**	Ferreira et al., (2017)
		Leaves, encapsulated	Germacrene D (9.9%) **(94)**, γ-elemene (7.4%) **(95)**, myrcene (48.6%) **(100)**, epicurzerenone (19.3%) **(107)**	Ferreira et al., (2020)
		Leaves	Myrcene (69.3%) **(100)**, 2-undecanone (9.6%) **(105)**	Lourenço et al., (2018)
		Leaves	*epi*-Shyobunone (18.9%) **(108)**, *iso*-shyobunone (23.9%) **(109)**	Martins et al., (2021)
S. muricata (Ruiz & Pav. A. DC.)	Ecuador	Aerial parts	Guaiol (14.6%) **(110)**, *cis*-cadina-1(6),4-diene (21.2%) **(111)**, atractylone (17.7%) **(92)**, germacrene B (19.7%) **(106)**	Burneo et al., (2021)
S. schimpffiii Diels	Southern, Ecuador	Leaves	γ-Muurulene (7.0%) **(90)**, germacrene D (35.3%) **(94)**, bicyclogermacrene (8.7%) **(101)**, germacrene B (6.4%) **(106)**, cadina-1,4-diene (5.2%) **(112)**	Rivera et al., (2014)
S. thecaphora (Poepp. & Endl.) A. DC	Costa Rica	Leaves	α-Pinene (16.3%) **(84)**, germacrene D (32.7%) **(94)**, β-pinene (13.8%) **(103)**, β-caryophyllene (4.1%) **(113)**	Cocció and Gómez-Laurito (2002)

4.4. Biological activity of *Siparuna* genus

Some *in vitro* and *in vivo* studies involving the biological activity of the *Siparuna* species were described, among them, antimicrobial, antiplasmodic, larvicide, antimalarial, antioxidant, and cytotoxicity activities against cancer cells have been well documented (Table 3). Of these, the most reported are antimicrobial tests. Referring to 30 reports of biological activities found, 16 report the biological activity of EOs. The extracts obtained from polar solvents showed antifungal, cytostatic, anthelmintic, antioxidant, anti-inflammatory, trypanocidal, leishimanicidal, antiplasmodic, cytotoxic and antibacterial activities. The least polar showed antiplasmodic and antibacterial activities.

The EOs of *S. camporum* (Tul.) A. DC., *S. cymosa* Tolm., and *S. macrotepala* Perkins also showed biological properties. However, most studies were performed with *S. guianensis* leaves. Only the EO of the leaves collected in Minas Gerais in Brazil, in several published works, showed antibacterial, antifungal, tick-resistance, anticariogenic, and insecticidal activity (Table 3).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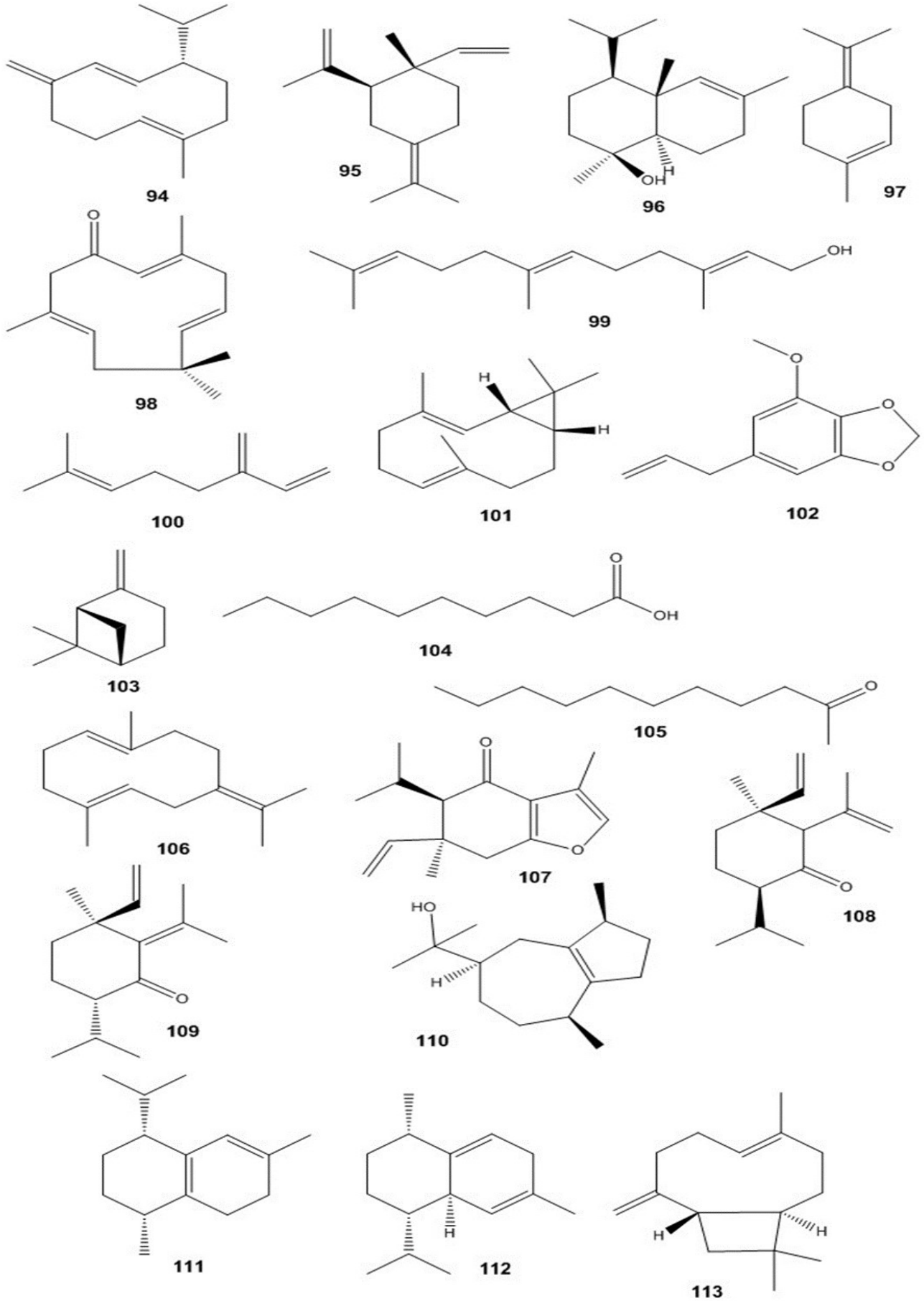

Fig. 3. Molecular structures of the main components present in *Siparuna* EOs.

Table 3
Biological activity of the genus *Siparuna*.

Species name	Distribuition	Organ of plant (Extracts/EO)	AA	ABA	AFA	Others
S. andina (Tul) A. DC[1], *S. pauciflora* (Beurl.) A. DC, *S. tonduziana* Perkins[1] *S. aspera* (Ruiz & Pav.) A. DC	Panama	Leaves (Petroleum ether/EtOAc)	-	-	-	Antiplasmodic, IC_{50}: 3.1 µg mL^{-1} (PoW), 5.4 µg mL^{-1}(Dd2) (Jenett-Siems et al., 2003)
S. arianeae V. Pereira (Syn: *S. guianensis* Aublet)[1]	Minas Gerais, Rio de Janeiro, Brazil	NI	-	*Mycobacterium malmoense*, MIC = 200 µg mL^{-1} (Fonseca et al., 2008)	-	-
		Leaves and barks (MeOH)	-	-	*Colletatrichum lindemuthianum* (MIC 0.72 mL^{-1} mL) (Pinto et al., 2010)	-
S. camporum (Tul.) A. DC[1]	Maranhão, Brazil	Leaves (EO)	-	-	-	Larvicid, LC_{50} = 251 (207-312) mg/L (Dias et al., 2015)
S. cymosa Tolm.	Bahia, Brazil	Leaves (EO)	-	-	-	Cytotoxic, IC_{50} = 25.44 ± 1.55 µg mL^{-1} (CML), 30.88 ± 2.45 µg mL^{-1} (AML) (Da silva et al., 2020)
S. guianensis Aublet	Amazon, Brazil	Leaves (EO)	-	*Streptococcus muttans, Enterococcus faecalis, E. coli*, MIC (µg mL^{-1}) = 125.0, 250.0, 500.0, respectively (De Oliveira et al., 2020)	*Candida albicans* MIC (µg mL^{-1}): 125.0. (De Oliveira et al., 2020)	
	Roraima, Brazil	Leaves (EO)	-	-	-	Cholinesterase-inhibition and *in silico* (Martins et al., 2021)
	Bahia, Brazil	Leaves (EO)	-	-	*Rhizoctonia solani, Sclerottium rolfsii* inhibition of 1.5 µl mL^{-1} and 2.0 µL mL^{-1}, respectively (Arruda et al., 2019)	-
	Cedeño, Bolívia	Leaves (EtOH)	-	-	-	Cytostatic LC_{50} (µg mL^{-1}) = 30.0 (PC-3), 23 (MCF7), 10.0 (MDA-MB-231), 36 .0 (4T1), 10.0 (RAW-267) (Taylor et al., 2012)

Table 3 Continued

Species name	Distribuition	Organ of plant (Extracts/EO)	AA	ABA	AFA	Others
S. guianensis Aublet	Minas Gerais, Brazil	Leaves (EtOH, AcOEt, EO)	-	-	-	Anthelmintic 0.05-1.0, 0.05-0.8, 0.2-1.0 mg/mL (Carvalho et al., 2019)
		Leaves (OE)	-	*Streptococcus mutans* (MIC, μg mL^{-1}) 50,0 *Mycobacterium avium* (MIC, 250.0 μg mL^{-1}) (De Melo et al., 2017); *S. aureus* (MIC = 125.0 μg ML^{-1}), *L. monocytogenes* (MIC = 250.0 μg ML^{-1}), *E. coli* (MIC = 500.0 μg ML^{-1}) (Andrade et al., 2015)	-	Anticariogenic, *S. mutans* (MIC = 50.0 μg mL^{-1}), *Streptococcus mitis* (MIC = 100.0 μg mL^{-1}) (De Melo et al., 2017); Inseticide: *Myzuz persicae* LC_{95} = 1.08 mg/cm^2 (Toledo et al., 2019)
		Leaves (MeOH)	Dioxyribose assay (100.0 μg mL^{-1}) (Conegundes et al., 2021)	-	-	Anti-inflammatory (10.0 mg/kg), antinociceptive (10.0 mg/kg) (Conegundes et al., 2021)
		Leaves (H_2O)	DPPH; radical inhibition of nitric oxide, 100.0 μg mL^{-1} (De Almeida et al., 2021)	-	-	-
	Paraná, Brazil	Leaves (EO)	-	-	-	Leishmanicide, IC_{50} = 162.25 μg mL^{-1} (Andrade et al., 2016)
	São Paulo, Brazil	Leaves (EtOH)	-	-	-	Trypanocidal, leishmanicide, 100.0 mg mL^{-1} (Tempone et al., 2005)
	Tocantins, Brazil	Leaves (EO)		*E. coli, S. aureus, P. aeruginosa, Streptococcus pyogenes*, MIC 1.30; 0.87; 0.87; 0.87 μg mL^{-1}, respectively (Moura et al., 2020)		
		Leaves (EO)	-	*S. aureus*, MIC 95.0 μg mL^{-1} (Bessa et al., 2005)	-	Ovicide, (0.025 to 0.550 μg/cm^2) (Aguiar et al., 2015); insecticide, (0.08 μg of EO/cm^2) (Ferreira et al., 2017)

Table 3 Continued

Species name	Distribuition	Organ of plant (Extracts/EO)	AA	ABA	AFA	Others
S. guianensis Aublet	Tocantins, Brazil	Leaves (EO, encapsuleted	-	-	-	Larvicid, 50% for 19 days with 100% mortality (Ferreira et al., 2019)
S. gigantotepala S. S Renner & Hausner	Valle del Cauca, Colombia	Leaves (EtOH)	DPPH 32.00 ±1.00 (Casteñeda et al., 2016)	-	-	-
S. macrotepala Perkins	Morona-Santiago, Ecuador	Leaves (EO)	Bioautography HPTLC with DPPH and ABTS, 29.37±1.15 and 0.80±0.03, respectively (Noriega et al., 2019)	-	-	-
S. poeppigi (Tul.) A. DC	Pará, Brazil	Barks (EtOH)	-	-	-	Antiplasmodic, IC_{50} = 5.95 ± 0.49 µg mL^{-1} (Pina et al. 2016)
S. sessiliflora (Kunth) A. DC	Cudinamarca, Colombia	Leaves (éter de petróleo)		-	*Fusarium oxysporum* (MIC 2 mg mL^{-1}), *Alternaria sp*, *Aspergillus niger* (MIC 4.0 mg mL^{-1}) (Guevara et al. 2010)	-
	Tolima, Colombia	Leaves (EtOH)	DPPH (304.1 ± 3.7), ABTS (47.2 ± 2.5) (Peréz-Jaramillo et al., 2017)	-	-	-
S. thecaphora (Poepp. & Endl.) A. DC	Costa Rica	Barks, unripe fruit, ripe fruit	-	-	-	Antimalarial: *P. Berghei* (IC_{50} = 2.0; 1.0; 3.9 µg mL^{-1}, respectively (Chinchilla et al., 2012)

EO: Essential oil; AA: Antioxidant activity; ABA: Antibacterial activity; AFA: Antifungal activity; ABTS: 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assay.
[1]The taxonomy of plant species is complex, and depending on botanical studies, species names undergo changes. Some of the species mentioned in this article currently have synonyms and/or names not accepted by botanists. Synonyms can be checked on The Plant List website (www.theplantlist.org).

4.4.1. Antibacterial

Due to the increasing occurrence of microorganisms resistant to current antibacterial compounds, the search for natural alternative substances has gained importance (Carvalho et al., 2014). Although many pharmaceutical industries produce new antibiotics and modify some existing drugs, in the past thirty years, microorganism resistance to these compounds has increased, resulting in serious public health issues (Santos et al., 2007). Some of the most common microorganisms in regard to bacterial resistance include the Gram-positive *Staphylococcus aureus*, and the Gram-negative *Escherichia coli*, *Escherichia coli* EPEC, *Salmonella enterica*, and *Acinetobacter baumannii* (Alves et al., 2016; Souza et al., 2016). Resistance of Gram-positive and Gram-negative bacteria to antibiotics or drugs with antibacterial properties is related to these

microorganism's cell wall structure. Gram-negative bacteria are usually more resistant to antibacterial action, as their cell wall is protected by a lipopolysaccharide layer. In Gram-positive bacteria, the antibacterial action mechanism of a plant extract most likely results from the interaction between bacteria and the peptidoglycan present in the bacteria cell wall, which is a weaker barrier than the Gram-negative bacteria cell wall (Rabêlo et al., 2014). Research involving the study of antibacterial activity in extracts from *Siparuna* species have revealed their biological potential. *S. guianensis* Aublet EO has exhibited antibacterial activity in the presence of *E. coli*, *S. aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* (Moura et al., 2020). *E. coli* and *S. aureus* were the most tested bacteria against the species, and *S. guianensis* Aublet showed greater efficiency. Few tests were performed with fungi. The action of *S. guianensis* against *Candida albicans* is noteworthy.

4.4.2. Antioxidant

The organisms of human beings constantly produce free radicals from their metabolic activities. Despite being a natural process, when these metabolic activities occur excessively, they may result in oxidative stress (Rodrigues et al, 2016), leading to tissue alterations responsible for several diseases, such as cancer, cardiovascular diseases, cataract, weakened immune system, and brain disorders (Sousa et al., 2007). This oxidative stress may be countered with antioxidants produced by the body or acquired from external sources, such as food and drugs (Nascimento et al., 2011). Antioxidants prevent free radicals from damaging cells and tissues and may be naturally present in food in the form of phenolic compounds (Milani et al., 2012). Studies of antioxidant activities were found in the literature for few species of the genus *Sipurana*. Using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method, leaf extracts from *Siparuna*, namely *S. gigantotepala* S.S Renner & Hausner and *S. macrotepala* Perkins were found to inhibit the scavenging of free radicals. Other methods were used to assess antioxidant activity between 2016 and 2021 (Table 3). Considering the report of isolation of several flavonoids in extracts of *Siparuna* species, these species may be promising in research involving antioxidant action.

5. Conclusion and future prospects

Although the genus *Siparuna* comprises few species, compared to other groups, this review reinforces the phytochemical and biological importance of its species which exhibit a wide variety of chemical structures. The species of *Siparuna* studied so far have proven to be promising for the isolation of flavonoids and alkaloids as well as chemical constituents with great biological potential. The use of more sophisticated chromatography techniques, such as high-speed countercurrent chromatography (HSCCC) and ultra-high performance liquid chromatography (UHPLC), may increase the number of isolated substances and also enable the elucidation of new substances. Research involving the synthesis of these substances, and the proposal of new structures can be carried out. In addition, tests with extracts and EOs from these plants and the isolated substances can still be extended in terms of the study of their biological properties. Brazilian biomes are rich in plants that have not yet been studied in terms of classes of chemical substances and their pharmacological properties, including many species of the genus *Siparuna* such as *S. krukovii* AC Sm. (found in the Brazilian states of Pará, Goiás, and Amazonas) and *S. tomentosa* (occurring in São Paulo, Rio de Janeiro, and Minas Gerais). Many studies can still be carried out with these species, contributing to the advancement of knowledge in natural products and medicinal chemistry. The continuity of natural product research involving this genus is promising.

List of abbreviations

AA: antioxidant activity; **ABA**: antibacterial activity; **AFA**: antifungal activity; **CC**: column chromatography; **CCC**: counter-current chromatography; **EO**: essential oil; **ESI-MS**: electrospray ionization-mass spectrometry; **EtOAc**: ethyl acetate; **GC-MS**: gas chromatography-mass spectrometry; **Hex**: hexane; **HPLC**: high performance liquid chromatography; **HPLC UV-vis**; **MALDI-TOF**: high performance liquid chromatography coupled with a ultraviolet-visible; matrix-assisted laser desorption/ ionization-time of flight mass spectrometry; **HPLC-HR-EI-MS**: high performance liquid chromatography coupled with high mass resolution electro-spray ionization mass spectrometry; **HPLC-DAD-ESI-MS/MS**: high-performance liquid chromatography-diode array detection-electro-spray ionization mass spectrometry/ mass spectrometry; **HR-ESI-MS**: high resolution electrospray ionization mass spectrometry; **IC**: inhibitory lethal concentration; **LC**: lethal concentration; **MIC**: minimum inhibitory concentration; **NMR**: nuclear magnetic resonance; **RP-HPLC**: reversed phase-high performance liquid chromatography; **TLC/EI-MS**: thin-layer chromatography/electrospray ionization mass spectrometry; **TLC**: thin layer chromatography; **UHPLC-MS**: ultrahigh-pressure liquid chromatography couple with mass spectrometry; **UPLC-PDA-ESI-MS/MS**: ultra-performance liquid chromatography-photodiodide array- electrospray ion source-mass spectrometry/mass spectrometry.

Conflict of interest

The authors declare that there is no conflict of interest.

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